Deep brain stimulation for the treatment of drug addiction

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Drug addiction represents a significant public health concern that has high rates of relapse despite optimal medical therapy and rehabilitation support. New therapies are needed, and deep brain stimulation (DBS) may be an effective treatment. The past 15 years have seen numerous animal DBS studies for addiction to various drugs of abuse, with most reporting decreases in drug-seeking behavior with stimulation. The most common target for stimulation has been the nucleus accumbens, a key structure in the mesolimbic reward pathway. In addition, the mesolimbic reward pathway undergoes a series of neuroplastic changes. Chief among them is a relative hypofunctioning of the prefrontal cortex, which is thought to lead to the diminished impulse control that is characteristic of drug addiction. The prefrontal cortex, as well as other targets involved in drug addiction such as the lateral habenula, hypothalamus, insula, and subthalamic nucleus have also been stimulated in animals, with encouraging results. Although animal studies have largely shown promising results, current DBS studies for drug addiction primarily use stimulation during active drug use. More data are needed on the effect of DBS during withdrawal in preventing future relapse. The published human experience for DBS for drug addiction is currently limited to several promising case series or case reports that are not controlled. Further animal and human work is needed to determine what role DBS can play in the treatment of drug addiction.

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WE are currently in the midst of a public health emergency, with opioid-related deaths skyrocketing over the past 15 years. In 2015 alone, there were upwards of 33,000 opioid-related deaths.²⁰ Beyond opioid addiction, alcohol, nicotine, and cocaine addiction also account for significant morbidity and mortality.^{15,25}

Given that current treatments—consisting of psychosocial and/or pharmacological interventions—for drug addiction have relapse rates as high as 50%–70%,⁵² additional treatments are needed. Neurosurgical procedures have been previously tried as early as the 1960s, with lesional procedures such as cingulotomy, hypothalamotomy, and resection of the substantia innominata having varying success in treating drug addiction.⁶⁰ These procedures (and psychosurgery as a whole) fell out of favor with the introduction of new pharmacological treatments and concerns for ethical treatment standards.^{50,71} Moreover, contemporary research suggests that such destructive procedures performed for drug addiction have limited efficacy.³⁸

Functional neurosurgery entered a new era with the in-

roduction of modern-day deep brain stimulation (DBS) in the late 1980s.⁶ Following successful thalamic DBS for parkinsonian tremor, DBS was used at other subcortical targets for Parkinson disease (PD) and other movement disorders. DBS has a favorable safety profile compared to lesioning, and this eventually led to the implementation of DBS as an investigational treatment for neuropsychiatric disorders including depression,²⁶ obsessive-compulsive disorder (OCD),¹⁶ and Tourette syndrome.⁵⁵ The indications for DBS may yet be expanding, with several positive reports of DBS for drug addiction.^{34,49} In this review of DBS for drug addiction, we will highlight the neurobiology of addiction, followed by an overview of animal and human studies of DBS for drug addiction, directions for future research, and possible ethical concerns.

Neurobiology of Addiction

Drug addiction develops through a series of stages, the first of which is the binge/intoxication stage.³¹ During

ABBREVIATIONS DBS = deep brain stimulation; DDS = dopamine dysregulation syndrome; ERN = error-related negativity; NAc = nucleus accumbens; OCD = obsessive-compulsive disorder; PD = Parkinson disease; PFC = prefrontal cortex; RI = reinstatement; SA = self-administration; STN = subthalamic nucleus.

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this stage, drug use produces a sense of reward, mediated by dopamine increases in the mesolimbic system.²⁹ The mesolimbic dopaminergic system is a reward circuit composed of the medial forebrain bundle, which connects the ventral tegmental area and hypothalamus with the olfactory tubercle, and the nucleus accumbens (NAc); drug-induced dopamine increases at the NAc ultimately facilitate reward.^{31,65} With continued drug use, prolonged and unregulated release of dopamine results in synaptic changes including elevations in mesolimbic dopaminergic excitability.^{31,73} This enhanced excitability is short-lived because repeated drug use leads to an attenuation of mesolimbic dopamine activity; i.e., decreases in dopamine at the NAc in response to drug use.^{46,66} As a result, increasing amounts of drug must be used to attain what amounts to a declining reward, or in other words, a tolerance develops.

Tolerance heralds the second stage of addiction: the withdrawal/negative affect stage. During this stage, decreased mesolimbic dopaminergic activity is hypothesized to be responsible for anhedonia and psychomotor depression.^{31,66,69} This negative emotional state is mediated by the activation of the extended amygdala, which includes the central nucleus of the amygdala, bed nucleus of the stria terminalis, and the medial portion (or shell) of the NAc, and is potentiated by increases in corticotropin-releasing factor, norepinephrine, and dynorphin. These neurotransmitters additionally activate stress responses, which can produce significant anxiety and irritability during withdrawal.³¹ Soon a conditioned negative response to withdrawal is formed, mediated by the extended amygdala and hippocampus. This learned negative response during withdrawal, coupled with tolerance, further feeds into compulsive drug-seeking behavior.

This marks the third and final stage of addiction: the preoccupation/anticipation (craving) stage. Here, the amygdala—a critical player in the withdrawal/negative affect stage—projects to the prefrontal cortex (PFC).⁹ The PFC—an area including the dorsolateral PFC, anterior cingulate gyrus, and medial orbitofrontal cortex—is postulated to be responsible for impulse control. However, during prolonged drug use, neuroplastic changes in the reward and memory circuits mediated by dopamine and glutamate can produce a hypofunctioning PFC, demonstrated by diminished impulse control.³¹ Diminished impulse control can help explain why those with addiction relapse despite known negative consequences, or why relapse may occur even after prolonged periods of drug abstinence.³⁶ The final stage of addiction ultimately cycles back to the first, whereupon each stage and cycle can become more and more intense, with drug abstinence harder to achieve.³⁰ Although the PFC appears to be a key player in the third stage of the addiction cycle, this final stage is fairly widespread, engaging multiple areas of the brain such as the striatum, hippocampus, insula, and habenula.^{42,50}

Although different drugs can produce various neuroadaptive changes, and other factors such as genetics and environmental factors play a role in addiction, the above explanation provides a basic framework of understanding behind the neurobiology of addiction.

Animal Studies

To date, numerous animal studies have investigated DBS for drug addiction (Table 1), with most reporting decreases in drug-seeking behavior. Most of these studies have targeted either the NAc core or shell.^{5,8,17–19,23,27,41,44,48,62,63,70} Although the NAc core and shell are both involved in the reward pathways and share many reciprocal connections, they are anatomically and functionally distinct, with the anterior cingulate cortex and dorsal prelimbic cortex mainly projecting to the core, and the infralimbic and ventral prelimbic cortex primarily providing afferents to the shell.⁷⁴ The shell is postulated to belong more to the limbic system, whereas the core is thought to act as an interface between the motor and limbic system. This has led some to postulate that the shell mediates desire, whereas the core translates the desire into a physical action.⁴

Additional studies investigating other targets implicated in the neurobiology of addiction such as the lateral hypothalamus, medial PFC,³⁹ lateral habenula,¹³ subthalamic nucleus (STN),^{58,67} and insula⁵⁶ have also shown reduction in addictive behaviors (Table 1). Addictive behaviors in animals are assessed through one of three common testing strategies (Table 2). A key demarcation between these strategies is whether the drug is experimenter-administered or self-administered. In a self-administered test—the most commonly used model in DBS for drug addiction—animals are placed in a chamber with access to the drug in the form of a bottle (e.g., ethanol) or a lever press that triggers an injection via a connected intravenous catheter (e.g., cocaine). Animals spend a prolonged period within the self-administration (SA) chamber until they reach a steady state of drug intake, referred to as the SA stage. Drug availability is often then terminated and during abstinence, animals may be subjected to extinction training wherein responding on the active lever no longer produces infusion of the drug. The next testing phase is reinstatement (RI), wherein animals are reexposed to the drug or to cues formerly associated with the drug (e.g., light paired with drug delivery; sound of the infusion pump). Interventions to treat addiction can occur during any stage. Self-administered models represent the gold standard for screening of potential treatments for drug addiction because such procedures induce features analogous to those seen in human drug addiction. Experimenter-administered testing (e.g., conditioned place preference and psychomotor sensitization), although less analogous to human drug addiction, can be useful for addressing effects on abuse potential and behavior-activating effects of drugs.

The majority of animal studies investigating DBS for drug addiction apply DBS in a self-administered model during the SA and/or RI stages. Although such experiments provide significant insights into the effect of DBS on drug addiction, they are limited in their ability to adequately replicate conditions of human drug addiction and the timing of potential DBS therapy. The SA stage correlates to the binge/intoxication stage in humans, whereas the RI stage is analogous to relapse—essentially another binge/intoxication stage. Patients who are actively abusing alcohol, opioids, stimulants, etc., would potentially be considered unfavorable candidates for DBS therapy. As

TABLE 1. Literature review of animal DBS studies for drug addiction

Authors & Year	No. of Animals	Target	Drug	Testing Paradigm	Was Stim Given During Drug Admin or WD?	Stim Paradigm	Stim Parameters	Laterality	Adverse Events	Outcome
Levy et al., 2007	40 (9 shams each, LH & PFC)	LH (n = 23), PFC (n = 17)	Cocaine	SA	Drug admin (SA phase)	30 min/day × 10 days	20 or 100 Hz, 0.1 msec, 200–400 μ A	Bilat	None reported	Reduced cocaine seeking at PFC & w/ 20 Hz
Liu et al., 2008	22 (12 shams)	NAc (core)	Morphine	CPP	Drug admin	3 hrs/day × 7–10 days	130 Hz, 0.21 msec, 0.2–0.5 mA	Unilat (side not specified)	ICH, infection, & contralateral spasm	Decreased morphine seeking
Vassoler et al., 2008	16 (9 shams)	NAc (shell)	Cocaine	SA	Drug admin (RI phase)	2 hrs/day × 16 days	160 Hz, 60 μ sec, 70–150 μ A	Bilat	None reported	Decreased cocaine seeking at 150 μ A*
Knapp et al., 2009	9 (sham stim in all animals)	NAc shell (n = 4), core (n = 5)	Ethanol	SA	Drug admin (SA phase)	Starting 5 min prior to & lasting the full access period (30 min)	160 Hz, 200 μ sec, 75–150 μ A	Bilat	1 animal became “highly active”	Decreased alcohol seeking at core & shell w/ 150 μ A
Henderson et al., 2010	11 (5 shams)	NAc (shell)	Ethanol	SA	Drug admin (RI phase)	Starting 1 hr prior to & lasting for the RI phase (24 hrs)	140–150 Hz, 60 μ sec, 200 μ A	Bilat	“Surprising amount of tissue damage” at electrode tip, postmortem histo findings	Decreased alcohol seeking
Friedman et al., 2010	54 (12 each at 10 & 100 Hz, 30 at combined 10 &/or 100 Hz)	Lat habenula	Cocaine	SA	Drug admin (SA & RI phases)	15 min during SA	10 &/or 100 Hz, 500 μ sec, 200 μ A	Rt-sided	None reported	Increased cocaine seeking w/ 10 Hz, no change w/ 100 Hz, decreased seeking w/ alternating 10- & 100-Hz stim
Rouaud et al., 2010	44; 28 in SA (12 shams), 16 in CPP testing (7 shams)	STN	Cocaine	SA & CPP	Drug admin (SA phase)	DBS applied for duration of SA & CPP testing	130 Hz, 60 μ sec, 50–130 μ A	Bilat	None reported	Reduced cocaine seeking in both SA & CPP testing
Vassoler et al., 2013	26 (5 shell shams, 8 core shams)	NAc shell (n = 10), core (n = 16)	Cocaine	SA	Drug admin (RI phase)	2 hrs/day × 16 days	160 Hz, 60 μ sec, 50–200 μ A	Bilat	None reported	Reduced cocaine seeking w/ shell but not core DBS
Pushparaj et al., 2013	24 (12 shams)	Granular insular cortex	Nicotine	SA	Drug admin (SA & RI phases)	5 min prior to & throughout testing session (1–4 hrs)	130 Hz, 90 μ sec, 50 μ A	Bilat	None reported	Decreased nicotine seeking
Guo et al., 2013	40 (6 shams in bilat & rt DBS grps, 5 shams in lt DBS grp)	NAc (core)	Heroin	SA	WD	1 hr/day × 14 days (stim given over 2 separate 7-day WD trials)	130 Hz, 100 μ sec, 150 μ A	Bilat (n = 17), lt (n = 11), & rt (n = 12)	None reported	Decreased cocaine seeking w/ bilat & rt DBS

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TABLE 1. Literature review of animal DBS studies for drug addiction

Authors & Year	No. of Animals	Target	Drug	Testing Paradigm	Was Stim Given		Stim Parameters	Laterality	Adverse Events	Outcome
					During Drug Admin or WD?	Admin or WD?				
Ma et al., 2013	20 (10 shams)	NAC (shell)	Morphine	CPP	WD	WD	130 Hz, 60 μ sec, 2 V	Bilat	None reported	Decreased morphine seeking on morphine RI; stimulated animals had faster resolution of WD Sxs
Wilden et al., 2014	7 (sham stim in all animals)	NAC (shell)	Ethanol	SA	Drug admin (SA phase)	5 min prior to & throughout testing session (1 hr); testing done across 5 days	150 Hz, 100 μ sec, 100 μ A (n = 3), 200 μ A (n = 4)	Lt-sided	None reported	Superior reduction in ethanol seeking w/ 200 μ A
Guercio et al., 2015	12 (6 shams)	NAC (shell)	Cocaine	SA	Drug admin (RI phase)	Throughout 2-hr RI session	160 Hz, 60 μ sec, 150 μ A	Bilat	None reported	Decreased cocaine seeking
Hamilton et al., 2015	24 (3 shams in shell grp, 4 in core)	NAC shell (n = 12), core (n = 12)	Cocaine	SA	WD	30 min/day $\times$ 14 days	20 or 160 Hz, pulse width NA, 50–200 μ A	Rt-sided	None reported	Decreased cocaine seeking w/ both 20 & 160 Hz, results w/ 160 Hz perhaps superior
Creed et al., 2015	46 (15 shams)	NAC (shell)	Cocaine	Psych sens	Drug admin (RI phase) & WD	24 hrs starting either at RI, or at 4 hrs or 24 hrs prior to RI	12 or 130 Hz, 90 μ sec, 50 μ A; 12-Hz DBS was also given w/ a D1 receptor antagonist	Bilat	None reported	Transient decrease in cocaine psych sens w/ 130-Hz DBS; long-lasting decrease in psych sens w/ 12-Hz DBS given w/ D1 receptor antagonist
Martinez-Rivera et al., 2016	43 (23 shams)	Ventral VS (n = 9), dorsal VS (n = 11)	Morphine	CPP	WD	1 hr/day $\times$ 11 days (130 Hz) or 9 days (20 Hz)	20 or 130 Hz, 0.1 msec, 100–200 μ A	Bilat	None reported	Decreased morphine seeking w/ 20 Hz at dorsal VS; increased morphine seeking w/ 120 Hz at dorsal VS
Batra et al., 2017	18 (8 shams)	NAC (shell)	Meth	SA	Drug admin (SA phase)	3 hrs/day $\times$ 5 days	130 Hz, 60 msec, 200 μ A	Bilat	None reported	Decreased meth seeking
Wade et al., 2017	36 (17 shams)	STN	Heroin	SA	Drug admin (SA & RI phases)	Applied through duration of SA (3 hrs) & RI (12 hrs) phases	130 Hz, 60 μ sec, 50–130 μ A	Bilat	None reported	Decreased heroin seeking

Admin = administration; CPP = conditioned place preference; grp = group; histo = histological; ICH = intracerebral hemorrhage; LH = lateral hypothalamus; meth = methamphetamine; NA = not available; psych sens = psychomotor sensitization; stim = stimulation; Sxs = symptoms; VS = ventral striatum; WD = withdrawal.

* Study investigated 70 and 100 μ A—however, saw no benefit at these amplitudes and did not report results in detail.

† Study also tested 75, 87, and 100 μ A, and saw no difference at these amplitudes compared to sham stimulation.

TABLE 2. Common experimental paradigms for animal drug addiction models

Study Type	Is Drug Self-Administered or Experimenter-Administered?	Outcome Measure
SA	Self-administered	Animal is placed in an operant conditioning test where the drug is available at set intervals. Determinations about addictive behavior are made based on the no. of lever pushes/nose pokes, latency btwn lever pushes/nose pokes, &/or total amount of drug consumed. Lever pushes or nose pokes are measured if drug is given intravenously via catheter; licks are measured if drug is given orally via a bottle.
CPP	Experimenter-administered	A drug of interest is given & associated w/ a specific context. For example, an animal is placed in a chamber w/ a different color in each half, & the drug is only given w/ the animal in the area w/ a particular color. Addictive behavior is then measured by how much time the animal spends in the part of the chamber associated w/ drug admin.
Psychomotor sensitization	Experimenter-administered	Animals are given repeated daily doses of drug until they develop increased locomotion, which is indicative of behavioral sensitization. Addictive behavior is then gauged based on the animals' locomotor activity, e.g., distance traveled.

such, animal studies in which DBS is applied during SA and/or RI may have limited generalizability to humans.

Perhaps a more useful DBS paradigm would be one in which stimulation was applied during withdrawal to help prevent potential relapse.¹⁹ Several studies have investigated DBS during withdrawal and have reported decreases in drug-seeking behavior. Both Guo et al.¹⁸ and Hamilton et al.¹⁹ reported reduction in heroin- and cocaine-seeking behavior, respectively, with DBS therapy administered during withdrawal. Withdrawal during these studies lasted a total of 14 days (in Guo et al. there were two separate 7-day trials of withdrawal interrupted by an RI session, whereas in Hamilton et al. the withdrawal lasted an uninterrupted 14 days), with stimulation applied for 30–60 minutes a day. Interestingly, these studies were also among the few to investigate unilateral NAc DBS. Right-sided NAc DBS was shown to reduce heroin-seeking behavior without a significant difference compared to bilateral NAc DBS, with left-sided NAc DBS shown to be ineffective.¹⁸ Hamilton et al. also investigated low-frequency NAc DBS. Here 160-Hz and 20-Hz DBS were applied during a 14-day withdrawal period, and both were effective at limiting subsequent cocaine seeking during RI.¹⁹ These results support previous work in which low-frequency stimulation (< 50 Hz) was found to suppress the NAc, albeit at a lower degree than high-frequency stimulation.²⁴ Nevertheless, other groups have also reported positive findings when using low-frequency settings.^{8,13,39} Notably, however, two of these studies used low-frequency stimulation at targets other than the NAc, specifically the PFC³⁹ and lateral habenula.¹³

The reason low-frequency DBS was investigated is interesting, given that many DBS stimulation parameters for movement disorders and neuropsychiatric disorders use high-frequency (> 100 Hz) stimulation. Although high-frequency stimulation is successful, its effects are generally transient, with symptoms recurring after cessation of stimulation.¹¹ Moreover, high-frequency stimulation is unlikely to reverse the neuroplastic changes that occur in response to addiction.⁸ Neuroplastic changes that occur in addiction include the potentiation of afferent axons—probably stemming from the medial PFC⁵³—onto D1 receptor-expressing neurons within the NAc.^{45,54} Creed et al.⁸

demonstrated that D1 receptor antagonism given with low-frequency (12 Hz) stimulation attenuated cocaine psychomotor sensitization and produced long-term depression of excitatory postsynaptic potentials. Stimulation was given once during withdrawal, and animals still demonstrated reduction in cocaine-induced behavior when RI occurred 7 days later. Interestingly, when either D1 receptor antagonism or low-frequency DBS was applied in isolation, no effects were observed. Low-frequency stimulation along with D1 receptor antagonism probably worked in concert to blunt the effects of afferents from the PFC synapsing on D1 receptor-expressing neurons in the NAc. Because this study used an experimenter-administered model instead of an SA model with multiple cycles of bingeing and relapse, it is possible that animals may have been early enough in the addiction cycle for there to have been up-regulation of the mesolimbic dopaminergic system.³¹ In that case, antagonism of the D1 receptors along with low-frequency stimulation curbed addictive behaviors. If D1 receptor antagonism were used with stimulation later on in the addiction cycle when mesolimbic dopaminergic activity is decreased,^{46,66} it is unclear whether this experimental paradigm would produce similar results.⁵⁷

This highlights an inherent weakness of many of the DBS animal studies on addiction. It is difficult to replicate the numerous cycles of bingeing and relapsing that characterize addiction in humans⁴³ in a laboratory setting. With these numerous addiction cycles come neuroplastic changes such as a hypofunctioning PFC. Although the PFC has not been as frequent a target for stimulation in the treatment of addiction compared to NAc DBS, its importance is nonetheless highlighted even during NAc DBS. During NAc DBS, c-Fos immunoreactivity (a surrogate for neuronal activity) was found to be elevated not only locally at the NAc but also at the infralimbic portion of the PFC.^{48,63} This activation of the PFC was postulated to occur in an antidromic fashion during NAc DBS.⁶³ This emphasizes the fact that NAc DBS may not function just through local effects only but rather through a widely dispersed network. This is additionally supported by work in which chemical silencing of the NAc (through γ -aminobutyric acid agonists and sodium channel blockers) failed to

produce results similar to NAc DBS.⁶³ It should be noted, however, that others have produced results comparable to NAc DBS with chemical silencing of the NAc,⁷⁰ and therefore the exact mechanism of NAc DBS for drug addiction remains to be fully elucidated.

Human Studies

The initial studies investigating DBS for addiction in humans were prompted by observations among patients with PD who were treated with DBS. Several small case series reported that STN DBS could curb symptoms of dopamine dysregulation syndrome (DDS)^{3,28,40,59,72}—a condition characterized by neuropsychiatric disturbances such as psychosis, pathological gambling, hypersexuality, mood swings, and compulsive dopamine replacement-seeking behavior.³⁷ Subsequent larger studies with longer follow-up have additionally supported STN DBS as therapy for reducing impulse control disorders characteristic of DDS in patients with PD.¹ The etiology of DDS is currently unknown,⁶⁸ and although loss of dopaminergic tone is a hallmark for PD, there is also a relative sparing of dopaminergic neurons that project to the NAc.⁷ The NAc does, however, represent the primary stimulatory target of interest in non-PD-related addiction; this again was discovered through a somewhat unforeseen manner.

NAc DBS had been previously investigated as a treatment for severe medication-refractory neuropsychiatric conditions such as anxiety, depression, and OCD.^{16,26} In several case reports, NAc DBS applied for these conditions resolved comorbid drug addiction.^{34,47} In the case of addiction superimposed with OCD it could be argued that the drug addiction may have been part of the patient's compulsive behavior and that resolution of addiction may have been a mere byproduct of improvement in OCD. In one case of OCD treated with NAc DBS, significant improvement in OCD symptoms occurred 10 months before the patient ceased nicotine use.⁴⁷ This suggests that the addiction may not have been part of the patient's underlying neuropsychiatric condition. In support of this, an additional patient who underwent NAc DBS for OCD and who experienced no improvement in OCD symptoms was nevertheless able to attain nicotine cessation.³² Moreover, another case report detailed resolution of alcohol dependency without any improvement in the patient's initial presenting symptoms (severe anxiety and depression) for which the NAc DBS was intended.³⁴ A larger case series in which patients were treated with NAc DBS for neuropsychiatric conditions reported less favorable results in terms of reducing concurrent drug addiction, with more than half experiencing no change in drug use.³²

Following these reports of NAc DBS improving drug addiction in the setting of comorbid neuropsychiatric disease, several small case series or case reports documented instances of NAc DBS being used primarily for drug addiction, all with decreases in drug use (Table 3).^{21,33,35,49,61,64,75} Although promising, these studies are limited by small patient numbers, variable long-term follow-up, possible publication bias, and lack of blinded stimulation. There was 1 double-blinded trial of NAc DBS for cocaine dependence that used the following paradigm:

Phase I (9 months)—initial DBS implantation with optimization of stimulation parameters; Phase II (9 months)—a 6-month period of double-blinded stimulation with a 3-month period of single-blinded stimulation; Phase III (12 months)—continued stimulation. At the conclusion of this 2.5-year trial, although there were objective declines in cocaine craving and usage, during the 9-month blinded period the results were equivocal, with no major differences between the “off” and “on” stimulation state, which led the investigators to conclude that there was a potential placebo effect.¹⁴

Although the placebo effect could be contributing to the results seen with NAc DBS for drug addiction, there are nevertheless neurophysiological changes that occur following NAc DBS that may explain its effect. These changes have been demonstrated by use of concurrent electroencephalography to characterize the activity of the anterior midcingulate cortex during NAc DBS. The anterior midcingulate cortex—part of the PFC—is postulated to be hypofunctioning in addiction, contributing to repeated relapse. Hypofunctioning of the PFC can be evaluated by error-related negativity (ERN). In brief, ERN represents a characteristic electrophysiological response produced after an erroneous answer is given, and has been shown to be reduced in patients who are in various addicted states.^{10,12} This decline in ERN amplitude in drug addiction has been shown to be ameliorated by NAc DBS.³³ This provides further evidence that the PFC may play a pivotal role in impulse control in drug addiction. Moreover, this result supports animal work in which NAc DBS was found to antidromically activate the PFC.⁶³

Neuroimaging has also demonstrated the critical role of the PFC in addiction. In 1 study, PET scans were performed during a gambling task in both the on and off stimulation state (the patient was blinded to the stimulation status during the testing) 2 years after the placement of NAc DBS for alcoholism. Testing revealed that the patient was more risk-averse and had preferential activation of the paracingulate cortex and hippocampus during stimulation.²² Although this work did not report the outcomes in regard to his alcoholism following NAc DBS, it does nonetheless highlight once again the importance of the PFC in addiction.

Future Directions

Additional preclinical and clinical studies need to be performed to establish the efficacy of DBS for drug addiction. Addiction testing in animal models consists of either experimenter-administered or self-administered paradigms. Given that self-administered experiments lend themselves more to the human state of addiction in which drugs of abuse are self-administered, this model seems more clinically relevant. Moreover, within these SA models, the vast majority of studies that have been conducted to date use DBS during the initial SA phase or the RI phase, which are analogous to the binge/intoxication phase and relapse, respectively. Instead of using DBS in these stages of addiction, future studies should investigate DBS given during the withdrawal stage, because this is the most likely stage in which DBS for addiction would be applied

TABLE 3. Literature review of human DBS studies for drug addiction (excluding DBS for PD in which DDS was improved)

Authors & Year	No. of Pts	Target	Primary Indication for DBS	Drug	Stim Parameters	Laterality	Adverse Events	Duration of FU	Outcome
Kuhn et al., 2007	1	NAC	Severe anxiety & depression	Alcohol	130 Hz, 90 μ sec, 3 V	Bilat	None reported	12 mos	No change in anxiety/depression, resolution of preop alcohol dependency
Müller et al., 2009	3	NAC	Addiction	Alcohol	130 Hz, 90 μ sec, 3.5–4.5 V	Bilat	Transient hypomania in 1 pt	12–18 mos	All pts improved; 2 w/ resolution
Kuhn et al., 2009	10	NAC	Anxiety (n = 1), OCD (n = 5), TS (n = 4)	Nicotine	130–145 Hz, 90 μ sec (1 at 180 μ sec), 3–6 V	Unilat & bilat (5 each)	None reported	22–33 mos	7 pts were unchanged, 3 (2 OCD, 1 TS) had nicotine cessation; of these 3 pts, 2 had unilat stim (OCD); 1 pt w/ OCD who quit nicotine had no improvement in primary OCD Sxs
Heinze et al., 2009	4	NAC	Addiction	Alcohol	130 Hz, 90 μ sec, 3.5–4.5 V	Bilat	DBS removed due to infection in 1 pt; transient hypomania in another	14 mos	Of the 3 pts w/ DBS, 2 had complete resolution, & 1 had prolonged periods of abstinence w/ occasional relapse
Mantione et al., 2010	1	NAC	OCD	Nicotine	180 Hz, 90 μ sec, 3.5 V	Bilat	None reported	24 mos	Improvement in OCD, smoking cessation achieved; did not occur until 10 mos post-DBS
Zhou et al., 2011	1	NAC	Addiction	Heroin	145 Hz, 90 μ sec, 2.5 V	Bilat	Transient confusion/urinary incontinence	6 yrs	Heroin cessation, which continued after DBS was removed (3 yrs postop) per pt wishes; additionally had decreased cigarette smoking
Kuhn et al., 2011	1	NAC	Addiction	Alcohol	130 Hz, 120 μ sec, 5.5 V	Bilat	None reported	12 mos	Alcohol intake decreased after stim, culminating w/ cessation at 1 yr postop
Valencia-Alfonso et al., 2012	1	NAC	Addiction	Heroin	180 Hz, 90 μ sec, 3.5 V	Bilat	None reported	6 mos	Heroin cessation w/ exception of 1 relapse
Voges et al., 2013	5	NAC	Addiction	Alcohol	130 Hz, 90 μ sec, 4.5 V	Bilat	Transient hypomania in 1 pt	31–47 mos (avg 38 mos)	All pts improved; 2 had continued cessation at 4 yrs postop
Kuhn et al., 2014	2	NAC	Addiction	Heroin	140 Hz, 120 μ sec, 5 V (n = 1); 130 Hz, 90 μ sec, 4.5 V (n = 1)	Bilat	None reported	24 mos	Both pts remained off heroin & levomethadone, aside from 1 relapse*
Gonçalves-Ferreira et al., 2016†	1	NAC‡	Addiction	Cocaine	150 Hz, 150 μ sec, 2.5–4 V	Bilat	Transient weight gain, diminished libido, & unpleasant warmth/flushing	30 mos	Decreased cocaine use/craving at 2.5 yrs postop; best results at contacts at NAC & BNST

Avg = average; BNST = bed nucleus of the stria terminalis; FU = follow-up; pts = patients; TS = Tourette syndrome.

* Besides heroin, both patients also used additional drugs (the first patient additionally used alcohol and amphetamines, and the second patient additionally used amphetamines and benzodiazepines). Following NAC DBS, both patients still occasionally used these other drugs.

† This study included 6 months of double-blinded stimulation and 3 months of single-blinded stimulation. All other studies listed were retrospective case series or case reports without blinded stimulation.

‡ Electrodes were placed such that contact 0 was at the NAC, contact 1 was at the BNST, and contacts 2 and 3 were at the anterior limb of the internal capsule.

in humans.¹⁹ To date, much of the human experience regarding DBS for drug addiction is based on case series or case reports without standardized outcome reporting, with limited long-term follow-up, and lack of blinding. Double-blinding was recently used by Gonçalves-Ferreira et al.¹⁴ in a study of NAc DBS for cocaine addiction. Although such studies have additional value, some have raised ethical concerns about double-blinded studies and sham surgery, because patients may be exposed to potential serious risks without any therapeutic benefits.⁵⁰ Beyond this are ethical and logistical concerns that pertain especially to DBS for addiction. DBS may not be well suited for patients who are actively abusing drugs, and furthermore if DBS were to be used in this population, there would be concerns regarding the patient's ability to give informed consent while under the influence of drug(s). Such matters may be mitigated provided that DBS is used for patients in withdrawal, seeking to prevent further relapse. However, some have noted that patients who rapidly undergo drug detoxification may still have alterations in mental status and/or executive function, limiting their ability to provide informed consent.⁵⁰

This highlights another ethical and logistical issue surrounding DBS for addiction: when is the appropriate time for this therapy? For patients who recently attained drug abstinence, the chance of drug relapse is relatively high compared to patients with long-term drug abstinence. Accordingly, DBS for patients in acute withdrawal has a higher chance of "failure," if one considers failure as drug relapse. However, newly drug-abstinent patients stand to benefit the most because DBS could prevent future relapse. For long-term drug abstainers, although DBS is less likely to "fail," its benefits may be marginal—some might argue that whatever treatments provided for prolonged drug abstinence would have continued to do so in the absence of DBS. Other ethical concerns regarding DBS for addiction surround the notion that, through targeting and alteration of the brain's reward centers, DBS may alter a person's sense of identity.⁵⁰ Last there is the issue of patient-controlled stimulation that, although common in DBS for movement disorders, may not be prudent in the addiction population because patients in theory could switch off their stimulation, leading to possible drug relapse. These ethical concerns are best addressed using a multidisciplinary team approach in which consensus criteria for inclusion or exclusion and standardized outcome measures are developed. Future studies may also benefit from multicenter collaborative efforts to help with patient recruitment.

Although the NAc has been the most popular target in both animal and human studies on DBS for addiction, other targets warrant further investigation. Chief among these would be the PFC, because animal studies have shown that direct stimulation of the PFC can reduce addictive behavior,³⁹ and that the effects of NAc DBS may be mediated in part by activation of the PFC.⁶³ Although the PFC has yet to be directly stimulated for addiction in humans, noninvasive studies of the PFC during NAc DBS have demonstrated that the PFC is responsible for modulating behavior that may be behind relapse.^{22,33} Beyond the PFC, the insula, which in one animal experiment was shown to be an efficacious stimulation target,⁵⁶ may also merit more preclinical investigation because human stud-

ies have demonstrated that those with insular lesions may have dramatic resolution of nicotine addiction and experience milder withdrawal symptoms, perhaps further implicating the insula's role in addiction.^{2,51}

Conclusions

Drug addiction remains a significant public health concern, with significant morbidity and mortality. Current therapies for drug addiction have high rates of relapse, and therefore within the past 15 years DBS has been investigated as a potential treatment. Much of the preclinical data has been promising; however, DBS has yet to be widely used in humans for drug addiction. The human experience with DBS for drug addiction is primarily limited to case reports without blinded assessments or standardized outcome measures. Additional preclinical and clinical research needs to occur in order to determine the role of DBS in the treatment of drug addiction.

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Author Contributions

Conception and design: Wang, Elias, Lynch. Acquisition of data: Wang. Analysis and interpretation of data: all authors. Drafting the article: Wang. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Wang. Study supervision: Elias, Lynch.

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