CHAPTER 08

General discussion
The aim of this thesis was to explore the effects of deep brain stimulation (DBS) on measures of heroin self-administration and impulsive behaviour, to evaluate the potential of DBS as a new therapy for treatment-resistant heroin use disorder. The studies in this thesis were carried out in translational animal models of drug addiction and impulsivity. A great advantage of the use of these animal models, is that behaviour can be investigated in a semi-isolated system. Genetic, social and environmental factors are controlled for and standardized to a larger extent than can be achieved in human studies. What do the observations from these animal models mean with regard to a potential DBS treatment for heroin use disorder? To answer this question, I will discuss some behavioural, translational and mechanistic aspects of the obtained results in light of clinical findings that are reported in recent case studies on DBS as a treatment for substance use disorder (SUD).

Since clinical studies on the effects of DBS in SUD are rather scarce, (case) studies of DBS treatment for obsessive-compulsive disorder (OCD) are also incorporated in the discussion. OCD and SUD share behavioural parallels, such as compulsive actions and compulsive drug intake, but also neurobiological parallels such as dopaminergic dysfunction in the ventral striatum. DBS studies in OCD patients are therefore of particular interest and may help to relate behavioural and neurobiological effects to SUD.

Effects of NA DBS on addictive and impulsive behaviour

High cue reactivity towards drug-related stimuli and poor impulse control are two core features of SUD that play an important role in the development and maintenance of drug addiction, as well as relapse sensitivity. Treatment interventions targeting these two features of SUD might therefore be successful to reach abstinence and reduce the risk for relapse.

Cue reactivity

Cue reactivity has shown to be very important in maintenance and relapse to drug addiction. Patients use drugs more often or relapse more likely when they are in an environment associated with drug use, implicating that substance dependent patients are particularly vulnerable to drug use, when they are exposed to drug-related stimuli (Carter and Tiffany 1999). The stimuli that are being paired with drug use become conditioned stimuli and can elicit a conditioned response resulting in continuation of drug use or relapse. Most cue reactivity studies have shown that the drug-related stimuli elicit a motivational state that is consistent with the positive-reinforcing properties of drugs (Carter and Tiffany 1999; Stewart et al. 1984). According to the incentive-sensitization theory of Berridge and Robinson (2016), cue-induced dopamine release attributes “incentive salience” to drug-associated cues, which they define as a “psychological process
that increases the valence of reward-associated cues and makes them attractive incentive cues” (Berridge and Robinson 2016). Therefore, reduction of cue reactivity is a key target for interventions for SUD. The question is whether DBS can successfully reduce cue reactivity in drug dependent patients.

The first patient who received NA DBS (in the Academic Medical Center, Amsterdam) for heroin use disorder was a 47-year-old man who had been using heroin for 22 years (Valencia-Alfonso et al. 2012). Stimulation of the two dorsal contact points of the implanted electrodes in the NA resulted in a significant reduction of heroin consumption and desire for heroin. In this study, intracranial EEG responses to drug-related pictures were measured directly after electrode implantation, and revealed a significant positive relationship between cue-induced activity at the electrode contact points and the most optimal therapeutic effect. In a similar fashion, local field potentials in the NA were modulated upon alcohol-related stimuli in two alcohol-dependent patients, who received NA DBS. This corroborates the findings that therapeutic effects of DBS rely on the location of electrodes in the NA where cue reactivity is measured (Heinze et al. 2009). Together, these results suggest that NA DBS attenuates cue-induced craving, supported by clinical and neurophysiological evidence. Clinically, NA DBS reduced craving for heroin or alcohol, and reduced substance consumption dramatically in all these patients. Intriguingly, both studies also showed that the NA expresses strong cue-induced activity, as indicated by electrophysiological recordings measured with the same electrodes that were used for DBS. Thus, stimulation of the area that expressed the strongest cue reactivity was shown to be most effective at reducing consumption and craving for heroin or alcohol.

The rodent self-administration model is based on cue-conditioning by addictive drugs (Fuchs et al. 2008). Using this rodent model, I showed that NACore DBS specifically attenuated cue-induced reinstatement of heroin seeking and that responses for heroin as measured in a progressive ratio schedule of reinforcement were suppressed. These results extend the findings of other preclinical studies reporting a reduction of cue-induced reinstatement of opioid seeking in the self-administration model (Guo et al. 2013) and the conditioned place preference model (Liu et al. 2008; Yan et al. 2013) by NA DBS. Although in our hands heroin intake was not affected by NA DBS, the findings support the clinical observations that NA DBS is effective in reducing cue-conditioned behaviour (Heinze et al. 2009; Valencia-Alfonso et al. 2012). Taken together, NA DBS appears successful in attenuating cue-conditioned behaviour in addiction, which is considered one of the core features of SUD responsible for craving and relapse.

Notably, we have shown that NACore DBS facilitated extinction of operant responding on the first day of extinction training, thus extending recent findings that NA DBS facilitated extinction learning in a fear conditioning paradigm (Rodriguez-Romagüera et al. 2012). Drug dependent patients display great difficulty in remaining abstinent,
suggesting that facilitation of extinction learning by DBS would explain the successful long-term abstinence as is reported in case studies (Kuhn et al. 2014; Valencia-Alfonso et al. 2012). It is therefore conceivable that the effects of NA DBS on extinguishing learned behaviour might have an additional positive effect on cue reactivity. NA DBS in combination with extinction-based therapy might be necessary to achieve complete clinical effects.

**Impulsive behaviour**

To date, one case report of an alcohol-dependent patient, who was successfully treated with NA DBS, specifically described the effects of DBS on impulsivity. This patient was tested in a gambling paradigm and DBS reduced risky choices during task performance (Heldmann et al. 2012). Risky choices in a gambling task can be regarded as a form of impulsive decision making, based on the uncertainty of a reward. In chapter 7, we showed that NA DBS decreased impulsive choice as measured in a delay-discounting task in heroin self-administering rodents, supporting the findings of Heldmann and colleagues (2012). Although decision making based on uncertainty and delay-discounting differ to some extent behaviourally and neurobiologically (Floresco et al. 2008), and the current clinical evidence is based on a case report, together these studies hint towards improved decision making following DBS in substance use. Thus, besides cue reactivity, NA DBS may also have beneficial effects on impulse control, another core feature of SUD.

However, the two patients treated at the Amsterdam Medical Center for their SUD showed increased disinhibition with increasing voltage at the contact points of the electrodes (Luigjes 2015), suggesting that DBS increases impulsivity, despite beneficial effects on drug consumption and abstinence. In this respect, methylphenidate was found to have beneficial effects on impulsive decision making in cocaine-trained rats, but at the same time methylphenidate was found to potentiate context-induced reinstatement of cocaine seeking without a correlation between these effects in individual animals (Broos et al. 2012a). This and similar observations (Broos et al. 2015) suggest that impulsivity and relapse vulnerability are independent phenomena and that (pharmacological) treatment of impulsivity does not necessarily result in a reduction of relapse vulnerability.

Despite a substantial body of evidence from both animal and human studies reporting a relationship between various measures of impulsivity and addictive behaviour, the precise direction of this relationship is still unclear. In this thesis, we showed that there is a unidirectional relationship between heroin addiction and impulsive decision making in that impulsive decision making was not predictive of aspects of heroin taking and seeking, but chronic heroin intake increased impulsive decision making. Although we showed that DBS altered maladaptive impulsive behaviour in heroin-trained rats, it remains to be investigated whether there is a correlation between the effects of NA DBS
on impulsive behaviour and cue-induced reinstatement of heroin seeking. This would add evidence to the question whether impulsivity and relapse vulnerability are really interrelated phenomena (Pattij and De Vries 2013).

In chapters 4 and 6, we showed that both pharmacological interventions and DBS affect measures of impulsive behaviour in a baseline-dependent fashion. High impulsive animals decreased impulsive responding upon either yohimbine administration in the SST or NA DBS in the 5-CSRTT and DRT. These findings are in line with accumulating evidence showing that high and low impulsive individuals differ on a genetic and neurobiological level (Jupp et al. 2013a), implying that the effect of pharmacological interventions or DBS is dependent on individual baseline impulsivity levels. Importantly, the notion that DBS normalizes behaviour, does not only account for high baseline impulsive behaviour, but also for low baseline impulsivity, since NA DBS was found to increase impulsivity in these individuals. Therefore, this might have unwanted implications when DBS is applied in low impulsive individuals. Such differential effects, based on individual differences in impulsivity, were also observed after pharmacological interventions in SUD. For instance, it was found that poor baseline response inhibition was associated with positive treatment outcomes for alcohol-dependent patients treated with modafinil, whereas modafinil treatment seemed rather detrimental for patients with good response inhibition at baseline (Joos et al. 2013).

A high impulsivity endophenotype is not only strongly related to SUD, but also to other psychiatric disorders for which NA DBS treatment is currently investigated, such as major depression and OCD (Moeller et al. 2001). These psychiatric disorders have a dysfunctional reward and motivational system in common, with an important role for the NA. The results obtained so far with NA DBS on impulsive behaviour suggest that there is a treatment potential for these disorders. A case study by Kuhn et al reports that NA DBS led to an amelioration of depressive and anxiety symptoms and increased perceived quality of life in two heroin-dependent patients (Kuhn et al. 2014), corroborating the notion that accumbal stimulation has a large treatment potential for reward and motivation related disorders. Nevertheless, a careful clinical assessment remains important, as was shown in two OCD patients who displayed increased impulsive and aggressive behaviour with voltage increase of NA DBS (Luigjes et al. 2011). Taken together, accumulating evidence shows that DBS normalizes both trait impulsivity and impulsivity induced by long-term drug use. However, whether normalization of impulse control is directly related to beneficial clinical effects on abstinence and reduced relapse vulnerability remains to be investigated.
Translational aspects: from rodents to humans

From a behavioural perspective, the findings described in this thesis are in line with clinical observations. All experiments were carried out in rats, which have been shown to be a valid model to investigate motivational and impulsive behaviour. In the next section, I will discuss translational questions regarding technical and neuroanatomical aspects of the model: 1) To what extent are the preclinical and clinical DBS electrodes comparable, 2) What is the translational importance of the stimulation procedure? and 3) To what extent are the rat and human nucleus accumbens functional homologues?

DBS electrodes

Size, shape and material of DBS electrodes largely affect the distribution of the current-density and the generated electric field, and thereby the overall effect of DBS on brain tissue (McIntyre and Grill 2001). Electrodes that are used in preclinical and clinical studies vary to a large extent, which needs to be taken into account when interpreting the data. DBS electrodes for clinical application usually consist of a quadripolar lead, with four electrodes that can be stimulated separately or in combination (Medtronic Diagnostics). However, in rodent models, the size and shape of the electrodes strongly differ from those used in the clinic (Figure 8.1). Many studies, including our own, use bipolar electrodes, which differ largely in material, contact diameter and inter-contact distance. In our studies, bipolar platinum electrodes were used, which are relatively non-toxic to the brain (Gubellini et al. 2009), combined with a stainless steel guide cannula (Plastics One). Due to the guide cannula, the electrodes had an estimated inter-contact distance of 500-750µm, enabling a horizontal orientation to stimulate structures in the antero-posterior axis. As such, this may yield a current field at the anatomical target comparable to the clinical situation (Gubellini et al. 2009). Thus, despite differences in size and shape of the DBS electrodes, the effect of DBS in rodent studies may be equivalent to the clinical situation, as is seen at a behavioural level discussed above.

![Figure 8.1 A Bipolar platinum electrodes, combined with a stainless steel guide cannula (product code 333-001, Plastics One, Roanoke, VA, USA) as used in this thesis. B Example of commonly used DBS electrode for clinical application (Lead model 3389, Medtronic, Minneapolis, Minnesota, USA).](image)
**Stimulation procedure**

Animal DBS studies typically use short stimulation durations (1-2 hours), usually during the execution of a task. However, the obtained results are extrapolated and interpreted to clinical results in which stimulation is typically applied on a chronic basis. Evidence from microdialysis studies and electrophysiological studies shows that short-term stimulation of the animal brain has immediate effects on prefrontal cortex (PFC) and orbitofrontal cortex (OFC) activity (McCracken and Grace 2007; 2009; van Dijk et al. 2012), effects that are consistent to what is observed in clinical studies (Figee et al. 2013; Smolders et al. 2013). This suggests that, in combination with behavioural findings, effects observed in animal models obtained with short stimulus durations can be extrapolated to clinical results.

In contrast, it has also been demonstrated that five days of continuous NAcore DBS in rats produced a significant increase in oscillatory power in multiple brain regions, which was no longer apparent after 6 hours of continuous stimulation (Ewing and Grace 2013). This observation would argue against the use of short-duration stimulation and the extrapolation of such data to clinical applications.

Not only the duration of stimulation, but also the pattern of stimulation is of great importance for clinical outcome. Usually, in clinical and preclinical applications, DBS is delivered in a continuous pattern of stimulation. Recently, it was hypothesized that continuous high-frequency stimulation does not always resemble the physiological situation, since many of the psychiatric disorders arise from abnormalities in brain activity patterns (Evans et al. 2015). In this thesis, we employed a continuous pattern of high frequency stimulation, to mimic clinical settings as closely as possible. However, intermittent, or otherwise non-continuous, stimulation yields similar results to continuous stimulation in animal models of cocaine (Friedman et al. 2010; Levy et al. 2007) and opioid addiction (Guo et al. 2013; Ma et al. 2013). In addition, low frequency stimulation has been shown to normalize synaptic transmission in cocaine-treated mice and reduce locomotor sensitization (Creed et al. 2015). Clearly, more research is needed to elucidate the optimal stimulation method.

**Nucleus accumbens**

In this thesis, DBS was applied to the nucleus accumbens (NA), since the NA is implicated in both cue reactivity and impulsive behaviour. Anatomically, the accumbens receives input from the PFC, amygdala, thalamus, hippocampus, ventral tegmental area and ventral pallidum. Output connections comprise ventral pallidal areas, hypothalamus, ventral tegmental area, substantia nigra pars compacta and pars reticulata. Most of these projections are non-homogeneously distributed among the core and shell sub-regions, thought of as neuronal ensembles (Groenewegen et al. 1999). Because of its anatomical positioning, the NA integrates cognitive information from the PFC, emotional information...
from the amygdala and contextual information from the hippocampus to mediate goal directed behaviour. This role as an “integration hub” makes the NA an attractive therapeutic target for addictive and impulsive behaviours.

Despite an overlap in afferent and efferent connections, the sub-regions of the NA appear to have distinct functions in behaviour. Animal studies have shown that the NAc core region plays a role in conditioned behaviour and goal-directed actions, whereas the NA shell seems to be predominantly involved in unconditioned responses and the assessment of attractiveness of a stimulus (Basar et al. 2010; Dalley et al. 2011). The NAc core has been shown to be primarily involved in mediating learned behaviour in response to conditioned cues with motivational properties (Ambroggi et al. 2011; Corbit and Balleine 2011; Jones et al. 2010; Theberge et al. 2010), which is in line with the present observations that specifically stimulating the NAc core region leads to attenuation of cue-conditioned reinstatement of heroin seeking, and baseline-dependent effects on impulsive behaviour. Our findings corroborate the clinical findings that effective stimulation is dependent on the location of stimulation (Valencia-Alfonso et al. 2012). In line with this, an animal study of impulsive action showed that NA DBS effects were dependent on the location (NA core vs NA shell) and amplitude of stimulation (Sesia et al. 2008).

Although similar patterns of the NAc core and NA shell subdivision can be histochemically distinguished in the human brain, it remains unclear whether these sub-regions are a functional homologue to the rodent NAc core and NA shell (Figure 8.2). This raises the question as to whether the rodent model can be used to translate the findings on behavioural and mechanistic effects of DBS to clinical applications. In general, the medial part of the human NA resembles histologically the NA shell, whereas the lateral part resembles the NAc core (Voorn et al. 1996). Clinical DBS studies for addiction, depression and OCD yielded the most promising results by targeting the border of the ventral striatum and the anterior capsula interna (Greenberg et al. 2010; Malone et al. 2009; Valencia-Alfonso et al. 2012). With respect to the ventral striatum, this would correspond to the rat NAc core.

The rat brain does not have an organized capsula interna as is found in the human brain. A recent tract-tracing study in rats, however, revealed that fibres from the PFC and OFC are organized within small white matter bundles and embedded within the striatum. The white matter bundles in the striatum are topographically arranged according to its origin and target location, comparable to the primate anterior limb of the capsula interna (Coizet et al. 2017). This suggests that these small white matter bundles can be viewed as the capsula interna in the rat. White matter bundles from the prelimbic cortex, infralimbic cortex, cingulate cortex and OFC descend mainly to the NAc core, the target site used in my DBS studies, and to more downstream brain areas such as the thalamus and brain stem.
(Coizet et al. 2017; Mailly et al. 2013). This suggests that there is a functional homology between the white matter bundles of corticostriatal projections in rodents and humans. However, due to the isolated white matter bundles in the rodent striatum, it is hypothesized that much larger volumes of rodent brain tissue would need to be stimulated to imitate the clinical effects of stimulation of the capsula interna (Feenstra and Denys 2012). Cautious interpretation and translation of the anatomical position of the electrodes is therefore warranted. Based on the previously discussed behavioural findings in this thesis, together with the comparable anatomical position and DBS electrodes, NA DBS in rodent models appears to have predictive value for the human situation.

**Figure 8.2** Atlas illustration of the nucleus accumbens sub-regions in the rat and human brain. A Coronal section of the rat brain, 1.6mm rostral to bregma. C nucleus accumbens core, S nucleus accumbens shell, AC anterior commissure. Picture adapted from Paxinos and Watson 1998. B Schematic picture of the human striatum, consisting of the caudate nucleus (CN), putamen (Put) and the nucleus accumbens (Nacs). IC capsula interna. Picture with permission from McLeman et al. 2000.

**The insula, an alternative potential target?**

The majority of research has focused on the NA as a potential target for DBS as a treatment for SUD. However, other brain areas implicated in addiction are also possible targets. Recent clinical observations showed that smokers who suffered from brain damage involving the insula were very likely to quit smoking easily and remain abstinent, which strongly implicates a role for the insula in (nicotine) addiction (Naqvi et al. 2014; Naqvi et al. 2007). From a neuroanatomical perspective, the insula is connected to brain regions that are well-known for their involvement in addiction, such as the NA, amygdala (Ohara et al. 2003), ventromedial PFC (Ongur and Price 2000) and anterior cingulate cortex (Augustine 1996). Functionally, the insula is thought to play an important role in the representation of the interoceptive effects of drug use, such as effects on the cardiovascular system and the airway (Naqvi and Bechara 2010).
To further explore the insula as a possible therapeutic target, we applied DBS to this region in our self-administration model. Since the first observations on the role of the insula in addiction were based on cigarette smoking (Naqvi et al. 2007), we conducted a pilot study to answer the question whether DBS of the insula is able to reduce nicotine taking and seeking behaviour in rats, without altering the motivation for natural rewards. Grain-based pellets (Bio-Serv, USA) were serving as natural reward, because they contain substantially lower amounts of sucrose, fructose and dextrose compared to regularly used sucrose food pellets, which have been shown to display large addictive potential (Lenoir et al. 2007).

The results showed that insula DBS did not alter responding for nicotine or food pellets on an FR3 schedule. In addition, insula DBS was ineffective on reinstatement provoked by pellets-paired or nicotine-paired cues (Figure 8.3). Also, local administration of baclofen/muscimol (GABA$_B$ and GABA$_A$ agonists, respectively) into the same brain region did not alter responding for nicotine. In contrast, intra-insula infusion of the preferential dopamine D1 antagonist SCH23390 and dopamine D1 agonist SKF82958 before cue-induced reinstatement reduced nicotine seeking behaviour (Figure 8.4).

Therefore concluding, in our hands insula DBS does not lead to favourable outcomes in an animal model of nicotine addiction. Although modulation of the dopamine D1 receptor indicated involvement of the insula in cue-induced reinstatement, local pharmacological inactivation of the insula and DBS were ineffective in altering nicotine taking and seeking behaviour. These findings are in contrast to other studies, showing that DBS of the insula decreased nicotine consumption on an FR5 and PR schedule of reinforcement, as well as cue-induced and drug prime-induced reinstatement, without effects on natural reward (Pushparaj et al. 2013). In addition, intra-insular pharmacological interventions have been shown to be effective in altering nicotine taking and seeking (Forget et al. 2010; Hollander et al. 2008) and other substances of abuse such as amphetamine (Contreras et al. 2007), alcohol (Pushparaj and Le Foll 2015) and cocaine (Di Pietro et al. 2008). The insula is a large and heterogeneous brain area, differences between our observations and other reports might therefore result from differences in stimulation parameters and location of electrodes, since electrode placements in our study seemed more rostrally located compared to previous studies.

Evidence from clinical and preclinical studies in delay discounting and gambling tasks highlight involvement of the insula in decision-making (Clark et al. 2008; Cocker et al. 2016; Pattij et al. 2014; Pushparaj et al. 2015). It is hypothesized that the insula evaluates the bodily sensations of drug use, and therefore the decision to refrain from drugs might be dependent on the representation of the positive and negative consequences by the insula (Naqvi and Bechara 2010). Similar to the NA, inhibition of insular activity is therefore hypothesized as a potential treatment for SUD. Based on the first observations
by Naqvi et al (2007), most research thus far has focused on the role of the insula in tobacco smoking, however, from a societal and medical perspective DBS treatment for smoking will be less likely. The knowledge based on nicotine addiction is likely to extrapolate to other substances of abuse, for which DBS treatment is considered. However, due to its dense and complex vascular network (Ture et al. 2000) and its role in the regulation of cardiac rate and rhythm (Oppenheimer 2006), DBS surgery in the insula poses many risks and does not seem suitable for widespread clinical application.

Figure 8.3 A Insula DBS did not alter self-administration of nicotine on an FR3 schedule of reinforcement (n=9, F(3,24)=3.40, p=0.034, post-hoc N.S.). B Likewise, insula DBS did not alter self-administration of grain-based pellets on an FR3 schedule (n=5, F(3,12)=3.33, N.S.). C Insula DBS was ineffective on reinstatement provoked by nicotine-paired cues (n=8, t(7)=0.14, N.S.) and D pellet-paired cues (n=4, t(3)=-0.071, N.S.).
Mechanism of DBS

Clinical and preclinical studies have shown that DBS has clear effects on several behavioural measures related to addiction and impulsivity. In this section, I will address some possible underlying neurobiological mechanisms.

It is hypothesized that DBS interacts with the pathological neuronal network, instead of a local activation or inhibition near the electrode (Deniau et al. 2010; McIntyre and Hahn 2010). Currently, most evidence for this hypothesis comes from subthalamic nucleus (STN) DBS as a treatment for Parkinson’s disease. Neuroimaging studies, electrophysiological recordings and computer models have shown that the pathological network in Parkinson’s disease can be reversed by DBS, generally through reducing burst activity and overriding disruptive oscillations (reviewed by Deniau et al. 2010; McIntyre and Hahn 2010). McIntyre and Hahn therefore propose the mechanism of DBS as “stimulation induced resetting of network oscillatory patterns, such that resonance at the stimulation frequency regularizes neural firing patterns” (McIntyre and Hahn 2010).

Along these same lines, etiological models of complex brain disorders such as SUD, depression and OCD have shifted to an emphasis on a dysfunctional neuronal network, as opposed to the traditional view of alterations in specific neurons or molecules (Fornito and Bullmore 2015). With regard to SUD, it is hypothesized that reduced plasticity in the frontostriatal circuitry promotes relapse to drug seeking (Kalivas and O’Brien 2008; Kalivas and Volkow 2005). The hypothesized effects of DBS on a neuronal circuitry are therefore very intriguing in comparison to pharmacological medication, which usually targets specific neural substrates, such as selected receptors. Current understanding of the neurobiological effects of NA DBS is increasing, supporting the results found in
Parkinson’s disease. The case report by Valencia-Alfonso and colleagues showed that the contact points at which the lowest connectivity between the NA and PFC in response to drug-related pictures was measured, were the contact points that gave the best therapeutic results in attenuating craving for heroin (Valencia-Alfonso et al. 2012). This observation suggests that interference of disturbed frontostriatal network connectivity is important for treatment success in SUD. Indeed, several preclinical and clinical studies have shown that NA DBS interferes with prefrontal cortical activity (Do-Monte et al. 2013; Figeé et al. 2013; McCracken and Grace 2009; Smolders et al. 2013; van Dijk et al. 2012). Additionally, a study combining clinical data with diffusion tensor tractography identified selective DBS activation of axonal pathways that correlated with the best therapeutic outcome measures in depressive patients (Lujan et al. 2012). Interestingly, a positive correlation between frontostriatal connectivity strength and improvement of obsessive-compulsive symptoms supports the hypothesis that the clinical beneficial effect of DBS relies on adjusting the pathological network (Figeé et al. 2013). Similar observations were found with respect to impulsivity. PET scans of an alcohol-dependent patient with NA DBS during execution of the gambling task revealed that brain areas connected to the NA and related to action-monitoring and behavioural control (paracingulate cortex, temporal poles, precuneus and hippocampus) were activated by DBS (Heldmann et al. 2012). Although we were not able to show that NA DBS alters neuronal activity in the PFC directly, altogether, the behavioural data from this thesis suggest that NAc core DBS reverses pathological frontostriatal activity, which would fit with the idea that compulsive drug seeking behaviour and decreased cognitive control over drug seeking result from neuroplasticity changes in corticostratial network (Jentsch and Taylor 1999; Kalivas and O’Brien 2008). However, an important question remains whether the stimulated network can still encode signals normally. Alternatively, DBS could prevent encoding of pathological information and therefore results in functional disconnection of the stimulated neuronal network (Deniau et al. 2010).

Concluding remarks

In conclusion, NA DBS reduced cue-conditioned heroin seeking and had baseline-dependent effects on impulse control. Based on our findings and those of others, NA DBS seems a promising treatment strategy for heroin addiction. The studies in this thesis focused on the NA as a potential target. It should be noted, however, that recent rat studies have suggested the STN as an alternative target for cocaine (Baunez et al. 2005; Pelloux and Baunez 2013; Rouaud et al. 2010) and heroin addiction (Wade et al. 2017). These studies reported a decreased motivation for cocaine and heroin, but facilitated motivation for sucrose upon STN DBS (Baunez et al. 2005; Rouaud et al. 2010). STN DBS has not been applied in substance-dependent patients yet, but there are several clinical
observations in patients with Parkinson’s disease. Some Parkinson patients develop a ‘dopamine dysregulation syndrome’, that is a dependence towards their dopamine medication, on which STN DBS was found to have beneficial effects (Lim et al. 2009; Witjas et al. 2005). However, STN DBS did not improve this syndrome in all patients, and sometimes even worsened behaviour (Lim et al. 2009). In addition, other case reports describe Parkinson patients who developed pathological gambling (Smeding et al. 2007) and increased impulsivity (Halbig et al. 2009). Taken the mixed results and the deteriorating effects of STN DBS on impulsive behaviour into account, the STN as a potential target for treatment of addiction should be questioned.

Important to note is that despite successful preclinical animal work and clinical case studies, implementation of DBS for addiction faces additional complicating factors. Our clinical partners from the Amsterdam Medical Centre question the current feasibility to implement DBS for addiction based on large difficulties experienced in consistent patient inclusion criteria. Inclusion difficulties presumably are due to less stable social environments in drug-addicted patients compared to for example OCD patients, as well as fluctuating and diminished perceived burden of the disease (Luigjes et al. 2015). In addition, the question remains whether DBS is a suitable treatment for poly-drug abuse, as is exemplified by a case study reporting successful abstinence of heroin by NA DBS, but not of comorbid drug-consumption of other psychotropic substances. Continuation of psychotropic drug consumption might be explained by remaining psychosocial difficulties, which are generally associated with heroin abuse, stressing the importance of accompanying psychotherapy for successful maintenance of DBS treatment (Kuhn et al. 2014). It is estimated that around 65% of problematic opiate users are abusing other substances such as cocaine and alcohol (Wisselink et al. 2016).

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. Although new emerging techniques such as optogenetics (Kim et al. 2017) and DREADDs (Roth 2016) have also proven very useful in elucidating underlying neurobiological mechanisms at a cellular level in vivo, implementation of these techniques in clinical practice will be a longer process. Therefore, DBS research is highly relevant to increase our understanding, and to optimize DBS as a therapeutic intervention in treatment-resistant psychiatric patients.