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Deep brain stimulation and magnetic resonance-guided focused ultrasound in Parkinsonism and related disorders: State-of-the-Art and future prospects

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ABSTRACT

Deep brain stimulation (DBS) has been a cornerstone treatment for pharmacologically refractory Parkinson's disease, essential tremor, and dystonia for over three decades. While it offers substantial symptom relief and medication reduction, its invasive nature introduces risks such as surgical complications and hardware-related issues. Magnetic resonance-guided focused ultrasound (MRgFUS) has recently emerged as a non-invasive neuromodulation alternative, providing incisionless lesioning for selected cases, particularly tremor-dominant phenotypes. However, the two modalities differ significantly in terms of mechanism, adaptability, safety profile, and long-term efficacy.

This review synthesizes recent developments in DBS and MRgFUS for Parkinsonism and related movement disorders, focusing on clinical efficacy, safety outcomes, and technological innovations. We evaluated the following key areas: adaptive and closed-loop DBS systems, advances in MRgFUS targeting and imaging, long-term outcomes, and the integration of machine learning in DBS personalization. These findings underscore the complementary roles of DBS and MRgFUS, supporting individualized, data-driven treatment approaches and highlighting the need for future large-scale, controlled trials to further optimize therapeutic strategies.

1. Introduction

Parkinsonism encompasses neurodegenerative movement disorders characterized by bradykinesia, rigidity, tremor, and postural instability. Parkinson's disease (PD) affects over 10 million individuals worldwide, representing the second most common neurodegenerative disorder [1].

PD pathology involves progressive dopaminergic neuronal loss in the substantia nigra pars compacta, causing striatal dopamine depletion and cardinal motor symptoms [1]. While levodopa remains the first-line treatment, long-term use causes motor complications, including wearing-off, fluctuations, and dyskinesias [2,3], driving the development of surgical interventions.

Deep brain stimulation (DBS), FDA-approved for advanced PD since 2002, targets structures such as the subthalamic nucleus (STN) or globus pallidus internus (GPi) to modulate abnormal neural activity. DBS offers adjustable, reversible, long-term efficacy in reducing motor complications [2].

Magnetic resonance-guided focused ultrasound (MRgFUS) provides incisionless thermal ablation of targets including the ventral intermediate nucleus (VIM), GPi, pallidothalamic tract (PTT) or zona incerta under real-time MRI guidance. Approved for essential tremor (2016) and tremor-dominant PD (2018), MRgFUS may be considered for elderly patients or those contraindicated for invasive procedures [3,4].

This review synthesizes current evidence on DBS and MRgFUS efficacy, safety, and clinical outcomes in Parkinsonism, providing comparative analysis to guide treatment strategies and future research [5–8].

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2. Deep brain stimulation (DBS)

2.1. Historical perspective, mechanism and indications

DBS was introduced in the late 1980s and received FDA approval for PD treatment in 2002 (Table 1). The procedure involves implanting electrodes into specific brain regions (commonly the STN or GPi) connected to an implanted pulse generator (Table 2). These targets are chosen based on their central roles in the cortico-striatal-thalamo-cortical motor circuit. In PD, abnormal oscillatory activity and excessive synchrony within this network contribute to motor dysfunction. DBS acts by modulating these dysfunctional circuit dynamics, rather than enhancing dopamine release, which is a common misconception [9,10]. High-frequency stimulation is thought to suppress pathologic bursting and restore physiological firing patterns, leading to improved motor control [11].

The EARLYSTIM trial demonstrated that early DBS provides greater quality of life improvements versus medical therapy alone in patients with early motor complications [12]. Eligible candidates include patients with idiopathic PD, significant motor fluctuations, and preserved levodopa responsiveness. Contraindications include severe cognitive impairment, uncontrolled psychiatric illness, and atypical Parkinsonism. Preoperative evaluation requires brain MRI, neuropsychological testing, and multidisciplinary assessment [13].

Recent technological advances focus on enhancing efficacy and expanding applications to broader neurological conditions. Key developments include novel stimulation targets, adaptive DBS systems, and improved hardware design.

2.2. New stimulation targets

The pedunculopontine nucleus (PPN), located in the mesencephalic locomotor region, modulates gait initiation and postural stability (Fig. 1). Stimulation of the PPN—often in combination with STN or GPi—has been shown to partially improve freezing of gait and postural instability in advanced PD, though responses remain heterogeneous and parameter-dependent [14,15].

The zona incerta (Zi) lies dorsal to the STN and connects with thalamic and cerebellar motor circuits. DBS of the posterior Zi has shown marked tremor reduction in tremor-dominant PD and essential tremor, sometimes exceeding that of STN stimulation, making it a valuable target when tremor is the predominant disabling feature [15].

The centromedian-parafascicular complex (CM-PF) of the thalamus is increasingly explored for rapid-onset dystonia-parkinsonism (DYT12) and refractory dystonia. This intralaminar nucleus influences basal-ganglia excitability and sensorimotor integration. Case studies have demonstrated clinically meaningful motor improvement and functional recovery following CM-PF stimulation [16].

In summary, these alternative targets expand the therapeutic scope of DBS toward axial and tremor-dominant phenotypes, emphasizing individualized, circuit-based target selection.

Table 1
Historical Perspective and Clinical Significance in Neuromodulation in the past decades (1987–2025). It highlights the chronological development of deep brain stimulation (DBS) and magnetic resonance-guided focused ultrasound (MRgFUS), detailing their respective modalities and clinical significance.

Year	Milestone	Modality	Clinical Significance
1987	First successful DBS for tremor (Benabid et al.)[a]	DBS	Pioneered modern neurosurgical therapy for movement disorders
1997	FDA approval of DBS for essential and parkinsonian tremor	DBS	Enabled widespread DBS use in tremor syndromes
2002	FDA approval for STN-DBS in PD	DBS	Standardized surgical treatment for advanced PD
2003	FDA approval for Gpi-DBS in PD	DBS	Standardized surgical treatment for advanced PD
2015	Directional DBS leads marketed (e.g., Vercise Cartesia)	DBS	Enhanced targeting precision and reduced side effects
2016	FDA approval for MRgFUS in essential tremor	MRgFUS	First incisionless lesioning for tremor control
2018	FDA approval for MRgFUS in tremor-dominant PD	MRgFUS	Expanded indication to Parkinsonian tremor
2021	Pilot clinical trials of MRgFUS subthalamotomy in mid-stage PD[b]	MRgFUS	Opened the possibility to treat rigidity/bradykinesia via non-invasive ablation
2023	Real-time closed-loop aDBS trials (e.g., ADAPT-PD)[c]	DBS	Dynamic symptom-responsive therapy
2025	FDA approval of Medtronic aDBS	DBS	Landmark in personalized stimulation protocols
2025	FDA approval of staged bilateral MRgFUS in PD	MRgFUS	Manage bilateral symptoms for advanced PD

[a] Obtained from reference [11].
[b] Obtained from reference [4].
[c] Obtained from reference [22].

Table 2
Clinical Comparison of DBS and MRgFUS for Parkinsonism and related disorders.
This table summarizes and compares the clinical features of Deep Brain Stimulation (DBS) and Magnetic Resonance-guided Focused Ultrasound (MRgFUS) therapies. It includes the respective mechanisms, common neuroanatomical targets (STN: subthalamic nucleus; GPi: globus pallidus internus; PPN: pedunculopontine nucleus; Zi: zona incerta; CM-PF: centromedian-parafascicular nucleus; VIM: ventral intermediate nucleus; PTT: pallidothalamic tract; PD: Parkinson's disease; ET: essential tremor), clinical indications, invasiveness, reversibility, programming flexibility, recovery times, potential adverse effects, and available long-term efficacy data.

Feature	Deep Brain Stimulation (DBS)	MR-Guided Focused Ultrasound (MRgFUS)
Mechanism	Electrical neuromodulation	Thermal ablation
Common Targets[a]	STN, Gpi, PPN (investigational), Zi (limited), CM-PF (limited)	VIM, PTT, GPi (investigational), STN (limited)
Indications	PD with motor fluctuations, dystonia, ET	ET, Tremor-dominant PD
Invasiveness	Invasive surgery with an implanted device	Non-invasive
Reversibility	Reversible and adjustable	Irreversible
Programming Flexibility	Adjustable	Non-adjustable
Recovery Time	2–4 weeks	1–2 days
Adverse Effects	Infection, hemorrhage, cognitive/mood changes	Gait imbalance, speech disturbance
Long-term Efficacy[b]	>10 years	2–5 years (limited data)

[a] Obtained from reference [3,14–16,42,84].
[b] Obtained from reference [62–64].

2.3. Adaptive and closed-loop DBS

Adaptive deep brain stimulation (aDBS) represents a shift from continuous, open-loop stimulation to responsive neuromodulation guided by physiological feedback (Fig. 2). Instead of delivering fixed pulses, aDBS dynamically adjusts stimulation amplitude or frequency in real time according to neural biomarkers (e.g., beta-band 13–30 Hz oscillations correlated with bradykinesia and rigidity, and gamma activity linked to dyskinesia) recorded from local field potentials in the basal ganglia or cortical interfaces [17–20].

The theoretical framework views aDBS as a closed control loop, where abnormal oscillatory activity triggers stimulation, which in turn suppresses pathological synchrony and restores circuit balance. This paradigm minimizes overstimulation, improves target specificity, and reduces energy consumption—extending device longevity by 30–40 % while maintaining clinical efficacy [19–21].

Advantages include individualized therapy, reduced side effects

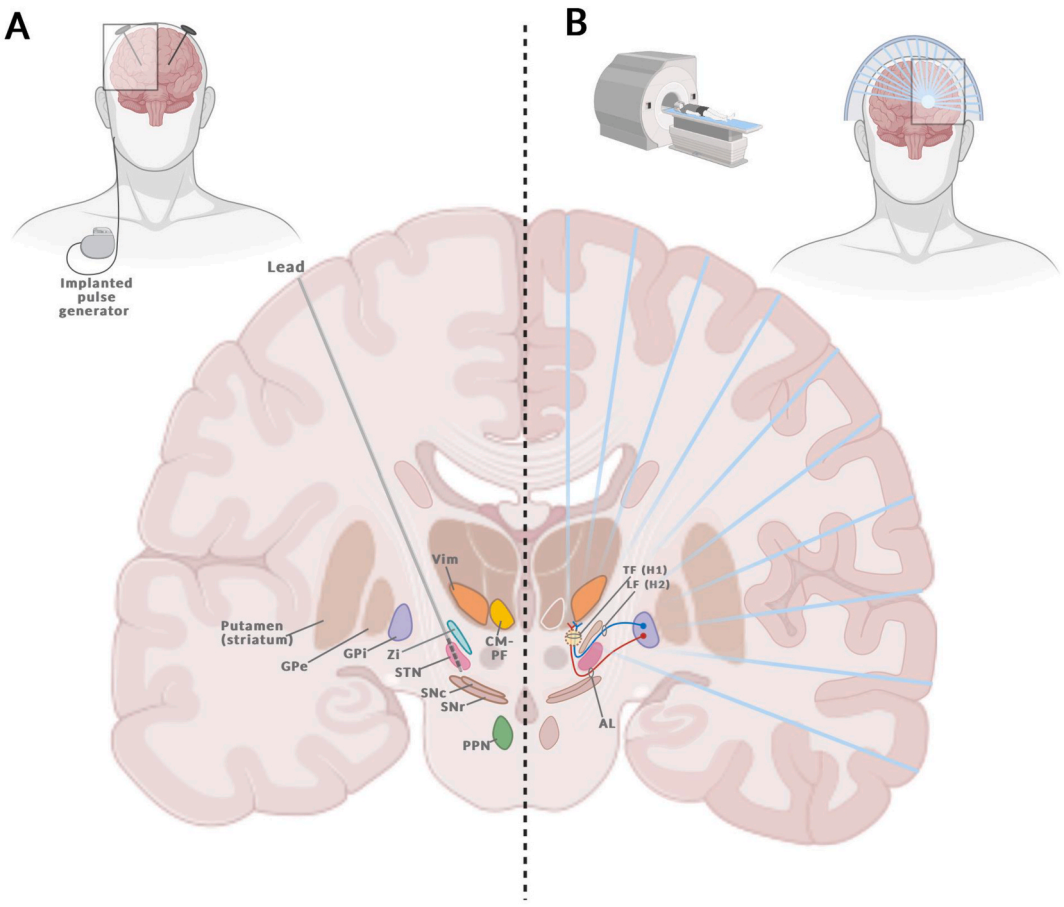

Fig. 1. Anatomical targets and mechanisms of deep brain stimulation (DBS) and magnetic resonance–guided focused ultrasound (MRgFUS).
(A) The DBS system consists of intracranial leads connected to an implanted pulse generator that delivers high-frequency stimulation to restore physiological network activity through electrodes implanted in deep brain targets. Key anatomical structures include the subthalamic nucleus (STN), globus pallidus internus (GPi), zona incerta (Zi), pedunculopontine nucleus (PPN), and centromedian–parafascicular complex (CM-PF) of the thalamus.
(B) MRgFUS delivers converging ultrasound beams, guided by real-time MRI thermometry, to create a focal thermal lesion in specific subcortical targets such as the pallidothalamic tract (PTT). The PTT, composed of the ansa lenticularis (AL) and lenticular fasciculus (LF, H2 field of Forel), converges within thalamic fasciculus (TH, H1 field of Forel), where the yellow dotted circle indicates the typical lesion zone. Other target choices includes ventral intermediate nucleus (Vim), GPi and STN.

(especially dyskinesia and speech disturbance), shorter programming sessions, and improved comfort. Limitations involve algorithm complexity, inter-patient variability of biomarkers, latency in signal detection, and high technological cost. Ongoing trials integrating machine learning and cloud-based adaptive systems aim to refine biomarker accuracy and enable fully autonomous stimulation [21,22].

2.4. Technological advancements

Directional leads enable current steering to optimize effects while minimizing side effects like dysarthria or paresthesia [23,24]. New hardware developments, including durable leads and wireless systems, address lead fractures that compromise long-term DBS efficacy [25].

2.5. Multi-modal imaging integration

Next-generation DBS planning integrates multi-modal MRI (T1, T2, SWI) and diffusion tensor imaging with functional imaging including resting-state fMRI and metabolic PET [26–28]. These techniques provide anatomical localization and network connectivity insights, improving target personalization.

2.6. DBS efficacy corresponding to a specific gene mutation in PD

2.6.1. Favorable outcomes in monogenic PD

DBS offers robust motor benefits in PD patients with *PRKN* or *LRRK2 p.G2019S* mutations, with studies showing >40–50 % improvement in UPDRS-III scores and significant medication reduction [29,30]. Long-term case reports also confirm durable benefits, such as a 15-year sustained response in a *PRKN* mutation carrier [31]. Similarly, *SNCA* duplication cases may benefit from tremor control in early phases, though outcomes appear more variable [32]. These findings support DBS as an effective treatment in select genetic subtypes, especially when levodopa responsiveness is good.

2.7. Cognitive and neuropsychiatric considerations

GBA1 carriers have raised concern due to reports of earlier cognitive decline following DBS [33]. However, recent data from a multicenter Italian cohort showed comparable cognitive trajectories between DBS and non-DBS *GBA*-PD patients, suggesting DBS does not independently worsen cognition [34]. However, improvements in quality of life may be blunted by faster non-motor progression. In contrast, *SNCA* and other rare mutations (e.g., *SLC9A6*) have been linked to rapid neuropsychiatric decline post-DBS [35,36], highlighting the importance of preoperative genetic profiling, cognitive assessment, and individualized

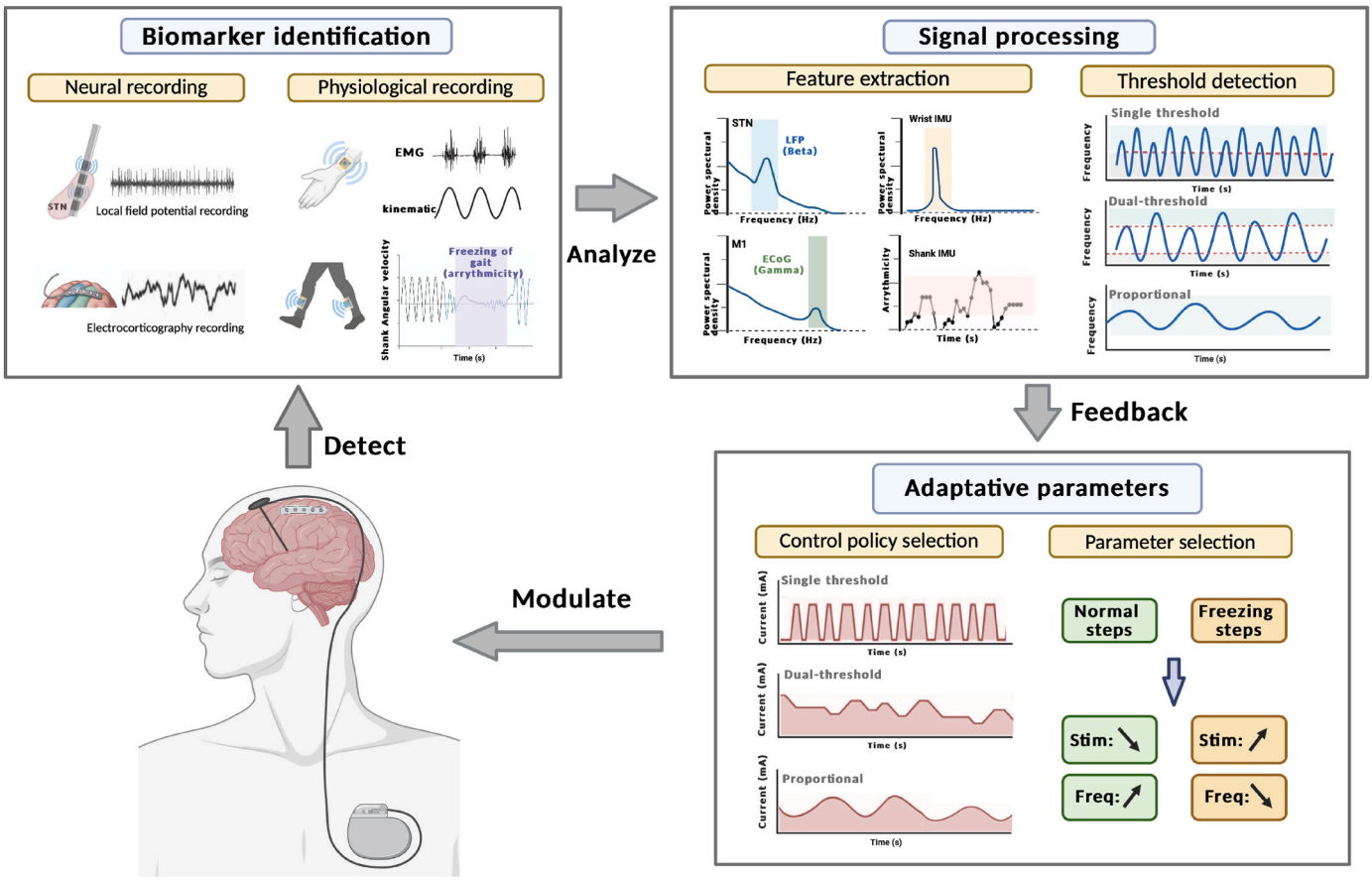

Fig. 2. Adaptive deep brain stimulation (aDBS) algorithm integrating biomarker detection, signal processing, and real-time stimulation adjustment. Neural biomarkers (local field potentials from the subthalamic nucleus and electrocorticography signals) and physiological recordings (EMG, kinematics, gait freezing metrics) are continuously detected and analyzed. Signal processing includes spectral feature extraction (e.g., beta and gamma oscillations) and threshold-based or proportional detection models. The adaptive system selects stimulation policies and symptom-specific parameters according to the patient's motor state—for example, increasing or decreasing stimulation amplitude and frequency during freezing phenomenon versus normal stepping. Closed-loop feedback enables real-time modulation of DBS output, improving symptom specificity and reducing stimulation burden compared with conventional open-loop DBS.

risk-benefit discussions.

2.8. DBS in other movement disorders

Beyond PD, DBS demonstrates efficacy in essential tremor, dystonia, and Tourette syndrome. For dystonia, GPi-DBS is preferred particularly in primary generalized dystonia. Emerging targets include cerebellar nuclei, CM-PF, ventralis oralis complex, and PPN [16,37–40].

2.9. Limitations and complications

DBS carries surgical risks including hemorrhage, infection, and hardware complications. Cognitive decline and mood changes occur, especially in vulnerable patients. Appropriate candidate selection is crucial to maximize benefits and minimize risks. DBS is expected to become more refined and personalized, improving outcomes across broader populations [41].

3. Magnetic resonance-guided focused ultrasound (MRgFUS)

3.1. Mechanism and new targets

MRgFUS uses multiple ultrasound beams focused on a single intracranial target for thermal ablation, with real-time MRI thermometry ensuring precision (Fig. 1). VIM is the most common target for tremor control, while GPi and STN are under investigation for broader PD symptoms [3].

Recent studies explore targeting the PTT for additional symptom benefits [42]. A stepwise dual-target approach (VIM and PTT ablation) shows promise for refractory tremors and akinetic-rigid features in PD.

3.2. Indications and contraindications

MRgFUS is indicated for patients with medication-refractory tremor who are ineligible or unwilling to undergo invasive surgery. Major considerations include skull density ratio, age, and comorbidities, as dense skulls impede ultrasound transmission [43].

3.3. Clinical efficacy

Most MRgFUS thalamotomy series report immediate tremor suppression in 96 % of patients, with 50–70 % reduction in tremor scores sustained up to 3 years in selected cohorts [3,44,45]. In Parkinson's disease, unilateral subthalamic or thalamic ablation produces approximately 50 % improvement in tremor, rigidity, and bradykinesia, while some studies note contralateral benefits suggesting interhemispheric modulation [46,47]. Clinical outcomes depend strongly on lesion volume, targeting accuracy, and patient age, with smaller or eccentrically placed lesions linked to poorer durability [48].

Recent series highlight tremor relapse as an important clinical issue. In a 2025 prospective cohort of 52 patients with tremor-dominant PD, 23 % relapsed within one month, most often younger individuals or

those with smaller lesions [48]. Other studies indicate that relapse usually reflects incomplete or misplaced lesioning along the dentato-rubro-thalamic tract rather than true disease progression [49]. These observations emphasize optimizing targeting through diffusion-tractography guidance and maintaining an effective lesion volume window (~145–220 mm^3) to balance efficacy and safety.

Management of tremor recurrence remains unsettled. Options include repeat MRgFUS, conversion to DBS, or stereotactic lesion revision, all supported mainly by small case series [50,51]. Repeat MRgFUS can restore tremor control in selected cases but requires cautious risk–benefit consideration due to cumulative tissue heating, yet standardized strategies for relapse prevention and re-intervention are still needed.

3.4. Safety and adverse effects

MRgFUS is generally well-tolerated with mild, transient side effects including involuntary movements and speech issues, manageable with medication adjustments [45,46]. Cognitive declines are minimal, with exceptions in verbal fluency and inhibition [52].

3.5. Multi-modal imaging integration

Preoperative SDR (skull density ratio) screening remains essential [53,54]. Current research investigates advanced acoustic modeling and machine learning to predict ultrasound penetration success and optimal sonication angles based on skull morphology [55,56].

3.6. Technological advancements and ongoing research

Recent MRgFUS developments have substantially enhanced both precision and therapeutic versatility. Refined sonication protocols and dual-target ablation techniques now permit tailored lesion volumes and improved symptom control while minimizing adverse effects [5,57]. The use of phased-array transducers enables dynamic electronic steering of ultrasound beams for targeting of deep nuclei, with real-time MRI thermometry providing continuous feedback to optimize lesion accuracy and ensure procedural safety [47,58].

Beyond lesioning, MRgFUS is rapidly expanding toward non-ablative applications. Low-intensity, pulsed ultrasound protocols can transiently open the blood–brain barrier (BBB), facilitating targeted drug or gene delivery to affected regions, while experimental low-energy paradigms explore neuromodulation without tissue destruction [5,59].

Ongoing clinical investigations are evaluating MRgFUS applications for bilateral tremor, dystonia, obsessive-compulsive disorder, and epilepsy. These advances mark a shift from lesion-based therapy toward precision-controlled, noninvasive circuit modulation, positioning MRgFUS as a versatile platform for future neurotherapeutic innovation [59].

4. DBS versus MRgFUS: comparative analysis

4.1. Efficacy, durability and long-term outcomes

Both DBS and MRgFUS show similar efficacy in tremor suppression without significant outcome differences (Table 2), though methodological heterogeneity persists [60,61]. DBS, particularly STN targeting, proves more effective for complex symptomatology, including rigidity and bradykinesia, with sustained effects at 5–15 years in long-term series [62–64]. MRgFUS excels in immediate unilateral tremor relief, especially in elderly patients or surgical contraindications, with mid-term durability (to ~3 years so far) [3,44,45]. However, durability is influenced by targeting accuracy and lesion volume [65], and early relapse is more likely with smaller/eccentric lesions and younger age [48,50]. In PD phenotypes with complex motor features, such as motor fluctuations and troublesome dyskinesias, DBS retains an advantage for comprehensive symptom control [60,61,64,66,67].

4.2. Safety profile and adverse effects

Both treatments report mild to moderate adverse events, typically transient and manageable; serious events are rare but require monitoring [48,68]. DBS entails surgical/anesthetic risks and hardware-related issues, such as lead fracture and infection, yet adverse stimulation effects are typically programmable/reversible and can be mitigated with directional or adaptive paradigms [19,23,24,69]. MRgFUS has fewer hardware-related complications than DBS, but lesioning risks include speech disturbances and gait issues, especially with bilateral lesioning [70,71]. Patient-specific skull characteristics (SDR) materially influence MRgFUS energy delivery and lesion formation; low SDR predicts lower efficacy and higher exposure requirements [53–56].

4.3. Patient selection for each modality

DBS—best suited when.

- Bilateral symptoms or multidomain motor symptoms (e.g., tremor with bradykinesia, rigidity, motor fluctuations, or dyskinesia) where programmability and reversibility are required [60,61,64,66,67].
- Younger to mid-life patients with good levodopa responsiveness, aiming for long-term control [62–64].
- ●Preserved cognition and controlled psychiatric status; multidisciplinary assessment completed.
- ●Genetic aspect: DBS yields strong motor benefit in *PRKN* and *LRRK2* p.G2019S carriers, moderate response in *GBA1* carriers with potential long-term cognitive vulnerability, and variable outcomes in *SNCA* or *SLC9A6* variants with higher neuropsychiatric risk.
- Future flexibility desired (parameter changes, battery upgrades, potential aDBS) [17,20,21].

MRgFUS—best suited when.

- Tremor-dominant phenotype (PD or ET) with unilateral disabling tremor, especially in older or medically fragile patients, or those declining implants [43–45,67].
- Rapid recovery and no hardware are priorities; MRI is feasible and SDR is adequate for safe/efficient sonication [53–56,58].
- Contraindications to open surgery/anesthesia, anticoagulation that cannot be interrupted, or infected hardware risk.
- ●Patient accepts irreversibility and understands limited bilateral capability and mid-term evidence horizon (durability typically reported to ~3 years) with potential early relapse that may warrant repeat MRgFUS or conversion to DBS [44,45,48,50,51,70,71].

4.4. Combined or sequential use

Sequential or hybrid approaches (e.g., MRgFUS for dominant tremor followed later by DBS for complex motor features; or DBS first with MRgFUS “touch-up” for residual tremor) are increasingly reported and may optimize outcomes in complex phenotypes, though prospective data are limited [42,43,72].

5. Future personalized treatment approaches

Personalized neuromodulation is an emerging paradigm in the management of Parkinsonism and related disorders. Growing evidence supports the importance of tailoring DBS and MRgFUS interventions to individual patient characteristics, including genetic background, motor phenotype, disease stage, and neuroimaging markers [73–75]. For instance, carriers of *LRRK2* p.G2019S and *PRKN* mutations generally achieve robust and durable motor improvements following DBS,

whereas *GBA1* carriers may require closer cognitive monitoring due to variable neuropsychiatric trajectories [34,73].

Recent imaging-based connectomic studies have demonstrated that individualized targeting guided by diffusion MRI and functional connectivity mapping can optimize electrode placement and lesion precision, directly correlating with motor outcomes and side-effect profiles [27,28]. In addition, machine learning algorithms trained on local field potentials and kinematic data are increasingly used to predict stimulation response and automatically adjust DBS parameters in adaptive systems [21,76].

For MRgFUS, ongoing work explores genotype- and phenotype-specific lesion planning, dual-target ablation strategies, and real-time feedback control to minimize off-target effects. On the other hand, integration of low-intensity ultrasound neuromodulation and blood–-brain barrier opening for targeted drug delivery offers a potential bridge between surgical and pharmacological precision therapies [5,59].

Looking ahead, a hybrid precision framework uniting genomic, electrophysiological, and neuroimaging data could guide clinicians in selecting between DBS and MRgFUS based on an individual's unique biological and clinical characteristics. Such integrative approaches could redefine therapeutic algorithms for Parkinsonism, improving both efficacy and long-term quality of life.

6. Integration with neurorehabilitation and adjunctive therapies

Integration of neurorehabilitation is essential to maximize functional outcomes following DBS or MRgFUS. While these interventions address abnormal motor circuitry, rehabilitation optimizes neuroplasticity, facilitating adaptation to altered neural output and restoring coordinated motor control.

DBS patients particularly benefit from task-specific physiotherapy, balance and gait training, and cueing-based programs to reduce freezing and postural instability, while speech and cognitive rehabilitation help mitigate stimulation- or disease-related deficits [77,78]. MRgFUS recipients, especially older adults or those with unilateral lesions, may require focused retraining to enhance compensatory mechanisms and prevent maladaptive disuse.

Emerging approaches such as wearable sensors, tele-rehabilitation, and AI-driven feedback systems allow remote, adaptive therapy programs that extend postoperative care to underserved populations [79,80]. Additionally, non-invasive brain stimulation (e.g., tDCS, rTMS) shows promise in enhancing post-lesion cortical reorganization and motor recovery after MRgFUS [81,82].

7. Limitations and research gaps

Limited long-term head-to-head studies comparing clinical efficacy and durability between DBS and MRgFUS in Parkinson's disease exist. Long-term MRgFUS durability and safety data remain unclear. Insufficient data exist on bilateral MRgFUS lesioning safety, particularly persistent adverse effects in PD patients. Both modalities require cost-effectiveness research in underserved populations. Global registries may standardize outcome tracking [83].

8. Conclusion

DBS and MRgFUS represent transformative tools in managing Parkinsonism and movement disorders. Each offers unique advantages, with application depending on disease phenotype, patient comorbidities, and preferences. Ongoing innovations in closed-loop systems, imaging guidance, and precision targeting will enhance outcomes, providing tailored treatment strategies worldwide.

Author contributions

Study concept and design: MK Lu.
Acquisition, analysis and interpretation of data: TL Lee, MK Lu.
Drafting of the manuscript: TL Lee.
Critical revision of the manuscript for important intellectual content: MK Lu.
Study supervision: MK Lu.

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Conflict of interest

All authors report no competing interests.

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