university of groningen / faculty of science and engineering

Deep brain stimulation as a treatment for substance addiction

Bachelor thesis
Kromojahjo, L.D.S. (S2908786)
University of Groningen, faculty of science and engineering - BSc Biomedical Sciences
Date: 31st of July, 2019
Supervised by prof. dr. A.J.W. Scheurink

ABSTRACT

Substance addiction is a disorder associated with intense feelings of craving, tolerance to the substance and withdrawal symptoms when substance use is being reduced. The reward system, including the Nucleus Accumbens (NAc) and the Ventral Tegmental Area (VTA), is highly involved in the development of addiction. Multiple therapies already exist, of which Cognitive Behavioural Therapy (CBT) is the most commonly used. Despite this, still half of CBT-treated patients remain addicted and have had relapses during or after therapy. It is time to consider a treatment that focuses on the neurobiology of addiction rather than its psychology. Therefore, this thesis will look at Deep Brain Stimulation (DBS) as a possible treatment for substance addiction. DBS is an already accepted treatment for different neurological disorders and is based on electrical stimulation through electrodes placed within structures deep in the brain. Even though the exact mechanism behind DBS is not discovered yet, it is likely that stimulation is able to induce synaptic and neuronal plasticity and to alter neuronal activity and neurotransmitter release. It is possible that DBS in addiction counteracts the downregulated dopamine (DA) receptors, together with normalization of prefrontal cortex (PFC) activity and a decrease of ΔFosB expression in the NAc. A variety of studies, both animal and human addiction models, demonstrated the successfulness of DBS. In general, no severe side-effects arise from stimulation itself, but surgical and hardware-related risks are still present and should be taken into account. DBS can be regarded as a safe treatment with positive results for the treated patients. However, DBS is a drastic intervention because of the required surgery and highly needed monitoring after initiation. Therefore it is concluded that DBS is a very promising treatment but is not expected to become the most preferred one in substance addiction.

Key words: deep brain stimulation, addiction, substance abuse, reward system, NAc

TABLE OF CONTENTS

1. INTRODUCTION

Addiction, or substance use disorder, is a common disorder which is seen all over the world and poses problems in multiple areas for the patient and his environment. Addiction is associated with craving, tolerance to the substance and withdrawal symptoms when substance use is being reduced (American Psychiatric Association, 2013). The rehabilitation clinic Jellinek estimates that in 2015 the Netherlands counted approximately 1,2 million substance addicts (alcohol, tobacco, cannabis, cocaine, crack, heroin, amphetamine, ecstasy, GHB and legal prescription drugs) of which merely 5% underwent treatment (Jellinek, 2019). It has been shown that 50-70% of these treated patients experienced relapse within a year after treatment, which is a substantial amount (GGZ Nederland, 2013).

Currently, patients with addiction are most commonly treated with CBT that focuses on alternating cognitive disturbances and behaviours. CBT can establish a more controlled or even ceased course of substance abuse in patients, however addictive behaviour recurred or still remained present in 40-50% of CBT-treated patients (NVO, BPSW, NIP, 2017). These numbers show that addiction is a disease with chronic features which makes it hard to cure in a considerable amount of patients. An alternative treatment is needed, perhaps one that emphasizes the neurobiology of addiction rather than one that focuses on the psychology. Deep brain stimulation (DBS) is such kind of treatment that is based on changing behaviour by electrically stimulating areas deep in the brain. It can already be known as it is an accepted treatment for Parkinson's disease and other neurological diseases. DBS could be the solution for the majority of treated patients to whom current treatments are not effective. Building on this hypothesis, this thesis will highlight the neurobiology of addiction and underlying mechanisms of DBS, it will underpin the hypothesis with already existing researches around this subject and it will discuss the potential for DBS to be a treatment for addiction.

2. ADDICTION

Prevalence

Over the world, the prevalence of substance use disorder varies from 2% of the population in Asia and Africa, to 6% in Eastern Europe and the United States (Ritchie & Roser, 2018). It is mentioned that these substance use disorders included addiction to alcohol and/or illegal drugs but excluded the addictions to tobacco or legal prescription drugs. If these addictions are also taken into account, the percentage of substance addicts will be much higher. In the Netherlands addiction to tobacco or prescribed medicine (especially benzodiazepines) are the most common, according to Jellinek (2019). They also show that the group of tobacco addicts is least likely to undergo treatment. Worldwide, alcohol is the substance that most people are addicted to as it is being estimated that the amount of alcohol addicts in the world is 65% higher than the amount of all drug addicts (Ritchie & Roser, 2018). In 2015, the Netherlands had a total of 60.979 substance addicts who were being treated, this means that only 1 out of 20 substance addicts is seeking for help (Jellinek, 2019).

Sensitivity

The risk of developing some type of addiction is approximately for 50% attributable to genotypic vulnerability that is predominantly a combination of variability of the drug metabolism and human sensitivity to conditioning (Volkow & Li, 2005). Also epigenetic factors such as stress, in which the hypothalamic-pituitary-adrenal (HPA) axis is involved, and pre-conceptional parental drug usage can influence the sensitivity to become addicted (Volkow & Boyle, 2018). Volkow & Boyle (2018) also state that an adverse environment during childhood can cause neurological changes, for example an alteration in neuronal connectivity or expression of a certain receptor due to social isolation. Furthermore, addiction is most likely to happen during adolescence as the brain in this period is not fully developed yet and is more neuroplastic than the matured brain (Jordan & Andersen, 2017). It is described that, within the young undeveloped brain, there is a lot of activity in the regions responsible for reward and motivation (striatal and limbic pathway) but hardly any activity in the prefrontal cortex (PFC) that influences among other impulsivity and risk-taking (Volkow & Boyle, 2018). This explains why adolescents, in comparison to adults, experimentalize more with drugs (high impulsivity and risk-taking) but also are more likely to continue with drug-taking (high reward-seeking behaviour). Thus, genetic, epigenetic and environmental factors (alone or together) can determine the individuals' risk of becoming addicted with the highest probability being in adolescence.

Diagnosis

As already mentioned in the introduction, addiction is initially associated with a strong desire to a certain substance (craving), increasing doses of the substance needed to achieve the same effect (tolerance) and a specific physiological state when the use of it has been reduced (withdrawal). When looking into the Diagnostical and Statistical Manual of Mental Disorders, 5th edition (DSM-V), there is a total of eleven diagnostic criteria of which at least two are needed to diagnose someone with substance use disorder (American Psychiatric Association, 2013). A linear relationship exists between the amount of criteria a patient fulfils and the severity of the disorder.

The DSM-V distinguishes types of substances to which patients could become addicted, noted by the different 'paragraphs' in the chapter *Substance-Related and Addictive Disorders.* These include alcohol; caffeine; cannabis; hallucinogen (phencyclidine and others); inhalant; opioid; sedative, hypnotic or anxiolytics; stimulant; or tobacco. Despite this distinction, there is no difference in the eleven criteria for substance use disorder. Therefore, the diagnostics criteria, seen in box 1, count for each of the above-named substances.

Box 1. DSM-V criteria for substance use disorder. At least two criteria need to be present to diagnose someone with substance use disorder. Adapted from American Psychiatric Association (2013).

Diagnostic criteria

A. A problematic pattern of use of a substance (alcohol; caffeine; cannabis; hallucinogen (phencyclidine and others); inhalant; opioid; sedative, hypnotic, or anxiolytics; stimulant; or tobacco) leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
    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 efforts 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 fulfil 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 substances (refer to criteria A and B of the criteria set for substance withdrawal).
        b. The substance is taken to relieve or avoid withdrawal symptoms.

Current therapies

Nowadays, the most prominent used method for treating addiction is CBT. This therapy can increase the patient's motivation to change and can learn patients to recognize hazardous situations for drug abuse and to applicate self-control techniques (NVO; BPSW; NIP, 2017). The therapy generally focuses on the importance of underlying thoughts and feelings that arise during a certain situation or action. In the case of addiction, this could be injection/inhalation of a drug or walking past the spot where the patient always took the drug, i.e. environmental cues (Zhang et al., 2017). Multiple rehabilitation clinics in the Netherlands (Jellinek; Novadic-Kentron; VNN, 2019) use CBT as a form of treatment for addiction and all have the option for individual sessions and/or group sessions. A general preference for treatment with CBT is seen on the websites of those clinics but certainly, other therapies are also proposed. Jellinek also suggests the Minnesota therapy, or the in the USA known Twelve Step therapy, which is a 24 weeks-enduring polyclinical therapy. Here, the patient is being stimulated to join meetings in self-help groups such as the AA (alcoholics anonymous) and the NA (narcotics anonymous), followed by a combination of individual and group therapy sessions with an addiction counsellor and psychologist (Jellinek, 2019). Novadic-Kentron (2019) also emphasizes the use of Community Reinforcement Approach (CRA) within their therapies. The aim of this approach is to look for other positive reinforcements in a client's daily living, e.g. employment, recreation and family systems, to put the importance of using a particular substance in perspective (Zhang et al., 2017). Eye Movement Desensitization and Reprocessing (EMDR), behavioural therapy, family therapy and aversion therapy are examples of other methods for treating addiction but are far less frequently used in clinics (Zhang et al., 2017).

It is obvious that current therapies are mostly based on the psychology of addiction, since they focus on creating awareness of certain thoughts and related emotions and behaviour. As previously mentioned, CBT is the most common therapy in lots of rehabilitation clinics. One would believe that because of the importance, CBT knows little weaknesses. However, it seems that CBT is only effective in a bare 50-60% of addicted patients in the Netherlands. Meaning that 40-50% are still not successfully treated and are in need of alternative treatments. To consider a neurobiology-based treatment for addiction such as DBS, the neurobiology of addiction first needs to be clear.

3. NEUROBIOLOGY OF ADDICTION

When investigating the effectiveness of DBS on addiction, it is important to know which brain areas are involved. For this to find out, the mechanism of addiction should be known, not only including the reward-pathway, its receptors/neurotransmitters and involving brain areas, but also the psychological background of addiction, including reinforcement and conditioning.

The reward system

Addiction is linked to a feeling of reward after administration of a substance, after all the individual constantly has the urge to take it. This feeling of reward is the result of dopaminergic neurons projecting from the ventral tegmental area (VTA) onto the nucleus accumbens (NAc) that cause dopamine (DA) release in this area (Volkow & Morales, 2015). Together with particular forebrain regions, these projections form the mesolimbic dopaminergic pathway, also called the reward system, and is proven to be highly involved in associative learning and reward as a consequence of natural stimuli and substances of abuse (Yohn et al., 2008).

The NAc is a brain structure that is part of the mesolimbic dopaminergic pathway, thus is involved in conditioning, and is responsible for actually experiencing the feeling of pleasure (Volkow et al., 2017). The NAc largely contains GABAergic medium spiny neurons (MSNs), as they are the main projecting neurons in the striatum. The MSNs can be divided into two groups: the D1-receptor containing MSNs (D1-MSNs) and the D2-receptor containing MSNs (D2-MSNs) (Yohn et al., 2008). Released DA in the NAc acts on these membrane receptors that belong to the G-protein-coupled receptors (GPCR) (Yohn et al., 2008). D1-receptors (D1R) have an activating effect as binding with DA induces production of cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA), where on the other hand D2-receptors (D2R) are inhibiting since binding with DA restricts cAMP production and limits PKA activation (Yohn et al., 2008). D2Rs are high-affinity receptors and can be activated with a lower level DA than needed for D1Rs, that are low-affinity receptors (Volkow & Morales, 2015). DA release in the NAc is the result of firing neurons with its onset located in the VTA. The VTA is the DA producing area in the brain that has projections on multiple brain structures, e.g. NAc, PFC, dorsal striatum and amygdala (Oliva & Wanat, 2016). The VTA predominantly consists of DA neurons since ~60% of its neurons contain tyrosine hydroxylase, which plays a role in the synthesis of it (Oliva & Wanat, 2016). DA neurons from the VTA know two types of firing, 1) tonic cell firing which is slow and stable and 2) phasic cell firing which is fast and short (Volkow & Morales, 2015). It is known that phasic firing happens with unexpected events (such as drug taking and its outstanding reward) and will increase DA levels with a higher extent than tonic firing, enabling low-affinity D1-receptors to also become activated (Uhl et al., 2019). It has been proven that signalling through both D1R and D2R is highly important for natural- and drug-reward and can only be established through phasic cell firing (Yohn et al., 2008). Activation of D1R is connected to the direct pathway that is associated with reward, whereas activation of D2R is connected to the indirect pathway that is associated with punishment (Volkow & Morales, 2015). As mentioned above, D1R signalling has an excitatory effect and thus contributes to a feeling of reward, while D2R signalling has an inhibiting effect on the indirect pathway and thus opposes the feeling of punishment (Volkow & Morales, 2015). This is possibly

the reason that phasic cell firing and activation of both D1R and D2R contribute to maximal drug reward. With associative learning, drug-linked cues become conditioned and will elicit phasic firing out of the VTA even before the drug is taken, with fast and large DA level increases in the NAc and the expectation of obtaining a reward as a result of D1R binding (Volkow & Morales, 2015). D2R however, is responsible for the long-term motivation needed for taking the drug as binding with DA will last longer and even continues after the peak (Volkow & Morales, 2015).

Conceptualization of addiction

Koob & Volkow (2016) describe addiction as a repetitive cycle that can be divided into three stages that all have their own set of involved brain areas and their own events characterizing the stage (figure 2). The first stage is binge/intoxication where conditioned reinforcement and incentive salience (both explained in box 2) lay the foundation for drug seeking and self-administration (Koob & Volkow, 2016). The phasic DA signalling after drug intake causes drug-paired cues to increase DA levels and eventually triggers neuroadaptations in the basal ganglia (Koob & Volkow, 2016). These neuroadaptations are the basis for individuals to experience compulsive behaviour towards drugs and feelings of craving when exposed to cues.

Box 2. Definition of conditioned reinforcement and incentive salience. Citation from Koob & Volkow (2016).

> Conditioned reinforcement is "when a previously neutral stimulus reinforces or strengthens behaviours through its association with a primary reinforcer and becomes a reinforcer in its own right".
>
> Incentive salience is "the motivation for rewards derived from both one's physiological state and previously learned associations about a reward cue that is mediated by the mesocorticolimbic dopamine system".

The second stage is associated with negative feelings, stress and loss of motivation for natural rewards and is called the withdrawal/negative affect stage. In this stage, the reward systems will have a decreased sensitivity for drug-taking related rewards as well as natural rewards due to deteriorated functioning of DA (Koob & Volkow, 2016). Also, a dysfunction in emotional regulation, where the HPA axis and the extended amygdala are involved, is typical in this stage. Withdrawal from drugs of abuse brings about the release of corticotropin-releasing factor (CRF) that can act on those brain structures which eventually will result in a negative emotional state and stress (Koob & Volkow, 2016).

The third stage of addiction is the preoccupation/anticipation stage which is linked to relapse and is associated with dysregulations of the PFC. The PFC has glutamatergic projections onto the VTA and since the VTA has lots of neurons extending to the basal ganglia, it is hypothesized that these glutamatergic projections indirectly can contribute to incentive salience (Koob & Volkow, 2016). Additionally, the reduction in PFC activity that has been found in this stage affects executive functioning, leading to problems with decision making and inhibitory control (Koob & Volkow, 2016). The combination of increased feelings of craving and a weakened inhibitory control and decision making enlarges the chance of relapses in the addicted individual.

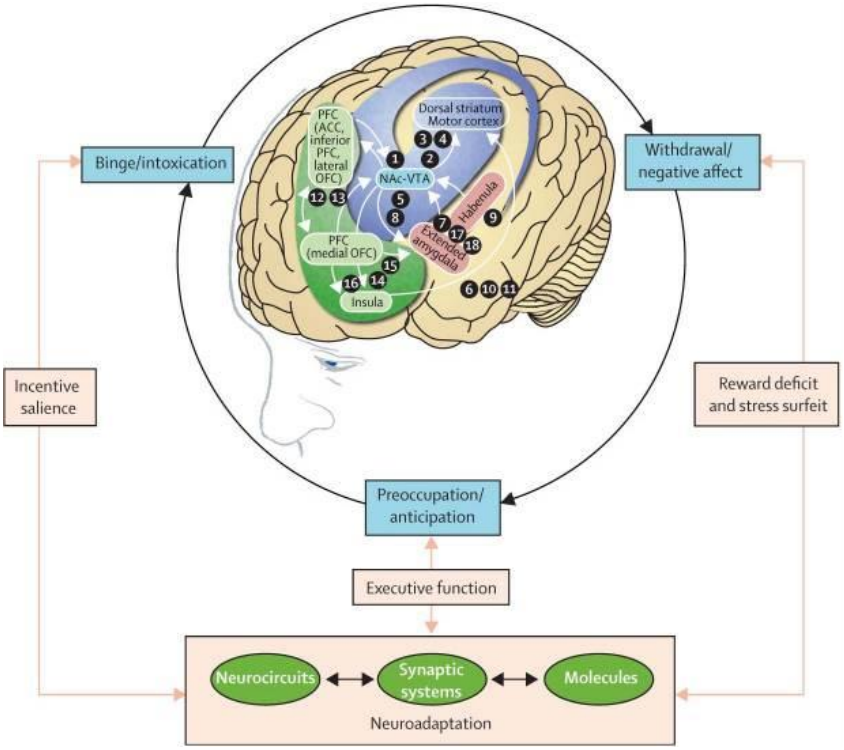

Figure 2. Three staged conceptualisation of addiction. Interacting circuits in the addicted brain. Characteristics for *binge/intoxication* (blue; basal ganglia) are conditioned reinforcement and incentive salience. Characteristics for *withdrawal/negative effect* (red; amygdala, habenula) are decreased reward sensitivity and negative emotional state. Characteristics for *preoccupation/anticipation* (green; PFC, insula) are craving and deteriorated executive function. Adapted from Koob & Volkow (2016).

Neuroadaptations in addiction

Drugs can elevate the level of neurotransmitters in the brain either directly or indirectly: directly through mimicking the neurotransmitter's effect so that concentrations will become higher and indirectly by stimulation or inhibiting certain systems that regulate the level neurotransmitters (Oliva & Wanat, 2016). For example, cocaine blocks the reuptake of DA in the synaptic cleft, resulting in a higher level of extracellular DA and a prolonged effect on the brain (Nestler, 2005). Either directly or indirectly, eventually intake of every type of drug will result in signalling from the VTA to the NAc causing an increase in DA release and a rewarding feeling. After repeated exposure to substances of abuse, reduced sensitivity for the drug and deteriorated functioning of the PFC will occur as a result of neuroadaptations, as mentioned above. But what exact neuroadaptations underlie these general changes, apart from desensitization of DA receptors?

Multiple studies show that striatal D2R are downregulated in addiction. Urban & Martinez (2012) state that this has been proven for addictions to cocaine, heroin, tobacco and alcohol and hypothesize that a lower D2R binding serves as a biomarker for addictive behaviour. Another study also found downregulated D2R and asserts that this is associated with decreased PFC activity in the brain (Volkow & Boyle, 2018). They have shown that improvement of these signals lead to mitigated compulsive drug-taking behaviour. Uhl et al. (2019) have also found that a D2R decrease is not only associated with poor decision making and emotion regulation, but also with compulsive behaviour and impulsivity. Studies done in rodents where NAc D2R expression was

being increased showed significant reductions in alcohol and cocaine consumption (Thanos et al., 2001).

Not only D2R downregulation is present in the addicted brain, also increased ΔFosB expression appears to be a biomarker for addictive behaviour. ΔFosB acts as a transcription factor and is only found in the NAc in healthy animals (Nestler, 2005). It appears that chronic cocaine intake elevates ΔFosB expression in the NAc, PFC and amygdala, however these elevations are the most prominent in the NAc (Nestler, 2005). Another research about the effect of opiate sensitization on ΔFosB expression is in line with this (Kaplan et al., 2011). They add to this that ΔFosB is thought to induce synaptic and neuronal plasticity in these brain areas after chronic drug-administration. A possible explanation could be that ΔFosB induces upregulation of Cdk5, which is known to be responsible for nerve cell growth and synaptic changes (Ruffle, 2014). However, this is only a hypothesis as evidence for this mechanism has not been found yet. Nevertheless, it could certify the increased spine density of dendrites in MSNs that were found after repeated cocaine exposure (Volkow & Morales, 2015). This increase seemed to induce longer-lasting memory for the drug-reward and its conditioning effects and thus could contribute in the neurobiology of addiction.

Furthermore, glutamate induced neuroadaptations are expected to be involved. Metabotropic glutamate (mGlu) receptors can be divided in two groups, group I mGlu receptors and group II mGlu receptors (Yohn et al., 2018). Group I mGlu receptors are expressed on striatal MSNs and DA neurons and activation of it contributes to long-term depression (LTD) and long-term potentiation (LTP) of synaptic strength that underlie learning and memory, thus are potential reasons for the addictive component of reward (Yohn et al., 2018). Volkow & Boyle (2018) add to this that glutamatergic projections onto the VTA and striatum causes sensitivity and reactivity for drug-related cues so that aversive emotions will emerge. They showed that restorage of these projections from the PFC and amygdala resulted in cessation of drug administration after exposure to drug-related cues. Additionally, Yen et al. (2013) proved that a morphine-conditioned status was linked to an increased level of Glu in the NAc and VP together with decreased levels of GABA in all three regions, suggesting this could be a biomarker for addiction in rodents.

Multiple changes in the addicted brain have been listed above, however lots of other alterations exist that are not named. The quantity of potential reasons for addicted behaviour in the individual makes it hard or even impossible to allocate addiction to only one alteration in the brain, once again showing that addiction is a very complex disorder that is still not being fully understood.

4. DEEP BRAIN STIMULATION

In order to determine whether DBS could be an effective treatment for addiction, not only the neurobiology of this complex disorder is important to clarify, but also DBS itself needs to be highlighted. This chapter explains what DBS is and considers which brain area should be stimulated and what underlying mechanisms are on the basis of stimulation.

What is deep brain stimulation?

Deep brain stimulation (DBS) is a method that is based on alternating neuronal components and neuronal activity using electrical pulses from electrodes in the brain (Chen et al., 2013). These electrodes are surgically placed within particular nuclear regions in the brain and deliver stimulating pulses (figure 4) (Chen et al., 2013). The electrodes are coupled to a kind of pacemaker that is subcutaneously implanted on the chest (figure 3) (Dougherty, 2018). Through this pacemaker different parameters can be adjusted, such as strength, frequency and pulse width, but also the exact location of stimulation (Dougherty, 2018). The most commonly used electrodes contain four contacts (quadrupole), so by varying in combination of stimulating contacts different parts around the electrode can be stimulated (figure 4B, 4C) (Dougherty, 2018).

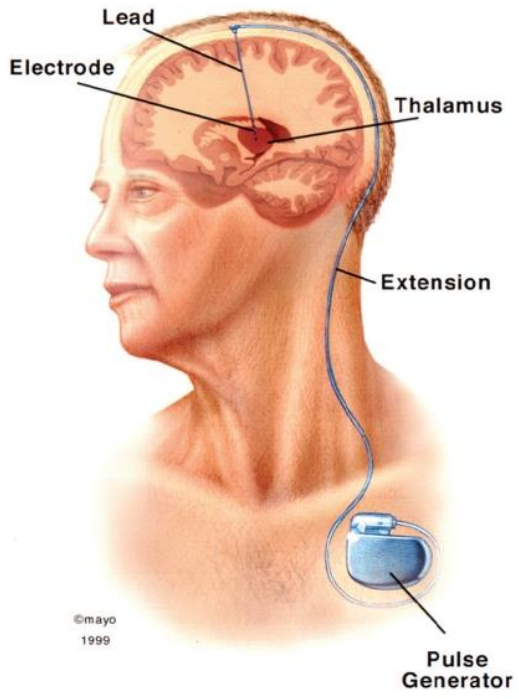

Figure 3. Components of deep brain stimulation. Including the electrode in the brain, the lead and its extension, and the pulse generator in the chest. Adapted from Lyons (2011).

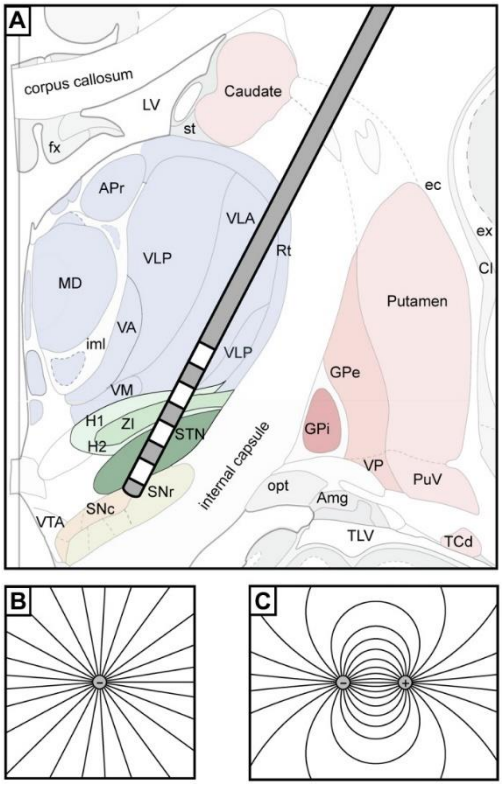

Figure 4. DBS electrode in the brain and its electric fields. A) Example of DBS electrode placed in the STN, B) electric field of monopolar stimulation, C) electric field of bipolar stimulation. With bipolar stimulation, a more focused electric field is being generated. Combinations in anode/cathode can adjust the field of DBS. Adapted from Herrington et al. (2016).

Lots of research has already been done into the effect of DBS on Parkinson's disease (PD). The first neuroscientists to find improvements on parkinsonism due to DBS were Siegfried and Lippitz (1994). Their research included three PD-patients to whom DBS of the globus pallidus internus (GPi) and the subthalamic nucleus (STN) was being applied. In

general, the severity of bradykinesia, speech problems and tremors were decreased during stimulation and the subjective assessment of the patients, using the Webster rating scale, was increased (Siegfried & Lippitz, 1994). These positive findings stirred up further research of DBS in PD as well as in other neurological diseases. Nowadays, in the Netherlands DBS is an accepted treatment for Parkinson's disease, obsessive compulsive disorder (OCD), epilepsy, Gilles de la Tourette and multiple motor neuron diseases (Hersenstichting, n.d.). These diseases all underlie structural, biochemical or electrical changes that arise within different neuronal circuits (i.e. are all neurological diseases), causing a variety of symptoms depending on the region affected. Since it is known that the same principle applies to addiction (Volkow & Boyle, 2018), it can be expected that DBS will also be a promising future treatment for this disorder, offering a solution for all substance use disorder patients to rehabilitate.

Underlying mechanisms

The exact mechanism of DBS in general is not yet fully discovered, but multiple findings and hypotheses do exist.

One of the hypotheses is that DBS can cause either inhibiting or exciting neuronal activation. One study states that DBS effects similarly to a reversible lesion and thus has an inhibiting effect (Herrington et al., 2016). They explain that it is possible for high-frequency stimulation to cause a depolarization block due to inactivated sodium channels and more potassium currents. However, a more legitimate explanation is the activation of inhibitory synapses (Herrington et al., 2016). Earlier research of Dostrovsky (2000) is in line with this and showed that GPi DBS causes a very rapid (100 ms after initiation) neuronal inactivation. However, work of Elder et al. (2003) challenges it. This study did not find neuronal *inactivity*, but neuronal *activity* in the GPi which was linked to higher excitatory output coming from the STN, the target region in that case (Elder et al., 2003). Another study hypothesized that NAc DBS is able to induce synaptic inhibition or excitation, with alterations of neuronal network activity as a result (Luigjes et al., 2012).

Not only electrical effects of DBS have been studied, but also lots of researches attribute the effectiveness of DBS to neurochemical effects. For example, DBS of the caudate nucleus or dorsal STN seemed to increase the level of extracellular dopamine and DBS of the anterior thalamus resulted in an induced release of adenosine (Herrington, 2016). Additionally, the review of Luigjes et al. (2012) hypothesized that DBS of NAc could establish normalization of striatal dysfunctions, suggesting that DBS could cause changes in dopamine levels. A rat study by van Dijk et al. (2012) that did research on monoamine neurotransmitters change in mPFC and orbitofrontal cortex (OFC) after DBS of the NAc, substantiates this speculation. Neurotransmitter levels were determined by examination of microdialysis samples taken before and after stimulation (van Dijk et al., 2012). An increased dopamine and serotonin release in the mPFC were found after DBS, as well as increased dopamine and noradrenaline release in the OFC (van Dijk et al., 2012). Even though stimulation was being applied in healthy rats (rather than addicted rats), the fact that stimulation did cause alterations in neurotransmitter release is already enough to take this hypothesis into consideration for DBS in addiction. Another study measured differences in Glu and GABA in morphine induced rats, since these neurotransmitters also seem to be involved in

addiction (Yan et al., 2013). Microdialysis probes in the VTA, NAc and ventral pallidum (VP) were analysed to determine neurotransmitter levels (Yen et al., 2013). It appeared that stimulation of the morphine-conditioned rats decreased Glu levels and increased GABA levels significantly in all three regions, suggesting that DBS is able to normalize the release of these neurotransmitters in rats with an induced addiction (Yen et al., 2013).

Finally, synaptic plasticity also seems to be responsible for the effects of DBS, especially long-term. Shen et al. (2003) showed that STN DBS in rodents resulted in different forms of synaptic plasticity, including short-term potentiation (STP), LTP and LTD. Another study that applied STN DBS in dopamine-depleted rats found similar results (Yamawaki et al., 2012). A very recent review mentioned that DBS of the anterior cingulate cortex (ACC) caused functional changes in its neuronal network one year after surgery (Jakobs et al., 2019). In addition, DBS of the STN was proven to desensitize its afferents, where on the other hand corticostriatal and direct pathways were strengthened (Jakobs et al., 2019).

These are only a few of many examples that each show different effects, reflecting the complexity of DBS's exact mechanism. Also, these examples all focussed on different areas of which some are not that important in addiction. As mentioned in chapter 3, the VTA and NAc are predominantly involved in addiction as abnormalities were found here, making either one of them a good target for DBS. Luigjes et al. (2012) reviewed seven animal studies and eleven human studies that considered different brain regions for stimulation. They indeed concluded that for addiction the NAc is the most eligible target area for DBS since stimulation of the NAc resulted in a reduction of addicted-related behaviour and cessation or significant reduction of drug intake (Luigjes et al., 2012). Additionally, no major side-effects occurred after stimulation (Luigjes et al., 2012).

5. DBS IN ADDICTION: ANIMAL STUDIES

It can be assumed that the NAc is the brain area yielding the most promising results, yet it is important to underpin this with already published researches. Lots of studies about DBS and addiction can be found, but most studies focus on drug seeking behaviour in rodents and addictions to either cocaine, heroin or ethanol. This chapter presents two animal studies that show the effect of NAc DBS on drug seeking behaviour and relapse in addicted rats.

Chronic unilateral stimulation of the nucleus accumbens at high or low frequencies attenuates relapse to cocaine seeking in an animal model (Hamilton et al., 2015)

This study investigates if unilateral DBS of the NAc attenuates drug seeking behaviour and the potential to relapse in rats using the drug self-administration (S-A) model of cocaine addiction. Also, Hamilton et al. answer the question whether or not there is a difference in effect between high-frequency stimulation (HF) and low-frequency stimulation (LF) of the NAc in these rats. Unilateral stimulation was chosen to minimalize possible complications due to electrode implantation in the brain.

Groups and methods

A total of 30 male Long-Evans rats of 10-12 weeks old were utilized in this study. All rats underwent surgery, including the sham stimulated rats. Rats were then divided into four groups: SA-sham (n = 6), Co-sham (n = 7), Co-LF (n = 9) and Co-HF (n = 8). SA stands for saline and Co stands for cocaine. Hamilton and colleagues made use of a saline-sham group to control for any potential side-effects of DBS and to check if DBS also has an effect on responses to a natural reinforcer. The rats were put into S-A chambers with active and inactive lever presses where they were trained and tested. Active lever presses resulted in cocaine (Co-sham, Co-LF, Co-HF) or saline (SA-sham) delivery and a stimulus light, while nothing happened with inactive lever presses. Rats were (being) trained until they progressed to a fixed ratio 3 (FR3) schedule of reinforcement which implies that the rats had to press the lever three times to receive one reinforcement. In case of five consecutive days of correctly following the FR3 schedule, rats were allowed to undergo the drug-taking test. Figure 5 shows a schematic timeline of the protocol. HF, LF and sham DBS was initiated for 30 minutes before the start of the drug-taking test (cocaine and saline were available) to determine the effects on drug-taking behaviour. After the drug-taking test, the withdrawal phase (30 days) could start in which the rats were constantly being (sham) stimulated in the first 14 days. During withdrawal, both active and inactive lever presses had no

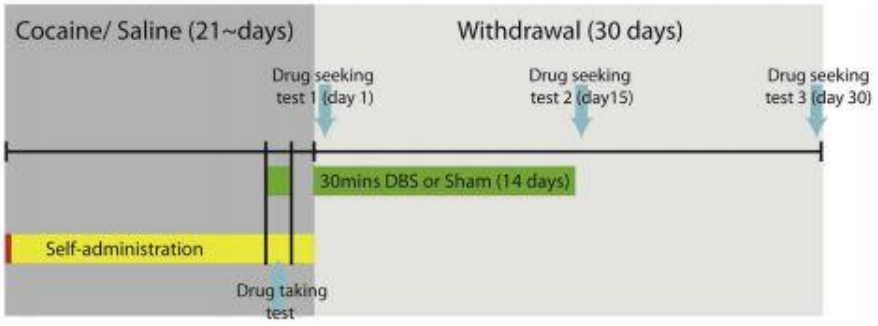

Figure 5. Schematic timeline of the protocol. The first 21 days, rats were trained on a FR3 schedule of reinforcement for either cocaine or saline. During the drug-taking test, DBS was being applied and cocaine was available. This was followed by the withdrawal period in which there were 14 days of DBS application and three moments where drug-seeking tests were conducted. Cocaine was not available during the withdrawal phase. Adapted from Hamilton et al. (2015).

consequences. Drug seeking tests were conducted at day 1, 15 and 30 after withdrawal to assess the effects of DBS on relapse (figure 5).

Results

The amount of obtained reinforcers within the drug intake test did not differ between Co-sham, Co-HF and Co-LF which means that DBS did not have any significant effect on drug-taking (figure 6). However, there was a significant difference between the cocaine groups and the saline group in the amount of obtained reinforcers. Results of the relapse tests are seen in figure 7. No significance in number of active lever presses was found across the cocaine groups on day 1 and day 30. The drug seeking test on day 15 however, did show significance across the cocaine groups. The HF- and LF-stimulated group had significantly less active lever presses than the sham-stimulated group, implying that DBS with high and low frequency reduced cocaine seeking behaviour in the rats. For HF stimulation, this was a reduction of 48% and for LF stimulation 36%. Note that this effect was only seen on the drug seeking test on day 15. In all three drug seeking tests, the cocaine groups significantly differed from the saline group. DBS of the saline group did not have any effect on responses to saccharin as the quantity of active lever presses was equal for baseline condition, HF-stimulation and LF-stimulation. For this to research, the same training and tests as for the cocaine were applied, but only cocaine was replaced with saccharin which was used as a natural reinforcer.

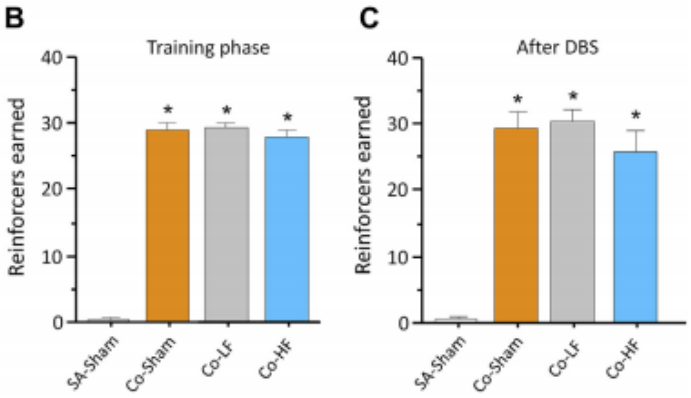

Figure 6. Unilateral NAc DBS had no effect on drug-taking. B) amount of reinforcements obtained by the groups in the training phase. Cocaine groups being significantly higher than the control group (*). C) amount of reinforcements obtained by the groups after DBS, based on results of the drug-taking test before the withdrawal phase. Cocaine groups are significantly higher than the control group in this phase as well (*). Adapted from Hamilton et al. (2015).

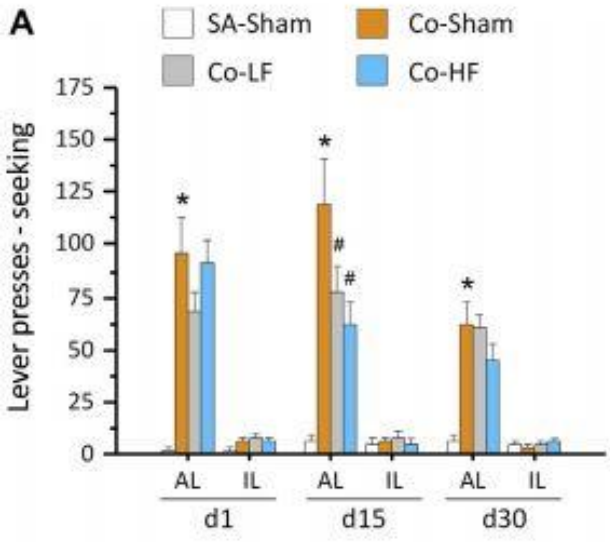

Figure 7. Unilateral NAc DBS reduces cocaine-seeking in withdrawal phase. Amount of active lever presses (AL) and inactive lever presses (IL) are seen for day 1, 15 and 30. HF and LF stimulation on day 15 significantly reduced cocaine seeking compared to C-sham (#). On day 1 and day 30, this had no significant effect (* = only significant from SA-sham). Adapted from Hamilton et al. (2015).

Conclusion

This study proves that unilateral DBS of the NAc with both HF and LF positively alters drug relapse after a mandatory abstinence period (15 days). This effect is strengthened by the fact that no significant differences were seen on day 30 when stimulation had already been stopped for 15 days. Stimulation with HF appears to be slightly more effective than

stimulation with LF, but the discrepancy is minor. NAc stimulation surprisingly had no significant effect on cocaine intake when the drug was available. Hamilton et al. also demonstrated that NAc DBS did not alter responses to natural reinforcers and that it did not evoke any side-effects. This study emphasizes that not only chronic bilateral, but also chronic unilateral stimulation of the NAc can positively influence drug relapse. Since bilateral electrode surgery is more likely to induce long-term complications but yet has been standardly applied in neuroscientific studies, it is of importance to also take unilateral stimulation into consideration.

DBS of nucleus accumbens on heroin seeking behaviours in self-administering rats (Guo et al., 2013)

This work of Guo et al. (2013) studies alterations in heroin seeking behaviours in rats after stimulation of the NAc. There has been chosen for bilateral and unilateral stimulation as well, similar to the previously explained study.

Groups and methods

For this study male Sprague-Dawley rats were used and underwent surgery where electrodes were placed either bilaterally or unilaterally. Rats then were put into heroin self-administration training following the FR1 schedule of reinforcement (previously explained study describes self-administration training). FR1 schedule of reinforcement means that rats received a reinforcement (i.e. heroin infusion) after every completion in the active nose-poke. Infusion went along with a LED light and the sound of the infusion pump, serving as conditioned stimuli. Total SA training lasted 14 days, with one session for each rat per day. A variation in response rates of less than 15% over three successive days was considered a stable response pattern. Rats that exhibited this were used for further experiments and were divided in different groups. An overview of the groups is seen in table 1.

Table 1. Overview of groups used in the study of Guo et al. (2013). Note that two rats (the bilateral 75μA DBS group and the unilateral left sham-DBS group) were excluded in statistical analysis due to misplacement of the electrode(s). The red marked groups are the groups that received actual DBS.

Bilateral *(n=24)*	Unilateral *(n=30)*	
Control *(n=6)*	Control *(n=6)*	
Sham-DBS *(n-6)*	Left sham-DBS *(n=5)*	Right sham-DBS *(n=6)*
75μA DBS *(n=5)*	Left 150μA DBS *(n=6)*	Right 150μA DBS *(n=6)*
150μA DBS *(n=6)*		

Rats underwent a period of heroin abstinence lasting seven days in which, depending on the group, they were being HF stimulated with varying intensity. This was followed by cue-induced reinstatement of heroin-seeking where conditioned stimuli were presented, and an active nose-poke response did not result in receiving infusion. After this, rats underwent a second period of abstinence similar to the first. Now heroin-induced reinstatement of heroin-seeking was tested in which rats received a small dose of heroin. Rats were placed in the SA chamber afterwards, but conditioned stimuli were not provided. In both experiments nose-pokes were being recorded for

respectively 1 and 2 hours. Two behavioural experiments were conducted after the heroin-induced reinstatement in the bilateral groups. Lastly, brain tissue of the sham-DBS groups and the 150µA bilateral DBS group were tested for immunohistochemical expression of ΔFosB and pCREB.

Results

Two rats were excluded in statistical analysis due to a misplacement of the electrodes. Within the bilateral groups, cue-induced reinstatement and heroin-induced reinstatement nose-poke responses of the 75µA DBS group and the 150µA DBS group were significantly lower than both the control group and the sham-DBS group (figure 8). Within the unilateral groups, cue-induced reinstatement and heroin-induced reinstatement nose-poke responses of only the right 150µA DBS group was significantly lower than other groups (figure 9). It seemed that there was no difference between nose-poke responses of the unilateral right 150µA DBS and bilateral DBS, meaning it was equally effective. No significant differences were found for the behavioural experiments between the groups. pCREB expression was significantly higher in tissue from the 150µA bilateral DBS group compared to the control group, whereas expression of ΔFosB was significantly lower compared to the control group.

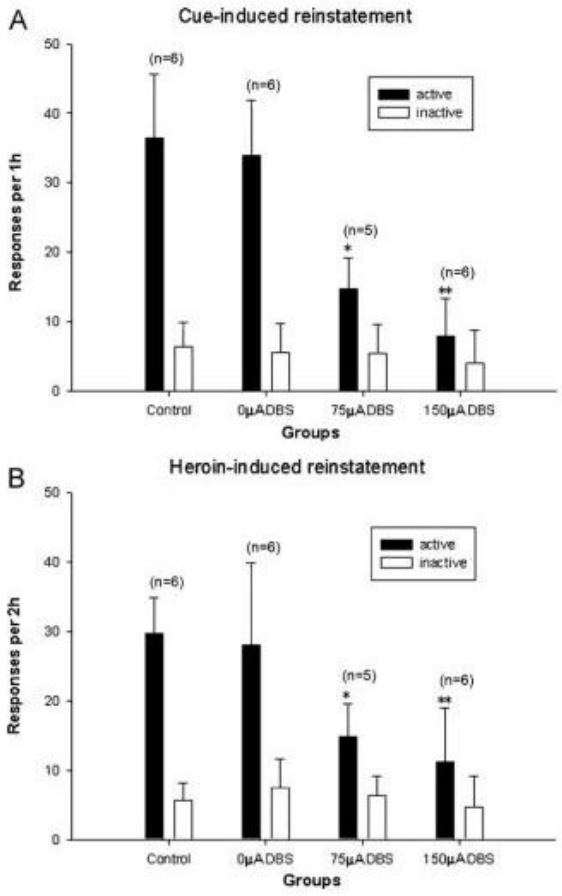

Figure 8. Bilateral NAc DBS attenuated cue- and heroin-induced reinstatement of drug-seeking. A) both the 75µA and 150µA DBS group were significantly different from the negative control and the 0µA DBS group. B) these differences were also found in heroin-induced reinstatement. Adapted from Guo et al. (2013).

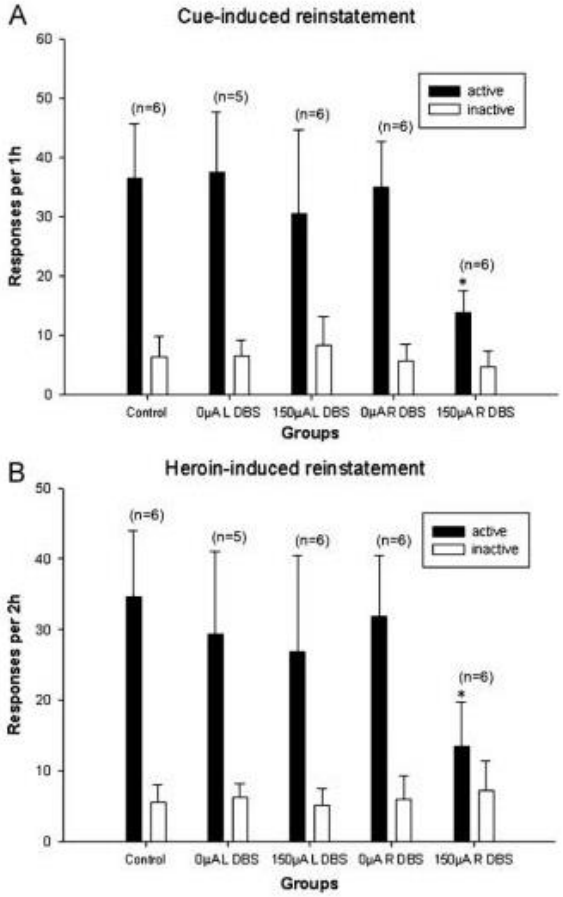

Figure 9. Unilateral right NAc DBS attenuated cue-and heroin-induced reinstatement of drug-seeking. A) the 150µA right DBS group differed significantly from the negative control and the 0µA DBS group. B) similar results were found in heroin-induced reinstatement. Adapted from Guo et al. (2013).

Conclusion

Guo et al. (2013) proved that DBS of the NAc reduced cue- and heroin-induced reinstatement of drug seeking. This holds true for bilateral stimulation with 75μA and 150μA, as well as unilateral stimulation of the right NAc with 150μA. It seemed that there were no significant differences between these three types of stimulation, suggesting that DBS of the left NAc does not significantly contribute to the positive results. Furthermore, no possible side-effects occurred as no significant behavioural differences were found. This study also explored an increased expression of pCREB and a decreased expression of ΔFosB in stimulated rats, indicating a possible underlying DBS mechanism in addiction. Guo et al. (2013) conclude that DBS of the NAc, either bilaterally or unilaterally (right), has positive effects on drug-seeking in rats without generating long-term side-effects and emphasize that it has potential to be an effective and safe therapy for heroin addiction.

6. DBS IN ADDICTION: HUMAN CASE STUDIES

When having a critical look at the animal studies, one can question whether or not it is possible to project these results onto situations in humans. The correctness of the transition from animal to human is and stays a dispute nowadays. Because of this, it is important to explain not only animal studies but also to shed a light on human studies. Since operation is required for a DBS treatment which is a somewhat serious intervention, no studies were found where controlled randomised trials are being used. Therefore the two human studies described below are case studies and respectively concern five and two persons.

Nucleus Accumbens Deep Brain Stimulation for Alcohol Addiction – Safety and Clinical Long-term Results of a Pilot Trial (Müller et al., 2016)

In 2009, Müller et al. (2009) already published an article in which three alcohol-addicted patients underwent treatment with DBS. Later two other patients took part in the research, which made a total of five patients with an alcohol addiction being treated with DBS. The article of Müller et al. (2016) shows the treatment's progress for at least five years. In those years there were multiple clinical follow-ups, however it is not clear how often these took place.

Patients and methods

A few criteria were set up for the selection of to be treated patients (Müller et al., 2009). As a consequence, all patients 1) were male and aged between 25 and 60 years old, 2) underwent detoxification followed by a two weeks period of abstinence, 3) had ten years of alcohol-induced addictive behaviour, 4) had at least two rehabilitation treatments and one unsuccessful therapy. Also, patients with comorbidities were excluded.

Before surgery, different neuropsychological tests and assessments were conducted (table 2). Neuropsychological tests primarily served as a measurement for the patients' IQ: there was exclusion of the patient when IQ was lower than 80. Symptom check list 90 (SCL), psychopathology, obsessive-compulsive drinking scale (OCDS), alcohol urge questionnaire (AUQ) were being assessed before and after surgery. Alcohol dependence scale (ADS) was being held only before surgery to check if alcohol dependence was severe enough to count it under addiction. Patients were then subjected to stereotactic surgery where electrodes were placed bilaterally in the NAc.

Table 2. Overview of patient information and results of neuropsychological tests on baseline; alcohol dependence scale (ADS), alcohol urge questionnaire (AUQ).

	Age	Addicted for	ADS	AUQ	Start DBS
Patient 1	40	23 years	34	37	Sept. 2007
Patient 2	35	17 years	41	29	Oct. 2007
Patient 3	37	22 years	28	53	Jan. 2008
Patient 4	51	21 years	22	20	Dec. 2008
Patient 5	55	19 years	33	14	Feb. 2009

Results

During DBS of the NAc, all patients experienced a complete disappearance of the craving for alcohol (figure 10). Two out of five patients have not had any relapses ever since and have been abstinent for almost 8 years (patient 1) and at least 7 years (patient 2). The last contact researchers had with patient 2 was at the end of 2014 where he said to still be abstinent and feeling well. The other three patients (patient 3, 4, 5) did have multiple relapses during the stimulation despite the loss of craving. Relapses generally were of few weeks length and were followed by longer periods of abstinence. They all experienced stressful or depressive feelings during or right before the relapse and the three patients themselves also attribute the relapses to stress. Two of the three patients (patient 4 and 5) that had relapses became depressed respectively three and two years after initiation of DBS, but were the result of personal events and were not related to DBS. Even though multiple relapses occurred in three out of five patients, all patients told to have a positive overall experience with DBS. One patient stated that "DBS changed his life", while another patient said that DBS helped him not to relapse continuously. Also, no negative consequences or side effects were reported by the patients at all.

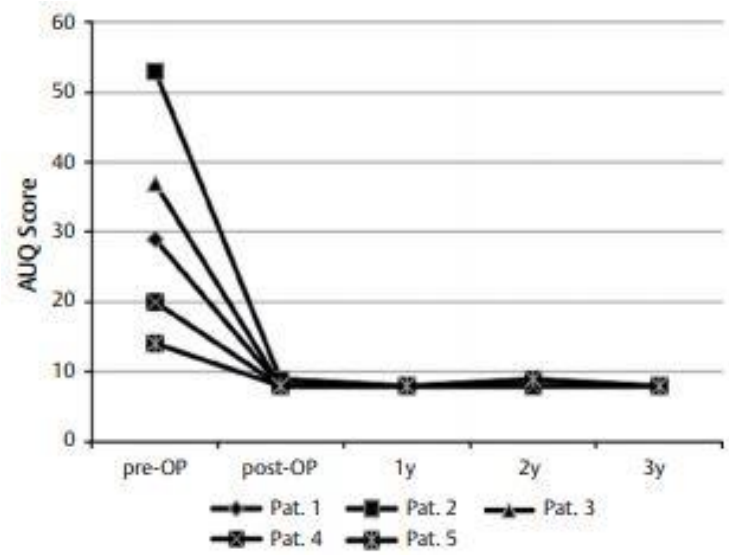

Figure 10. NAc DBS reduced cravings for alcohol on long-term. AUQ score as a measure for the urge to consume alcohol. Questionnaires were conducted pre-operative (pre-OP), post-operative (post-OP) and 1, 2 and 3 years after initiation of DBS. A score of 8 is considered normal and indicates no craving. Adapted from Müller et al. (2016).

Conclusion

DBS of the NAc reduced alcohol craving in all five patients on long-term, based on AUQ scores conducted until 3 years after initiation of DBS. Two patients did not have any relapses afterwards, while three patients did. It is striking that these relapses were of short duration and all occurred when the patient experienced stress. Even though three patients relapsed, all patients reported their cravings for alcohol had reduced considerably. Additionally, all patients said to have a positive overall experience with DBS. Also, no adverse side-effects were found associated with DBS.

Deep Brain Stimulation of Nucleus Accumbens for Methamphetamine Addiction: Two Case Reports (Ge et al., 2019)

This article shows the effects of NAc DBS in two patients with a methamphetamine (MA) addiction. Ge et al. (2019) mention that various studies can be found about the effectiveness of DBS on patients with an addiction to alcohol, heroin and cocaine whereas for MA addiction this is not the case. The reason for this is that MA can cause the patient to develop an addiction that differs in mechanism from other substance use disorders (e.g. of the above-named substances). Reason for Ge et al. to publish two case reports in this subject.

Patients and methods

All patients were male, aged between 25-60 and addicted to MA for at least 8 years. Severity of addiction is being expressed in level of craving using the Visual Analog Scale (VAS), where a score of 0 is equal to no craving and a score of 10 is equal to intense craving. This assessment was done pre- and post-operative, as well as the Hamilton Depression Rating Scale (HAMD), with scores meaning the following: normal ≤ 8, mild depression 9-19, moderate depression 20-23, severe depression ≥ 35. The Symptom Checklist-90 (SCL-90) was also used before and after surgery to measure psychiatric and addiction symptoms in the patients. For this, a score is considered normal when below 2 and abnormal when higher than 2. A score even higher than 3 indicates serious psychiatric and addiction symptoms. Table 3 shows an overview of patient information.

Before surgery, MRI scans were made to target the exact location of the NAc in the patients. Post-operative MRI scans were made to check whether the electrodes were placed appropriately and to evaluate the potential for abutting brain structures to become stimulated as well (/to evaluate to what extent abutting brain structures would become stimulated as well). After bilateral placement of the electrodes, the monitoring of the patients could start. This was done by taking urine MA tests, family reports (telephone) and face-to-face interviews.

Table 3. Overview of patient information and results of neuropsychological tests on baseline; visual analog scale (VAS), Hamilton depression rating scale (HAMD), symptom checklist-90 (SCL-90).

	Age	Addicted for	VAS	HAMD	SCL-90	Start DBS
Patient 1	38	10 years	5	6	3.0	Nov. 2016
Patient 2	49	8 years	5	17	3.1	Nov. 2015

Results

Patient 1 had withdrawal symptoms before DBS such as chest tightness and hallucinations and he also had a poor sex life. After DBS, the patient felt more energetic and he also had a better sex life. He achieved total abstinence that remained until the last moment of monitoring (i.e. 1,5 years after initiation). The patient's VAS score, which was 5 before DBS, decreased to 0. Also, according to the SCL-90 score, the patient was considered to have serious psychiatric and addiction symptoms before surgery. This score dropped to 1,3 afterwards, thus indicates a normal score.

Patient 2 experienced complications regarding impulsivity, tantrums and other addictions beforehand. Also, a mild depression was present in the patient since his HAMD score was 17. After

initiation of DBS, the patient had feelings of anxiety and hypomania (stimulation of 4,5 V). Reduction to 3,7 V had teeth grinding, insomnia and a hypomanic period as consequences, hence the adjustment of the stimulation to 3,3 V. After completely fine-tuning the DBS parameters, the side-effects disappeared and the patient's depression symptoms and need for drugs diminished. His HAMD score reached a normal level after DBS and his VAS score dropped from 5 to 2. However, these effects were temporary because 6 months later the patient began to relapse intermittently, especially in stressful periods. Eventually, his VAS score and HAMD score returned to pre-DBS levels. Again, multiple stimulation adaptations were being done, but did not affect the patient's behaviour positively.

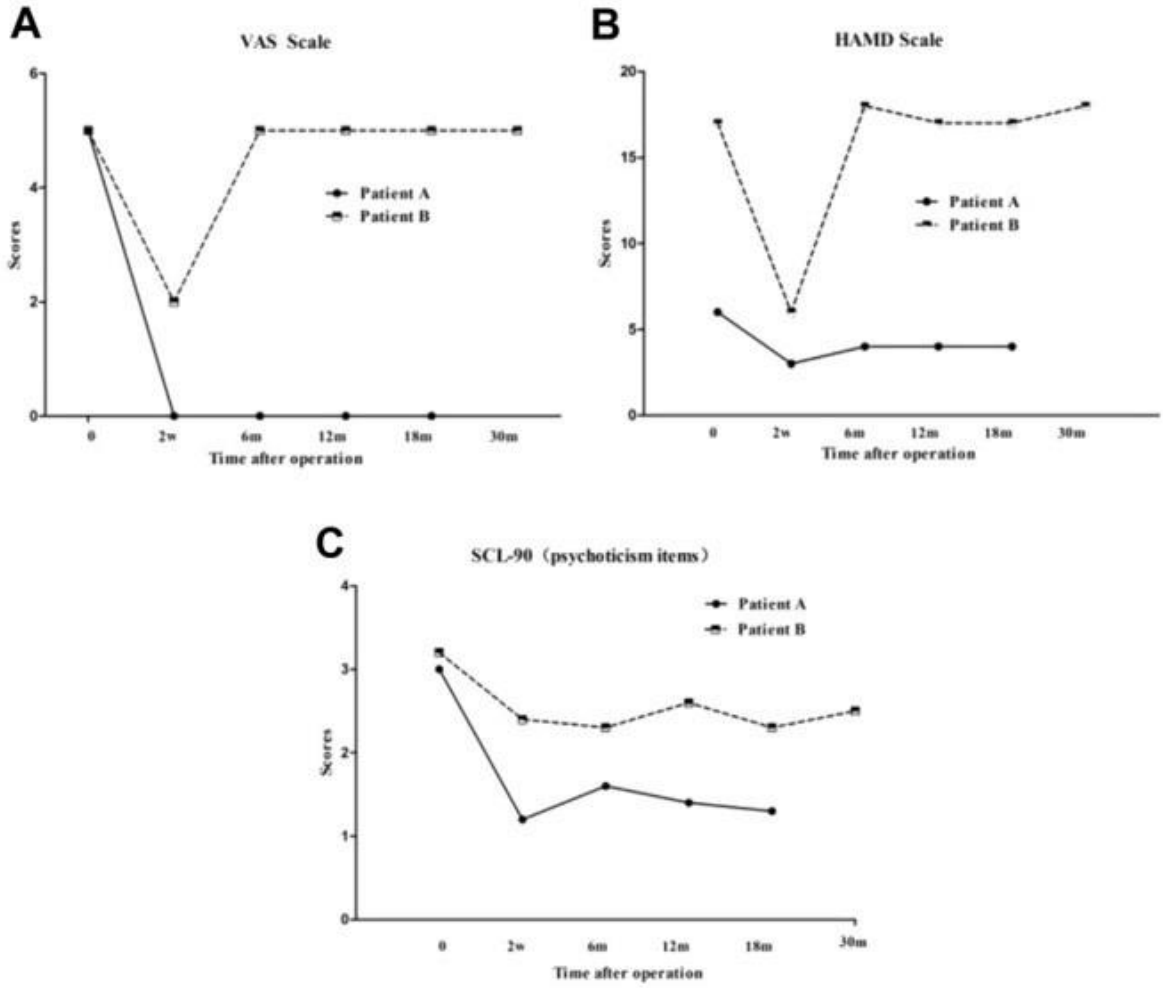

Figure 11. Results of VAS (A), HAMD (B) and SCL-90 (C) on six time points. A) Patient A (1) and B (2) had reduced feelings of craving two weeks after initiation of DBS. Patient A retained this level, while patient B returned to baseline level at six months after initiation. B) Baseline of patient A was considered normal and stayed on this level during DBS. Patient B went from mild depression to a normal level after two weeks of initiation but returned to baseline level at six months after initiation. C) Patient A went from abnormal to normal levels after two weeks of initiation and stayed on this level. Patient B stayed on abnormal levels during the whole DBS period. Adapted from Ge et al. (2019).

Conclusion

One patient experienced positive effects on his addictive behaviour and became drug-free for at least 1,5 years. The patient's feeling of craving disappeared completely, and psychiatric symptoms diminished. On the other hand, the second patient did not profit from DBS. Multiple side-effects arose from stimulation and also, the patient relapsed after 6 months. Dislocation of the electrode was likely to be the cause as post-MRI scans made clear that the ventral electrode contact in the right hemisphere was shifted outside the NAc and was located rather close to the GPi. Ge et al. emphasize that bilateral DBS of NAc-related circuits could not only play an important role in preventing relapse in addicted patients but can also be valuable for treating psychiatric symptoms involved in addiction. However, it is concluded that further research with a larger sample size is needed to unravel and prove predictive factors of therapeutic effects, for example the exact target location.

7. POSSIBLE MECHANISMS OF NAC DBS IN ADDICTION

Earlier in this thesis (Ch.4), the general underlying mechanisms of DBS were discussed. Once provided that the NAc is the most ideal region for stimulation in addiction, the possible DBS mechanisms can be specifically applied to changes in this brain area. Lots of hypotheses exist about the mechanism of DBS, however a combination of a few seemed to dominate. It is likely that DBS induces 1) activation of inhibitory or excitatory neurons and/or 2) alteration of neurotransmitter release and/or 3) neuronal and synaptic plasticity. When these mechanisms hold true for DBS in addiction, the following changes could occur.

Stimulation in the NAc could increase DA release in this region, leading to activation of D1Rs and D2Rs. However, D2Rs are downregulated in addiction and it is proven that DA release in the NAc has very little effect on DA neurons (Urban & Martinez, 2012). Also, frequent and long-term exposure of D1Rs and D2Rs to DA is known to cause desensitization of the receptors, meaning that a DBS-induced increase of DA could only contribute to this. Perhaps it is more likely that rather the D2Rs expression or sensitivity will be enhanced after DBS. Two studies actually found increased D2Rs expression after DBS of respectively the medial forebrain bundle (MFB) and the NAc (Dandekar et al., 2017; Herrington et al., 2016). Therefore it is possible that D2Rs directly become upregulated in the NAc due to stimulation. This D2Rs upregulation can also be the result of synaptic plasticity which was the third hypothesized mechanism. It has been shown that synaptic plasticity is mainly based on changes in the amount of receptors at synapses (Gerrow & Triller, 2010), which makes it probable for NAc DBS to indirectly alter D2Rs expression so that a normal functioning of the reward system will be established.

Additionally, in the case of activation of inhibitory or excitatory neurons, brain areas such as PFC and the limbic system can be either inhibited or stimulated considering their connections with the NAc. Through this, the characteristic hypofunctioning of the PFC and hyperfunctioning of the limbic system could be normalized by DBS, resulting in restoration of the deteriorated inhibitory control and less strengthened emotions.

A hypothesis other from the ones previously mentioned, is based on the research of Guo et al. (2013) which is explained in Ch.5. They concluded that bilateral NAc DBS with 75µA and 150µA and unilateral right NAc DBS with 150µA reduced cue- and heroin-induced reinstatement of drug-seeking in heroin self-administering rats. After the tests, brain tissue of the sham-DBS group and the bilateral 150µA DBS group were tested for immunohistochemical expression of ΔFosB. As earlier mentioned, ΔFosB is a transcription factor that is upregulated in the NAc and seems to be a biomarker for addictive behaviour. Guo et al. (2013) found that ΔFosB expression of the bilateral 150µA DBS group was lower compared to the sham-DBS group. It is not clear whether DBS is able to completely normalize ΔFosB expressions since no baseline was measured, but at least DBS is able to establish a decreased expression. It is highly possible that the decrease in ΔFosB expression contributed to the reduced drug-seeking, since ΔFosB upregulation is linked to addictive behaviour. Therefore, alteration of ΔFosB expression should also be considered a possible mechanism for the effectiveness of NAc DBS in addiction.

8. SYNTHESIS

In conclusion, the NAc seems to be the area with the most promising results after stimulation. This is in line with the importance of the NAc in the reward system and thus addiction. The two animal studies previously explained both concluded that DBS of the NAc reduced drug-seeking. Within the described human case studies, one patient did not profit from the stimulation in the end. However, in this patient the NAc was probably not stimulated due to dislocation of the electrode. The six other patients all had a positive overall experience with DBS. However, it must be said that complete cessation of drug-taking did not happen in each patient since multiple patients have had relapse(s). Though it is striking that these were always followed by a (longer) period of abstinence and also only occurred in periods of high stress. It could be possible that stress can outweigh the stimulation's positive effects, perhaps through neuronal interference with the HPA-axis. However, the underlying mechanism of DBS together with stress should be studied more accurately before this assumption holds true. All explained studies reported that DBS had positive results on drug-seeking in a period where drugs were not available and did not focus on drug-taking when drugs were available. Hamilton et al. (2015) did study DBS's effects on drug-taking, but unfortunately were not promising. They reported that NAc DBS did not reduce drug-taking when the drug was available. Although, this stimulation was only for short-term and it was the first stimulation the rats received. It could be possible that NAc DBS indeed is not able to reduce drug-taking when the drug is available. The human case studies however, applied long-term DBS and showed that half of the patients did not have relapses after initiation of DBS, implying that DBS is able to reduce actual drug-taking. Still, it is important to take this matter into account as availability to the drug could reduce DBS's effectiveness.

Although the studies highlighted in this thesis had overall positive results of NAc stimulation in the treatment of addiction, lots of other successful studies exist where other brain areas were targeted. For example regions as the STN (Pelloux & Baunez, 2013; Rouaud et al., 2010), the PFC (Levy et al., 2007) and the lateral habenula (LHb) (Yadid et al., 2013). Additionally, Müller et al. (2013) explain that lots of brain areas are involved in the reward system, e.g. the ventral pallidum (VP), amygdala, hippocampus and the raphe nucleus. The fact that these areas are not outlined in this thesis, is the result of delineation of the thesis. Also, Luigjes et al. (2012) took these other areas into consideration by thoroughly reviewing a total of 18 studies with 6 different target areas, including the above-named brain regions. They concluded that stimulation of the NAc had the most promising results regarding drug-seeking and drug-administration and had the least side-effects. This supports the safety of stimulation in the NAc and is one of the reasons why this thesis focuses on DBS in the NAc.

As mentioned in the previous paragraph, multiple mechanisms of NAc DBS in addiction are possible. It is likely that NAc DBS is effective because it can upregulate D2Rs indirectly through synaptic plasticity, resulting in a normal functioning of the reward system. Also, functioning of the PFC and the limbic system could be normalized as a result of activation of NAc surrounding excitatory or inhibitory neurons. This can possibly establish an increased inhibitory control and less strengthened emotions. Moreover, NAc DBS could be effective because of its ability to

decrease ΔFosB expression in the NAc, reducing addictive behaviour such as drug-seeking. Despite the fact that these are all speculations and obviously further research is needed to confirm these, it is very likely that a combination of suchlike mechanisms underlies the successfulness of NAc DBS as seen in the earlier described animal and human studies.

The two animal studies described in Ch.5 concluded that NAc DBS did not evoke any notable side-effects. However, Hamilton et al. (2014) only based this on results of the saline control group rather than behavioural and cognitive experiments, which means they can only conclude DBS did not affect normal motivational behaviour. Guo et al. (2013) did conduct behavioural and cognitive experiments: the locomotor activity test and the Morris water maze behavioural test. Even though DBS did not have negative effects on cognition and locomotor behaviour as well, it can be discussed whether DBS of the NAc has no notable side-effects at all. Side-effects can also include changes in the emotional wellbeing of the patient or in this case the rodent. It is understandable that subjective assessments of rodents are difficult to identify, but still there are ways to make a rough estimate. An article about the psychological well-being of non-human primates mentions that evidence for behavioural oddities, e.g. self-biting, hair-plucking or back-flips, are a good measure for an animal's well-being (National Research Council, 1998). Thus, to optimally determine potential side-effects of DBS in rodents, behavioural observations could be done as well. The human case studies explained in Ch.6 on the other hand, are more reliable when looking at side-effects of DBS. A total of seven patients were treated within the two studies, but only one of them experienced long-term side-effects and had depressive feelings similar to before stimulation. Ge et al. (2019) attributed this to the dislocation of the right electrode. Also, general short-term side effects such as hypomania and anxiety happened with the second patient in the study of Ge et al. (2019). However, after adjusting DBS parameters, these side-effects disappeared. Taking all determined side-effects together (i.e. of both animal and human studies), it can be said that DBS does not evoke long-term side-effects in general, provided that the electrodes are positioned precisely. Short-term side-effects are possible to occur, but since DBS has the advantage to be adjustable and even reversible, these side-effects can be easily remedied.

Despite the fact that DBS in the NAc will bring about positive results in the addicted patient, it is of high importance to also discuss the safety of the treatment. As mentioned above, stimulation itself did not evoke severe side-effects in general in human patients and rodents. However, DBS is a treatment where (brain) operation is required to place the electrodes and the pulse generator, lowering its accessibility. Similar to other treatments in which this is needed, hardware-related and surgical risks are involved that must be taken into account. Major risks for DBS are intracranial haemorrhage and seizures (surgical), infections and electrode misplacement (hardware-related) (Chen et al., 2013). According to analysis of Vergani et al. (2010), surgery-related complications occurred in 5,6%, infections in 5,6% and hardware-adverse effects in 7% of the 522 DBS-treated PD patients. Work of Saleh & Fontaine (2015) reviewed that 6,2% of patients had complications related to hardware *and/or* surgery. This was based on reports of 272 patients with different neurological disorders. It is likely that Vergani et al. (2010) did not take comorbidity into account, while Saleh & Fontaine (2015) did. Both reviews found that direct surgical mortality was zero. Incidence of these risks seem to be very low and can, in addition, become even lower

when surgical experience is increased and devices are improved (Chen et al., 2013). As stated earlier, side-effects related to stimulation can be reversed easily by adjusting stimulation parameters or by complete cessation of DBS. Overall, DBS can be considered a safe treatment based on a relatively low incidence of risks and the reversible characteristic of DBS. However more than with other treatments, it important to keep close surveillance of DBS-treated patients during the follow-up period to minimalize possible minor side-effects.

Thus, it seems that DBS of the NAc is a very promising treatment for patients with substance addiction. Various studies found a DBS-induced reduction of drug craving and drug-seeking in both human and rodent models, and sometimes it even led to complete abstinence even though conditioned cues were present. Additionally, required surgical procedures make DBS less accessible than other therapies. Therefore, it can be expected that DBS will not become the first choice of treatment in the future but rather a second option for patients that do not respond to therapies such as CBT. Also, a few questions remain unanswered. For example, does DBS in addiction need to focus on the NAc core or rather the shell? And with HF stimulation or LF stimulation? Also, can stress and stressful periods directly increase the chances on getting a relapse? And, is NAc DBS still effective when the patient is exposed to substances of abuse? Obviously, further research is needed to answer these relevant questions. Also, these results can optimize DBS's effects and must reveal whether DBS can become the most preferred treatment for patients with substance addiction.

9. REFERENCES

American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders, 5th ed. American Psychiatric Publishing

Chen, X.L., Xiong, Y.Y., Xu, G.L., Liu, X.F. (2012). Deep Brain Stimulation. *Interventional Neurology* 2012(1), 200-212. doi: 10.1159/000353121

Dandekar, M.P., Luse, D., Hoffmann, C., Cotton, P., Peery, T., Ruiz, C., Hussey, C., Giridharan, V.V., Soares, J.C., Quevedo, J., Fenoy, A.J. (2017). Increased dopamine receptor expression and anti-depressant response following deep brain stimulation of the medial forebrain bundle. *Journal of Affective Disorders* 217, 80-88. doi: 10.1016/j.jad.2017.03.074

van Dijk, A., Klompmakers, A.A., Feenstra, M.G.P., Denys, D. (2012). Deep brain stimulation of the accumbens increases dopamine, serotonin, and noradrenaline in the prefrontal cortex. *Journal of Neurochemistry* 123, 897-903. doi: 10.1111/jnc.12054

Dostrovsky, J.O., Levy, R., Wu, J.P., Hutchison, W.D., Tasker, R.R., Lozano, A.M. (2000). Microstimulation-induced inhibition of neuronal firing in human globus pallidus. *Journal of Neurophysiology* 84(1), 570-574. doi: 10.1152/jn.2000.84.1.570

Dougherty, D.D. (2018). Deep brain stimulation: Clinical applications. *Psychiatric Clinics of North America* 41, 385-394. doi: 10.1016/j.psc.2018.04.004

Ge, S., Chen, Y., Li, N., Qu, L., Li, Y., Jing, J., Wang, X., Wang, J., Wang, X. (2019). Deep Brain Stimulation of Nucleus Accumbens for Methamphetamine Addiction: Two Case Reports. *World Neurosurgery* 122, 512-517. doi: 10.1016/j.wneu.2018.11.056

Gerrow, K., Triller, A. (2010). Synaptic stability and plasticity in a floating world. *Current opinion in Neurobiology* 20(5), 631-639. doi: 10.1016/j.conb.2010.06.010

GGZ Nederland (2013). Een visie op verslaving en verslavingszorg: focus op preventie en herstel. 2013/392

Guo, L., Hongyu, Z., Ran, W., Jiwen, X., Whenua, Z., Fuqiang, Z., Shuaien, T., Huifen, L., Jiyao, J. (2013). DBS of nucleus accumbens on heroin seeking behaviors in self-administering rats. *Drug and alcohol dependence* 129, 70-81. doi: 10.1016/j.drugalcdep.2012.09.012

Hamilton, J., Lee, J., Canales, J.J. (2015). Chronic unilateral stimulation of the nucleus accumbens at high or low frequencies attenuates relapse to cocaine seeking in an animal model. *Brain Stimulation* 8(1), 57-63. doi: 10.1016/j.brs.2014.09.018

Hegeman, D.J., Hong, E.S., Hernández, V.M., Chan, C.S. (2016). The External Globus Pallidus: Progress and Perspectives. *European Journal of Neuroscience* 43(10), 1239-1265. doi: 10.1111/ejn.13196

Herrington, T.D., Cheng, J.J., Eskandar, E.N. (2016). Mechanisms of deep brain stimulation. *Journal of Neurophysiology* 115(1), 19-38. doi: 10.1152/jn.00281.2015

Hikida, T., Mortia, M., Macpherson, T. (2016). Neural mechanisms of the nucleus accumbens circuit in reward and aversive learning. *Neuroscience research* 108(2016), 1-5. doi: 10.1016/j.neures.2016.01.004

Jellinek (2019). Cognitieve gedragstherapie. Available at: https://www.jellinek.nl/behandelingen/behandeling-volwassenen/cognitieve-gedragstherapie/. Accessed 14/3/2019

Jellinek (2019). Hoeveel mensen in Nederland zijn verslaafd en hoeveel zijn er in behandeling? Available at: https://www.jellinek.nl/vraag-antwoord/hoeveel-mensen-zijn-verslaafd-en-hoeveel-zijn-er-in-behandeling/. Accessed 14/3/2019

Jellinek (2019). Poliklinische behandeling Jellinek Minnesota. Available at: https://www.jellinek.nl/behandelingen/behandeling-volwassenen/minnesotabehandeling/poliklinische-behandeling-jellinekminnesota/. Accessed 14/3/2019

Jordan, C.J., Andersen, S.L. (2017). Sensitive periods of substance abuse: early risk for the transition to dependence. *Developmental Cognitive Neuroscience* 25, 29-44. doi: 10.1016/j.dcn.2016.10.004

Kaplan, G.B., Leite-Morris, K.A., Fan, W., Young, A.J., Guy, M.D. (2011). Opiate sensitization induces FosB/ΔFosB expression in prefrontal cortical, striatal and amygdala brain regions. *PLoS One* 6(8), e23574. doi: 10.1371/journal/pone.0023574

Koob, G.F., Volkow, N.D. (2016). Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* 3(8), 760-773. doi: 10.1016/S2215-0366(16)00104-8

Levy, D., Shabat-Simon, M., Shalev, U., Barnea-Ygnael, N., Cooper, A., Zangen, A. (2007). Repeated electrical stimulation of reward-related brain regions affects cocaine but not "natural" reinforcement. *Journal of Neuroscience* 27(51), 14179-14189. doi: 10.1523/jneursci.4477-07.2007

Luigjes, J., Van den Brink, W., Feenstra, M., van den Munckhof, P., Schuurman, P.R., Schippers, R., Mazaheri, A., de Vries, T.J., Denys, D. (2012). Deep brain stimulation in addiction: a review of potential brain targets. *Molecular psychiatry* 17, 572-583. doi: 10.1038/mp.2011.114

Lyons, M.K. (2011). Deep brain stimulation: current and future clinical applications. *Mayo Clinic Proceedings* 86(7), 662-672. doi: 10.4065/mcp.2011.0045

Müller, U.J., Sturm, V., Voges, J., Heinze, H.J., Galazky, I., Büntjen, L., Heldmann, M., Frodl, T., Steiner, J., Bogerts, B. (2016). Nucleus Accumbens Deep Brain Stimulation for Alcohol Addiction – Safety and Clinical Long-term Results of a Pilot Trial. *Pharmacopsychiatry* 49, 170-173. doi: 10.1055/s-0042-104507

Müller, U.J., Sturm, V., Voges, J., Heinze, H.J., Galazky, I., Heldmann, M., Scheich, H., Bogerts, B. (2009). Successful Treatment of Chronic Resistant Alcoholism by Deep Brain Stimulation of Nucleus Accumbens: First Experience with Three Cases. *Pharmacopsychiatry* 42, 288-292. doi: 10.1055/s-0029-1233489

National Research Council. (1998). *The Psychological Well-Being of Nonhuman Primates.* Washington, DC: The National Academies Press. doi: 10.17226/4909

Nestler, E.J. (2005). The neurobiology of cocaine addiction. *Science & Practice Perspectives* 3(1), 4-10. PMCID: PMC2851032

Novadic-Kentron (2019). Cognitieve gedragstherapie bij problematisch middelengebruik. Available at: https://www.novadic-kentron.nl/hulp-en-advies/cgt-middelen/. Accessed 14/3/2019

Novadic-Kentron (2019). Een positiever leven met CRA. Available at: https://www.novadic-kentron.nl/hulp-en-advies/een-positiever-leven-met-cra/. Accessed 14/3/2019

NVO, BPSW, NIP (2017). Factsheet Middelengebruik.

Oliva, I., Wanat, M.J. (2016). Ventral Tegmental Area Afferents and Drug-Dependent Behaviors. *Frontiers in Psychiatry* 7(30). doi: 10.3389/fpsych.2016.00030

Pelloux, Y., Baunez, C. (2013). Deep brain stimulation for addiction: why the subthalamic nucleus should be favoured. *Current Opinion in Neurobiology* 23(4), 713-720. doi: 10.1016/j.conb.2013.02.016

Ritchie, H., Roser, M. (2018). Substance use. Available at: https://ourworldindata.org/substance-use. Accessed 14/3/2019

Rouaud, T., Lardeux, S., Panayotis, N., Paleressompoulle, D., Cador, M., Baunez, C. (2010). Reducing the desire for cocaine with subthalamic nucleus deep brain stimulation. *Proceedings of the National Academy of Sciences of the United States of America* 107(3), 1196-1200. doi: 10.1073/pnas.0908189107

Ruffle, J.K. (2014). Molecular neurobiology of addiction: what's all the (Δ)FosB about? *The American Journal of Drug and Alcohol Abuse,* 40(6), 428-437. doi: 10.3109/00952990.2014.933840

Saleh, C., Fonatine, D. (2015). Deep Brain Stimulation for Psychiatric Diseases: What Are the Risks? *Current Psychiatry Reports* 17(5), 33. doi: 10.1007/s11920-015-0565-1

Shen, K.Z., Zhu, Z.T., Munhall, A., Johnson, S.W. (2003). Synaptic plasticity in rat subthalamic nucleus induced by high-frequency stimulation. *Synapse* 50, 314-319. doi: 10.1002/syn.10274

Siegfried, J., Lippitz, B. (1994). Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. *Neurosurgery* 35(6), 1126-1130. doi: 10.1227/00006123-199412000-00016

Thanos, P.K., Volkow, N.D., Freimuth, P., Umegaki, H., Ikari, H., Roth, G., Ingram, D.K., Hitzemann, R. (2001). Overexpression of dopamine D2 receptors reduces alcohol self-administration. *Journal of Neurochemistry* 78(5), 1094-1103. doi: 10.1046/j.1471-4159.2001. 00492.x

Uhl, G.R., Koob, G.F., Cable, J. (2019). The neurobiology of addiction. *Annals of the New York Academy of Sciences* 0(0), doi: 10.1111/nyas.13989

Urban, N.B.L., Martinez, D. (2012). Neurobiology of Addiction: Insight from Neurochemical Imaging. *Psychiatric Clinics of North America* 35(2012), 521-541. doi: 10.1016/j.psc.2012.03.011

Vergani, F., Landi, A., Pirillo, D., Cilia, R., Antonini, A., Sganzerla, E.P. (2010). Surgical, Medical, and Hardware Adverse Events in a Series of 141 Patients Undergoing Subthalamic Deep Brain Stimulation for Parkinson Disease. *World Neurosurgery* 73(4), 338-344. doi: 10.1016/j.wneu.2010.01.017

Volkow, N.D., Boyle, M. (2018). Neuroscience of Addiction: Relevance to Prevention and Treatment. *American Journal of Psychiatry* 175(8), 729-740. doi: 10.1176/appi.ajp.2018.17101174

Volkow, N.D., Wang, G., Fowler, J.S., Tomasi, D., Telang, F. (2011). Addiction: Beyond dopamine reward circuitry. *Proceedings of the National Academy of Sciences of the United States of America* 108(37), 15037-15042. doi: 10.1073/pnas.1010654108

VNN (2019). Samen je behandeling bepalen. Available at: https://www.vnn.nl/vnn-basisggz. Accessed 14/3/2019.

Volkow, N.D., Li, T.K. (2005). The neuroscience of addiction. *Nature neuroscience* 8, 1429-1430. doi: 10.1038/nn1105-1429

Volkow, N.D., Morales, M. (2015). The Brain on Drugs: From Reward to Addiction. *Cell* 162, 712-725. doi: 10.1016/j.cell.2015.07.046

Volkow, N.D., Wise, R.A., Baler, R. (2017). The dopamine motive system: implications for drug and food addiction. *Neuroscience* 18, 741-752. doi: 10.1038/nrn.2017.130

Yadid, G., Gispan, I., Lax, E. (2013). Lateral habenula deep brain stimulation for personalized treatment of drug addiction. *Frontiers in Human Neuroscience* 7(806). doi: 10.3389/fnhum.2013.00806

Yamawaki, N., Magill, P.J., Woodhall, G.L., Hall, S.D., Standorf, I.M. (2012). Frequency selectivity and dopamine-dependence of plasticity at glutamatergic synapses in the subthalamic nucleus. *Neuroscience* 203, 1-11. doi: 10.1016/j.neuroscience.2011.12.027

Yan, N., Chen, N., Zhu, H., Zhang, J., Sim, M., Ma, Y., Wang, W. (2013). High-Frequency Stimulation of Nucleus Accumbens Changes in Dopaminergic Reward Circuit. *PLoS One* 8(11), e79318. doi: 10.1371/journal.pone.0079318

Yohn, S.E., Galbraith, J., Calipari, E.S., Conn, P.J. (2018). Shared Behavioral and Neurocircuitry Disruptions in Drug Addiction, Obesity, and Binge Eating Disorder: Focus on Group I mGluRs in the Mesolimbic Dopamine Pathway. *American Chemical Society Neuroscience.* doi: 10.1021/acschemneuro.8b00601

Zhang, X., Shi, J., Tao, R. (2017). Substance and Non-substance Addiction (1010). *Advances in Experimental Medicine and Biology* 1010. doi: 10.1007/978-981-10-5562-1