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Research Progress on the Pathogenesis of Parkinson's Disease and the Neuroregulatory Mechanism of Deep Brain Stimulation Based on Animal Models

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Abstract. The core pathological features of Parkinson's disease (PD) are the loss of dopaminergic neurons in the compact part of the substantia nigra and the abnormal aggregation of α-synuclein; animal models can reproduce the pathological phenotype of this disease at multiple levels and serve as important tools for exploring its aetiology and evaluating intervention strategies. Deep brain stimulation (DBS) is currently widely used in the clinical management of motor symptoms in moderate-to-advanced Parkinson's disease; however, its complete regulatory mechanisms remain to be thoroughly elucidated. Based on relevant studies in animal models, this review summarizes a series of pathological changes, including dopaminergic neuron degeneration, abnormal α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, and basal ganglia circuit dysregulation.This paper systematically reviews the experimental evidence supporting the regulatory role of deep brain stimulation (DBS) at multiple levels, including the correction of abnormal neural discharges, the attenuation of pathological neural oscillations, the modulation of neurotransmitter transmission, the remodelling of synaptic plasticity, and the intervention in neuroinflammation. Furthermore, the paper compares the differences between current animal models and the clinical features of Parkinson's disease in humans, and looks ahead to future directions such as closed-loop deep brain stimulation and precision neuromodulation

Keywords: PD, animal models, deep brain stimulation, α-synuclein, basal ganglia circuits

1. Introduction

1.1. Clinical features of PD

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder with a high prevalence amongst middle-aged and elderly people [1]. With the accelerating pace of population ageing, the number of people affected worldwide continues to rise; the patient population in China is particularly large, and the resulting social burden is becoming increasingly onerous. The disease has a protracted course; in its advanced stages, patients' motor function is severely impaired and is often

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accompanied by a variety of complications, placing a heavy strain on patients themselves, their families providing care, and social healthcare resources.

The clinical manifestations of PD can be broadly categorised into two main types: motor symptoms and non-motor symptoms [2]. Among these, motor symptoms primarily manifest as resting tremor, rigidity, bradykinesia and postural and gait disturbances; patients often experience limb tremors, stiffness and difficulty initiating movement, whilst unsteady gait increases the risk of falls, thereby directly impairing their ability to perform activities of daily living. In contrast, non-motor symptoms often manifest earlier—in some cases several years before motor symptoms—and affect multiple systems, such as hyposmia, intractable constipation and sleep-behavioural disorders; they may also be accompanied by psychological changes such as anxiety, depression and cognitive decline. For some patients in the advanced stages of the disease, the distress caused by emotional and sleep disturbances may exceed that caused by motor symptoms; these two categories of symptoms intertwine to collectively constitute the complete clinical picture of PD. The hallmark pathological changes of the disease include the progressive loss of dopaminergic neurons in the compact part of the substantia nigra, as well as the abnormal aggregation of α-synuclein to form Lewy bodies, which also serve as important basis for clinical diagnosis and pathological research [3].

1.2. Current treatments and their limitations

As the cornerstone of pharmacological treatment for Parkinson's disease (PD), levodopa effectively alleviates key motor symptoms such as rigidity and bradykinesia by replenishing the dopamine deficient in the brain. It also significantly restores patients' daily functioning in the early stages of the disease and is therefore classified as the treatment of first choice [4]. However, this medication only provides temporary symptom relief and does not halt the progressive degenerative loss of dopaminergic neurons. As treatment continues, the majority of patients gradually develop motor fluctuations—characterised by 'on-off' fluctuations in the drug's effect—as well as treatment-related complications such as dyskinesias; some patients may also experience psychiatric adverse reactions, such as hallucinations and impulse control disorders. Following long-term use, the efficacy of the drug tends to decline, and it becomes difficult to effectively control the condition with medication alone [5]. DBS is an important surgical option for patients with mid- to late-stage PD who have developed motor complications and are experiencing diminishing benefits from their medication. This therapy may significantly decrease core motor symptoms such as rigidity, bradykinesia, and resting tremor by electrical modulation of specific brain nuclei, reduce the levodopa dose, and reduce drug-induced dyskinesia and fluctuations of the therapeutic effect [6]. The advantages of DBS over ablative surgery are that it is adjustable, reversible, and the stimulation parameters can be dynamically changed in response to the changes in the patient's condition . However, DBS is mainly efficacious in improving the motor symptoms and its benefits for non-motor symptoms (such as cognitive decline and mood disorders) are limited. DBS cannot stop the progression of the disease itself.

Deep brain stimulation is now a well-established procedure in the clinical treatment of PD, but its precise mechanism of action is still to be elucidated. Initial assumptions were that electrical stimulation would only have a functional inhibitory effect on the target nuclei. However, extensive animal experiments and clinical studies have since revealed a more complex mode of action [7]. DBS modulates not only the local neuronal firing pattern but also activates the surrounding nerve fibers, so it has a broad regulatory effect on the basal ganglia and even the neural network of the whole brain. Some partial explanations from different perspectives, including the neural electrical

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activity, neurotransmitter release, synaptic plasticity and neuroinflammation have been given in previous studies, but the results obtained under different experimental models, stimulation targets and parameters have some discrepancies. The different hypotheses are not yet fully reconciled and further analysis of the underlying regulatory mechanisms is still required, using animal models in combination with multimodal techniques.

1.3. The significance of research using animal models

The establishment of appropriate animal models of Parkinson's disease enables the reproduction of the disease's pathological hallmarks and phenotypic characteristics at multiple levels [8]. At the molecular level, these models are capable of reproducing pathological changes closely associated with the onset and progression of the disease, such as the abnormal deposition of α-synuclein and mitochondrial dysfunction. At the cellular level, they reflect pathological events, including dopaminergic neurone damage and glial cell activation; whilst at the neural circuit level, they facilitate the study of basal ganglia dysfunction and disrupted neural oscillations. In terms of behavioural manifestations, model organisms also exhibit characteristics similar to those of Parkinson's disease (PD), including bradykinesia, tremor and gait disturbances. Given that the aforementioned pathological features can be replicated at multiple levels, whilst allowing for interventions that are difficult to implement in human studies, animal models have thus become an indispensable experimental platform for exploring the mechanisms underlying the onset and progression of the disease.

Standardised animal models are likewise instrumental in clarifying how deep brain stimulation (DBS) exerts its effects at the level of both local nuclei and distributed brain networks. Within the immediate vicinity of the stimulating electrode, electrical pulses can reshape neuronal discharge patterns, influence axonal excitability and propagation, and ameliorate pathological local activity. Yet the influence of DBS extends well beyond the directly contacted target; stimulation-induced signals may travel along anatomical projections to remote regions, promoting large-scale reorganisation of the basal ganglia–thalamocortical circuitry and adjusting oscillatory synchronisation across brain areas. Given that invasive whole-brain electrophysiological recordings in patients are constrained by considerable ethical limitations, animal studies offer a practical alternative, enabling the use of local field potential recordings and multi-channel unit recordings to monitor dynamic changes in both local structures and distant networks.

This article provides a review of recent advances in the application of animal models in Parkinson's disease research, with a particular focus on their contribution to understanding the pathophysiological processes of the disease and the mechanisms of action of deep brain stimulation. The article begins by summarising the advantages, limitations and appropriate applications of different types of animal models for Parkinson's disease, before examining the pathogenic processes revealed by existing experiments at three levels: molecular, cellular and neural circuit.The subsequent sections focus on experimental evidence concerning the neuromodulatory actions of DBS in animal models, examine the translational gaps that remain between preclinical findings and clinical application, and consider emerging directions such as closed-loop stimulation and precision neuromodulation, with the aim of informing future mechanistic studies and the optimisation of therapeutic strategies for Parkinson's disease.

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2. Common animal models for PD and their characteristics

2.1. Structure neurotoxin-induced model

Neurotoxin-induced models rely on exogenous toxin intervention to directly damage the dopaminergic system; they have a relatively short modeling period and produce stable behavioral phenotypes, making them the most commonly used models in basic research on DBS.

2.1.1. 6-hydroxydopamine model

This model involves the stereotactic injection of 6-hydroxydopamine into the brain, which directly disrupts the substantia nigra–striatal dopaminergic pathway, leading to massive loss of dopaminergic neurones [9]. Model animals exhibit typical motor disorders, such as rotatory behaviour and impaired motor function. Owing to the well-established and relatively low-cost nature of the modelling method, this model is widely used in research into the mechanisms of dopaminergic pathway damage, the assessment of motor behaviour, and the preliminary validation of the efficacy of deep brain stimulation (DBS). However, as this model represents a rapidly progressing acute injury, it is difficult to replicate the slow-progressing degenerative pathological process observed in human Parkinson's disease; furthermore, the brains of these models typically lack the characteristic pathological aggregates of α-synuclein, resulting in significant discrepancies between the model and actual clinical lesions.

2.1.2. MPTP model

Following metabolic conversion within the body, the active metabolites of MPTP inhibit the activity of mitochondrial complex I, thereby causing selective damage to dopaminergic neurones in the substantia nigra [10]. To date, this model has been successfully established in mice and non-human primates. Among these, the mouse MPTP model is particularly suitable for exploratory mechanistic studies requiring large sample sizes, owing to its relative ease of use.

Conversely, the basal ganglia have a similar anatomical structure in non-human primates as in humans and the motor symptoms observed in these models are more comprehensive. This provides substantial advantages for translational research on deep brain stimulation (DBS). However, note that this model often leads to acute damage and experiments with non-human primates can be expensive and involve strict experimental conditions.

2.1.3. Models of rotenone and other toxins

Rotenone Rotenone, paraquat and lipopolysaccharide are commonly used toxins for disease modeling, respectively inducing mitochondrial inhibition, oxidative stress and neuroinflammation which result in pathological damage [11]. The toxic effects of rotenone and paraquat are primarily localised to the mitochondria, where they cause cellular damage by inducing oxidative stress; lipopolysaccharide, on the other hand, mainly promotes the activation of glial cells in the brain, thereby triggering a neuroinflammatory response. The aforementioned models are of some value in elucidating the roles of mitochondrial dysfunction, oxidative stress and neuroinflammation in the pathogenesis of Parkinson's disease (PD). However, this type of modelling is often associated with significant inter-individual variability, lacks model stability and has limited experimental reproducibility; therefore, strict control over dosages and modelling conditions is required during the research process.

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2.2. Hereditary animal models

The modification of susceptibility genes associated with Parkinson's disease (such as SNCA, LRRK2, PINK1, Parkin and DJ1) using gene-editing techniques is the primary approach for constructing genetic animal models [12]. Such models aid in elucidating the aggregation behaviour of α-synuclein, pathways related to mitochondrial quality control, and the genetic basis of susceptibility to the disease. However, their limitations are equally pronounced: in most model strains, neither a clear loss of dopaminergic neurones has been observed, nor is it possible to consistently reproduce the motor dysfunction characteristic of Parkinson's disease. Consequently, genetic models are predominantly used to explore molecular pathological mechanisms and are not commonly employed as experimental tools for evaluating the therapeutic efficacy of deep brain stimulation (DBS).

2.3. Preformed α-synuclein fibrils and viral vector models

The *α*-synuclein preformed fiber inoculation model and the viral vector overexpression model are capable of simulating the misfolding, aggregation, and trans-regional prion-like propagation of α-synuclein; as the pathological progression exhibits certain chronic characteristics, these models are suitable for studying the evolution of the disease course and can also be used to investigate the therapeutic efficacy of DBS at different intervention timepoints [13]. However, no uniform standards have yet been established for the modeling methods or pathological evaluation criteria for this type of model, and there is considerable variation in modeling results between different laboratories.

2.4. Principles for the selection of animal models

Different animal models have their respective advantages and disadvantages; in practical research, the appropriate model should be selected based on the research objectives. It is necessary to comprehensively consider the model's pathological characteristics, the rate of disease progression, behavioral phenotypes, and experimental reproducibility, while also taking into account differences in brain anatomy and physiology between species. It should be noted that, at present, no single animal model is capable of fully reproducing all the pathological features, disease progression, and clinical symptoms of human PD; when conducting complex research, the use of multiple models to corroborate one another may be considered. Among animal models used to study deep brain stimulation (DBS) for Parkinson's disease, the 6-hydroxydopamine (MPTP) model induces acute damage to the substantia nigra–striatal pathway via stereotactic injection. This model is well-validated, relatively inexpensive and capable of inducing stable motor behavioural abnormalities; however, as its pathological process is characterised primarily by acute damage, the disease progresses rapidly and lacks the typical α-synuclein aggregation observed in human cases. It is therefore mainly used to assess the extent of dopaminergic pathway damage, detect changes in motor behaviour and preliminarily validate the efficacy of DBS. MPTP selectively damages dopaminergic neurones by inhibiting mitochondrial complex I. The preparation of mouse models is relatively straightforward, whilst non-human primate models possess brain structures more closely resembling those of humans and are capable of exhibiting a more complete range of motor symptoms; however, primate models still predominantly involve acute injury and are characterised by high experimental costs and significant technical barriers. In addition to preclinical translational research, these models are also frequently used to screen for DBS targets and optimise stimulation

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parameters.Toxin models (e.g. rotenone model) cause neuronal damage via mechanisms including mitochondrial inhibition, oxidative stress and neuroinflammation. These models are useful to investigate processes related to mitochondrial dysfunction and neuroinflammation but they show high interindividual variability and problems with stability and reproducibility are frequent. Given the above characteristics, the application of such models focuses on investigating the modulatory effects of deep brain stimulation (DBS) on inflammatory responses and oxidative stress. Genetically modified animal models are typically established through the editing of disease-causing genes such as SNCA, LRRK2 and PINK1, which helps to elucidate genetic susceptibility factors and the pathological mechanisms associated with α-synuclein and mitochondrial quality control. However, most of these models lack a significant loss of dopaminergic neurones, and their motor phenotypes are often subtle; they are therefore more suitable for studies of genetic mechanisms and are rarely used directly to evaluate the therapeutic efficacy of DBS.In contrast, models constructed using pre-fabricated α-synuclein fibres or viral vector delivery offer more pronounced advantages in simulating the abnormal aggregation and inter-regional propagation of this protein and can replicate the characteristics of a slowly progressive disease course; they are therefore better suited to investigating the optimal timing for interventions. However, there are currently no standardised protocols for the construction or evaluation of such models, and there is considerable variation in the results obtained across different laboratories. At present, these models are primarily used to investigate the potential mechanisms underlying deep brain stimulation (DBS) interventions within different time windows.

3. Pathogenesis of PD as revealed by animal models

3.1. Selective degeneration of dopaminergic neurons

A defining pathological feature of Parkinson's disease is the degeneration of the nigrostriatal dopaminergic pathway. Neurons in the substantia nigra pars compacta are characterised by high metabolic energy requirements and elevated intracellular calcium levels. In addition, oxidative metabolism of dopamine readily generates toxic intermediates, rendering these cells particularly vulnerable to injury and apoptotic death. The extensive loss of dopaminergic neurons results in a marked reduction of striatal dopamine, which in turn gives rise to core motor deficits including bradykinesia and rigidity.

3.2. Abnormal aggregation and spread of α-synuclein

Misfolded α-synuclein progressively assembles into oligomeric species, which later organise into fibrillar structures [14]. Both the oligomers and the resulting fibrils interfere with synaptic signalling, undermine membrane integrity, and disturb the physiological activity of multiple organelles. Evidence from animal experiments indicates that α-synuclein exhibits prion-like spreading behaviour, whereby the aberrant protein propagates from its initial site to interconnected brain areas. This process enables pathological lesions to extend across the central nervous system, thereby hastening disease advancement [15].

3.3. Mitochondrial dysfunction and oxidative stress

In the pathological progression of Parkinson's disease, functional defects in Complex I of the mitochondrial respiratory chain play a pivotal role; this defect directly impairs ATP production and

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disrupts intracellular energy balance [16]. Dysfunctional mitochondria also generate large amounts of reactive oxygen species (ROS); these free radicals, combined with the oxidation of dopamine, further exacerbate oxidative damage [17]. Once PINK1/Parkin-mediated mitochondrial autophagy becomes abnormal, damaged mitochondria cannot be accurately identified and removed, thereby creating a self-reinforcing vicious cycle in which energy metabolism disorders and oxidative stress mutually reinforce one another, leading to the progressive worsening of neuronal damage [18].

3.4. Protein homeostasis and dysfunction of autophagy–lysosomal systems

Parkinson's disease (PD) is associated with reduced activity of the ubiquitin-proteasome system and concurrent impairment of the autophagy-lysosomal route, both of which markedly diminish the capacity of cells to eliminate aberrant proteins [19]. Because these degradative pathways are compromised, α-synuclein is not efficiently cleared and instead progressively builds up intracellularly, exerting pronounced neurotoxic effects. Moreover, pathogenic variants in genes such as GBA can further compromise lysosomal performance, aggravating the deficit in protein removal and thus hastening both the pathological evolution and clinical progression of PD.

3.5. Neuroinflammation and the glial response

Under pathological stimulation, microglia and astrocytes in the brain become extensively activated and release large quantities of pro-inflammatory factors, thereby compromising the structural integrity of the blood-brain barrier [20]. Activated glial cells and inflammatory mediators directly damage neurons, whilst the molecules released by the damaged neurons, in turn, further enhance glial cell activation. This cycle continues to amplify, with the inflammatory response and neuronal degeneration mutually reinforcing one another, leading to progressively worsening damage to the central nervous system [21].

3.6. Basal ganglia neural circuits and abnormal oscillations

In Parkinson's disease, the functional balance of the direct, indirect and ultra-direct pathways of the basal ganglia is disrupted, leading to abnormal discharges in the thalamic nuclei and the globus pallidus. There is an enhanced synchronisation of β-band oscillations and excessive synchronisation of neural activity across different brain regions [22]; such disturbances cause deviations in the encoding and transmission of motor commands and are directly associated with bradykinesia and rigidity [23].

3.7. Interactions between multiple mechanisms

Abnormal α-synuclein deposition, defects in the mitochondrial respiratory chain, oxidative stress and neuroinflammation are not independent phenomena. These four pathological events are interlinked, forming a self-amplifying loop in which each form of damage amplifies the effects of the others through a cascade of reactions. At the molecular level, imbalances in protein homeostasis and organelle damage jointly drive neuronal death, resulting in impaired function of basal ganglia-related circuits. The process by which initial molecular damage progressively extends to widespread disruption of neural circuits exemplifies the characteristic of Parkinson's disease as a multifactorial disorder—where multiple pathogenic mechanisms converge within a single pathological network. Figure 1 summarises the multi-level pathogenic process of Parkinson's disease based on evidence from animal models.

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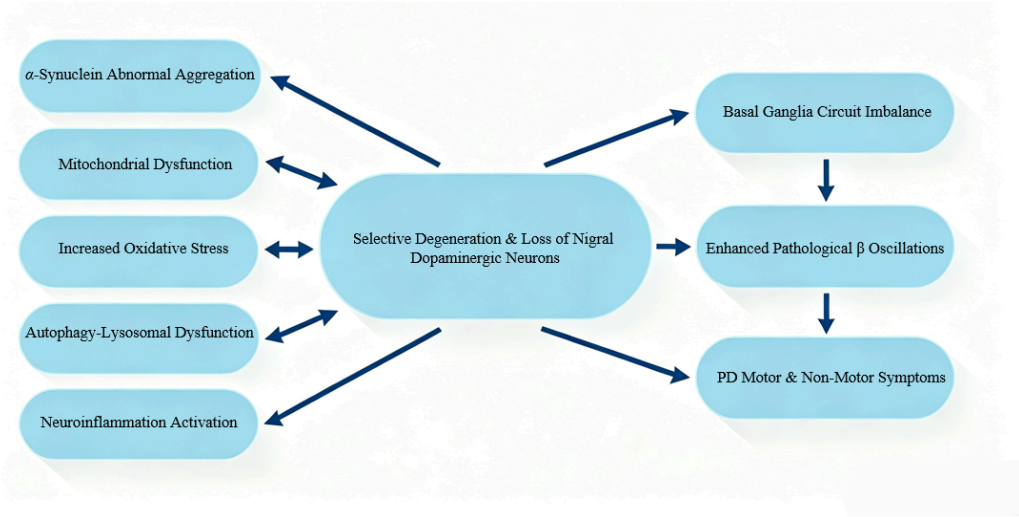

Figure 1. Schematic diagram illustrating the multi-level pathogenesis of PD as revealed by animal models

4. The animal research basis for deep brain stimulation

4.1. The basic principles and common parameters of DBS

Deep brain stimulation (DBS) is a surgical procedure in which electrodes are implanted into the brain to deliver electrical pulses to targeted regions [24]. Its key parameters include stimulation frequency, amplitude, pulse width and stimulation pattern. Stimulation at different frequencies can induce markedly different neuromodulatory effects; high-frequency stimulation is widely used clinically to alleviate the motor symptoms of Parkinson's disease (PD) and is currently the mainstream stimulation pattern.

4.2. Common stimulation targets

At present, the commonly used targets for deep brain stimulation (DBS) primarily include the subthalamic nucleus (STN) and the medial globus pallidus (GPi); in addition, the ventral intermediate nucleus of the thalamus and the pontine nucleus have also been used as stimulation sites in some experiments. These targets exhibit significant differences in their anatomical structure and projection pathways; consequently, their efficacy in alleviating motor symptoms is not entirely consistent, and they also display distinct functional characteristics when modulating activity within whole-brain neural circuits.

4.3. Key evaluation methods in animal experiments

The evaluation framework for animal experiments covers several complementary dimensions. Motor function can be assessed through behavioural paradigms such as the rotarod test, open-field exploration, gait analysis and quantification of rotational behaviour. Electrophysiological assessments include recordings of single-unit activity and local field potentials. In addition, neurotransmitter measurements, histopathological examination and functional imaging analyses can be performed. Upon completion of the experiments, the anatomical location of the implanted

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electrodes should be confirmed, so as to exclude potential confounding effects arising from electrode migration or surgically induced local tissue injury.

5. Mechanisms of DBS neuromodulation revealed by animal models

5.1. DBS's modulation of local neural activity

DBS can alter the firing rate and pattern of neurons in the target region, suppressing pathological bursts of firing and restoring a more regular firing rhythm. Electrical stimulation exerts both excitatory and inhibitory effects on local neural tissue; therefore, DBS cannot simply be understood as 'functional destruction,' which also explains its reversible and adjustable therapeutic characteristics [25].

5.2. DBS regulation of axonal and basal ganglia circuits

Neuronal axons and nerve fibers are highly sensitive to electrical stimulation; DBS can activate nerve fibers both anterograde and retrograde, thereby extensively modulating the direct, indirect, and ultra-direct pathways of the basal ganglia, restoring the efficiency of information transmission within the basal ganglia–thalamus–cortex network, and improving functional dysregulation of these circuits [26].

5.3. DBS's suppression of abnormal oscillations and synchronisation

DBS can modulate the release of dopamine, glutamate, and γ-aminobutyric acid (GABA) at local and loop levels, thereby improving the balance between excitatory and inhibitory neurotransmitter transmission in the brain.However, stimulus-induced fluctuations in neurotransmitter levels depend on factors such as the type of model, the choice of target and the stimulus parameters, and the findings reported in various experiments are inconsistent.

5.4. The effects of DBS on neurotransmitters

Deep brain stimulation can regulate the release of dopamine, glutamate and γ-aminobutyric acid (GABA) at both the local and circuit levels, thereby optimising the balance between excitatory and inhibitory neurotransmitter transmission in the brain. However, the extent of neurotransmitter changes induced by stimulation is influenced by multiple factors, including the animal model, choice of target and stimulation parameters, and the findings of existing studies, which are not entirely consistent.

5.5. The regulation of glial cells, neuroinflammation and synaptic plasticity by DBS

Deep brain stimulation (DBS) is capable of influencing the activation state of microglia and astrocytes, downregulating the expression of selected pro-inflammatory mediators and thereby attenuating the exaggerated inflammatory reactions within cerebral tissue. Moreover, DBS facilitates plasticity at corticostriatal synapses, encouraging long-term reorganisation of neural circuitry. These changes are thought to contribute to the enduring alleviation of motor symptoms.

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5.6. Whether DBS has neuroprotective effects

Some animal studies suggest that deep brain stimulation (DBS) may be able to mitigate the extent of damage to dopaminergic neurones; the mechanism may be related to the upregulation of neurotrophic factor expression, the suppression of neuroinflammation, and the improvement of axonal function. However, the results obtained by different laboratories are not entirely consistent, and the relevant evidence remains controversial. It is therefore necessary to distinguish between the short-term symptomatic benefits of DBS and its potential long-term disease-modifying and neuroprotective effects; furthermore, findings from animal models should not be directly extrapolated to clinical contexts. Figure 2, 'Schematic of DBS: From Local Stimulation to Whole-Brain Network Modulation', illustrates the basic principles underlying this technology.

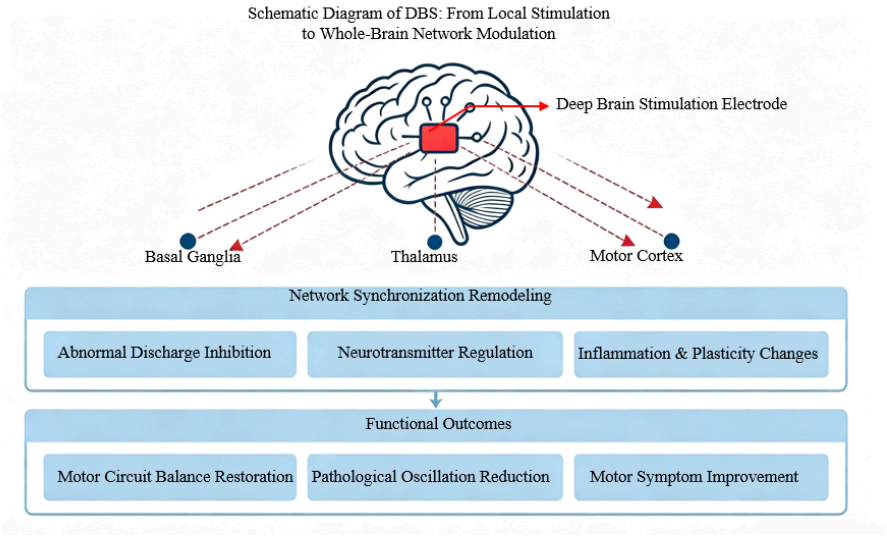

Figure 2. Schematic diagram of DBS: From local stimulation to whole-brain network modulation

6. Current issues and future prospects

6.1. Limitations of animal models

At present, most animal models are still unable to accurately replicate the slow progression that is a key characteristic of the course of human Parkinson's disease (PD). There are marked species-specific differences between rodents and humans in terms of brain anatomy and the composition of the basal ganglia neural networks, whilst the rapid rate of damage induced by acute toxin models may lead to an overestimation of the actual efficacy of deep brain stimulation (DBS), ultimately resulting in bias when translating experimental findings into clinical practice.

6.2. DBS research lacks standardization

In current experiments on deep brain stimulation (DBS) using laboratory animals, there are marked differences in experimental conditions between studies, and no uniform standards have yet been established for key variables such as electrode specifications, stimulation parameters and stimulation duration; there is also a lack of consistency in behavioural and electrophysiological assessment methods, which hinders cross-comparison of results from different experiments. In future, efforts

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should focus on standardising aspects such as the selection of animal models, the design of stimulation protocols and the reporting of experimental data.

6.3. Research into mechanisms requires the integration of multiple technologies Citations and references

Future research should integrate a variety of technical approaches, such as multi-channel electrophysiological recording, optogenetic modulation, chemogenetics and calcium imaging, in order to systematically investigate the response characteristics of various neuronal subtypes and nerve fibre pathways to deep brain stimulation (DBS). If these approaches are further combined with spatial transcriptomics and single-cell sequencing, the underlying mechanisms by which DBS exerts its regulatory effects can be elucidated at the cellular and molecular levels.

6.4. Closed-loop and personalised DBS

If biomarkers such as β-oscillations are incorporated into the feedback control loop, it may be possible to establish a closed-loop deep brain stimulation (DBS) system. This system would dynamically adjust stimulation parameters in real time according to the animal's movement status, thereby transforming the original continuous stimulation mode into an on-demand triggering mode. This approach would not only reduce the device's energy consumption but also minimise stimulation-related adverse effects whilst maintaining therapeutic efficacy [27].

6.5. Enhancing the clinical translational value of animal experiments

There is a need to vigorously develop animal models of chronic, progressive diseases characterised by multiple overlapping pathologies; experimental designs must take full account of confounding factors such as age, sex and disease stage; at the same time, cross-validation between experiments involving rodents and non-human primates and clinical research must be strengthened in order to bridge the gap between basic research and clinical application.

7. Conclusion

In the basic research landscape of Parkinson's disease (PD), animal models remain indispensable, supplying critical experimental data for clarifying how the disease evolves pathologically and for dissecting the mechanisms through which deep brain stimulation exerts its effects. PD cannot be attributed to a single pathogenic trigger; rather, it arises from the convergence and progressive intensification of multiple pathological events, including α-synuclein misfolding and aggregation, mitochondrial impairment, elevated oxidative stress, defective protein clearance, exaggerated neuroinflammatory responses and disrupted basal ganglia circuitry. Findings from animal experiments suggest that the clinical benefit of deep brain stimulation (DBS) cannot be reduced to mere suppression of target nucleus activity. Instead, its therapeutic action appears to rely on coordinated effects across several domains: altering the electrical behaviour of neurones and axons within the stimulated region, dampening pathological oscillatory activity, restoring basal ganglia circuit function, modulating neurotransmitter output and enhancing synaptic plasticity, all of which collectively contribute to the amelioration of motor deficits.

Nevertheless, current animal models have notable limitations. Their pathological trajectories do not fully mirror those observed in patients, and DBS-related studies still lack harmonised protocols and evaluation standards. Future investigations should therefore prioritise the development of

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models that better approximate the chronic and progressive nature of human PD. Equally important will be the integration of multimodal methodologies and a stronger emphasis on closed-loop, precision and individually tailored DBS strategies, so as to establish a more robust theoretical foundation for neuromodulation-based treatment of Parkinson's disease.

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