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Review

Mechanisms of nucleus accumbens deep brain stimulation in treating mental disorders

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ABSTRACT

Growing evidence supports the effectiveness of deep brain stimulation (DBS) in treating various psychiatric disorders. DBS has the potential to selectively stimulate specific subcortical brain areas thus providing high-frequency electric stimulation of these regions. The nucleus accumbens (NAc), a frequent DBS target, has shown promise in treating psychiatric conditions like depression, obsessive-compulsive disorder, and addiction. In this review, we provide an overview across studies investigating the effects of NAc DBS in humans and animals and discuss potential mechanisms underlying its clinical efficacy. We address the anatomical properties of NAc and discuss, in particular, the frequently reported differential effects of NAc shell and NAc core DBS. Moreover, by outlining the various NAc cell types, transmitter systems (i.e., predominantly GABAergic and dopaminergic systems) and anatomical pathways that have been shown to be relevant for NAc DBS stimulation effects, we aim to further elucidate the neurobiological determinants of NAc DBS efficacy. Finally, since treatment effects of NAc DBS are most probably also related to alterations in NAc connected circuits or networks, we review studies focusing on the investigation of NAc DBS network effects. By examining these various components that are assumed to be of relevance in the context of NAc DBS, this review will hopefully contribute to increasing our knowledge about the mechanisms underlying NAc DBS and optimizing future selection of optimal DBS targets.

1. Introduction

Decades after its initial application in psychiatric disorders [1], deep brain stimulation (DBS) has proven highly effective for the treatment of these disorders. Using a stereotactic neurosurgical procedure, DBS can be implanted into specific subcortical brain areas that non-invasive therapies such as transcranial direct current stimulation (tDCS) cannot reach, to provide programmed electric stimulation. After valuable experience with implanting in subthalamic nucleus (STN) [2], targets of DBS were extended to globus pallidus internus (GPi) [3], nucleus accumbens (NAc), anterior limb of internal capsule (ALIC), subgenual cingulate cortex (SCC) [4] and the medial forebrain bundle (MFB) [5]. These regions mainly belong to the limbic system or the striatum, and are thought to regulate emotion, behavior or cognitive processes [6,7].

The NAc, influenced by dopaminergic inputs from the ventral tegmental area (VTA), acts as a critical 'motivation gateway' connecting emotional and motor control systems [8]. The NAc acts as a functional hub in reward, habit and emotion related behavior. It has been found to be altered in addiction, depression, or obsessive-compulsive disorder (OCD) [9–11], with DBS targeting the NAc proving effective for many treatment-resistant patients suffering from these disorders [12–14]. Given its significant treatment effects across multiple applications, NAc DBS is emerging as a promising treatment option for patients resistant to conventional psychiatric therapies. The aim of this review is to synthesize studies and findings to enhance our understanding of the mechanisms of NAc DBS in mental disorders and to suggest future directions for its clinical application.

2. Nucleus accumbens–cell types, transmitters and anatomical pathways

Over 90% of the local neurons in the Nucleus Accumbens (NAc) are GABAergic medium spiny neurons (MSNs), which play pivotal roles in motor control and addictive behaviors through both direct and

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indirect pathways [15,16]. Direct pathway MSNs are characterized by expressing D1 type dopamine receptor (D1R), dynorphin and substance P. These D1R-MSNs directly target the ventral mesencephalon or, more specifically, the VTA and the substantia nigra (SN), then disinhibit the thalamus and promote motivation and reinforcement learning [17,18]. The indirect pathway first reaches the ventral pallidum (VP) and then innervates the midbrain causing an opposite effect going along with an inhibition of specific behavioral, affective or cognitive processes [19,20]. MSNs of the indirect pathway express D2 type dopamine receptors (D2R), together with enkephalin and adenosine-2 receptors. MSNs are crucial in the pathophysiology of stress-induced depression symptoms and addictive behaviors, with each subtype responding differently to stress and having varied effects. Traditionally, D1R MSNs are associated with mediating reward and reinforcement, whereas D2R MSNs are linked to punishment and aversion [21,22]. The response to addictive substances also varies between these subtypes: D1R MSNs, during withdrawal, show changes in membrane excitability and translatomes, reduced dendritic complexity, and can induce negative emotion [23,24]. In the context of chronic stress, alterations in D1R MSNs not only occur following stress exposure but direct manipulation of these neurons can also trigger stress-induced depression-like outcomes. Suppressing D1R MSNs or activating D2R MSNs in mice leads to a stress-susceptible phenotype characterized by social avoidance, depressive or anxiety-like behaviors, and sleep disturbances [25–28].

However, the theory of two anatomically and functionally distinct pathways has recently been challenged by in vivo studies. Firstly, D1R and D2R are not exclusively distributed among MSNs; however, the exact ratio of their co-location remains unclear [29–31]. Secondly, optogenetic studies revealed a mixed projection pattern of NAc to midbrain. In fact, direct and indirect pathways are not strictly segregated by MSN cell types [32]. Recent findings also demonstrate that the VP receives inputs from both D1R and D2R MSNs [33], and some D2R MSNs can even project directly to the mesencephalon. Moreover, these two subtypes do not functionally segregate during the processing of stress and reward as previously thought. Manipulating different receptors on D1R and D2R MSNs in various regions leads to similar effects [22,34]. Furthermore, advanced techniques like single-cell RNA sequencing and multiplexed error-robust fluorescence in situ hybridization have identified a more complex categorization of MSNs, based on molecular differences, suggesting significant heterogeneity within these cells [35]. This complexity implies that the simple dichotomy of MSN types is insufficient. Although several studies have confirmed distinct functional differences in MSNs with specific molecular expressions [36,37], further research is required to deepen our understanding of the functional organization within NAc MSNs.

The interneurons are cholinergic and GABAergic. Cholinergic interneurons (CINs), including a small amount of midbrain cholinergic projection, are the main provider of acetylcholine in NAc [38]. Albeit scarce, accounting for only approximately 1% of NAc neurons, CINs are the largest neurons in the neostriatum [39]. Muscarinic and nicotinic acetylcholine receptors of MSNs constitute the main target of CINs, while GABAergic interneurons and other CINs also receive cholinergic input. CINs obtain inputs from various brain regions including the frontal cortex and the VTA [40,41], modulate the neurotransmitters including GABA, dopamine and glutamate, and finally regulate the MSN output. Previous animal studies had indicated a vital role of CINS in reward processing, motivation, cognitive function and motor control through those interactions [42–44]. Thus, a malfunction of CIN activities is usually linked with pathological behaviors like addictive and depressive-like behaviors [45,46]. Apart from CINs, there are three types of GABAergic interneurons, including parvalbumin-releasing (PV^+), somatostatin-releasing and calretinin-expressing [47]. NAc GABAergic interneurons receive cortical input and send feedforward inhibitive signals to MSNs [48,49]. Although less studied, these interneurons are also thought to be related to emotion and motivation regulation [50,51].

3. Local neurophysiological stimulation effects

DBS modifies pathological neural activities by delivering high-frequency stimulations (HFS), typically exceeding 100 Hz, to study its effects on targeted or relevant brain areas. Local effects of NAc DBS can be complex. Initially, DBS was believed to simulate lesion surgery since it led to local inhibition in the stimulated region. For instance, in the treatment of Parkinson's disease, DBS targeting STN or GPi lowers the firing rates of nearby neurons [52–54]. This suppression of hyperactivity in the target area effectively alleviates motor symptoms [55]. Several theories have been proposed to explain this inhibitory effect, including depolarization block [56], inactivation of voltage-gated currents [57–59], and activation of inhibitory afferents [60–62].

As previously noted, NAc activation is altered in several mental disorders, and DBS or HFS has the merit of simply producing localized inhibition. Studies in humans and animals have confirmed that NAc DBS is an effective treatment for disorders involving deficiencies in reward, emotion, or motor control systems [11,63–65]. Table 1 summarized DBS or HFS parameters and locations, as well as research diseases and subjects for those studies we included. It is suggested that HFS may facilitate GABA release in the target area [66,67]. NAc HFS has been shown to induce a hypoactivation of NAc local neural activities through $GABA_B$ receptors [62]. Researchers further indicated that NAc HFS mainly affects MSNs and causes a subsequent increase of GABA outflow in NAc [61]. These findings support the inhibition theory as a mechanism of NAc DBS's effectiveness.

Beyond the GABAergic system, NAc DBS significantly influences the dopamine system. NAc DBS can attenuate cocaine-induced increase of tonic dopamine in NAc [68]. DBS has also been found to increase dopamine D2 receptor expression in the NAc shell (NAcS) of diet-induced obesity(DIO) rats and to alleviate binge-eating behavior [69]. DIO rats showed lower extracellular dopamine level at baseline, and DBS increased this reduction while it showed no effect on control rats, suggesting the treatment effect may be the result of restoration of dopamine system. Further research indicates that NAcS DBS elevates dopamine levels in the NAc and increases impulsive behaviors in mice [70]. In mice with emotional deficits, NAc DBS not only improves behavioral performance but also correlates with an upregulation of dopamine D1 and D2 receptors in the NAc and enhanced functional connectivity in the dopaminergic pathway. These effects are further modulated by increased BDNF expression triggered by NAc DBS [71]. Therefore, while there is growing evidence of DBS's impact on the dopaminergic system, the results vary, and the precise mechanisms remain to be fully understood.

Although direct evidence detailing the microscale mechanisms of NAc DBS in improving anxiety disorders is scarce, emerging studies shed light on potential pathways. For instance, optogenetic activation of the presynaptic H3 heteroreceptor on glutamatergic afferent terminals in the NAc has been shown to alleviate anxiety and obsessive-compulsive-like behaviors in rats [72]. This points to a potential role of the glutamate pathway in the anxiolytic effects of NAc DBS. Additionally, previous research has shown that DBS modulates neural activity patterns by regulating the activation of gate channels in receptors within the targeted area [73]. Given these findings, further research is essential to clarify how DBS-induced changes in receptor activity contribute to its therapeutic efficacy in treating anxiety disorders.

The effects of HFS or DBS are primarily attributed to the stimulation of MSNs, which is expected given that MSNs comprise the majority of all neurons in the NAc. MSNs exhibit characteristics akin to a low-pass filter, only responding to stimulation at higher frequencies [74]. Furthermore, the stimulation pattern plays a crucial role; only repeated HFS of MSNs has been shown to be effective, whereas acute activation of the total NAc or specific MSN subtypes does not influence behavioral outcomes [26]. Interestingly, repeated HFS of the entire NAc or D1-

Table 1
Summary of DBS stimulation parameters, disorders, targets, and research subjects of the articles. DIO: diet-induced obese; MDD: major depressive disorder; NAcC: nucleus accumbens core; NAcS: nucleus accumbens shell; OCD: obsessive compulsive disorder; SUD: Substance use disorder.

First author (yr)	Disorder	Research subject	Target	DBS parameter
Lopez-Sosa [84]	OCD	Human	NAcS/NAcC	130 Hz, 3.5 V, 60 μs
Hartmann [86]	OCD	Human	ALIC/NAc	60/135 Hz, 1.5-8.5 V, 90-210 μs
Treu [87]	OCD	Human	NAc	/
Schlaepfer [88]	MDD	Human	NAcS/NAcC	145 Hz, 4 V, 90 μs
Volker Sturm [11]	OCD/Anxiety	Human	Right NAcS	130 Hz, 2-6.5 V, 90 μs (square-wave impulses)
Christiane Grubert [64]	MDD	Human	Bilateral NAcC	/
Figee [101]	OCD	Human	NAcC/ALIC	130/185 Hz, 3.5-6.2 V, 90/120/150 μs
Smolders [102]	OCD	Human	NAc	/
Sesia [91]	/	Rat	NAcC	130 Hz, 200 μA, 100 μs
van Dijk [93]	/	Rat	NAcC	120 Hz, 300 μA, 80 μs
McCracken [94]	/	Rat	NAcC	130 Hz, 100–300 μA, 100 μs
Wei [96]	Obesity	Rat	NAcS/NAcC	200 Hz, 3 V, 100 μs
Yijing Xie [62]	OCD	Rat	NAc	2–140 Hz, ± 65 μA, 100 μs
Ramya Varatharajan [61]	/	Rat	NAc	high frequency DBS-like optogenetic stimulation
Jason Yuen [68]	SUD	Rat	NAcC	60 Hz, 0.2 mA, 0.2 ms, 2 s duration
Chao Zhang [69]	DIO	Rat	left NAcS	130 Hz, 500 μA, 90 μs
Thibaut Sesia [70]	/	Rat	NAcS/NAcC	130 Hz, 3/30/150 μA, 60 μs
Wenhan Hu [77]	SUD	Rat	NAcS/NAcC	20/50/80/130/200 Hz, 0.4 mA, 60 μs
Anett Schumacher [78]	MDD	Rat	NAcS	124 Hz, 0.5 mA, 60 μs (monopolar positive rectangular pulses)
FM Vassoler [79]	SUD	Rat	NAcS/NAcC	160 Hz, 150μA, 60μs
S. E. Swinford-Jackson [80]	SUD	Rat	NAcS	HFS-like optogenetic stimulation
Adrian Mundt [63]	OCD	Rat	Bilateral NAcS/NAcC	130 Hz, 75/100/150μA, 60μs (constant current)
Yifeng [99]	OCD	Rat	Left NAcC	130 Hz, 150 μA, 90 μs
Ewing [100]	/	Rat	NAcC	130 Hz, 100 μA, 100 μs
McCracken [104]	/	Rat	NAc	10/130 Hz, 200 μA, 100 μs
Ssu-Ju Li [71]	MDD	Mouse	Bilateral NAc	130 Hz, 200 μA, 60 μs
Hong Zhou [75]	MDD	Mouse	Right NAcC	130 Hz, 100 μA, 60 μs
Schmuckermair [92]	Depression/Anxiety	Mouse	NAc	130 Hz, 100 μA, 60 μs

like MSNs has demonstrated an antidepressant effect in mice exhibiting depression-like behaviors [26,75]. However, when the stimulation of D2-like MSNs showed the opposite effect, it promoted the susceptibility of stress naïve mice to subthreshold social defeat stress. Research has shown that targeting HFS at a specific MSN subtype can suppress the activity of another subtype. Francis et al. [76] found that strong activation of D1-like MSNs triggers the release of substance P, which then excites D2-like MSNs and cholinergic interneurons (CINs) in the NAc core, suggesting a mechanism by which local circuitry rebalances excitation between MSN subtypes in a lasting manner.

However, despite this increasingly more detailed knowledge about DBS effects on NAc MSNs, many open questions remained. Particularly, taking into consideration the anatomic properties of NAc, researchers have recently started to investigate the following, highly relevant question: Are there any therapeutic differences between NAc core (NAcC) and NAc shell (NAcS) stimulation?

Although some studies suggested that both NAcC and NAcS HFS are able to alleviate pathological behavior [63], most studies elicited different effects resulting from stimulating the two parts. Hu et al. [77] found that targeting NAcC was more effective in reducing morphine preference in mice model and inhibiting NAc. Schumacher et al. [78] investigated NAcS DBS effects on depressive-like rats and found that DBS actually did not significantly affect depressive behavior as well as neurotransmitters level in NAcS. Some other researchers reported opposite results. Vassoler et al. [79] found that NAcS DBS has greater effects in alleviating cocaine seeking in rats. Furthermore, selective stimulation of NAcS D2DR-containing neurons was found to attenuate cocaine seeking in male rats, whereas stimulation of D1DR containing neurons showed no such effects [80].

The mechanisms underlying the differential effects of regional NAc DBS are still not clear. The different anatomic organization of NAc neurons might be one explanation. Another possible explanation is that NAcS is more “receptive” to stimulation [81]. NAcS is believed to contain a multitude of neuroactive substances, including various receptors, drug-regulated transcripts and peptides. For example, peptides require high-frequency stimulation for their release, in the case of repeated, long-lasting stimulation, deplete peptides within various striatal subregions to rebalance excitation [82]. Thereby, overall effects of peptides may differ across the NAcC and NAcS. And specifically, the selective stimulation of NAcS will produce stronger effects in altering reward circuits and behavior [83].

4. Long-distance stimulation effects

The local effect of NAc DBS produced contradictory results between different studies. Differences in stimulation sites or neurons of the NAc might be one reason for these inconsistencies. However, NAc DBS actually provides some extra therapeutic effect in other cognitive processes [84], and neuroimaging studies of DBS patients pointed out that the activation pattern in other brain regions is also affected [85–87]. Based on these results, some researchers believed that the treatment effects of NAc DBS in psychiatric disorders may be the result of circuit- or network-wise modulation [12,88].

It has been suggested that the network effects of DBS are transferred through structural or functional brain networks. A typical, well-known, reward circuit includes VTA, VP, NAc, amygdala, hippocampus, and prefrontal cortex [9,89,90]. Studies using mouse models have shown that neurons in both the VP and VTA are also inhibited by HFS [10,77]. Following NAc HFS, glutamate levels decrease while GABA levels increase in the NAc, VP, and VTA, indicating a circuitry effect on the mesolimbic reward system [10]. F However, further research indicates that NAc core (NAcC) DBS does not alter VTA activation [91].

Interesting findings have also been reported regarding the hippocampus: repeated NAc DBS enhances c-Fos expression in the dentate gyrus and stimulates neurogenesis in the hippocampus of rats exhibiting depression- and anxiety-like behaviors [75,92]. This effect could not

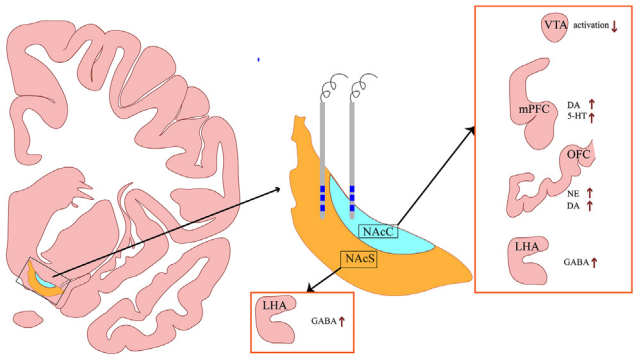

Fig. 1. Effects of deep brain stimulation (DBS) on neurotransmitter levels and brain region activation. Deep brain stimulation (DBS) of the nucleus accumbens core (NAcC) and shell (NAcS) produces distinct neurochemical and functional changes in various brain regions. DBS electrode stimulation of the target in the NAcC caused an increase in dopamine (DA) and serotonin (5-HT) in the medial prefrontal cortex (mPFC), an increase in norepinephrine (NE) and DA in the orbitofrontal cortex (OFC), an increase in gamma-aminobutyric acid (GABA) in the lateral hypothalamic area (LHA), and an inhibition of ventral tegmental area (VTA) activation. Conversely, stimulation of the NAcS leads to a significant increase in GABA levels in the LHA.

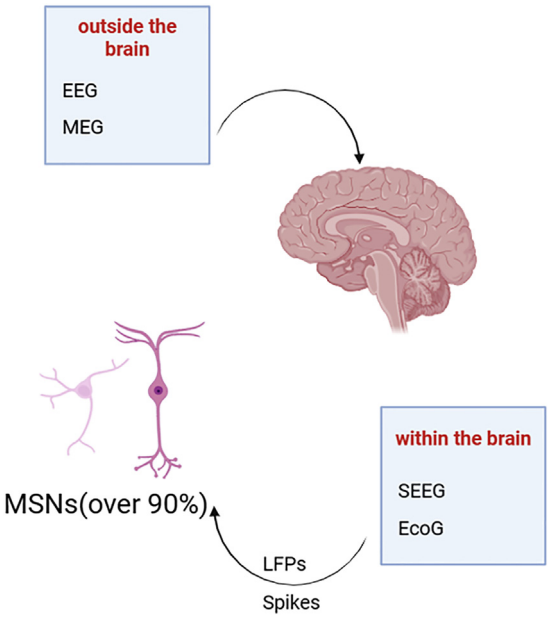

Fig. 2. Data acquisition methods.

be reproduced when giving acute HFS, which was corresponding with a local effect [83]. In the frontal cortex, NAcC DBS rapidly increases dopamine and serotonin levels in the medial prefrontal cortex (mPFC) and dopamine and noradrenaline levels in the orbital prefrontal cortex (OFC) [93]. Further studies suggest that NAc DBS-induced activity in the OFC is mediated by antidromic activation of recurrent OFC collaterals, which excite inhibitory interneurons leading to the suppression of principal cell output, thereby normalizing hyperactivity in the OFC [94]. Taken together, these findings underscore the potential of NAc DBS to modulate aberrant activities within the cortico-accumbal and mesolimbic reward systems, which are critical in various psychiatric disorders.

It is important to consider that the network effects of DBS may also arise from the distinct distributions of afferent and efferent neurons within the core and shell sub-territories (Fig. 1). The NAcS is connected to the limbic system, indicating its involvement in emotional processing, while NAcC is more related to regions involved in motor function [95]. Vassoler et al. [79] suggested that NAcS DBS antidromically activates inhibitory interneurons in the prefrontal cortex. Additionally, NAcS HFS has been shown to significantly increase GABA levels in the lateral hypothalamic area (LHA) more than NAcC or sham HFS, and to decrease the firing rate of neurons in the LHA specifically under NAcS HFS conditions [96]. The inhibitory effect is still detectable thirty minutes after the HFS. Despite a non-negligible result heterogeneity, results from local effect studies clearly indicate that NAcS can be regarded as a central target for HFS in mental disorders.

5. Electrophysiological effects of stimulation

As discussed previously, the complex neuronal composition of the NAc means that HFS treatment effects are a reflection of the sum of neuroactivity changes within this structure. Electrophysiological techniques such as electroencephalogram (EEG) and magnetoencephalography (MEG) assess neural activities on a macroscopic level, providing insights into the overall local and network effects of DBS. Additionally, the use of brain depth electrodes to record local field potentials (LFP) and spikes offers another method to examine local effects. Intracranial brain signal acquisition techniques, including electrocorticography (ECoG) and stereoelectroencephalography (SEEG), capture signals such as LFPs and spikes, enabling a more precise and intuitive evaluation of intervention-related changes in brain electrical activity (Fig. 2). It is generally understood that LFPs represent the collective electrical activity of neurons near the recording electrode, while spikes indicate the action potentials of individual neurons within the population [97,98]. Unlike EEG and MEG, which are conducted externally, LFP recordings measure extracellular fields directly within the brain, thus providing a more direct insight into NAc activities.

Consistent with the findings from several cited studies, electrophysiological methods have also demonstrated that NAc DBS exerts therapeutic effects by modulating neural activity [94]. Shi et al. [99] found that in rats with quinpirole (QNP)-induced OCD, NAc DBS significantly increased the firing rate of neurons and reformed the pathological pattern of neuron activity associated with OCD-like behaviors, with these changes reverting to baseline post-DBS. Another study observed that acute NAc DBS caused a transient increase in low frequency power in situ, while prolonged stimulation led to an increase in high frequency power [100]. In addition to these frequency changes, other DBS-related alterations, such as increased coherence between the left and right NAc, persisted even after the stimulation ceased. This persistence aligns with clinical observations of long-term plastic changes in DBS patients, underscoring the potential for sustained therapeutic effects.

On the network level, researchers found that DBS ameliorated OCD symptoms by mitigating the excessive frontostriatal connectivity [101]. Here, NAc DBS normalized a symptom-provoked increase in frontal low frequency oscillation. Smolders et al. [102] discovered that when NAc DBS was turned on, it decreased the phase stability of frontal theta oscillations, while leaving theta power unaffected. This reduction in phase stability has the potential to significantly diminish the likelihood of neural communication between brain regions within the stimulated network, in this case, the frontostriatal network. Researchers suggested that DBS leads to reduced low-frequency coupling without disrupting the local neural activity that gives rise to oscillations [103]. Svenja Treu et al. [87] uncovered an elevated phase-amplitude coupling between beta and gamma oscillations in frontocentral scalp sensors which were localized at the ventromedial prefrontal cortex among patients with OCD. However, this phenomenon was not observed in intracranial EEG recordings.

Using animal models, studies were able to figure out LFP changes in other brain regions to investigate DBS-induced network effect. Researchers found that after acute NAc DBS, the mean firing rate of OFC

was significantly suppressed and slow frequency oscillation in OFC was enhanced, suggesting an inhibitory effect on the OFC [94]. They further found that suppression of the OFC was focused on putative pyramidal neurons, and the putative interneurons were left unaffected. Additional research reported that NAc DBS also produced time-dependent increases in beta and gamma band oscillation in other OCD-related regions (mPFC, mediodorsal thalamus) [104]. Ewing et al. [100] reproduced the short-term effect of acute DBS in increasing low frequency power in prelimbic area, OFC, mediodorsal thalamus. However, long term NAc DBS did cause a long-lasting effect of reducing alpha coherence between NAc and mediodorsal thalamus as well as between NAc and OFC.

6. Discussion and conclusion

Although considerable success has been made in the clinical usage of DBS, the exact mechanism underlying the effects of this method remain to be elucidated. Various theories have been prompted by previous reviews, yet no consensus has been reached. In this review, we have focused on the mechanisms of NAc DBS by examining the anatomical properties of the NAc and relating these to the specific effects of stimulation.

Most of the studies described above showed that NAc DBS induced an inhibitory effect within the stimulation target. However, given that NAc serves as a hub in multiple functional networks, the overall outcome will extend beyond mere alterations in a single region. We proposed that the therapeutic effect of NAc DBS stems mainly from modulating NAc related networks. Interestingly, the distant brain areas affected by NAc DBS can vary significantly across different diseases, suggesting that NAc DBS may selectively alter abnormal activity in specific brain regions, independent of the disorder. Studies using non-depressive or normal depression/anxiety animal models have shown that NAc DBS does not induce behavioral improvements [92,105]. However, these model animals do not experience the pathological alterations that can be found in typical depression or anxiety models. In this context, NAc DBS NAc DBS appears to function distinctly from traditional drugs or psychotherapies. However, this remains to be debated, as some research indicates that DBS can induce changes even in healthy subjects [106]. This theory requires further validation through future studies involving healthy or sub-clinical models.

Additionally, NAc DBS might induce indirect but long-lasting treatment effects according to some studies. Kim et al. [107] found that NAc DBS enhances mitochondrial function in depressed rats. As a potential target of depression, active glycogen synthase kinase-3β (GSK3β) is thought to be related to synapses sizes and to decrease excitabilities of neurons, and researchers have proved the efficacy of GSK3β inhibitors in ameliorating depression [108]. The mammalian target of rapamycin (mTOR), a serine/threonine kinase, has also been implicated in synaptic plasticity, neurogenesis, and interactions with inflammation and stress response [109]. Traditional and novel antidepressants which are able to activate mTOR have a fast onset and long-lasting antidepressant effects [110]. Kale et al. used adrenocorticotropic hormone (ACTH) to induce an antidepressant-resistant mice model, and found that NAc DBS increased phosphorylated GSK3β and mTOR level in ventral hippocampus, and successfully alleviated depressive symptoms [111]. These neuroplasticity related alterations further indicate that NAc DBS can be regarded as a treatment method causing sustainable, long-term effects on different levels.

Most research on DBS has focused on its long-term modulatory effects. However, acute DBS has also been observed to cause short-term effects. During clinical practice, transient mood changes, such as emotional elevation or euphoria, have been noted immediately after DBS initiation in some patients [112,113]. Subsequent investigations have confirmed these acute alterations in brain activities, although such changes are typically not sustained [100,114,115]. Some other studies failed to elicit acute effects or found distinct long-term effects. Moreover, evidence from neurogenesis or neuroplasticity studies suggested a prolonged pattern of DBS. Based on this, we propose that the network-modulation effect of NAc DBS is primarily achieved through long-term stimulation. As per this assumption, clinicians need to wait for a certain period for DBS to be fully functional, and an extended follow-up is needed for each patient. Accordingly, long-term efficacy and safety have been proved by clinical trials [116,117], which highlights the importance of careful consideration regarding the timing of parameter adjustments or therapy changes in non-responding patients in future studies.

During clinical practices in treatment-refractory patients, the implantation site within the NAc is usually not precisely specified. The different cell composition and functions between NAcC and NAcS have been discussed before [81,118], and many animal studies have pointed out that DBS in the NAcS is more effective than in the NAcC. This effectiveness is thought to be due to the richer neuroactive components and closer connections to the limbic system in the NAcS. Still, this has not been proved and should be investigated by further studies. The selection of the appropriate NAc sub-region for implantation is a complex but crucial factor in improving surgical outcomes. As such, additional research is urgently needed to provide clearer guidance for future surgical procedures.

In conclusion, NAc DBS shows promising results across animal and human studies, and produces stable treatment outcomes in different mental disorders by affecting functional networks. Single target DBS treatment will help to generalize the use of this therapy for treatment refractory psychiatric patients over the world. To optimize treatment outcome, future studies may focus on increasing our knowledge about the underlying mechanisms as well as on determining an optimal subregion-selection of implant target. Finally, more efforts are needed to improve the adjustment of stimulation parameters during follow-up.

Declaration of competing interest

The authors declare that they have no conflicts of interest in this work.

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