CHAPTER 01

General introduction
General rationale

Substance use disorder (SUD) is considered a chronic, relapsing brain disorder, which is characterized by a continuation of compulsive drug taking even in the presence of severe negative side-effects (Leshner 1997). Despite currently available treatments, many substance abusers display high rates of relapse. Deep brain stimulation (DBS) is a promising alternative treatment for therapy-resistant SUD. Although DBS as therapeutic intervention is already approved by the Food and Drug Administration (FDA) for Parkinson’s disease, and is clinically applied on a small scale in other psychiatric disorders such as OCD and depression, the effectiveness and optimal brain target for DBS as a treatment for SUD is still under debate.

The aim of this thesis is to explore and better understand 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. This, 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 (Moeller et al. 2001).

Heroin use disorder

This thesis mainly focusses on addiction to the opioid heroin. Heroin is considered to be one of the most harmful substances to users and others, as was found by expert panels in the United Kingdom and The Netherlands (Nutt et al. 2010; van Amsterdam et al. 2015). Harm to heroin users appeared mainly related to drug-specific and drug-related mortality, which is much more than for most other drugs (Nutt et al. 2010). In relation to this, the Amsterdam Cohort Study among drug users reported that at least 27% of heroin users had died within 20 years after starting regular drug use (Termorshuizen et al. 2005).

In the Netherlands, opiates, alcohol and cannabis use constitute the main group of drugs abusers, disregarding nicotine. Around 97% of opiate-dependent patients have been in treatment for a period longer than three years, due to harm reduction strategies. The number of people suffering from opiate dependence has substantially decreased over the past ten years, from 13,500 in 2006 to 9,000 in 2015. In addition, a shift in age group has been observed in the past ten years, currently the largest group of opiate users is between 40-54 years of age and there are very new users in comparison to other drugs of abuse (Wisselink et al. 2016). In sharp contrast, the number of people suffering from heroin use disorder in the USA has doubled from 314,000 in 2002 to 681,000 in 2013 (Substance Abuse and Mental Health Services Administration 2014). These numbers are presumably underestimated, because heroin is mostly abused amongst problematic drug...
users, who are less represented in public screenings and surveys. In addition, heroin is frequently used by polydrug users, often in combination with cocaine or alcohol. This makes interpretation of these numbers difficult (European Monitoring Centre for Drugs and Drug Addiction 2013; Wisselink et al. 2016). Demographic studies show that current heroin users entering treatment are primarily older, white men and women living primarily in non-urban areas, in contrast to 50 years ago, when heroin abuse was mainly an inner-city, minority-centred problem (Cicero et al. 2014; Wisselink et al. 2016). Together, these studies emphasize the large health, social and economic burden of heroin dependence, resulting in a substantial global public health problem. Despite currently available treatments which are mainly focussed on harm reduction, prevalence of stable abstinence from opioid use is low (Hser et al. 2015). Thus, the development of new prevention and treatment strategies is of great importance.

**Translational animal models of addiction**

In order to develop novel treatment interventions for SUD, the underlying behavioural and neurobiological mechanisms need to be better understood. Several animal models have been developed over the past years that are suitable to study these mechanisms. The drug self-administration model and the conditioned place preference model are the most commonly used models. An extensive overview of these models and their translational validity is described in chapter 2. In short, the drug self-administration model, which is used in this thesis, relies on the propensity of stimuli which become conditioned and associated with a drug memory over the course of drug taking (Shaham et al. 2003). In this model, it is possible to study different aspects of drug taking and drug seeking separately. In the acquisition phase, drug taking is monitored. In addition, the motivation for a reward can be investigated by making use of a progressively-increasing schedule of responses necessary in order to obtain one drug reward. Lastly, reinstatement to drug use after an extinction period is modelled by exposing the subjects to conditioned stimuli, drug priming or stress; factors that are well-known to trigger craving and relapse in drug addicted patients (Fuchs et al. 2008; Shaham et al. 2003).

**Neurobiology of addiction**

Drugs of abuse share the ability to increase dopamine levels in the nucleus accumbens (NA) (Di Chiara and Imperato 1988). Here, I will briefly summarize the main brain pathways in SUD. An extensive overview of the neurobiology of addiction is provided in chapter 2.

Opiates increase dopamine levels by inhibiting GABAergic interneurons in the ventral tegmental area (VTA), thereby indirectly activating dopaminergic cell bodies in this
brain region (Johnson and North 1992). These dopamine neurons in the VTA send projections to the NA, the amygdala and the medial prefrontal cortex, brain regions which are thought to be critical for immediate reward and the initiation of drug-seeking (Koob and Volkow 2010). In addition, glutamatergic projections from the prefrontal cortex (PFC), important for executive control and decision making, to the NA have been shown to be important in maintenance and relapse of substance dependence (Kalivas and Volkow 2005). Drug-induced neuroadaptations in the mesocorticolimbic dopamine system and the glutamatergic corticolimbic circuitry are thought to mediate compulsive drug use and relapse (Kalivas and O’Brien 2008; Nestler 2001; Van den Oever et al. 2010b).

**Impulsive behaviour**

Impulsive behaviour is generally defined as: “Actions which are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and often result in undesirable consequences” (Durana and Barnes 1993). Thus, impulsivity is regarded as acting or making decisions without appropriate forethought. Quick decision making can represent an evolutionary advantage, for instance to increase opportunities or respond to a quickly changing environment (Winstanley et al. 2010). However, long-lasting elevated levels of impulsive behaviour can be unfavourable. Maladaptive impulsivity is recognized as a key feature of many psychiatric disorders, such as attention deficit/hyperactivity disorder (ADHD), SUD and behavioural addictions, obsessive-compulsive disorder (OCD), borderline personality disorder and bipolar disorder (Moeller et al. 2001). Due to this transdiagnostic symptom of many psychiatric disorders, interventions that effectively target impulsive behaviour are considered for treatment of these psychiatric disorders.

Distinct forms of impulsive behaviour have been identified (Evenden 1999). Roughly, impulsivity can be divided into impulsive action and impulsive choice (Figure 1.1). Impulsive action, or motor impulsivity, is characterized as the inability to inhibit either inappropriate (action cancellation) or planned (action inhibition) motor responses. Inappropriate responses are thought to arise as a consequence of anticipation of a reward or reward-related cue, whereas planned motor responses are already initiated responses that need to be volitionally controlled and inhibited (Dalley et al. 2011). On the other hand, impulsive choice is defined as a preference for an immediate, but less favourable, reward over a delayed, but more beneficial, reward. Besides delayed gratification, risk or uncertainty based decisions can also be regarded as a form of impulsive choice, and can be measured by probability discounting tasks and gambling-related decision making tasks. Interestingly, the different forms of impulsive behaviour do not correlate on the individual level (Broos et al. 2012b; Robinson et al. 2009; Solanto et al. 2001), supporting the notion that distinct forms of impulsive behaviour partly rely on different brain circuits and neurochemical mechanisms (Evenden 1999; Pattij and Vanderschuren 2008).
Translational animal models of impulsive behaviour

A large variety of translational animal models have been developed to study different forms of impulsivity in rodents. The paradigms that have been used in this thesis to study impulsive action and impulsive choice will be discussed below.

**Action inhibition – Five-choice serial reaction time task**

To study impulsive action in a laboratory setting, typically the five-choice serial reaction time task (5-CSRTT) is used (Robbins 2002). The 5-CSRTT is analogous to the human continuous performance task (CPT). This CPT was originally developed to monitor attention in humans, in which subjects had to continually monitor the location of a visual stimulus in one of five locations (Wilkinson 1963). Comparable to the CPT, in the 5-CSRTT rodents learn to respond to a stimulus light, which is presented in one of five holes in a curved wall of the operant chamber to earn a food reward (Figure 1.2). A prematurely expressed response, i.e. before a stimulus is presented, is considered a measure of impulsive action, reflecting the inability to inhibit pre-potent actions (Robbins 2002). Another measure of inhibitory control which can be monitored in the 5-CSRTT are perseverative responses, a persistent continuation of an action, despite presentation of a reward. Perseverative responses are often referred to as “compulsive responses” (Robbins et al. 2012).

**Action cancellation – Stop-signal task**

Action cancellation is oftentimes assessed in the stop-signal task (SST). The rodent version of this task is adopted from the SST used for clinical assessment in humans in which subjects need to respond as quickly as possible to a stimulus. However, on a subset of trials, a stop-signal is presented at varying delays after the stimulus presentation and the

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Figure 1.1 Distinct forms of impulsivity and in brackets the translational animal models that are used to study these impulsive behaviours. 5-CSRTT five-choice serial reaction time task; DRT delayed reward task; GT gambling task (not used in this thesis); SST stop-signal task.
subject must cancel the response to the stimulus. In the rodent version, animals learn to respond to a stimulus light to earn a food reward. Analogous to the human SST, in 25% of the trials a stop-signal is presented in the form of a tone, and the planned response must be inhibited to perform correctly (Figure 1.3). The estimated stop-signal reaction time (SSRT) reflects the ability to inhibit an already initiated action (Verbruggen and Logan 2008).

**Impulsive choice – Delayed reward task**

Delay-discounting tasks are used to model the inability to prioritize a future reward over satisfying the desire for an immediate reward (Ainslie 1975). In these tasks, the subject needs to choose between a small immediate reward and a large but delayed reward, with varying delays. Typically, the preference for the large reward decreases with increasing delay, yielding a hyperbolic discounting curve. The delay at which the preference for the small and large reward is equal is called the indifference point (Mazur 2006). In clinical settings, mostly questionnaires are used with fictitious rewards, such as money, to establish discounting behaviour (e.g. (Kirby and Petry 2004). The rodent version of the delayed reward task (DRT) is performed in operant chambers and makes use of within-session increasing delays for a large food reward compared to an immediate small food reward (Figure 1.4) (Evenden and Ryan 1996).

**Validity of the animal models**

All rat models for impulsive behaviour that have been used for this thesis are translated from human neuropsychological tasks and are therefore to a large extent analogous to the original clinical tasks, presuming a high face validity for all three tasks. Comparison of behavioural effects resulting from pharmacological and lesion studies in rodents with clinical neuroimaging studies reveals similar brain circuitries (Eagle and Baunez 2010; Eagle et al. 2008; Winstanley 2011; Winstanley et al. 2006). This consistency between rodent and human tests indicates that impulsive behaviour as measured in the above-mentioned tasks relies on comparable underlying neurobiological constructs, which is important for the construct validity of the tasks. However, it has been shown that the predictive validity of different rat models may vary in terms of the class of tested drugs, noradrenergic drugs seem to be most comparable between the CPT and 5-CSRTT, whereas psychostimulant drugs are more reliable in the SST and DRT (Winstanley 2011).
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**Figure 1.2** A schematic overview of the five-choice serial reaction time task. The task starts with an entry in the food magazine, which is followed by an intertrial interval of 5s. Next, one of the five holes is illuminated for 1s. A response during the intertrial interval, before stimulus presentation, is recorded as a premature response. A response in the illuminated hole during stimulus presentation or within 2s after stimulus presentation (limited hold) is registered as a correct response and rewarded with a food pellet. Responses in a non-illuminated hole is counted as an incorrect response. No responses during stimulus presentation or limited hold are counted as an omission. Omissions, premature, and incorrect responses are followed by a time-out period of 5s in which the house-light is switched off.

**Figure 1.3** A schematic overview of the stop-signal task. Animals learn to respond to a stimulus light in outer left or right hole to earn a food reward. However, in 25% of the trials a stop-signal is presented in the form of a tone at various delays, and the planned response must be inhibited to perform correctly. The estimated stop-signal reaction time (SSRT) reflects the ability to inhibit an already initiated action.

**Figure 1.4** A schematic overview of the delayed reward task. In every trial, the second and fourth nose poke hole are illuminated. Responding in one hole results in a small immediate reward (one food pellet), whereas responses in the other hole result in a large but delayed reward (four food pellets). The delay for the large reward is increased over five blocks of 10 trials from 0 to 40s.
Neurobiology of impulsive behaviour

Both human and animal studies have shown that corticostriatal circuits play an important role in impulsive behaviour (Jupp et al. 2013a). The NA is implicated as a key brain region involved in the expression of impulsive behaviour (Basar et al. 2010). Within the NA there is functional compartmentalization (Groenewegen et al. 1999). In general, the NAcortex region is considered to be primarily involved in impulsive behaviour, although the NAShell region also plays a role. The NAcortex region appears to play a role in conditioned behaviour and goal-directed actions, whereas the NAShell seems to be predominantly involved in unconditioned responses and the assessment of attractiveness of a stimulus (Basar et al. 2010; Dalley et al. 2011). Besides the NA, other regions such as the PFC, orbital frontal cortex (OFC) and amygdala are important brain regions in the modulation of impulse control (Dalley et al. 2011). The contribution of the brain regions and neurotransmitter systems partly varies between different impulsivity subtypes (Jupp et al. 2013a), supporting the notion of neurobiologically distinct constructs. Within corticostriatal brain regions, the monoaminergic neurotransmitters play an important role in impulsive behaviour (Pattij and Vanderschuren 2008). Mainly dysfunctional dopamine and noradrenaline signalling have been implicated in disorders related to impulsive behaviour, such as ADHD (Del Campo et al. 2011).

Substance use disorder and impulsivity

Many criteria of the DSM-5 for SUD refer to impaired impulse control (see Box 1). Indeed, clinical studies have shown that substance dependent subjects display elevated impulsivity compared to healthy control subjects (de Wit 2009; MacKillop et al. 2011; Perry and Carroll 2008). In addition, a high co-morbidity exists between substance abuse and psychiatric disorders characterized by compulsive or impulsive behaviour, such as ADHD (Wilson 2007). Also, decreased levels of impulse control are hypothesized to contribute to the risk for addiction (Ersche et al. 2010), relapse vulnerability and poor treatment outcomes (Jentsch and Taylor 1999; Pattij and De Vries 2013; Stevens et al. 2014).

On a neurobiological level, there is a large overlap in brain regions that are involved in SUD and poor decision-making, such as the PFC, amygdala and the striatum (Noel et al. 2013). It is hypothesized that both SUD and impulsive responding result from failures in top-down control from the PFC to NA (Dalley et al. 2011; Kalivas and Volkow 2005). This intriguing link between SUD and impulsivity provides new opportunities for interventions aimed at reducing impulsive behaviour and thereby conceivably decreasing the propensity for relapse to drug seeking.
Box 1. DSM-5 criteria for substance use disorder

1. The substance is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful effort to cut down or control use of the substance.
3. A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects.
4. Craving, or a strong desire or urge to use the substance.
5. Recurrent use of the substance resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use.
7. Important social, occupational, or recreational activities are given up or reduced because of use of the substance.
8. Recurrent use of the substance in situations in which it is physically hazardous.
9. Use of the substance is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
   a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
   b. A markedly diminished effect with continued use of the same amount of the substance.
11. Withdrawal, as manifested by either of the following:
   a. The characteristic withdrawal syndrome for that substance (as specified in the DSM-5 for each substance).
   b. The substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

Although clinical data strongly suggest a relationship between impulsivity and substance dependence, it remains unclear whether elevated levels of impulsivity are a pre-existing trait or a consequence of drug abuse (de Wit 2009; Verdejo-Garcia et al. 2008; Winstanley et al. 2010). In this regard, preclinical rodent models have revealed a causal relationship between pre-existing impulsivity traits and vulnerability to psychostimulant drug self-administration including cocaine and nicotine. Moreover, these studies demonstrated that different subtypes of impulsive behaviour predict different stages of the addiction process (Belin et al. 2008; Broos et al. 2012a; Dalley et al. 2007; Diergaarde et al. 2008; Perry et al. 2008).

In contrast to psychostimulants, the relationship between impulsive behaviour and opioid use disorder has received less attention. Thus far, clinical studies have demonstrated that heroin dependent subjects display elevated levels of impulsive
decision making (Clark et al. 2006; Kirby and Petry 2004; Kirby et al. 1999; Madden et al. 1997), but the direction of this relationship is not clearly identified. It has been shown that rats selected on impulsive action did not differ in heroin intake (McNamara et al. 2010), suggesting that this type of impulsive behaviour is not predictive of heroin intake. In chapter 3 of this thesis, we aim to identify whether impulsive choice is predictive of aspects of heroin taking and seeking. This will provide more insight in relationship between heroin addiction and impulsive behaviour, and consequently the treatment potential of impulsive behaviour in new therapies for heroin use disorder.

**Deep brain stimulation**

Deep brain stimulation was originally developed for movement disorders (Benabid et al. 1987). For approximately 20 years DBS has been investigated as a potential therapy for treatment-resistant patients suffering from psychiatric disorders such as major depression and OCD (Goodman and Alterman 2012). More recently, DBS for treatment of therapy-resistant substance dependence has been suggested (Luigjes et al. 2012). In contrast to other (less invasive) stimulation techniques such as transcranial magnetic stimulation and transcranial direct-current stimulation, DBS electrodes are implanted in the brain and deliver electrical pulses to a specific brain target. This offers the opportunity for continuous stimulation, and to reach deep subcortical structures that are implicated in psychiatric disorders. Several studies have shown that treatment with DBS for different types of psychiatric disorders tremendously improves quality of life (Benabid et al. 2009; Denys et al. 2010; Greenberg et al. 2010).

DBS electrodes receive electrical pulses via insulated wires from a pulse generator implanted subcutaneously below the clavicle. Stimulation parameters such as amplitude, pulse width and frequency are adjustable to the individual patient, and the interaction of these parameters determines the volume of stimulated tissue and which neuronal elements are modulated (Gubellini et al. 2009). In the clinic, stimulation is applied at high frequency (>100 Hz), with a short pulse width (60-90 µs) and amplitude of around 3 V, which are thought to modulate myelinated axons (Gubellini et al. 2009) in a proximity of 3 mm around the electrode (Gielen and Molnar 2012). Moreover, stimulation is reversible, which is another major advantage of this technique.

Until now, a few case reports have been published on successful DBS treatment of SUD including alcohol (Heinze et al. 2009; Kuhn et al. 2011; Muller et al. 2009) and heroin use disorder (Kuhn et al. 2014; Valencia-Alfonso et al. 2012; Zhou et al. 2011). Together with promising studies in rodent models of SUD (Knapp et al. 2009; Levy et al. 2007; Rouaud et al. 2010; Vassoler et al. 2008), these studies suggest that DBS is a potential treatment for SUDs. A majority of the studies have investigated the NA as a
putative therapeutic target, based on its important role in motivated behaviour (Luigjes et al. 2012).

The current leading hypothesis on the mechanism of DBS states that DBS does not only influence local neurons around the electrode, but also influences passing neurons and thereby a wider neuronal circuitry (Figure 1.5) (Deniau et al. 2010). During DBS, evoked synaptic effects, antidromic activation and neurotransmitter release has been found in structures connected to the stimulated area (e.g. (McCracken and Grace 2007; 2009). Psychiatric disorders, which have been hypothesized to rely on a dysfunctional neuronal network, such as the corticostriatal network in SUD and OCD, might therefore benefit from altered neuronal activity by DBS treatment.

Although impulsive behaviour is an important feature of psychiatric disorders for which the application of DBS is currently investigated, the effects of DBS on impulsive behaviour have not been extensively studied so far. To date, two preclinical and two clinical studies have been published on NA DBS on impulsive action (Heldmann et al. 2012; Luigjes et al. 2011; Sesia et al. 2010; Sesia et al. 2008), with contradictory effects. Clearly, more research on this topic is necessary to get more insight into the mechanism of DBS on impulsivity related disorders and improve DBS treatment.
Chapter 1 | General introduction

Outline of the thesis

The aim of this thesis is to explore the effects of DBS on heroin addiction and impulsive behaviour, in order to evaluate DBS as a new therapy for treatment-resistant heroin use disorder. First, a literature review of DBS studies using preclinical models of SUD is given in chapter 2. In addition, the underlying neurobiology of addiction is discussed in this chapter.

As discussed above, the relationship between impulsive choice and heroin addiction is not yet understood. To investigate whether elevated impulsive choice in heroin dependent subjects is a cause or a consequence, a study was performed in which a group of rats was selected on their trait impulsive choice behaviour and subsequently subjected to different stages of the heroin self-administration paradigm (chapter 3).

Many pharmacological interventions that target cue-induced or drug-primed relapse are also effective in models of impulsive behaviour (Jupp and Dalley 2014). However, the role of acute stress, which is known to increase the risk for relapse, in impulsive behaviour has not been well characterized. In chapter 4, we explored the effects of pharmacologically induced acute stress on different aspects of impulsive behaviour. Pharmacological stress was induced by injection of yohimbine, a competitive α2 adrenoceptor antagonist (Charney et al. 1984).

In the second part of this thesis, the effects of NA DBS were assessed on different aspects of heroin self-administration (chapter 5) and impulsivity (chapter 6). Since the NAcore and NAshell have been shown to play a role in heroin taking and seeking, in chapter 5, DBS of both NA sub regions was investigated in a rodent model for heroin self-administration. Based on the specific effects of NAcore DBS on cue-induced reinstatement of heroin seeking in chapter 5, the effects of NAcore DBS on impulsive choice and impulsive action were investigated in chapter 6.

The data from chapters 3, 5, and 6 revealed that 1) elevated impulsive decision making is a consequence of long-term heroin intake, 2) specifically NAcore DBS is successful in reducing cue-conditioned reinstatement of heroin seeking and 3) NAcore DBS has baseline-dependent effects on impulsive behaviour, reducing impulsivity in high impulsive individuals and vice versa. In the final experimental chapter of this thesis (chapter 7), I aimed to integrate the results obtained in the previous chapters and explore the effects of NAcore DBS on heroin-induced impulsive choice (Figure 1.6).
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Figure 1.6 Schematic overview of the various experiments conducted in this thesis. (1) The relationship between impulsive choice and heroin addiction is described in chapter 3. (2) The effects of NA DBS on different aspects of heroin addiction are described in chapter 5. (3) The effects of NA DBS on impulsive choice and impulsive action are described in chapter 6. (4) In chapter 7, the results of the previous chapters are integrated and the effects of NAcore DBS on heroin-induced impulsive choice are described.