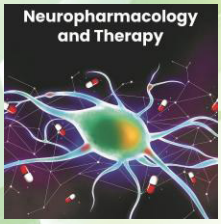

Neuropharmacology and Therapy, 2024;1(1):18-30
DOI: 10.15212/npt-2024-0003

REVIEW ARTICLE

Deep Brain Stimulation for Substance Use Disorder: Current Status

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Received: June 7 2024; Revised: July 3 2024; Accepted: July 26 2024; Published Online: August 21 2024

Abstract

Substance use disorders (SUDs) precipitate a loss of control over substance use, thus compromising daily functioning and social behavior. Current addiction treatment relies primarily on medication. Relapses may occur after extended periods of abstinence upon exposure to substance-associated stimuli or environments. More must be done to prevent relapsing. Deep brain stimulation (DBS) is used to treat a spectrum of medical conditions through insertion of electrodes into specific brain regions and administration of impulses that regulate brain activity. Considerable evidence suggests that DBS may be helpful in treating addiction, but the targets and treatment parameters remain ambiguous. This review describes research progress and the associated targets of DBS in managing alcohol, cocaine, opioid, and nicotine addiction, to lay groundwork for future research. It additionally examines the risks and safety aspects of DBS in SUD treatment, to optimize DBS for enhanced clinical efficacy in managing addictive disorders.

Keywords: Deep brain stimulation, Nucleus accumbens, Substance use disorder, Neuromodulation

1. INTRODUCTION

Substance use disorders (SUDs), mental illnesses caused by the use of psychoactive substances, are characterized as chronic with recurrent phases. SUD manifests as a cycle comprising three stages: intoxication, withdrawal, and craving and relapse [1–3]. Despite being cognizant of the perils of addiction, individuals may struggle to control their behavior. Substance use severely decreases quality of life and increases the risk of contracting infectious diseases, because of compromised safety during drug use [4,5]. According to the World Drug Report, in 2023 [6], more than 39.5 million individuals were estimated to have drug use disorders. Research has indicated infection rates of 19.22% for HIV, 44.82% for hepatitis C virus, and 19.22% for hepatitis B virus among injection drug users [7]. The current mainstay therapy for SUD is psychological and adjunctive pharmacological treatment, but its effectiveness is limited [8]. Development of new therapeutic strategies is urgently needed to improve outcomes.

Deep brain stimulation (DBS) is a surgical technique using electrodes implanted in the brain to precisely target specific regions (Fig 1) such as the subthalamic nucleus (STN) and nucleus accumbens (NAc); the electrodes are connected to a battery-operated pulse generator implanted in the chest [9,10]. DBS has found extensive applications in addressing neurological disorders such as Parkinson's disease [11], tremors [12], epilepsy [13], and dystonia [14]. With the development of DBS, the potential for treatment of mental illnesses such as depression [15], addiction [16],

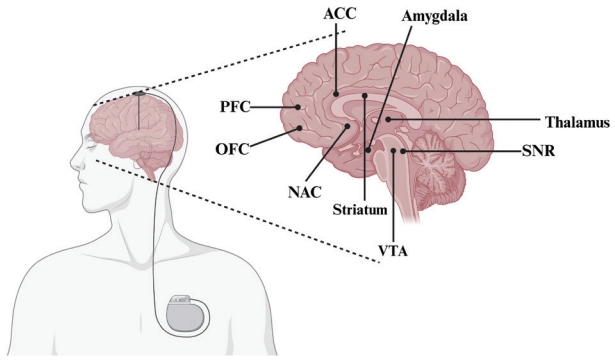

Figure 1 | DBS installation diagram. Abbreviations: ACC, anterior cingulate cortex; PFC, prefrontal cortex; OFC, orbitofrontal cortex; NAC, nucleus accumbens; VTA, ventral tegmental area; SNR, substantial nigra pars reticulate.

Alzheimer's disorder [17], and schizophrenia [18] has been described. Whereas SUD relapse is difficult to prevent with traditional treatments, DBS has provided a new means of preventing relapse in people with drug addiction after withdrawal [19].

DBS has shown promising efficacy in addiction treatment by targeting crucial brain regions such as the NAc [20,21], STN [22,23], and amygdala [24]. This approach has been investigated in both preclinical and clinical studies [25–28], thus positioning DBS as a promising therapeutic intervention for SUD.

The main current hypotheses regarding the mechanism of DBS include direct neural inhibition (wherein DBS suppresses neural activity), direct neural activation (wherein DBS directly excites neural activity), information lesion (wherein electrical stimulation obstructs the transmission of information through the targeted brain structure), and synaptic filtering (wherein synapses act as low-pass filters for low-frequency signals) [29–31]. Furthermore, DBS can increase dopamine levels, thus supporting the dopamine replacement hypothesis [32]. DBS affects the glutamate system as well as the dopamine system [27]. Glutamate levels increase in mice under DBS stimulation, as determined by solid-phase microextraction technology [33]. Therefore, DBS is a treatment strategy aimed at rectifying abnormal neural activity and restoring normal physiological function. Given the multifaceted nature of addiction, involving various brain regions and neurotransmitter systems, the potential efficacy of DBS in addiction treatment is also likely to be multifaceted. An in-depth investigation of the complicated interplay between DBS and the intricate architecture of neural networks is imperative for advancing understanding of its therapeutic potential.

In this review, we delineate the mechanisms through which DBS can treat addiction and the limitations of current therapies; elucidate the viability of DBS techniques in addiction treatment; provide an overview of research advancements in DBS for alcohol, cocaine, opioid, methamphetamine, and nicotine addiction; and explore potential risks and optimization strategies that DBS may encounter in the future. The aim of this review is to guide the direction of DBS in SUD treatment, including deepening understanding of addiction mechanisms, and establishing a systematic and reliable theoretical framework. Finally, we highlight several limitations of the application of DBS in SUD and propose avenues for future improvement.

1.1. Alcohol

DBS treatment for neuropsychiatric disorders has shown unexpected effects on decreasing alcohol consumption [25]. This finding has opened new opportunities for research and potential treatments for people struggling with alcohol addiction. The primary focus of research on DBS for the treatment of alcohol addiction is the NAc. Both animal experiments and clinical trials have shown that DBS targeting the NAc decreases alcohol consumption in mice [34,35]. Furthermore, a direct correlation has been observed between treatment efficacy and the intensity of alcohol addiction [35]. Notably, unilateral DBS is also effective in treating alcohol addiction [36].

The activation of the secondary cingulate cortex during DBS treatment suggests emotional involvement in behavior control [37]. Studies have indicated that DBS therapy affects the anterior midcingulate cortex through ERN (an event-related potential associated with mistakes) [38]. Additionally, NAc DBS has been found to reverse the activation of the secondary cingulate cortex and temporal pole. Possible mechanisms underlying this process include DBS decreasing NAc metabolism; functional down-regulation disrupting the connection between visually associated cortices; and DBS interfering with the striatal response, thus leading to a decrease in dopamine release [39]. Furthermore, alcohol addiction lowers baseline dopamine levels and leads to anhedonia [40]. The NAc may increase dopamine release, thus supporting alcohol dependence [41]. However, direct injection of dopamine into the NAc has been demonstrated to be ineffective in treating alcohol addiction [36]; therefore, alcohol addiction is determined by a combination of factors. In summary, DBS has emerged as a potential therapeutic modality for the treatment of alcohol addiction, by decreasing metabolic activity in the NAc. This neurostimulator approach is associated with enhanced executive function, suppressed alcohol cue reactivity, and dopamine homeostasis restoration.

1.2. Cocaine

The NAc and STN are the main targets of current research on DBS in cocaine addiction. The NAc consists of two areas: the shell and the core. DBS to the shell rather than the core region attenuates cocaine-induced drug seeking without affecting food seeking [42]. Although many studies have shown that DBS decreases cocaine-seeking behavior, a case report has suggested that STN-DBS does not decrease cocaine craving and use, even under previously well-tolerated stimulation parameters. Additionally, this treatment results in hypomania after several weeks of cocaine use [43]. DBS effectively decreases cocaine craving

behavior and alleviates negative emotions during withdrawal. However, continued cocaine use during treatment may worsen patient condition [20].

The mechanisms of DBS in the treatment of cocaine dependence have not been clearly established. DBS to the NAc shell inhibits the neural activity of neurons projecting to the NAc and/or deactivates neurons projecting to the prefrontal cortex, thus attenuating cocaine-seeking behavior [44]. Whereas some studies have suggested that targeting the nucleus or channel fiber inactivation may be effective, microinjection of GABA agonists or sodium channel blockers into the NAc shell does not produce the expected effects of DBS [42]. Moreover, acute cocaine can damage the responsiveness of the medial prefrontal cortex to stimulation of the VTA [45]. DBS applied to the NAc can have counteractive effects on the intermediate neurons located in the prefrontal cortex, thereby inhibiting the activity of glutamate projection neurons, which are responsible for transmitting signals from the prefrontal cortex to the NAc [46]. This normalization of activity within the cortex-NAc pathway has been found to decrease cocaine-seeking behavior [42]. After DBS treatment, cocaine-related SUD shows increased glucose metabolism in the frontal lobe region, as visualized through FDG-PET neuroimaging [47]. The frontal lobe region, associated with behavioral control, may be improved by DBS through normalizing activity in the cortex-NAc pathway, in a potential therapeutic mechanism of DBS. Many studies have shown that behavioral changes in addiction are caused by drug-induced synaptic plasticity in the mesolimbic dopamine system [48,49]. Cocaine self-administration can increase levels of the glutamate receptor subunits NR1, GluR1, and the scaffolding protein PSD95, but does not affect GABAAβ protein levels in the VTA. After DBS treatment, these subunits return to baseline levels [50]. DBS to the NAc or medial prefrontal cortex increases GluR1 levels in the central amygdala or cingulate cortex, respectively [20]. High-frequency DBS-like optogenetic stimulation of d2dr neurons has been shown to decrease cocaine-seeking behavior in male rats [46]. However, whereas high-frequency DBS is ineffective, low-frequency DBS has been shown to reverse behavioral sensitization [27]. Understanding the differential outcomes of high-frequency stimulation (HFS) and low-frequency stimulation (LFS) on cocaine-seeking behaviors and neural activity across various neuron types will be essential for elucidating the mechanisms underlying DBS's ability to diminish drug-seeking. STN-targeted DBS diminishes motivation for cocaine primarily by decreasing the reinforcing effects of the drug while increasing motivation for food. One potential mechanism through which STN DBS decreases the cocaine response is through changes in midbrain dopamine neuronal activity [23].

LFS (12 Hz) combined with optogenetic techniques effectively eliminates cocaine-induced behavioral sensitization by reversing the enhancement of excitatory synaptic transmission mediated by D1R spiny neurons [27]. This treatment might potentially be effective for cocaine addiction. Abnormal low-frequency oscillations of the STN predict cocaine resistance in mice [22]. In addition, the lateral pallidum and the absence of vertebral bands may be potential targets for DBS in the treatment of cocaine addiction [51,52].

DBS has emerged as a valid therapeutic modality for cocaine addiction, albeit one whose multifaceted mechanisms of action require a comprehensive theoretical scaffold. Combining innovative techniques with DBS may provide new avenues for elucidating its therapeutic mechanisms, thus more effectively helping patients overcome cocaine dependence.

1.3. Opioids

Morphine and heroin are the main focus of DBS research on opioid dependence. These medications are frequently prescribed for the management of discomfort but unfortunately may be misused by individuals seeking their intoxicating effects [53]. Bilateral DBS targeting the NAc is the main target in morphine research. Implantation of a homemade DBS device into the NAc in rats first revealed that long-term high-frequency DBS to the NAc decreases morphine's reinforcing effects [54]. Notably, DBS inhibits only drug craving in mice, but has no influence on learning or memory [55]. In addition, DBS prevents the development of morphine reward in mice without decreasing natural reward motivation in multiple brain areas, including the striatum [56], orbitofrontal cortex (OFC) [57], anterior insula [58], and lateral hypothalamic area [59].

Drug reward and reinforcement involve up-regulation of CREB and FosB expression, thus resulting in tolerance to the reinforcing effects of drugs. NAc DBS significantly increases pCREB expression in rats after self-administration and subsequently leads to changes in drug-seeking behavior [60], probably through regulating the entire neural network, rather than stimulating or inhibiting specific nuclei. Moreover, low frequency DBS applied to the ventral striatum increases the expression of c-fos in the central amygdala [24]. Of note, the relationship between specific behaviors and cell types is beginning to be explored with a combination of optogenetics and DBS. Optogenetic stimulation of the same GABAergic pathway from the lateral hypothalamic area through VTA-induced feeding at 5 Hz or reward at 40 Hz has demonstrated that the same pathway displays completely different behavioral effects [61]. Subtle frequency is crucial for achieving the effects of optogenetic stimulation. Both frequencies were not high yet had opposite effects. Diverse neural pathways control different symptoms of opioid withdrawal. The BLA-NAc D1 medium spiny neuron (MSN) pathway regulates morphine withdrawal-induced depression, whereas the paraventricular nucleus of the thalamus-NAc D2 MSN pathway controls acute withdrawal symptoms caused by naloxone. A new therapy using brain stimulation, KOR antagonism, and D1 receptor activation has been found to alleviate depression and prevents morphine relapse in animals [53].

DBS effectively treats opioid addiction by modulating reward and reinforcement pathways, thereby decreasing drug-seeking. The neural pathways and cell subtypes that govern opioid addiction provide valuable insights into the mechanism of DBS.

1.4. Methylamphetamines

At present, the NAc is the main target of DBS in the treatment of methamphetamine dependence. Studies in mice have shown that administering DBS outside the drug-related environment aids in decreasing drug use and methamphetamine-seeking behavior. This discovery has the potential to lead to better treatment options for addiction in humans [62]. A patient with SUD with methamphetamine dependence who received 1 year of DBS treatment targeting the NAc and ventral capsule reported a disappearance of drug-taking behavior [63].

Methamphetamine is a highly addictive psychotropic drug associated with the dopamine system [64]. This drug increases synaptic dopamine levels by blocking dopamine reuptake and enhancing reverse transport of the dopamine transporter (DAT) [63], in agreement with reports of increasing cognitive and motor deficits similar to those in Parkinson's disease among long-term methamphetamine users [65]. No proven psychological, social, or pharmacological treatments are available for methamphetamine dependence [66]. DBS may be a promising treatment for methamphetamine addiction.

Clinical evidence has demonstrated that DBS increases levels of dopamine and related enzymes in the central nervous system; this response may underlie its therapeutic effects in treating Parkinson's disease and obsessive-compulsive disorder [62]. DBS targeting the NAc in patients with obsessive-compulsive disorder increases striatal dopamine release, and DBS treatment for methamphetamine addiction increases striatal DAT levels [63]. In treating addiction through DBS, treatment frequency and timing play crucial roles in determining therapeutic effectiveness. Recent studies have shown that both asynchronous and synchronous high-frequency DBS effectively prevent methamphetamine-induced reinstatement, whereas only low-frequency synchronous DBS prevents the reinstatement of methamphetamine-seeking behavior [67]. Notably, the potential therapeutic target of stimulant DBS continues to be actively explored. High-frequency DBS to the substantia nigra reticulata promotes the extinction and prevents reinstatement of methamphetamine-induced conditioned place preference [68]. The acquisition of methamphetamine-seeking behavior can also be prevented by OFC DBS (high or low frequency) [28].

Currently, research on DBS in methamphetamine focuses primarily on the dopamine system, and is aimed at understanding treatment effects on dopamine release and transporter levels. Additional insight into these mechanisms will be essential to improve treatment strategies in the future.

1.5. Nicotine

A case report has described a 47-year-old woman who received DBS to the NAc for obsessive-compulsive disorder and unexpectedly stopped smoking [69]. This report suggests that DBS to the NAc might be a potential treatment for nicotine dependence. In animal studies, inactivation of the insular cortex with a drug mixture of baclofen/muscimol blocks the recovery of cue-evoked nicotine-seeking and nicotine priming without affecting food-seeking relapse [69], thereby indicating that the insular cortex is a potential target for the treatment of nicotine dependence.

Nicotine, the main psychoactive component of tobacco smoke, binds acetylcholine receptors and causes the release of dopamine [70]. Chronic nicotine exposure leads to neural adaptation, by resulting in tobacco dependence characterized by drug seeking, tolerance, withdrawal, and craving [71]. DBS to the insular cortex significantly decreases nicotine intake and cue- and priming-induced nicotine-seeking behavior [72]. The inactivation of insular neurons in brain slices containing the insular cortex suggests that the mechanism of DBS in the insular cortex may be associated with neuronal inactivation.

To date, limited research has examined use of DBS for treating nicotine addiction. Because nicotine addiction is less harmful than other drug addictions, and because of the invasive nature of DBS, patients might hesitate to pursue this treatment. Existing studies have focused primarily on the NAc to achieve withdrawal goals by inducing neuronal inactivation. Research on potential DBS targets, exemplified by insulae, is currently underway.

2. MECHANISM OF DBS

In most experimental results and data, DBS has been observed to specifically mitigate addiction without impinging on other rewarding behaviors. Table 1 provides a comprehensive summary of the stimulation parameters, targets, results, follow-up durations, and observed adverse effects in humans. Table S1, in contrast, summarizes the species, targets, stimulation parameters, paradigms, and results observed in animal models. Importantly, the mechanisms underlying DBS in the treatment of addiction remain incompletely understood. The following section briefly introduces several potential mechanisms of DBS in addiction.

2.1. Local inhibition

DBS may inhibit neural tissue in motor and psychiatric disorders through depolarization blockade, synaptic inhibition, and synaptic depression [77,78]. Sustained high-frequency DBS deactivates neurons in the targeted brain regions [58]. For example, high-frequency DBS suppresses activity in the STN [22,79], and the therapeutic effects of heroin addiction may be due to sustained inhibition of the substantia nigra pars reticulata and nucleus accumbens shell [56]. Studies have shown that DBS consistently uses a γ-aminobutyric acid agonist mixture to

Table 1 | Human DBS trials for SUD.

References	Substance	Country	Numbers of participants	Target(s)	Stimulation parameters	Result	Follow-up time	Adverse effects
Kuhn et al. [25]	Alcohol	Germany	1	Nucleus accumbens	130 Hz, 90 μs, 3 V	No change in primary disease but significant improvements in alcohol dependence were observed.	12 months	Treatment was not accompanied by adverse reactions.
Kuhn et al. [38]	Alcohol	Germany	1	Nucleus accumbens	130 Hz, 120 μs, 5.5 V	DBS of the NAc led to a significant decrease in drug consumption and modulated associated deficits in cognitive control.	1 year	Adverse effects were not reported.
Heldmann M et al. [37]	Alcohol	Germany	1	NAc, BSTM and the VP	130 Hz, 90 μs, 3.5 V	DBS to the NAc improved behavioral control in decision-making processes.	18 months	The patient experienced a short period of hypomania.
Davidson et al. [39]	Alcohol	Canada	6	Nucleus accumbens	130 Hz, 90 μs	All six patients experienced marked decreases in alcohol craving and alcohol-related compulsive behaviors.	12 months	Patient 3 developed an infection 12 months postoperatively. Non-serious adverse events included transient hypomania, scalp pruritis, fatigue, and headaches.
Bach et al. [35]	Alcohol	Germany	12	Nucleus accumbens	130 Hz, 90 μs, 3.5 V	DBS positively affected important secondary outcomes, including the proportion of abstinent days, heavy drinking days, alcohol craving, and anhedonia.	18 months	Most adverse events were mild to moderate.
Rezai et al. [47]	Cocaine	America	4	NAc/ventral capsule (VC)	125–145 Hz, 90–300 μs, 3.0–4.5 ma	The findings suggest the safety and feasibility of NAc/VC DBS, with a potential for decreasing substance use, craving, and emotional symptoms in treatment-refractory OUD.	52 weeks	No SAEs or any surgical or DBS-related complications were observed in any participant.
Vorspan et al. [43]	Cocaine	France	1	Subthalamic nucleus	130 Hz, 60 μs, 3 V	Over the treatment period, the patient decreased his crack use and finally achieved abstinence. However, this outcome was not correlated with DBS-ON periods.	30 months	Mild hypomania and dyskinesia/ akathisia were observed.
Valencia-Alfonso et al. [73]	Heroin	Netherlands	1	Nucleus accumbens	180 Hz, 90 μs, 3.5 V	Patient is currently clean for more than 6 months with the exception of a 14-day relapse.	6 months	Adverse effects were not reported.
Chen et al. [74]	Heroin	China	8	Nucleus accumbens, the anterior limb of the internal capsule	NAc: 145 Hz, 180–240 μs, 2.2–2.8 V; ALIC: 185 Hz, 150–240 μs, 1.5–2.4 V	Simultaneous DBS of the NAc and ALIC may prevent long-term heroin relapse after detoxification in certain patients.	24 months	Stimulation-related adverse events were few and reversible.

Table 1 | (continued)

References	Substance	Country	Numbers of participants	Target(s)	Stimulation parameters	Result	Follow-up time	Adverse effects
Zhang et al. [63]	Methamphetamine	China	1	Nucleus accumbens and ventral capsule	130 Hz, 90 μs, 2.5 V	Extinction of drug-taking behavior along with a marked increase in striatal DAT levels was observed in a patient with MUD after 1 year of DBS.	1 year	No significant adverse effects or complications were observed.
Zhang et al. [75]	Heroin	China	1	Ventral capsule/ ventral striatum	130 Hz, 90 μs, 3.5 V	Comorbidity with ASPD requires special attention when DBS treatment is considered for patients with addictive disorders.	3 months	This is the first reported death caused by opioid overdose after VC/VS DBS.
Mantione et al. [76]	Nicotine	Netherlands	1	Nucleus accumbens	185 Hz, 90 ms, 3.5 V	The patient was treated with DBS for obsessive-compulsive disorder. Unintended, effortless, and simultaneous smoking cessation and weight loss were observed.	2 years	Adverse effects were not reported.

inactivate the granular insular cortex [69]. Whether the therapeutic effect of DBS is due to the stimulation or the damage caused to brain tissue by the DBS is worthy of consideration. Notably, brain tissue can be damaged by DBS. Clinical trials have indicated little difference in effects between patients receiving DBS and those with surgical injury [35]. Additionally, a case report has indicated that the on/off status of DBS does not significantly influence therapeutic effects [43]. However, some studies have reached different conclusions. For instance, the injection of inhibitors into the NAc has been found not to mimic the effects of DBS [42], possibly because the mechanism of action of DBS differs among anatomical sites. In summary, an important mechanism underlying the effects of DBS is direct inhibition of neuronal activity.

2.2. Reverse activation

DBS influences neural networks beyond local targets via direct or reverse activation [74]. Metabolic changes are observed in the prefrontal cortex in patients with SUD receiving high-frequency STN DBS. These changes have also been found in the lateral habenula nucleus (LHb) [80]. STN DBS results in the reversal of interneuron stimulation in the prefrontal cortex and inhibition of glutamatergic neurons; simultaneously, inhibitory interneuron neurons are activated [81], and pharmacological inactivation of the limbic subcortex by GABA agonists attenuates cocaine-induced reinstatement of drug seeking, thus confirming previous findings [42]. In conclusion, DBS has a wide range of effects on neural networks and can decrease drug-seeking behavior. These effects are achieved through inverse activation of other brain regions. DBS can also activate inhibitory neurons or inhibit excitatory neurons.

2.3. Modulation of reward circuits

Reward circuits, which are responsible for pleasure and satisfaction, are associated with addiction [82]. DBS treatment targeting brain regions in reward circuits, such as the STN, NAc, and lateral hypothalamus, has shown promising results [28]. However, understanding of the mechanisms involved remains incomplete. STN-DBS decreases motivation for cocaine and addiction by enhancing behavioral control through the reward circuitry [83]. This treatment approach is promising in mitigating drug-seeking behavior. The anastomosing lateral part of the paracortical cortex, the temporal pole, the precuneus, and the hippocampus [84,85], which are associated with processing affective information in a behavioral control task, showed a significant increase in activity after DBS activation [37]. The increase in ERN amplitude after NAc DBS in alcohol-dependent patients may imply restoration of behavioral control and decreased alcohol craving [38]. DBS may modulate dopamine in reward circuits, restore normal activity in the NAc, improve decision-making and self-regulation in the prefrontal cortex [47], or integrate rewarding stimuli and their associated cues separately from their expected outcomes, goal-directed behavior is difficult to complete

to form a closed loop [57,59]. Nevertheless, DBS is specific for regulating reward circuits but does not affect natural rewards.

2.4. Disruption of pathological network activity

One possible mechanism through which DBS may decrease drug-seeking behavior is the dissociation of input and output signals, and the interruption of abnormal firing [86]. Decreased metabolism in the NAc and the altered functional connectivity of the visual cortex in patients with alcohol dependence are directly related [39]. Additionally, the disruption of the structure of the stimulated region is similar to the therapeutic effect of DBS [30]. In Parkinson's disease, DBS interrupts abnormal brain activity and restores normal movement [10,87]. It is also consistent with the fact that the mechanisms of action of HFS and LFS are inconsistent [24,57]. In conclusion, HFS may act as a filter blocking abnormal low-frequency pathological discharges.

2.5. Dopamine system

Dopamine is closely associated with SUD [88,89], and all addictive drugs affect dopamine concentrations in the VTA region [49]. Drug addiction has been shown to alter dopaminergic neurotransmission in the NAc and its associated circuits [90]. Increased dopamine levels in the striatum after STN HFS have been observed in DBS treatment of Parkinson's disease [91]. Infusion of dopamine D2/D3 receptor agonists in CEA decreases drug-seeking behavior [92]. Moreover, cocaine inhibits the dopamine transporter, thus increasing extracellular dopamine concentrations; the dopaminergic system is particularly important in mediating the addictive system for cocaine [93]. Cocaine enhances excitatory transmission through ERK signaling in mouse D1 receptor-expressing medium spiny neurons (D1R-MSNs). Selective synaptic potentiation in the D1R-MSNs is a mechanism underlying the core component of addiction [94]. However, recent studies have found that selective mimicry of high-frequency DBS optogenetic stimulation in D2DR-containing vomeronasal NAc neurons (but not D1DR-containing neurons) attenuates cocaine seeking in male rats, thus apparently contradicting former findings [46]. In addition, optogenetic stimulation of the basolateral amygdala (BLA) to the NAc D1 MSN pathway controls depressive-like behavior after morphine withdrawal, and the paraventricular nucleus of the thalamus to NAc D2 MSN pathway controls naloxone-induced acute withdrawal symptoms [53]. The dopamine system is closely associated with the therapeutic efficacy of DBS, and will be a beneficial focus for further revealing the mechanism of DBS.

2.6. Glutamate system

Glutamate is a crucial neurotransmitter with a key roles in the molecular and neurochemical mechanisms underlying addiction to drugs [95]. This neurotransmitter is involved in cue-induced cocaine seeking after withdrawal [96]. Studies have shown that overexpression of the GluA1 subunit of the AMPA receptor in the CeA (central nucleus of the amygdala) decreases morphine place preference. In contrast, downregulation of the GluA1 subunit in the same region has opposite effects [97]. DBS targeting LHb in cocaine-addicted rats restores the glutamatergic elements NR1, GluR1, and PSD95, which are involved in the LTP process, to normal levels [50]. Metabotropic glutamate receptors may participate in cocaine treatment with LHb DBS [27]. Furthermore, NAc-shell DBS increases GluR1 levels in synaptosomes and the cytoplasm, particularly in CeA, and does not affect GluR2 [20]. The specific molecular therapeutic mechanism associated with DBS must be further explored.

In conclusion, the therapeutic mechanism of DBS does not involve a single system; existing research indicates a multi-molecular, multi-systemic network therapeutic system [98]. In addition, the ongoing development of optogenetics will help refine the therapeutic mechanism of DBS toward cellular subpopulations as well as specific neural pathways.

3. LIMITATIONS

DBS research has predominantly involved male participants, and more than 80% of studies have focused exclusively on males. However, a growing body of evidence indicates that the manifestation and progression of addiction may significantly differ between sexes [58]. The current body of research comprises non-randomized, open-label studies, or small case-control series, with some degree of chance [99]. Moreover, safety concerns persist as a major consideration. For instance, a case report has described a patient who died of a heroin overdose due to opioid dependence 3 months after DBS implantation, despite cessation of initial opioid exposure after DBS activation [75]. Most case reports suggest that DBS has favorable effects in the treatment of addiction, but long-term safety remains the most crucial issue in moving DBS from preclinical to clinical trials.

4. DISCUSSION AND FUTURE DIRECTIONS

The repercussions of addiction are extensive, engendering a cascade of health deterioration, a precipitous decline in the overall quality of life, an elevated susceptibility to infectious diseases [100], and a concerning rise in the number of suicides [101]. Although medication forms the cornerstone of addiction treatment, the unsettling reality is that relapse rates persist at alarmingly high levels [102]. New therapeutic interventions are needed to help people overcome addiction. DBS has demonstrated promising therapeutic effects in diseases including Parkinson's disease, and has shown potential in preventing relapse in addiction, as

evidenced by animal studies and case reports of addiction treatment [21,73,76,103,104]. This article presents a comprehensive review of DBS research progress in the context of alcohol, cocaine, opioids, methamphetamines, and nicotine.

In the field of addiction treatment, precise, energy-saving, miniaturized, networked, intelligent, and individualized treatment strategies are becoming increasingly important. The NAc has emerged as the predominant anatomical target for addiction treatment, whereas the efficacy of DBS varies depending on the specific anatomical location of stimulation [44]. The application of DBS at these sites influences both the target nucleus and the surrounding structural tissues, thus underscoring the importance of precise anatomical targeting for therapeutic benefits [28]. Surgical localization relies on imaging techniques such as electrode localization using magnetic resonance imaging. However, the accuracy of these techniques is limited. Future developments may include more precise electrode positioning methods and a greater variety of channel information sources such as EEG, magnetoencephalography, and cerebral hemodynamics to improve therapeutic outcomes. The advancement of DBS technology must focus on addressing issues such as battery life, integrated wireless technology, and minimizing trauma [105]. Directional electrodes and optimization of the stimulation field for IPGs could potentially be used [18]. Combining DBS technology with the Internet and artificial intelligence enables remote monitoring and regulation of treatment effects. Physicians can monitor patient condition and treatment results in real time via smartphones or other devices, and make personalized treatment adjustments.

Tailored treatment plans are essential, given the diverse nature of addiction and the unique characteristics of each patient [106]. Addiction is a complex phenomenon involving a variety of mechanisms, including Pavlovian conditioning, goal-directed theory, and stimulus-response associative learning [107]. Recent research on the mechanisms of addiction has focused on the roles of specific cell types and projections between brain regions in addiction and relapse. For instance, BLA-RPL and BLA-NAc play crucial roles in morphine-induced memory recall [108]. Projection pathways between brain regions regulate various post-withdrawal symptoms [53]. The therapeutic effects of DBS are affected by various parameters, including stimulation type, amplitude, voltage, frequency, and pulse width [58,109]. In studies of DBS, both in clinical trials and in animal models, most experiments have favored electrical stimulation at frequencies of 130 Hz or higher (Table 1 and Table S1). Whether the fewer positive results with lower frequency treatments contribute to this observed discrepancy is worthy of consideration. Studies have generally shown that higher-frequency electrical stimulation is a more effective treatment. Interestingly, cocaine levels are likely to be exacerbated if drug use continues during DBS treatment [20]. In addition, DBS shows varying efficacy in different Parkinson's disease genotypes [110]. Repeated exposure to addictive substances can modify gene expression [60,111]. Chronic use of addictive drugs may also alter the gut microbiota, thereby affecting the central nervous system via the brain-gut axis [112]. Diverse types of DBS are targeted according to the cognitive or neurological characteristics of individual patients or patient subgroups [113]. Pre-testing individuals' genotypes and tailoring treatments on the basis of the results can predict treatment effects and prevent potential harm. The advancement of personalized treatment strategies relies on analyzing brain imaging and using large-scale data resources.

The combination of DBS and new technologies can lead to developments in treatment programs. The use of optogenetic techniques in DBS has refined understanding of the roles of different cell types and neural circuits in the treatment of addiction, and their combination with DBS will open new possibilities for therapeutic protocols [53,92,114]. Acevedo et al. have used a mixed linear model to study the direction of symptom change in patients with obsessive-compulsive disorder [115]. A combination of ERN53, PET, fMRI, and other tests is necessary to accurately assess the therapeutic effects of DBS [39]. DBS is advancing toward adaptive DBS to enhance treatment efficacy, decrease complications, and avoid costs due to frequent battery changes. This innovative approach involves integrating a responsive system into the DBS framework that actively monitors physiological signals and adjusts stimulation parameters in real time to optimize treatment outcomes [116,117]. aDBS requires biomarkers that differ before versus after treatment to monitor the condition [118]. A study has identified 17 proteins differentially expressed in the anterior part of the insulae during morphine exposure and after withdrawal [58]. Moreover, a notable advancement in neural stimulation technology is temporal interference (TI) stimulation, a non-invasive method to modulate neural activity. TI stimulation uses the interference of two HFS fields to generate a low-frequency field in the brain, thus providing a precise and non-invasive method for neural stimulation [119–121].

Neuromodulation techniques are not limited to DBS, but also include non-invasive methods such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and magnetic resonance-guided focused ultrasound (MRgFUS) [122,123]. TMS penetrates the skull with a strong magnetic field generated by transient currents, to induce induced electrical currents that affect metabolic and nerve electrical activity in the brain [124]. MRgFUS uses constant, low-intensity direct current to modulate neuronal activity in the cerebral cortex [123]. MRgFUS combines the precise guidance of magnetic resonance imaging with the energy delivery capabilities of focused ultrasound technology. tDCS uses a continuous, low-intensity direct current to modulate neuronal activity in the cerebral cortex [125]. A meta-analysis has shown that TMS is more effective and localized than tDCS, whereas DBS is more effective and applicable in treating

refractory substance use [19]. Unlike other surgical procedures, long-term DBS does not damage brain tissue, but its invasive nature can lead to infection, seizures, or stroke [126]. In contrast, MRgFUS thermal ablation has fewer overall effects on the brain and does not require surgery [123]. However, it carries a risk of irreversible neurological complications, and its long-term benefits are unclear [127].

In summary, the development of DBS by considering multiple dimensions offers tremendous potential and broad prospects for the further optimization of DBS.

5. ETHICAL CONSIDERATIONS

DBS, approved by the FDA in 2015 for treating Parkinson's disease [128], is an invasive procedure involving the implantation of a neurological device. Risks include bleeding and infection after surgery [129]. Additionally, some individuals may have concerns about their social identity because of the brain implant's resemblance to a robot [130]. Clinical trials are a critical phase of applying DBS as a therapeutic intervention in human patients. Compared with drug trials for DBS are more risky and involve more ethical controversies [131]. For example, setting up a placebo-controlled trial for surgery might deprive patients of the opportunity to receive beneficial treatment, and participants may be required bear the risks associated with surgery rather than benefit from it. Surgical placebos should be permitted if they meet five basic criteria: clinical equipoise; initial evidence indicating significant improvement from the procedure, along with the possibility of a placebo or nocebo effect or bias; minimization of risk and prevention of unnecessary harm; absence of deception; and a research question that is clinically significant and likely to have substantially influence clinical practice [131]. Critically, certain individual case studies may come to light primarily because of their secondary outcomes, and an excessive focus on positive results can result in publication bias [132]. Although positive results may garner attention, negative results are also integral to scientific progress. Numerous ethical controversies surround DBS, and every stage of its development requires careful consideration and discussion.

In addiction therapy, the investigation of DBS must be refined through practical applications to fully elucidate its mechanisms, optimize treatment protocols, and improve clinical outcomes and safety. Finally, adherence to ethical standards is critical for safeguarding patients and promoting progress in medical research.

ACKNOWLEDGMENTS

The authors thank BioRender.com for charting. This work was financially supported by the National Natural Science Foundation of China (grant No. 82101247).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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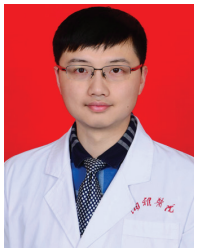

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