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*Review Article*

# Role of deep brain stimulation (DBS) in addiction disorders

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## ABSTRACT

**Background:** Addiction disorders pose significant challenges to public health, necessitating innovative treatments. This assesses deep brain stimulation (DBS) as a potential intervention for addiction disorders.

**Methods:** A literature review was carried out with a focus on the role of DBS in addiction disorders and its future implications in neurosurgical research.

**Results:** The online literature shows that DBS precisely modulates certain brain regions to restore addiction-related neural circuits and promote behavioral control.

**Conclusion:** Preclinical evidence demonstrates DBS's potential to rebalance neural circuits associated with addiction, and early clinical trials provide encouraging outcomes in enhancing addiction-related outcomes. Ethical considerations, long-term safety, and personalized patient selection require further investigation.

**Keywords:** Addiction, Deep brain stimulation, Health care, Neuromodulation, Nucleus accumbens, Stereotactic neurosurgery

## INTRODUCTION

The term "addiction" encompasses various heterogeneous disorders, including substance-related dependencies on various pharmacological agents. These substances differ in their addiction potential and the health hazards they pose to individuals in the short- and long-term. Psychoactive drugs are categorized into several groups, such as psychostimulants (e.g., amphetamine and cocaine), sedatives and hypnotics (e.g., alcohol and benzodiazepines), opiates and their derivatives (e.g., heroin and methadone), cannabinoids, and nicotine.[63]

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The current era is marked by a significant public health crisis characterized by drug abuse and addiction. The combined impact of smoking, alcohol consumption, and illicit drug use results in the annual death of approximately 11.8 million individuals, surpassing the mortality rate associated with all types of cancers.[38] Of particular concern is the emergence of the opioid addiction epidemic, which has become the primary cause of non-accidental deaths. According to data from the Centers for Disease Control and Prevention, between 1999 and 2016, drug overdose-related fatalities surpassed 630,000, reflecting a fivefold increase compared to 1999. Notably, around 66% of these deaths were attributed to opioid overdoses.[7,94]

Addiction treatment is crucial to addressing substance dependencies, such as nicotine, alcohol, or drugs. However, the current addiction treatment through different medications often fails due to relapses experienced by individuals after completing a treatment program. Studies examining abstinence rates one year after treatment completion indicate that only 30–50% of patients have remained completely abstinent, while an additional 15–30% have reduced their compulsive drug use without resuming addictive behaviors.[91]

The urgent need for new modalities to treat and enhance substance use disorder (SUD) treatment is emphasized, particularly for substances that lack medication options. Non-pharmacological approaches are of interest, especially for individuals who cannot tolerate medication or have an inadequate response. Deep brain stimulation (DBS), one of the invasive forms of neuromodulation, is a surgical procedure where electrodes are implanted in specific brain regions and stimulated through implanted pulse generators. It has been Food and Drug Administration -approved for Parkinson's disease, essential tremor, dystonia, and obsessive-compulsive disorder (OCD). DBS has shown promise in clinical investigations for conditions such as depression, Tourette's disease, eating disorders, traumatic brain injury, Alzheimer's disease, and chronic pain. The stimulation parameters are programmable based on the targeted brain region and patient response. DBS is also being explored as a potential approach for SUD.[18,46,47,50]

In this article, we provide a concise review of the relevant scientific literature on DBS for the treatment of addiction disorders. We focus specifically on the mechanism of DBS in the treatment of addiction disorders and summarize the findings from clinical trials investigating the use of DBS for addiction to various psychoactive substances, including nicotine, alcohol, cocaine, opioids, and methamphetamine/amphetamine. In addition, we explore the therapeutic effects of DBS in other brain regions, such as the subthalamic nucleus (STN), striatum, lateral habenula (LHb), medial prefrontal cortex (mPFC), and hypothalamus. The status of DBS as a treatment modality for addiction disorders is discussed, along with the challenges associated with its implementation.

## DISCUSSION

### Neurocircuitry of addiction

The progression of drug addiction involves distinct stages, with the initial phase known as the binge/intoxication stage, which involves complex neurobiological processes.[60] The mesolimbic dopaminergic pathway, encompassing the medial forebrain bundle and its connections to key brain regions such as the ventral tegmental area (VTA) and nucleus accumbens (NAc), is central to the rewarding effects of drugs.[93] Extended and unregulated release of dopamine resulting from persistent drug use leads to synaptic alterations, including heightened excitability of the mesolimbic dopaminergic pathway.[60] However, recurrent drug administration eventually reduces dopamine activity within the NAc, diminishing the dopamine response to drug intake. Consequently, individuals develop tolerance, necessitating higher drug doses to attain increasingly diminished rewards.[113]

As addiction progresses, a conditioned negative response to withdrawal is formed, mediated by the extended amygdala and hippocampus. This learned negative response, combined with tolerance, fuels compulsive drug-seeking behavior. During this stage, decreased activity in the mesolimbic dopaminergic system leads to anhedonia and psychomotor depression. The extended amygdala mediates this negative emotional state, specifically the central nucleus of the amygdala, the bed nucleus of the stria terminalis (BNST), and the medial portion of the NAc. The activation of these regions is potentiated by neurotransmitters such as corticotropin-releasing factor (CRF), norepinephrine, and dynorphin. In addition, these neurotransmitters activate stress responses, contributing to anxiety and irritability during withdrawal.[60,93,113]

The third and final stage of addiction is the preoccupation/anticipation or craving stage. During this stage, the amygdala projects to the prefrontal cortex (PFC).[28] The PFC, including the dorsolateral PFC (DLPFC), anterior cingulate gyrus (ACC), and medial orbitofrontal cortex (mOFC), is responsible for impulse control.[60] However, prolonged drug use can lead to neuroplastic changes in the reward and memory circuits, mediated by dopamine and glutamate, which result in impaired functioning of the PFC and diminished impulse control. This diminished impulse control helps explain why individuals with addiction often relapse despite knowing the negative consequences or even after periods of drug abstinence. The final stage of addiction becomes a cycle where each stage intensifies, making drug abstinence increasingly difficult to achieve. The

preoccupation/anticipation or craving stage has long been considered a crucial element of relapse in addiction, defining it as a chronic relapsing disorder.[68]

**The mechanism of DBS treatment in addiction disorders**

In the context of addictive disorders, research suggests that altered activity in brain regions connected to the NAc, such as the mPFC, plays a role in the effects of DBS.[111] Exposure to drugs of abuse leads to increased excitatory connections onto dopamine D1 receptor-expressing medium-sized spiny neurons (D1R MSNs) in the NAc, which is associated with drug-induced behavioral changes.[24,95]

Recent studies using optogenetic techniques in mice have shown that drug-adaptive behaviors can be reversed by restoring normal synaptic transmission at specific synapses. Activation of metabotropic glutamate receptors (mGluRs) leads to depotentiation of excitatory inputs onto D1R MSNs and normalization of drug-adaptive behavior. Acute low-frequency DBS, combined with selective blockade of dopamine D1 receptors, can replicate the effects of optogenetic stimulation on mGluRs. This refined DBS protocol normalizes synaptic transmission onto D1R MSNs and eliminates behavioral sensitization.[15,79]

While DBS increases neuronal activity and activates the NAc shell, it has been observed that enhancing neuronal activity in the NAc promotes cocaine seeking, suggesting that shell activation is not responsible for reducing cocaine reinstatement.[14,83] Other theories propose that DBS inhibits the stimulated nucleus through depolarization inactivation or activation of inhibitory neurons.[6,57,59] Experiments using GABA agonists or lidocaine to inhibit specific NAc regions have shown that only inhibition in the core, not the shell, attenuates cocaine reinstatement. This indicates that the effect of shell DBS on cocaine reinstatement is not due to local inactivation or impaired neuronal transmission in axons of passage.[112]

The effects of DBS extend beyond simple excitation or inhibition at a local level. DBS preferentially stimulates axon terminals, resulting in broader circuit-wide influences.[80,90] It can reduce the spontaneous activity of glutamatergic neurons in the corticoaccumbal system while stimulating cortical interneurons through recurrent inhibition. Prolonged accumbens DBS may induce long-term potentiation in cortical interneurons, contributing to the sustained action of DBS. Activation of the infralimbic cortex by DBS of the accumbens shell and subsequent activation of GABAergic interneurons may also play a role in reducing cocaine seeking.[112]

It is important to note that these mechanisms are specific to the NAc, and the local and circuit-wide effects of DBS depend on the stimulated brain structure, including its inputs, outputs, cell types, neuron ratios, transmitter systems, and other factors.

**Different targets of DBS in addiction disorders**

The major components of the reward system, identified based on neuroanatomical definitions, consist of the ACC, the orbitofrontal cortex (OFC), the ventral striatum (which includes the NAc), and the VTA.[45] Other brain regions such as the amygdala, hippocampus, pedunculopontine nucleus, LHb, the ventral pallidum, dorsomedial thalamic nucleus, and the raphe nucleus have also been associated with regulatory influences on the reward system. These regions are the targets of DBS for the treatment of addiction.[1]

***Nucleus accumbens***

A study conducted by Gao *et al*. explored a novel approach to treat drug addiction using stereotactic surgery to ablate the NAc, a region linked to drug-induced psychological dependence. Targeting the mesocorticolimbic dopamine circuit, the surgery aimed to reduce drug cravings and prevent relapse post-detoxification. Among 28 patients followed for an average of 15 months, 11 remained relapse-free, with drug-free periods exceeding six months in four cases and over a year in three cases. In 15 cases, relapse occurred, with drug-free periods exceeding six months in three cases, between 1 month and six months in ten cases, and <1 month in two cases. Therapeutic effectiveness was rated as excellent in seven cases, good in ten cases, and poor in two cases, with seven cases still under investigation. Relapse rates were 7.7%, 38.5%, and 57.5% within one month, between 1 month and six months, and after more than six months, respectively. Surgery-related complications were minimal, with minor character type changes in two cases and temporary memory loss in four cases, which did not affect daily life or learning and recovered within one month. In summary, stereotactic surgery for bilateral NAC lesions effectively reduced drug addicts' psychological dependence, with a mean follow-up time of 15 months and minimal complications.[36]

Vassoler *et al*. conducted a study demonstrating that DBS targeting the shell region of the NAc effectively reduced cocaine reinstatement in rats.[112] In another study by Liu *et al*., DBS of the NAc was found to diminish morphine reinforcement by blocking morphine-conditioned place preference (CPP).[74] It is worth noting that Liu *et al*. utilized a self-constructed stimulation device that was affixed to the rat's skull, whereas most other animal studies administered DBS using an external stimulator.

Kanaka *et al*. observed a significant decrease in alcohol consumption with NAc DBS, and this effect disappeared when the stimulation was discontinued.[56] Similarly, Henderson *et al*. reported a noteworthy reduction in overall alcohol intake following NAc DBS.[49]

In 2007, Kuhn *et al*. published a case report on a person with severe anxiety disorder who received bilateral DBS of the

NAc. The patient, who had developed a secondary alcohol addiction to cope with anxiety, reported stopping drinking without any further assistance after the DBS procedure. It is noteworthy that the patient's anxiety disorder did not improve following the DBS treatment.[65]

In a pilot study by Müller *et al*., five individuals with severe alcohol addiction underwent bilateral DBS targeting the NAc. The study aimed to assess the effects of this intervention on alcohol cravings. The results revealed that all participants reported a complete and lasting elimination of their alcohol cravings after receiving DBS treatment. Notably, two of the subjects remained abstinent for over four years following the procedure, while the remaining three exhibited a substantial reduction in both the frequency of drinking days and the amount of alcohol consumed.[87]

In a review conducted by Kuhn *et al*., patients who received DBS targeting the NAc for the treatment of conditions such as OCD, anxiety disorder, and Tourette's disorder were evaluated for their smoking habits. Among the ten patients included in the review, 30% of them achieved permanent smoking cessation without any additional treatment after NAc DBS.[62] This abstinence rate is significantly higher than the spontaneous abstinence rate of 9% observed in the general smoking population.[86]

A study by Kallupi *et al*. found that high-frequency DBS (HF-DBS) of the NAc shell did not decrease cocaine intake but instead slightly increased it. This suggests that HF-DBS of the NAc shell is not an effective treatment for reducing cocaine intake in active cocaine-dependent individuals.[55]

In a study with eight patients who had a long history of heroin use and relapses, simultaneous DBS of the NAc and anterior limb of the internal capsule (ALIC) was investigated for addiction treatment. DBS began two weeks after surgery, and patients were followed for at least 24 months. DBS resulted in five patients maintaining abstinence for over three years, two relapsed after six months, and one was lost to follow-up at three months. Patients who remained abstinent experienced significantly reduced drug cravings ($P < 0.001$). Simultaneous NAc and ALIC DBS improved quality of life (QoL), alleviated psychiatric symptoms, and increased glucose metabolism in addiction-related brain regions. Stimulation-related adverse events were minimal and reversible.[11] These findings suggest that DBS of the NAc may have a suppressive effect on addictive behaviors.

### *The anterior cingulate cortex (ACC)*

The posterior cingulate cortex, OFC, amygdala, NAc, and other important brain areas are structurally connected to the ACC, making it a crucial piece in the understanding of addiction. Compulsive internet, alcohol, heroin, and cocaine usage are all associated with abnormal white matter FA values in the ACC, whereas impulsive and compulsive behaviors are related to structural hyperconnectivity with the thalamus and OFC. In addition, persons with alcohol use disorder (AUD) and SUDs had lower levels of gray matter in the ACC.[96]

The dorsal ACC (dACC) and DLPFC together make up a network that regulates executive control functions, including inhibition and attention in the resting state. The processing of emotions, rewards, and motivation is related to the ventral ACC (vACC), which contains the rostral ACC (rACC), subgenual ACC, and perigenual ACC (pgACC).[96] The rACC encodes aversive emotional emotions and ambiguity in decision-making. An increased incentive salience for drugs and drug-related signals has been shown by higher resting-state functional connectivity between the rACC, mOFC, and NAc in addiction.[26] On the other hand, the pgACC, which encodes the dependability of behavioral methods, is frequently hyperactive in people with an addiction, which results in impulsive actions. Synchrony analysis indicates changes in connectivity with the limbic system and inhibitory control network during abstinence, implying possible neural plasticity in long-term recovery.[22]

The information on ACC-DBS for the treatment of addiction is relatively few and largely based on case studies. Findings from two cases presented by De Ridder *et al*. indicate that ACC-DBS may be a successful method for treating addiction.

In the first case report, a male patient who had co-occurring anxiety disorders and alcoholism got bilateral ACC-DBS. Functional magnetic resonance imaging and resting-state EEG data were used to help choose the target for DBS, which was the dACC. After six weeks of repetitive transcranial magnetic stimulation (rTMS) therapy, the patient saw a brief but clinically significant improvement. This improvement persisted throughout the patient's 18-month follow-up period, during which time they continued to abstain from alcohol and had less anxiety. Surprisingly, the favorable outcome lasted for seven years.[21]

In the second example, a female patient who was alcohol dependent and had refractory OCD, anxiety, and depression had bilateral ACC-DBS. After nine months of ACC-DBS, there were notable reductions in alcohol seeking (88% reduction) and OCD symptoms (66% reduction). Overall results showed a good influence, even if the patient's weekly alcohol intake was somewhat less affected after therapy.[20]

Cingulotomy, a surgical technique that involves lesioning underneath the ACC, was formerly considered a viable addiction therapy. Early trials revealed encouraging outcomes, with drug-dependent individuals no longer needing medicines following the surgery. Cingulotomy, however, was abandoned due to worries regarding long-term functional deficits, such as those related to emotional stability and cognitive control.[31] Since then, DBS, a neuromodulation

technology, has dominated addiction therapy, replacing surgical methods and emphasizing the modulation of ACC activity for therapeutic objectives.[70]

Bilateral stereotactic cryo cingulotomy has been used to treat drug addiction since 1998 by the Institute of the Human Brain of the Russian Academy of Sciences. This method has been applied to 348 patients throughout time, allowing for the examination of long-term effects, psychological evaluations, and an extensive analysis of the results. In interviews with 187 patients with follow-ups of more than two years, it was discovered that 45% of them had completely stopped using addictive drugs after surgery, while 17% had used drugs once or twice in the first two months after surgery but had not used them since. There is insufficient data available for 13% of the patients. The remaining individuals have experienced either partial improvement, such as finding temporary employment and reducing drug usage and frequency, or no change at all, accounting for 13% and 12% of the cases, respectively. The results of this follow-up study have indicated that cryocingulotomy is particularly effective in addressing heroin addiction and is associated with minimal complications.[85,124]

### *Insular cortex*

The insula cortex is a crucial brain region involved in the neurocircuitry of addiction.[61] Dopaminergic neurons from the VTA and substantia nigra influence dopamine reactivity and release in the NAc, critical for addictive behavior.[54] The insula's granular subregion exhibits high dopamine utilization, particularly in the anterior insular cortex, with D1 receptors surrounding dopaminergic terminals.[37] These terminals project to the agranular subregion, which houses large pyramidal neurons with GABA B receptors projecting to the amygdala and NAc.[78,92] CRF plays a role in drug motivation, substance dependence, withdrawal distress, and stress-induced relapse.[13] The agranular subregion of the insula contains a high density of CRF subtype one receptor.[100]

Studies have shown that damage to the insula due to stroke can lead to a sudden and profound disruption of addiction, such as smoking cessation without relapsing or craving.[89] Similarly, patients with insula lesions have shown higher rates of quitting heroin use compared to control groups.[125]

The results of a study conducted by Chang *et al*. show that the continuous HF-DBS applied to the bilateral anterior insula prevents the relapse of morphine place preference following withdrawal, facilitates its extinction, blocks reinstatement triggered by morphine priming, and reverses the expression of morphine-regulated proteins.[10] These findings, combined with previous research, suggest that modulating insular activity through pharmacological or other methods, such as DBS, holds promise as a potential treatment for SUD.

### *The sub thalamus nucleus*

The STN is a brain structure that is connected to both the striatum and the prefrontal cortex. It plays a crucial role in the integration of signals necessary for behavioral control. STN DBS may inactivate the STN, and high-frequency stimulation (HFS) of the STN inhibits certain brain regions in rats.[5] These regions include the substantia nigra, entopeduncular nucleus, and NAc shell.[114]

In a study by Witjas *et al*., two young Parkinson's patients with severe motor fluctuations and dyskinesia due to dopamine dysregulation syndrome were treated with DBS of the STN. The DBS not only improved their motor disability but also greatly reduced behavioral disorders and completely eliminated their addiction to dopaminergic treatment.[118]

In a study by Lardeux and Baunez, STN lesions selectively modulated alcohol motivation in rats based on their alcohol preference. Lesions in "High-Drinker" rats increased alcohol motivation, as shown by higher breaking points and increased time spent in the alcohol-associated environment. In contrast, lesions in "Low-Drinker" rats decreased alcohol motivation, resulting in lower breaking points and increased time spent in the water-associated environment. These results demonstrate that STN lesions can enhance alcohol motivation in rats with a high alcohol preference while reducing it in rats with a low preference for alcohol.[69]

HFS of STN in rats reduces cocaine taking and heroin seeking. A conflicting study showed that only low-frequency stimulation (LFS) at 30 Hz modulates cocaine taking under foot-shock punishment. Abnormal oscillatory activity during cocaine intake predicts compulsive-like seeking in shock-resistant animals. STN stimulation outcomes depend on punishment presence. Further research is needed to understand the effects of LFS versus HFS.[99]

### *Orbitofrontal cortex*

The OFC plays a significant role in the development of compulsive drug-seeking and relapse.[101] Neuroimaging studies consistently reveal the activation of the OFC in individuals with addiction during phases of intoxication, craving, and binging while observing its deactivation during withdrawal.[117] Extensive research has demonstrated enduring structural and functional changes in the OFC following exposure to drugs of abuse.[40]

In 2006, the researchers conducted experiments using rats to study the effects of opiates on drug craving. MRI scans showed a decrease in activity in the OFC during opiate administration, which gradually recovered during withdrawal. EEG recordings indicated a decrease and subsequent increase in gamma-band activity during opiate administration and withdrawal, respectively. These results

suggest that OFC activity decreases during morphine administration and progressively recovers during withdrawal, potentially correlating with drug craving.[106]

HF-DBS applied to the OFC in rats has shown promising results in preventing the development of morphine-associated place preference, reducing its persistence, facilitating extinction, and blocking reinstatement. Importantly, HF-DBS did not have negative effects on memory acquisition, retrieval, locomotor activity, or anxiety levels.[29]

Stimulation of the mPFC in rats reduces cocaine consumption and motivation, suggesting it as a potential treatment for addiction.[71] However, its translational use in human DBS is limited. Other prefrontal areas, such as the OFC, are implicated in addictive behaviors, but DBS of the lateral OFC can increase compulsive behavior. Further research is needed to explore the effects of prefrontal cortex stimulation in addiction treatment.[58]

### *The lateral habenula*

The LHb is implicated in negative reinforcement. DBS of the LHb at low frequencies, which enhances LHb activity, has been found to promote cocaine self-administration. In contrast, conventional HFS does not exert any significant effect. However, an unconventional alternating stimulation paradigm consisting of alternating frequencies (10 and 100 Hz) has been shown to reduce cocaine self-administration.[34] In addition, LHb stimulation leads to reduced sucrose intake, whereas LHb lesions result in increased sucrose consumption, indicating a general decrease in motivational drive.[33] These observations suggest that non-standard stimulation parameters for LHb DBS might induce a decline in motivational states.

### *Substantia nigra*

The substantia nigra (SNr) serves as a convergence region for the striatal output pathways, consisting of striatonigral neurons from the direct pathway and striatopallidal neurons from the indirect pathway.[19] D1-expressing medium spiny neurons in the direct pathway project to SNr GABA neurons and exhibit D1-mediated presynaptic facilitation.[12,95] The direct pathway is crucial for drug-seeking behaviors, and inhibiting its activity can suppress cue-induced cocaine-seeking behaviors without affecting addiction formation.[16,121] Modulating SNr activity can regulate addiction by influencing striatum activity. HF-DBS of the SNr produces negative changes in cerebral blood volume (CBV) in the striatum, along with positive CBV changes in various brain regions, including basal ganglia nuclei, zona incerta, and VTA. These regions have been implicated in addiction, suggesting that electrical stimulation of the SNr may affect addiction by modulating neural activity in these related brain regions.[103,110]

HF-DBS of the substantia nigra (SNr) was found to be beneficial in the treatment of methamphetamine-induced CPP. It facilitated the extinction of CPP and blocked methamphetamine-primed reinstatement. On the other hand, low-frequency DBS of the SNr had a negative impact on the extinction process. Notably, HF-DBS did not cause any changes in locomotor activity, induce anxiety-like behaviors, or affect the initial formation of methamphetamine-induced CPP.[127]

### *Amygdaloid complex*

The extended amygdala, as described by Heimer and Alheid (1991), is a neuroanatomical entity that integrates brain arousal-stress systems with hedonic processing systems, resulting in the generation of negative emotional states. These negative emotional states contribute to the promotion of negative reinforcement mechanisms associated with the development of addiction.[48] In individuals with cocaine addiction, amygdala volume has been found to be associated with drug craving. These findings suggest that alterations in amygdala volume may contribute to the intensity of drug craving and the risk of relapse in individuals with SUDs.[119]

In animal studies, blocking the extended amygdala in rats prevents the anxiety-inducing effects of self-administered cocaine. It promotes compulsive drug-seeking behavior, leading the animals to continue using cocaine despite negative consequences.[116] Conversely, inhibiting the basolateral amygdala in rats reduces the reinstatement of cocaine-seeking triggered by drug-associated cues, aligning with clinical observations of amygdala activation during cue-induced relapse.[120] Based on this evidence, Langevin has recently suggested DBS of the amygdala as a potential treatment approach for addiction.[67]

## The role of DBS in the treatment of specific drug addictions

### *Alcohol*

DBS has been investigated as a potential treatment for alcohol addiction since the early 2000s. In a 2010 clinical trial by Henderson *et al*., alcohol-preferring P-rats with a stable alcohol intake of about 5–7 g/day over approximately two weeks were studied. The researchers found that DBS of the NAc using specific parameters resulted in a significant reduction in alcohol preference and consumption in these rats. They suggested that similar effects could be expected in patients with alcohol addiction.[49]

In 2009, a small case series examined the use of DBS of the NAc in treating chronic alcoholism. Three male patients participated in the study, while one patient could not receive DBS due to a surgical infection. Patient HM,

aged 36, had a long history of unsuccessful detoxification and other treatments but achieved abstinence after DBS. Patient GM, aged 37, remained abstinent with reduced cravings following DBS. Patient TM, aged 40, experienced a brief relapse but reported a significant reduction in alcohol cravings.[87]

In 2016, a study assessed the long-term outcomes of five patients who received DBS of the NAc for treatment-resistant alcohol addiction. Over up to 8 years, all patients reported a complete absence of alcohol cravings. Two patients remained abstinent, while the other three showed a significant reduction in alcohol consumption. No severe or long-lasting side effects were observed.[88]

These findings indicate that DBS could be a promising treatment option for severe alcohol addiction. However, further research through larger clinical trials is necessary to confirm and better understand the effectiveness of DBS in addressing addiction.

### *Nicotine*

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are two non-invasive brain stimulation (NIBS) techniques being investigated as potential therapy for nicotine addiction. Studies show that nicotine affects the DLPFC by inhibiting alpha-7 NAc receptors in glutamate network synapses. Thus, modulation of the DLPFC by NIBS can result in the release of neurotransmitters and can help smokers to quit smoking. Preliminary empirical evidence has emerged, suggesting that NIBS can be valuable as a potential treatment for nicotine addiction.[123]

A study conducted by Fregni *et al*. on the effect of tDCS on nicotine addicts demonstrated that applying weak currents over the DLPFC resulted in decreased smoking craving and consumption and increased rejection of cigarettes. Besides DLPFC, the front-parietal-temporal association area is being investigated as another potential target of NIBS for modulating smoking-related behavior.[32]

Eichhammer *et al*. demonstrated that HF-rTMS over the DLPFC significantly decreases the smoking rate and craving in smokers, although the effects are neither immediate nor long-lasting. Nonetheless, rTMs could potentially complement cognitive-behavioral therapy as adjunctive treatment during the intermediate nicotine abstinence phase.[27]

These findings suggest that NIBS has promising potential for treating nicotine addiction. However, further studies involving underlying neural mechanisms, brain connectomics, individualized protocols, and cultural differences are needed to comprehend better the effectiveness of NIBS in treating nicotine addiction.[122]

### *Opioids*

Liu *et al*., in a preclinical study, evaluated the role of DBS of rat NAc in relation to morphine reinforcement. Thirty-two adult rats were divided into three groups: a DBS group, a sham DBS group, and a control group. A 130 HZ high HFS was applied to rats in the DBS group and data showed significantly lower preference scores in the DBS group as compared to the other groups.[74]

A study conducted by Stephen *et al*. focused on establishing the effectiveness threshold at which a hypothetical DBS treatment would yield comparable QoL improvements and cost-effectiveness as methadone maintenance treatment (MMT) for individuals with heroin dependence. This study demonstrated that a trial of DBS is more cost-effective as compared to untreated or relapsed heroin dependence but still more expensive than MMT. For a theoretical course of DBS to be on par with MMT, a success rate of 36.5% would be required. However, to achieve cost-effectiveness, a higher success rate of 49% is estimated. Therefore, a success rate of 49% would make DBS a similarly cost-effective treatment for opiate addiction as MMT.[105]

Another study by Kuhn *et al*. demonstrated a significant reduction in heroin cravings of two drug-resistant persons and resulted in heroin withdrawal.[66] However, further research through larger clinical trials is necessary to confirm and better understand the effectiveness of DBS in addressing opioid addiction.

### *Methamphetamine*

A case report by Zhang *et al*. showed that patients with methamphetamine addiction who were treated with NAc DBS remained abstinent from methamphetamine one year after surgery, and their social functioning also improved.[126]

Two other case reports by Ge *et al*. of two patients demonstrated that patient A maintained abstinence and experienced positive emotional changes after undergoing DBS of NAc, while patient B did not exhibit significant psychobehavioral improvements. A comparison of preoperative and postoperative MRI showed that the DBS electrode was accurately placed in the NAc of patient A, while the inpatient B electrode was deviated to the side.[39]

These case reports showed that DBS has immense potential as a treatment option for methamphetamine addiction, but further clinical trials are necessary to better understand the effectiveness and possible psychobehavioral side effects.

### *Cocaine*

Gonzales-Ferreira, in 2016, treated a chronic cocaine-addicted patient by placing DBS electrodes in the medial

NAc juxtaposed with the BNST. The 36-year-old patient was a multi-drug addict during his teenage years. However, by the age of 20, his addiction was limited to heroin and cocaine. He achieved remission from heroin addiction at the age of 31 due to methadone treatment, but his cocaine addiction worsened. All the inclusion criteria for cocaine dependence (DSM-IV-TR criteria, 304.20) were positive in this patient, and his dependence was refractory and severe clinical global impression (CGI = 6). Six months after treatment, there was a significant decrease in cocaine dependence and consumption. This was demonstrated by the study results, which showed that the percentage of weeks free of consumption increased from 40.9% to 80.5%, the percentage of negative urinalysis results increased from 12.5% to 66.7%, and craving visual analog scale decreased from 3.4% to 1%.[41]

This was the first refractory cocaine-dependent patient treated by DBS and the study showed that DBS may indeed be a potential treatment option for cocaine addiction. However, further studies and control trials are needed to better understand its efficacy and viability as a treatment for cocaine addiction.

## Target localization for DBS

Recent neuroimaging studies have shown that people who battle with addiction and substance use have significant alterations in their brain activity and structure. The neural networks that connect certain gray matter brain regions that are involved in reward, memory, motivation, executive function, emotion, and metacognition are affected by these changes. However, it is still challenging to anticipate, diagnose, and track addiction using brain imaging, in part due to the paucity of studies on white matter, which is crucial for cortical communication.[60]

### *Diffuse tensor magnetic resonance imaging (DTI)*

DTI has developed as a non-invasive DTI has developed as a non-invasive method for examining white matter and its connection to substance abuse in the human brain. White matter is assessed using DTI at both the macrostructural (e.g., volume and tracts) and microstructural levels. Microstructural abnormalities such as Wallerian degeneration or altered neuronal membrane permeability are detected using metrics like fractional anisotropy (FA). The biology of addiction is increasingly being studied using the magnetic resonance (MR) imaging technique known as diffusion tensor imaging (DTI). White matter's macrostructure, microstructure, and connectivity may all be inferred from DTI data.[104] By calculating mean diffusivity, radial diffusivity, and axial diffusivity (AD), DTI can also detect demyelination, axonal degeneration, and maturation. These DTI metrics improve our understanding of substance-related white matter alterations, enhancing our understanding of the neurological substrate of addiction.[53] The relationship between substance abuse and white matter microstructure varies across different substances:

### *Alcohol*

Teenagers who binge drink have lower FA than controls, according to study.[84] In addition, FA makes a distinction between high- and low-severity heavy drinkers among adolescents, with lower FA being associated with higher AUD scores.[108] Lower FA has frequently been seen in alcohol abusers.[102] Alcohol abuse has been observed to positively correlate with AD measures, suggesting that alcohol use is associated with higher AD in alcohol-abusing people.[109]

However, a more nuanced relationship between drinking and the microstructure of the white matter has recently come to light. In a well-powered study ($n$ = 377), an inverted-U relationship was found, showing that light and moderate alcohol use was connected to increased FA but that heavy consumption (28 drinks or more over 2 weeks) was related to substantial decreases in FA.[82] These results highlight the need to consider alcohol use as well as age when examining the relationship between alcohol and alterations in the white matter.

### *Cannabis*

Studies have revealed that regular cannabis users tend to have decreased FA, a metric of the integrity of the white matter's microstructure.[2] Regular cannabis usage has also been linked to reduced FA in particular brain areas.[52] It is not fully clear how cannabis usage affects the white matter microstructure, though. The idea of a quadratic connection was first proposed in research by Filbey *et al*., which suggested that FA may initially rise with cannabis use but fall with continued and heavy usage.[30] The intricacy of cannabis' effect on white matter architecture is highlighted by this data, which suggests that the quantity and frequency of usage may be important considerations.

### *Cocaine*

According to certain research, cocaine users exhibit decreased FA in particular brain areas, which may be a sign of changes to the white matter's architecture.[3] These results imply that individuals with a history of cocaine use may experience changes in the coherence and integrity of their white matter tracts.

The normal process of brain development may result in reduced gains in white matter volume in cocaine-dependent people, according to a study.[4] This finding raises the possibility that cocaine use alters the brain's normal white

matter formation and growth, which might have an impact on cognitive and behavioral performance.

### *Nicotine*

Numerous researches have looked at the effects of chronic nicotine use on the architecture of white matter, with varying degrees of success. Chronic nicotine use has been linked in certain studies to both lower and greater FA levels.[72] This variation in FA results can be caused by variations in the research populations and methodology used.

In addition, studies looking at how frequent nicotine use affects white matter have yielded contradictory results. Regular nicotine use has been associated with decreased FA levels in some studies,[51] whereas regular nicotine users have been shown to have greater FA. These differences highlight the intricate link between nicotine exposure and the architecture of the white matter.

### *Opiates*

Numerous investigations have consistently shown a strong correlation between opiate usage and changes in white matter microstructure.[8,35] These studies consistently show reduced FA, indicative of impaired white matter integrity, in those with a history of opiate misuse. Another interesting discovery is the lower AD seen in opiate users, which denotes less directed water diffusion along the main axonal routes.[8] This pattern of altered AD suggests that opiate users may have axonal anomalies or disruptions.

## Focused ultrasound (FUS) therapy

A novel tool for neuromodulation that appears to have promising effects in SUDs is FUS. In this non-invasive technique, specific subcortical brain structures could be targeted, and relevant neural circuits could be modulated.[9,23] FUS has been shown to be capable of temporarily disrupting the blood-brain barrier (BBB) and allowing for the delivery of neuroactive substances to a specific brain region. The application of this method has been tested in animal rat models, demonstrating a potential for similar effects in human subjects. As opposed to direct current stimulation, which is an invasive intervention that involves inserting wires into the brain matter, FUS offers a rather non-invasive alternative.[81]

Two major modalities of FUS exist, including low-intensity focused ultrasound (LIFU) and high-intensity focused ultrasound (HIFU). LIFU appears to be an emerging tool for non-invasive neuromodulation as it creates reversible lesions with no associated functional deficits or histopathologic changes, unlike the permanent lesions created by HIFU.[17] It is delivered in pulse mode with a low intensity. It is delivered in pulse mode with a low intensity, hence, minimizing tissue overheating and damage. With its highly accurate spatial resolution, it can specifically target deep subcortical structures of the brain.[98]

A study published in 2018 attempted to replicate the application of MR-guided FUS on five patients with early to moderate Alzheimer's disease following the demonstration of reduced amyloid deposition in disease animal models. Combined with the injection of microbubbles, FUS could safely disrupt the BBB without causing any clinically significant worsening in cognitive scores. The study prompted the need for continued investigation of FUS as a potential novel therapeutic option or medication delivery mechanism for patients with Alzheimer's disease.[73]

Another study published in 2022 by Wang *et al*. utilized MR-guided LIFU in combination with glial cell-derived neurotrophic factor (GDNF) microbubbles to cause a local opening in the BBB in the VTA brain region of rat animal models. Previous studies have shown that GDNF is considered a promising treatment option for drug addiction despite being limited by its low BBB permeability. In this study, it was shown that LIFU and microbubbles injection significantly increased the concentration of GDNF in the VTA region, destroyed morphine-induced CPP, and reduced the withdrawal symptoms of morphine addiction evaluated by behavioral observation. Moreover, a significant reversal was seen in the usually up-regulated expression of tyrosine hydroxylase and increased dopamine and norepinephrine content induced by morphine. This study further demonstrated the promising role of FUS therapy in the treatment of addiction disorders, including morphine addiction.[115]

In a recent study conducted by Mahoney *et al*. in September 2023, two doses of LIFU (60 and 90 W) targeting the bilateral NAc were evaluated in four patients with SUD. The results demonstrated that both doses were safe and well-tolerated with no associated MRI changes at the time of the procedure, 24 h after, and at 1-week postprocedure images. The two patients who received the 90 W dose showed reduced cravings for their primary substance of choice relative to before receiving LIFU. This reduction persisted during the 90-day post-LIFU follow-up evaluation. The study demonstrated that LIFU targeting the NAc adequately reduced substance craving with potential long-term favorable outcomes. It was also safe and well-tolerated. However, further evaluation of its utility and potential long-term outcomes, including relapse, was recommended.[76]

By utilizing the magnitude of neuromodulation that could be achieved with LIFU, its exceptional spatial resolution, its ability to target deep subcortical structures such as the NAc, and its capacity to reversibly and safely relieve the continuity of the BBB, it could be a viable treatment option for SUD through one or more of those mechanisms.[77]

### Ethical and legal considerations

DBS is being investigated as a potential treatment for several psychiatric and addiction disorders. However, ethical and legal considerations related to DBS treatment are yet to be explored by medicolegal healthcare workers.

Patients with psychiatric and substance abuse disorders might have their judgment impaired and might not be able to give informed consent. In some cases, due to the severity of the disease, these patients may be more willing to take risks associated with invasive DBS procedures, especially after the failure of conservative treatments.[75] Informed consent should be autonomous and free of coercion. However, some experts have the opinion that people with an addiction have limited capacity to be autonomous due to their addiction, which may coerce their behavior.[42] Patients who are coerced to have DBS treatment may not be able to better understand the risks and side effects related to this modality of treatment.

Some studies have shown that DBS treatment for drug abuse or psychiatric conditions also results in enhanced mood, raising the concern of DBS abuse by normal people for the mere purpose of mood enhancement. Likewise, people with normal BMI may be lured to DBS for weight loss after seeing the effects of DBS as a treatment for obesity. Some authors argue that the domain of DBS should be restricted to treatment purposes only and should not be extended to enhancement.[107]

DBS targets for treating addiction are the hypothalamus and NAc, which also drive mood, behavioral, and personality phenomena. Some studies have shown a loss of sexual drive and unusual personality changes after undergoing DBS for addiction. In addition to these serious psychological changes, DBS can also cause some undesirable physical changes, such as changes in blood pressure and heart rate. The psychological and personality changes remain a concern and present a limitation for using DBS to treat addiction.[25] Moreover, some studies have shown that modulating the activity of NAc can affect innate reward and pleasure pathways. This may be useful in treating pleasure and reward associated with addiction but may also affect other innate reward motivation behaviors, such as sexual pleasure.[43]

Some researchers have put forward deeper ethical and philosophical questions regarding DBS treatment and proposed that placing stimulating electrodes can lead to cognitive, behavioral, and emotional disturbances. Some researchers have proposed that patients may accredit their behavior to the electrodes placed and not to themselves, thus putting their autonomy in grave danger.[64]

Patient selection for DBS treatment in case of addiction is also a question of concern. In the case of psychiatric patients, DBS is reserved for severe and treatment-resistant cases. Such a scale of severity must be defined in the case of addiction. Other researchers believe that patients in moderate stages rather than severe should be enrolled in small clinical trials for better results, as neural circuits in such diseases may deteriorate over time.[97]

Another ethical issue related to DBS treatment is compensation and follow-up. Some researchers suggested that despite funding of clinical trials, participants are not offered compensation in case of recurrence and relapse. Moreover, while follow-up is essential for better estimating patient outcomes, studies have shown that follow-up and access to care are limited in addiction patients, often due to poor socioeconomic factors.[44]

Conference consensus statements on DBS shed light on the significance of a multidisciplinary team approach consisting of experts from different fields, including psychiatry, neurology, neurosurgery, and surgery, to collaborate in assessing and treating patients. This can significantly address and reduce the ethical considerations of this treatment. DBS should be carried out at highly equipped and experienced centers, and an ethical committee should oversee the interventions for further improvement of patient outcomes.

## CONCLUSION

DBS is a promising method for treating addiction disorders. Specific brain regions, such as the NAc, mPFC, insula cortex, OFC, LHb, and substantia nigra (SNr), play crucial roles in addiction's neurocircuitry, making them ideal targets for DBS interventions.

DBS shows promise in treating addiction to various drugs, including alcohol, nicotine, opioids, methamphetamine, and cocaine, by focusing on the reward system involving the OFC, NAc, and VTA. However, the effects of DBS heavily rely on the stimulated brain structure and its connections. Ethical and legal concerns are vital when using DBS for addiction treatment, especially when dealing with patients with impaired judgment who may struggle to provide informed consent. Potential abuse for mood enhancement or weight loss purposes is another concern. To address ethical concerns and enhance patient outcomes, a multidisciplinary team approach involving compensation, follow-up, and careful patient selection is recommended.

DBS shows significant promise for treating addiction disorders and has the potential to transform our understanding and treatment of addiction. However, further research and ethical considerations are necessary to ensure its safe and responsible application in addiction treatment.

### Author contributions

JA carried out the conception and design and participated in the final approval of the version to be published. MNMM participated in the acquisition of data or analysis and

interpretation of data. HAS participated in the acquisition of data or analysis and interpretation of data. JS participated in the acquisition of data or analysis and interpretation of data. MAL, MHZ, and MHH drafted the manuscript and participated in the sequence alignment. MA and MM participated in the study design. DM and MA did manuscript editing and review. All authors read and approved the final manuscript.

### Ethical approval

Not applicable.

### Declaration of patient consent

Patient's consent was not required as there are no patients in this study.

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### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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