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REVIEW

Deep brain stimulation in addiction: a review of potential brain targets

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Deep brain stimulation (DBS) is an adjustable, reversible, non-destructive neurosurgical intervention using implanted electrodes to deliver electrical pulses to areas in the brain. DBS is currently investigated in psychiatry for the treatment of refractory obsessive–compulsive disorder, Tourette syndrome and depressive disorder. Although recent research in both animals and humans has indicated that DBS may be an effective intervention for patients with treatment-refractory addiction, it is not yet entirely clear which brain areas should be targeted. The objective of this review is to provide a systematic overview of the published literature on DBS and addiction and outline the most promising target areas using efficacy and adverse event data from both preclinical and clinical studies. We found 7 animal studies targeting six different brain areas: nucleus accumbens (NAc), subthalamic nucleus (STN), dorsal striatum, lateral habenula, medial prefrontal cortex (mPFC) and hypothalamus, and 11 human studies targeting two different target areas: NAc and STN. Our analysis of the literature suggests that the NAc is currently the most promising DBS target area for patients with treatment-refractory addiction. The mPFC is another promising target, but needs further exploration to establish its suitability for clinical purposes. We conclude the review with a discussion on translational issues in DBS research, medical ethical considerations and recommendations for clinical trials with DBS in patients with addiction.
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Introduction

Deep brain stimulation (DBS) is a neurosurgical intervention in which implanted electrodes deliver electrical pulses to stereotactically targeted areas of the brain. It has been used as treatment for movement disorders for over 20 years[1] and has recently shown promising results as experimental treatment of psychiatric disorders such as obsessive–compulsive disorder (OCD), Tourette syndrome and depressive disorder[2–4] (for review, see Greenberg *et al.*[5]). A wide range of other possible applications for DBS have been suggested over the last years[6–8]—one of which is addiction.

The reasons to consider DBS as an intervention for addiction are threefold. (1) Preclinical studies and case studies have reported promising results for DBS as a treatment for addiction.[9–11] (2) The recent understanding of neural pathways that are affected in addiction has created a new range of possibilities for treatments that directly target and normalize affected brain circuits. And (3) new effective interventions are needed for patients who do not benefit from current treatments, since addiction is a chronic relapsing brain disorder seriously affecting both individual and public health.[12] A substantial number of patients suffer multiple relapses and show a chronic course of the disorder despite several treatments: abstinence rates after 1 year of completing treatment are about 30–50%.[13,14]

A well-documented rationale for the choice of the target area in the brain is required in order to investigate the effectiveness, safety and feasibility of DBS in treatment-refractory addiction. Therefore, the objective of this review is to find the most promising target area for DBS in addiction. For this purpose, we examined original published reports on empirical studies about DBS in addiction in animals and humans. In the first step, a PubMed search was conducted using various terms for 'addiction' and

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'deep brain stimulation'. In the second step, the reference lists of all papers from the first step were screened for additional articles fitting the inclusion criteria. Only papers that focused on the effects of DBS on addiction that were written in English were included. This search resulted in 7 animal studies (summarized in Table 1) and 11 human studies (summarized in Table 2).

We separately discuss the findings from preclinical and clinical studies taking into account both efficacy and safety for each of the target areas. Specifically, we discuss (1) which of the target areas used for DBS in animal research directed at the reduction of drug-seeking behaviour has been most effective and resulted in the least severe side effects, and (2) which of the target areas used for DBS in humans have been most effective in terms of a lasting reduction of drug consumption and resulted in the least severe side effects.

Neurocircuitry underlying addiction

Although the neuropathophysiology of addiction can be appreciated at multiple levels, from the molecular and cellular level to the interplay of networks systems in the brain, here, given the nature of DBS we focus on the neuroanatomical brain circuits that were elucidated by different types of animal and human imaging research. A useful framework has been provided by Koob and Volkow[15] in a recent review. According to the authors, the addiction cycle is characterized by three stages: 'binge/intoxication', 'withdrawal/negative affect' and 'preoccupation/anticipation' (craving), and involves aspects of both impulsivity and compulsivity. In the binge/intoxication stage, the nucleus accumbens (NAcs) is considered to have a key role together with the ventral tegmental area, whereas the extended amygdala is seen as central structure in the withdrawal/negative affect phase. A more dispersed network of brain regions is associated with the preoccupation/anticipation phase that is involved in craving and relapse, processes responsible for the chronic nature of the disorder. The main brain structures involved in these processes include the (orbito) frontal cortex, striatum, amygdala, hippocampus and insula, which are involved in subjective experiences of drugs while disrupted inhibitory control involves the cingulate gyrus, dorsolateral prefrontal cortex and inferior frontal gyrus. All the brain structures involved could be potential targets for DBS. Effective DBS would optimally interfere with the neuroanatomical circuits of all three stages.

Animal studies

At time of writing, seven studies have investigated the effects of DBS in animal models of addiction, using six different target areas; NAc, subthalamic nucleus (STN), dorsal striatum, lateral habenula, medial prefrontal cortex (mPFC) and lateral hypothalamus (see Table 1 and Figure 1c to h). To test the impact of DBS on drug-seeking behaviour, different models of addiction were used in these studies (for a description see Table 3). In order to have a valid control group, all animals in these experiments were implanted with electrodes but only the experimental group was stimulated (DBS 'on') whereas the control group was not (DBS 'off'). Typically, the animals were stimulated only before and/or during experiments. Most studies used continuous high-frequency stimulation (>100 Hz), although two additionally tested low-frequency stimulation: 20 and 10 Hz,[10,16] while three gave trains of pulses with pauses in between.[10,16,17] With the exception of two studies[16,17] rats were stimulated bilaterally. Three different substances were used in the addiction paradigms; ethanol, cocaine and morphine. DBS effects on sucrose self-administration or water consumption were evaluated to control for possible side effects in some studies, while effects on learning/memory or depression-like behaviour were tested in others.

NAc and dorsal striatum

Four out of seven animal studies targeted the NAc for DBS (see Figure 1c).[17–20] All four studies showed a significant reduction of drug-related behaviours following high-frequency DBS in either core or shell. Two studies examined the effect of DBS on ethanol consumption,[18,19] a third examined the effects of DBS on reinstatement of cocaine-seeking behaviour,[20] and in one study[17] rats were given morphine in a conditioned place preference paradigm. There were no effects of NAc DBS on sucrose self-administration or water consumption and none of the studies reported unusual behaviours in the experimental compared with the control groups. Overall, these animal studies suggest that high-frequency NAc DBS attenuates drug-related behaviour in rats with no apparent side effects. It should be noted that in addition to NAc DBS, Vassoler *et al*.[20] also examined DBS effects in the dorsal striatum (Figure 1h) on cocaine reinstatement in rats. In contrast to the NAc experiment, they failed to find any significant effects on cocaine reinstatement.

STN

Rouaud *et al*.[21] examined the effect of high-frequency STN DBS (Figure 1d) on cocaine and sucrose (food) self-administration. The DBS 'on' group showed increased motivation to work for sucrose but decreased motivation to work for cocaine using a progressive ratio self-administration experiment. However, when every lever-press was followed by a reward (fixed-ratio 1) no difference was found between the 'on' or 'off' group, suggesting that STN stimulation did not affect the consumption of readily available drugs or sucrose, but made them less willing to work for cocaine. In addition, no effect of STN DBS was found on regular food (chow) intake.

Table 1 Animal studies that examined DBS effects on addiction-related behaviour

Reference	*Target area*	*Substance*	*Paradigm*	*Sign DBS effects*	*Side effects*	*Electrode*	*Intensity (μA)*	*Freq. (Hz)*	*PW (μs)*	*Duration stimulation*
Henderson *et al.*[18]	NAc (shell)	ethanol	SA (2 bottle)	study 1: alcohol preference decreased study 2: alcohol consumption and preference decreased	no unusual behaviours noted	bipolar concentric stainless steel (Plastics One) inner: ∅ 127 μm	200	140–150	60	study 1: 1 h on/1 h off during session study 2: 1 h before and during 24-h session
Vassoler *et al.*[20]	NAc (shell) DS	cocaine	RI (drug)	decrease in cocaine-induced reinstatement in NAc group; no effect DS group	no effect on food seeking, no abnormal behaviours	bipolar stainless steel (Plastics One)	70–150	160	60	1 h during RI session
Knapp *et al.*[19]	NAc (core or shell)	ethanol	SA (2 bottle)	reduction in alcohol consumption (shell and core)	no unusual behaviours noted	bipolar stainless steel (Plastics One)	50–150	160	200	35 min incl 30 min of task session
Liu *et al.*[17]	NAc (core)	morphine	CPP	reduction in time spent in drug paired side	side effects related to surgery in recovery phase	bipolar concentric stainless steel, inner: ∅ 200 μm	200–500 Mono-phasic	130 in trains of 15 min each hour	210	3 h incl 1 h task session
Rouaud *et al.*[21]	STN	cocaine	SA (FR1/PR) CPP	no effect on SA (FR1) reduced SA (PR) reduction in time spent drug paired side	no effect on food intake and sucrose SA (FR1). Increased sucrose SA (PR). Increased time spent in sucrose paired side	bipolar platinum-iridium ∅ 110 μm, 0.1 mm between poles	50–130	130	60	during all sessions (15–60 min)
Levy *et al.*[10]	mPFC Hypo-thalamus	cocaine	SA (FR1/PR) EP	PFC: 100/20 Hz: reduction of LP in EP and of SA (PR) Hyp: reduction of LP in EP but not of SA (PR)	no effects on sucrose seeking, spatial learning or motor activity.	monopolar (Plastics One) ∅ 200 μm	200–400	100/20 in trains of 10–50 pulses	100	30 min daily for 10 days after which testing starts
Friedman *et al.*[16]	Lateral habenula	cocaine	SA (FR1) RI (drug)	10 Hz: increase in SA 100 Hz: no change Combined: reductions in SA, LP in EP and RI	no unusual behaviours noted in Friedman *et al.* (2002)[22]: decrease in sucrose-seeking behaviour	bipolar stainless steel, ∅ 10 μm, 1 mm between poles	200	10/100/ combined in trains of 4–60 s	500	15 min during 1 h SA session 15 min during RI session

Abbreviations: CPP, conditioned place preference; DS, dorsal striatum; LP in EP, lever presses in extinction phase; NAc: nucleus accumbens; DBS, deep brain stimulation; mPFC, medial prefrontal cortex; PW, pulse width; RI, reinstatement; EP, extinction phase; SA (FR1), self-administration with reward for each response; SA (2 bottle), self-administration with drinking bottle; SA (PR), self-administration progressive ratio; STN, subthalamic nucleus.

Table 2 Human case reports describing effects of DBS on addiction-related behaviour

Reference	N	*Target area*	*Addiction substance or behaviour*	*Comorbid disorder*	*Addiction behaviour after DBS*	*Side effects*	*Med before DBS*	*Med after DBS (last follow-up)*	*PW (μs)*	*Freq. (Hz)*	*Voltage (V)*	*Bi/Uni lateral*
Müller *et al.*[11]	3	NAc	alcohol	—	2 resolved 1 improved	no reported	—	—	90	130	3.5–4.5	bilateral
Zhou *et al.*[25]	1	NAc	heroin	—	1 resolved	transient (<12 h) mild confusion and urinary incontinence	—	—	90	145	2.5	bilateral
Mantione *et al.*[24]	1	NAc	nicotine	OCD	1 resolved	no reported	60 mg paroxetine 250 mg quetiapine	not reported	90	180	3.5	bilateral
Kuhn *et al.*[9]	10	NAc	nicotine	AD/OCD/TS	3 resolved 7 unchanged	no reported	Different med	1 stopped BZ 1 changed med (good outcome) 2 changed med (poor outcome)	90 (one 180)	130–145	3–6	5 bilateral 5 unilateral
Kuhn *et al.*[23]	1	NAc	alcohol	AD/DEP	1 improved	no reported	—	—	90	130	3–4.5	bilateral
Ardouin *et al.*[27]	7	STN	PG	PD	7 resolved	2 patients had transient worsening of manic symptoms 3 patients had transient episode of depression 2 patients persistent mild apathy	1395 LED (mean)[a]	571 LED (mean)	60	130	2.8/2.9 (mean)	bilateral
Bandini *et al.*[28]	2	STN	PG, DDS	PD	2 resolved	no reported	1500 1220	200 800	—	—	—	bilateral
Knobel *et al.*[29]	1	STN	DDS	PD	1 improved	no reported	1830 LED	560	—	—	—	—
Witjas *et al.*[30]	2	STN	DDS	PD	2 resolved	one episode of compulsive alcohol intake	2500 1450	0 300	—	—	—	bilateral
Smeding *et al.*[31]	1	STN	PG	PD	worsened (only occurred after DBS) and stopped after changing settings and medication	emotional lability, vivid dreams	880 LED	760 LED (when gambling) 560 (gambling stopped)	60	130–185	2.5 left 2.6–3.2 right	bilateral
Lim *et al.*[32]	19	STN	DDS, PG	PD	5 worsened 8 unchanged 6 resolved	no reported	not reported	329 LED (mean) good outcome group 2745 LED (mean) poor outcome group	—	—	—	18 bilateral 1 unilateral

Abbreviations: AD, anxiety disorder; DBS, deep brain stimulation; DDS, dopamine dysregulation syndrome; NAc, nucleus accumbens; OCD, obsessive–compulsive disorder; PD, Parkinson's disease; PG, pathological gambling; STN, subthalamic nucleus; TS, Tourette syndrome.
[a]L-dopa equivalent dose in mg per day.

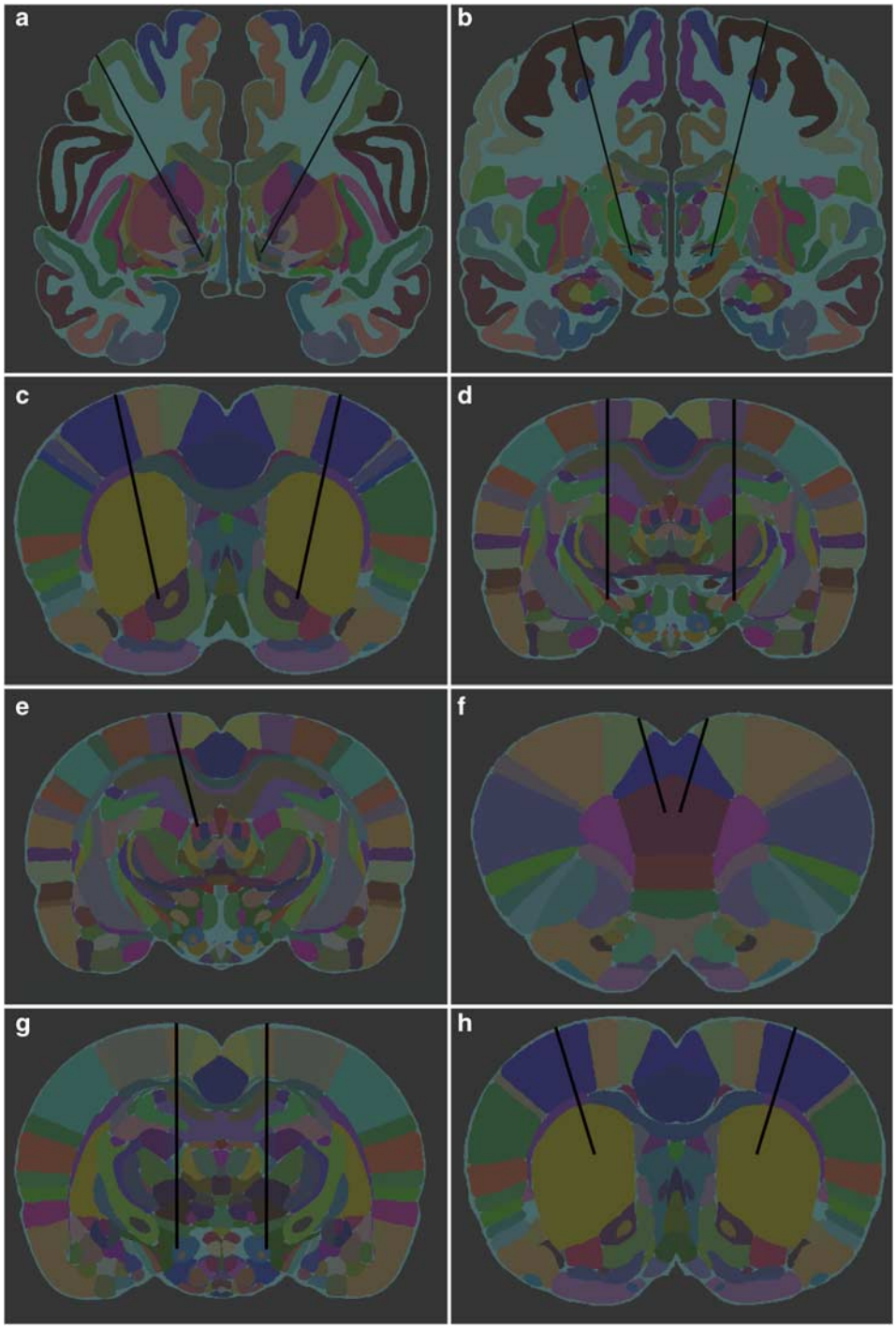

Figure 1 Atlas illustrations of electrode placement. These Atlas illustrations show the location of electrode placement in the used brain areas for both animals and humans. Human brain (**a**) bilateral nucleus accumbens (NAc) (**b**) bilateral subthalamic nucleus (STN). Rat brain (**c**) bilateral NAc 1.2 mm anterior to bregma (**d**) bilateral STN −3.7 mm anterior to bregma (**e**) unilateral lateral habenula −3.8 mm anterior to bregma (**f**) bilateral medial prefrontal cortex 3.2 mm anterior to bregma (**g**) bilateral hypothalamus −2.5 mm anterior to bregma (**h**) dorsal striatum 1 mm anterior to bregma. Brain Navigator release 2.0 (2009), Paxinos G and Watson C, editors-in-chief, Elsevier, Boston, MA, USA, www.brainnav.com.

Lateral habenula

One study used the lateral habenula (Figure 1e) as target for DBS in a self-administration experiment with cocaine.[16] Stimulation with alternating sets of high- and low-frequency patterns (combined pattern DBS) resulted in a decrease in lever presses during self-administration and during extinction. The effect of DBS applied on the first day of extinction was

Table 3 Animal models of addiction

Model	*Substance administration*	*Description*	*Outcome measurement*
Fixed ratio	Self-administration	The animal has to perform an action or a fixed number of instrumental responses (such as pressing a lever) to obtain a rewarding substance	Number of lever presses/nose pokes or rewards
Progressive ratio	Self-administration	The animal has to progressively increase their effort to obtain a rewarding substance	Number of lever presses/nose pokes. The final ratio completed is defined as break point
Extinction phase	Self-administration	Instrumental responses do no longer result in the delivery of the rewarding substance	Number of lever presses/nose pokes
Drug-induced reinstatement	Self-administration	After the extinction phase, instrumental responding is reinstated by administering a priming dose of the drug to the animal	Number of lever presses/nose pokes
Conditioned place preference	Experimenter administration	A substance is repeatedly administered in a specific context. In the test phase the animal is free to choose between the drug-associated context and a neutral context	Time spent in drug-associated context
Psychomotor sensitization	Experimenter administration	After repeated administration of a substance, an increased locomotor response is observed indicative of a sensitized response to the substance	Locomotor activity

still present on drug-induced reinstatement after six extinction sessions (up to 7–8 days). It should be noted that no effects were found with only high-frequency stimulation (100 Hz) on cocaine self-administration, whereas only low-frequency stimulation (10 Hz) resulted in an increase in self-administration. Additional experiments showed that the effects that were observed with combined pattern DBS were not the result of a decreased ability to press a lever or depressive-like manifestations. Furthermore, in a separate study from the same group,[22] a significant decrease in lever presses for sucrose after combined pattern DBS of the lateral habenula was found.

mPFC and lateral hypothalamus

A somewhat different approach was used by Levy *et al.*,[10] who stimulated the medial PFC (Figure 1f) of rats 30 min a day for 10 consecutive days during abstinence after a period of cocaine self-administration. DBS reduced the number of lever responses for cocaine, but not for sucrose, in the extinction phase and under a progressive ratio schedule. Similar effects were obtained using low-frequency stimulation (20 instead of 100 Hz). These results imply that repeated stimulation of the medial PFC could be effective in reducing addiction-related behaviours at both high- and low-frequency stimulation. Other behaviours, including spatial learning and memory and general locomotor activity were unaffected. Finally, high-frequency stimulation of the lateral hypothalamus (Figure 1g) during 10 days of abstinence from cocaine self-administration also resulted in reduced lever responses during extinction phase, but no effect was found in a progressive ratio schedule. DBS of the lateral hypothalamus did not affect sucrose seeking.[10]

Taken together, stimulation of the NAc, STN, lateral habenula and mPFC all seemed to be effective in reducing various aspects of drug-seeking behaviour or drug consumption. This was generally achieved without clear signs of side effects other than food or water intake. An increase in sucrose-seeking behaviour was observed in the study using STN stimulation[21] and a decrease in sucrose seeking was found in the study with lateral habenula stimulation.[16] Both can be considered undesirable side effects because it might indicate a changed motivation for natural reinforcers. No effects were found of STN stimulation on low cost self-administration behaviour suggesting that stimulation of the STN might reduce the incentive value of the drugs but not the consumption

when the drug is available. Although a cautionary remark should be made concerning the differences in stimulation parameters used in these studies (see Table 1), our conclusion is that stimulating the NAc with high-frequency DBS or the medial PFC with both high- and low-frequency DBS seems to result in the most robust effects. The NAc is the only area that has been used in different studies, underscoring the need for preclinical confirmation studies for the mPFC.

Human case studies

As of today, there are no published randomized controlled trials on the effect of DBS in alcohol- or drug-dependent patients. The available clinical evidence is restricted to 11 case reports or case series. In these studies, two target areas have been used: the NAc and the STN (see Table 2 and Figures 1a and b). Five reports described the NAc as target area for DBS—three reported on the remission of addiction as a non-intended side effect of DBS during the treatment another psychiatric disorder[9,23,24] and in two studies the indication for DBS was addiction.[11,25] We found six reports that described the effects of STN DBS on addiction; in all these studies the indication for DBS was Parkinson's disease. Here, we provide a summary of these case studies.

NAc

The first study that examined the effects of NAc DBS on addiction was a retrospective case series by Kuhn *et al.*[23] They found that 3 out of 10 patients treated with high-frequency NAc DBS (five bilateral and five unilateral) for different disorders (for example, depression, OCD) stopped smoking; a much higher quit rate than unaided smoking cessation in the general population. All patients that retrospectively reported any attempt to quit smoking after surgery were successful. Successful quitters were less addicted, more motivated to quit and were stimulated at higher mean voltages than non-attempters (5.7 versus 4.4 V). None of the quitters relapsed during the 30 months follow-up period.

In a single case study,[9] a patient was treated with bilateral high-frequency NAc DBS for severe agoraphobia with panic attacks and depression. Before surgery, the patient also met criteria for alcohol dependence. DBS had a negligible effect on the anxiety symptoms, but rapidly and drastically reduced alcohol consumption without any particular motivation. The patient claimed to have lost the desire to drink and felt no longer a pressing need to consume alcohol. He did not reach abstinence but reduced his intake to moderate amounts and continued this pattern during a 1-year follow-up period.

Müller *et al.*[11] were the first to report on three patients who were treated with bilateral, high-frequency NAc DBS for alcohol dependence. Patients were between 36 and 40 years, had been drinking from their early teens and had not responded to different types of therapy. In all three patients, craving fully disappeared after NAc DBS; two patients remained abstinent during 1-year follow-up and the other patient reduced his alcohol consumption considerably. In one patient, a hypomanic episode of 2 weeks was reported that remitted after adaptation of stimulation parameters. This patient also reduced his nicotine consumption from 40 to 15 cigarettes per day. No other side effects were reported.

In another single case study, a patient was successfully treated for OCD with bilateral high-frequency NAc DBS.[24] She was a heavy smoker and reported repeated unsuccessful attempts to quit smoking before surgery. Ten months after the DBS surgery, she decided that she no longer wanted to be a smoker and quit the next day. In the 2-year follow-up evaluation, she was still not smoking and there was no desire to start again.

Finally, Zhou *et al.*[25] described a patient addicted to heroin who refrained from drug use after bilateral, high-frequency NAc DBS during follow-up period of 6 years in total. The patient was 24 years old, had been using 1–1.5 g of heroine for over 5 years and did not respond to any previous interventions. Additionally, he decreased the number of cigarettes he smoked from 40 a day before surgery to 10 a day after surgery. After 2 to 3 years, the pulse generator was first put off and later removed. Subsequently patient remained drug free throughout the 3-year follow-up period. Mild confusion and urinary incontinence were reported as transient side effects after surgery from which he fully recovered within 12 h.

STN

Finally, there are several reports in which high-frequency STN DBS in patients with Parkinson's disease either induced or reduced addictive behaviours. Some Parkinson patients treated with dopamine replacement therapy develop an addictive pattern of medication use called 'dopamine dysregulation syndrome', which in turn is associated with the onset of impulse control disorders, including pathological gambling, hypersexuality and compulsive shopping.[26] In four case studies[27–30] with a total of 12 patients with dopamine dysregulation syndrome or pathological gambling, bilateral STN DBS resolved these addictive behaviours. Importantly, all of these patients drastically reduced or stopped the use of levodopa or dopamine agonist treatment. However, another case report[31] described a patient without a history of addictive behaviours who developed a pattern of pathological gambling after high-frequency bilateral STN DBS despite a clear reduction of levodopa and dopamine agonist treatment. In another study, 19 Parkinson patients with dopamine dysregulation syndrome or impulse control disorders were followed after STN DBS treatment (18 bilateral and 1 unilateral).[32] The study showed mixed results: in a small proportion of these patients the addictive behaviour improved, whereas in the majority of the

patients the addictive behaviour did not improve or even worsened.[32] Moreover, the poor outcome on behavioural symptoms was associated with higher post-operative use of dopaminergic medication. Side effects of STN DBS reported in these case studies were mild apathy (two patients[27]), emotional instability and vivid dreaming (one patient[31]). From these studies it is difficult to deduce how STN DBS influences addictive behaviours and what role adaptation of dopaminergic medication has in it. Moreover, two reports[31,32] suggest that high-frequency STN DBS may in fact increase or induce addictive behaviour. Finally, several studies have associated STN DBS with increased impulsivity,[33–35] which has been linked to addictive behaviours.[36] In sum, the potential efficacy and safety of STN DBS for the treatment of addiction can be called into question.

On the basis of these cases, the NAc appears to be the most promising and safe target for the use of DBS in patients with addictive behaviours. However, we like to emphasize that no firm conclusions can be drawn from uncontrolled case reports and case series. Although there is a bias towards publishing positive results in all scientific articles, selective bias is even stronger for case reports where positive results will be published at the expense of negative data making a balanced judgement difficult if not impossible.[37] Therefore, from these case reports one could only cautiously conclude that the use of STN stimulation to treat addiction seems questionable while stimulation of the NAc is promising.

Most promising target area: NAc

The NAc is the most frequently used target area for addiction, and has consistently shown promising results across human case studies and animal research. We, therefore, conclude that NAc DBS is currently the most promising candidate target for therapy-refractory addiction. Four different animal studies using several substances showed a reduction of different aspects of addiction-related behaviour, while in five human case studies (16 individuals treated), a reduction or cessation of drug intake was observed that lasted at least a year. No important side effects were reported in any of these studies, confirming more extensive studies on the application of NAc DBS in other psychiatric disorders where most adverse events were transient and generally resolved after adjustments of stimulation parameters or were tolerated because of the beneficial effects of treatment.[38] For an overview of adverse events with DBS in the ventral striatal area for the treatment of OCD or depression the reader is referred to Supplementary Table S1 in supplementary material.

Possible mechanisms of action of NAc DBS in the treatment of addiction

The NAc has an established central role in reward processing in the context of addictive behaviours—it shows both acute drug-related activity changes and long-term alterations in structure and function on prolonged drug use, is involved in the transition from voluntary to compulsory drug use and in relapse after extinction.[15,39–42]

The precise mechanisms behind DBS are still a matter of investigation and we can only speculate about the mechanism of action of NAc DBS in the treatment of addiction. Here, we elaborate on two plausible mechanisms. First, NAc stimulation could normalize dysfunction in striatal areas of which the NAc is an important part. Recent studies show reduced striatal dopamine activity in individuals with drug addiction that might be responsible for decreased sensitivity to natural reinforcers whereas long-lasting drug-induced increases of dopamine are likely to activate the reward circuits.[43] This situation might strengthen the relative salience of drugs over natural reinforcers leading to fixed motivational choices. Normalizing striatal functionality by DBS might reduce craving and increase the relative salience of natural reinforcers. Second, NAc DBS might activate afferent and efferent pathways leading to distant synaptic inhibitory and excitatory effects, modulating dysfunctional neuronal network activity. For example, electrophysiological animal studies suggest a reduced firing in orbitofrontal cortex pyramidal cells and enhanced synchronicity of the thalamo-cortical circuit after high-frequency NAc DBS.[44,45] The NAc is connected to the prefrontal and cingulate cortices and to limbic areas such as the amygdala, hippocampus, thalamus and midbrain.[46] Studies with addicted individuals have shown a decreased activity in the cingulate gyrus and the dorsolateral prefrontal cortex presumably affecting the process of inhibitory control.[43,46] Modulating neuronal activity within this network could lead to an increase in self-control. We must note that these mechanisms are not mutually exclusive and could both contribute to the reported effects. Moreover, different brain regions and different classes of cells may be affected differently by high-frequency stimulation.[47] The effects of NAc DBS on monoamine neurotransmitters in the target area and in other regions of the network were examined in two recent animal studies.[48,49] The first study suggested that stimulation of the NAc shell can decrease dopamine and serotonin turnover (measured as the metabolite-transmitter ratio's in post-mortem tissue) locally, whereas stimulation of the NAc core did not.[48] Neither core nor shell stimulation affected the turnover of these monoamines in the mPFC.[48] A recent *in vivo* micro dialysis study did not detect any alterations in dopamine, serotonin or noradrenaline release in the NAc core during stimulation in the same area.[49] Unpublished findings, however, show increases in the release of all three monoamines in both medial and orbital prefrontal cortex (A van Dijk, personal communication). Together with the results of McCracken and Grace,[44,45] these results emphasize the importance of distant effects. Furthermore, these findings suggest that the mechanism of action of

NAc DBS is not dependent on one but probably on various effects that modulate the underlying pathophysiology in different ways.

Other potentially effective target areas

In animal studies, stimulation of the mPFC was also associated with reductions in drug-seeking behaviour or drug intake without side effects. However, to date, only one study for this potential target region has been conducted and, therefore, more preclinical research is needed to confirm these findings. It is of note that two potentially interesting target areas have not been studied at all, neither in human nor in animal studies: the insula and cingulate cortex. The insula has received more attention from addiction researchers following a publication showing that smokers who had a brain stroke of the insula were over a 100 times more likely to stop smoking than smokers who had their brain infarction in other areas.[50] Imaging studies have shown activation of the insula during drug craving and a correlation of reported subjective craving with insula activity.[51] The insula is thought to be involved in encoding interoceptive effects of drug use rituals, which in turn could have a role in craving for drugs and promoting addiction behaviour.[51] Chemical inactivation of the insula has been shown to disrupt addictive behaviours in rats.[52,53] The cingulate cortex is another potentially interesting area. Abnormalities in this area are likely to have a role in disadvantageous decision making, increasing the risk for drug use and relapse.[54] Hypoactivation of this area has been consistently observed in addicted patients during inhibition or selective attention tasks,[54] whereas hyperactivation was observed during craving.[54] Furthermore, disrupting the cingulate cortex either by lesions or stroke have reduced or ceased addiction.[55,56] It is of special interest that one of the target areas for DBS in depression is located in the cingulate region: Brodmann area 25.[57,58] Results suggest that this area might be involved in the emotional response to drugs and contributes to the craving for drugs.[59] However, no studies are available on cingulate cortex DBS in addiction and further preclinical research is needed.

Translational issues in DBS research

Animal studies are indispensable in uncovering the mechanisms behind the effects of DBS and elucidating neuronal circuitries underlying the disorder. They can also help us identify potentially safe and effective new brain targets and new stimulation paradigms for the treatment of patients with addictive behaviours.[60] However, translational research of DBS in addiction has its limitations as well; animal models of addiction do not represent the full complexity of the disorder and the practical application of DBS in rodents is different from DBS in humans. Animal models used in preclinical studies often do not distinguish 'recreative' drug use from the compulsive drug taking that characterizes addiction.[61] Models that include drug-seeking and drug taking when the animal is faced with adverse consequences such as foot shocks should therefore be considered.[62,63] Using such a model in DBS research might be a better predictor for the effects of DBS in individuals with chronic treatment-refractory drug addiction.

Another translational issue is the difference in anatomical brain regions between rodents and humans. The anatomical subdivision of the NAc in shell and core is often made in animal (rodent) research. Although histochemically the shell and core are also distinguishable in humans,[64] it is not known whether there are functional similarities between animal and human NAc shell and core. Moreover, currently the spatial resolution in imaging techniques is not sufficient to differentiate between the core and shell in humans.[65] Although the differences between shell and core in animal research can be of conceptual interest, it is questionable whether they are translational meaningful for the targeting of DBS in humans, because the placement of electrodes depends on these imaging techniques.

It should also be noted that many technical aspects of rodent DBS differ significantly from the clinical parameters. All animal studies except for the one by Levy *et al*.[10] use acute stimulation (restricted to the duration of experiment), whereas all human studies rely on chronic stimulation. Previous studies have shown that mechanisms of acute stimulation can differ from those of chronic stimulation.[66] Furthermore, although the tips of the electrodes used in rats can be fairly small, they are still relatively large compared with those used in humans, specifically when placed in brain areas that are relatively bigger in humans than rats such as the prefrontal cortex and insula. This could create a larger area of stimulation with lower specificity as a possible consequence. Moreover, animal studies often use bipolar stimulation, whereas in human studies monopolar stimulation is favoured leading to differences in stimulation field. Finally, stimulation amplitudes have traditionally been higher in animal compared with human studies. These differences should be taken into account when extrapolating findings from preclinical studies to humans.[66]

Medical ethical considerations

In accordance with Carter *et al*.,[67] we would like to emphasize that DBS for addiction can only be considered when the highest medical ethical standards are applied. These include careful patient selection, responsible publishing and media reporting, and free and non-coerced choice to be treated with DBS. For more detailed ethical guidelines, we refer to previous papers.[67–72] In DBS for addiction, patient selection deserves special attention because of the serious social and physical problems that often accompany chronic alcohol or drug dependence. In the screening process, patients will have to undergo

careful physical examination and laboratory testing to determine their fitness for anaesthesia and surgery. Furthermore, patients should be seriously motivated and be able to keep their appointments since DBS is an intensive procedure that requires extensive follow-up and careful observations of symptoms and possible side effects. DBS should, therefore, be restricted to chronically addicted, treatment-refractory patients stable enough to comply with an intensive period of treatment and research. Lastly, patients should have (had) unrestricted and free of charge access to alternative treatments, that is, DBS has to be a free and non-coerced choice, which is important since serious concerns have been expressed about some neurosurgical lesion studies in addicted patients on these issues.[73,74]

Recommendations

Ultimately, the evidence for new DBS indications and targets has to come from clinical studies and, therefore, carefully designed pilot studies are needed as a next step for those target areas that have shown to be effective and safe in preclinical research and clinical research in patients with other psychiatric disorders. Based on the discussed literature, we conclude that NAc DBS was effective and safe in animal research and has shown encouraging results in human case reports. Moreover DBS of the NAc has proven to be safe in the treatment of OCD and depression[75–77] (see Supplementary Table S1). Therefore, we would like to propose that small and carefully designed pilot DBS studies using the NAc as target area for the treatment of chronic addiction are indicated.

However, Carter *et al*.[67] recently reached the opposite conclusion on the basis of largely the same literature—minus four more recent published papers.[16,18,24,25] They argue that (1) there is insufficient clinical evidence and more preclinical research has to be conducted to identify the optimal brain target; (2) more clinical experience has to be gained with other psychiatric disorders to better estimate risks involved in DBS; and (3) other effective treatments are available for addiction and addiction does not carry a high enough probability of significant harm to justify invasive interventions such as DBS.

We would like to argue that (1) four studies from four different research groups consistently found significant decreases of addiction-like behaviour following NAc DBS in rats, assessed by three different paradigms and using three different substances (2); the described case reports support the safety and possible efficacy of NAc DBS. Furthermore, NAc DBS has proven to be safe and to be associated with very few side effects in the treatment of other psychiatric disorders;[75–77] and (3) although there is a variety of (moderately) effective interventions to treat patients with addiction, research shows that many patients do not respond to currently available treatments even in countries where addiction treatments are accessible and free of charge. Additionally, high mortality rates (>27%) are associated with drug addiction because of overdose, drug-associated illnesses, violence and suicides.[78–81]

In summary, the use of DBS for the treatment of mental disorders is ground-breaking development in psychiatry and NAc DBS may create new opportunities for the treatment of treatment-refractory addicted patients.

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