

**REVIEW ARTICLE**

MRI-Guided Focused Ultrasound in Parkinson's Disease and Essential Tremor: Incisionless but Invasive. A Narrative Review

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ABSTRACT

Magnetic resonance-guided focused ultrasound (MRgFUS) is an emerging and promising technology for treating movement disorders, such as essential tremors and tremor-dominant Parkinson's disease. MRgFUS utilizes advanced ultrasound transducer emitters to condense sound waves at a precisely defined point. This technology can target various brain areas, such as the pallidothalamic tract, thalamus, and pallidum, to ameliorate some of the symptoms of Parkinson's disease and other movement disorders, such as dystonic and action-induced tremors. We review the current status of preclinical and clinical trials on the clinical use, treatment outcomes, and indications of MRgFUS.

Keywords Magnetic resonance-guided focused ultrasound; Essential tremor; Tremor dominant Parkinson's disease; Blood-brain-barrier; High-intensity focused ultrasound ablation.

INTRODUCTION

Since its inception in the 1940s, stereotactic surgery has significantly altered the landscape of medical procedures. Before the advent of stereotactic technology, surgical interventions for the brain were often imprecise and relied on a general understanding of the anatomy of the brain. This lack of precision means that the risk of damage to healthy tissue is high, leading to uncertain outcomes. One of the key developments in this field was the introduction of the stereotactic frame by Spiegel et al.¹ This innovative device allows surgeons to map the brain in three-dimensional space, providing them with a reliable refer-

ence for targeting specific deep-seated structures in several neurological condition structures, paving the way for advancements in neurosurgery. Practical applications of stereotactic surgery began to emerge in the 1960s and 1970s, particularly in the treatment of Parkinson's disease (PD) and other movement disorders.

Following the discovery and widespread use of levodopa (from the mid-1970s to the 1990s, which revolutionized the therapeutic outcome of this challenging disease), the need for stereotactic surgery almost disappeared.^{2,3} Long-term medical treatment-resistant sequelae, including fluctuations and dyskinesia, have resulted in the reintroduction of stereotactic surgeries and other surgical methods, such as deep brain stimulation (DBS).⁴⁻⁶ De-

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spite the inherent risks associated with DBS, it offers the advantage of minimizing damage to normal brain tissue.⁷

The initial application of magnetic resonance-guided focused ultrasound (MRgFUS) marked a significant advancement in lesional therapies. It was first utilized for the treatment of movement disorders, particularly tremor, in 2013.⁸⁻¹⁰ The goal is to review all available research that has been conducted on this subject, including clinical trials.

METHODOLOGY

We conducted a PubMed search that encompasses both animal model and human studies published between 1989 and 2025, focusing on the term “focused ultrasound (FUS)” in relation to essential tremor (ET), PD, and dystonic tremor (DT). A comprehensive literature review was performed across major medical journals and trial databases, including Medline, EMBASE, CINAHL, EBSCO, and ClinicalTrials.gov. We prioritized studies that clearly described their cases, included a reasonable number of patients, and presented robust methodologies.

TECHNICAL IMPLEMENTATION OF MRgFUS

MRgFUS employs ultrasound emitters to concentrate sound waves at a precisely defined point within stereotactically determined target tissue, inducing various biological effects that depend on the temperature achieved. At low intensities and temperatures of up to 45°C, a reversible conduction block was created, likely due to the inactivation of sodium channels. Additionally, low-frequency ultrasound (220 kHz) can be used to reversibly open the blood-brain barrier (BBB) and can be visualized using contrast agents; this effect typically lasts for approximately 6 hours. Numerous studies are underway to explore the use of growth factors for the treatment of neurodegenerative diseases and other potential applications.^{11,12}

The current primary application of MRgFUS involves creating FUS lesions in the diencephalic and midbrain regions using devices that operate at mid-frequency ultrasound (650 kHz) with varying intensities.¹³ Lower intensity levels generate moderate temperatures, inducing a reversible blockade that may mimic sodium channel blockade. Conversely, higher intensities resulted in protein denaturation and necrosis. The outcomes depend not only on temperature but also on the duration of sonication, which is quantified by a parameter known as the “thermal dose.” On magnetic resonance imaging (MRI), three concentric types of lesions can be identified by a central necrotic core sur-

rounded by a hyperintense zone along with peripheral edema that leads to reversible functional blockage within weeks.¹⁴ After 12 to 24 months, the final imaging outcome typically presents as either a hypodense small dot or no significant change. A rabbit model has been used to investigate the effects of FUS, revealing a similar three-zone pattern identifiable on serial MRIs.^{15,16}

To date, anatomical changes resulting from therapeutic ultrasound lesions have been studied in two patients who died from unrelated conditions and underwent autopsies. One of these patients was treated with peak temperatures exceeding 60°C, and the FUS lesion exhibited a typical MRI pattern¹⁷ that corresponded pathologically to a spherical lesion. The patient died 10 days posttreatment, the inner core displayed necrosis surrounded by a ring of homogeneous changes and apoptotic cells, and the third concentric structure indicated edema. The second patient received treatment at lower sonication temperatures for a longer duration and was autopsied after several months. Unlike the first patient, this individual did not exhibit classical necrosis but rather preserved cells with significant demyelination.¹⁸ Notably, both patients experienced clinically significant improvements in their tremors. The effects of MRgFUS on tissue are not uniform; for example, perfusion through relatively large vessels may create heat sinks that result in a more complex pattern.¹⁹ Further studies are needed in this area, and available animal models could enhance our understanding of the underlying molecular processes.²⁰

MRgFUS is a noninvasive procedure that does not require incisions, burr hole trephination, or electrode insertions. It is hypothesized that lesioning through high-intensity FUS allows precise targeting while minimizing thermal damage to the surrounding skull and scalp. The procedure follows a standardized protocol for lesioning, which begins with administering escalating doses of low-power sonication to increase the target temperature to approximately 45°C, below the threshold for coagulation necrosis. At this stage, both radiological assessments of the thermal lesioning location and clinical evaluations for safety are performed. Once the accuracy of the target is confirmed, several high-power sonications are applied under magnetic resonance (MR) thermometry guidance, gradually increasing the acoustic power and energy until the temperature at the target reaches between 55°C and 60°C.

MRgFUS: TARGETED SITES

MRgFUS thalamotomy

The procedure is performed with the patient lying in an MRI scanner, following head shaving and the attachment of a stereotactic head frame (Figure 1A). Although light sedation is an op-

tion, patients can remain awake, allowing them to provide feedback during the process. The procedure uses continuous MRI and thermal mapping to locate the target area in the brain. Low-power ultrasound was used to confirm the selected site, followed by high-power ultrasound to irreversibly ablate the target tissue. Chilled water is circulated around the scalp to protect it from heat. The treatment lasts approximately 3 hours, with immediate symptom relief. The advantages of this method include a less invasive approach, quicker recovery, and the ability to assess effects before full ablation. It is primarily used for unilateral tremors, as it targets only one side of the brain.²¹

MRgFUS-ventral intermediate nucleus

Another promising approach is ablation of the ventral intermediate nucleus (VIM) thalamic nucleus. Several approaches have been recommended; however, the standard method uses an approximate, atlas-based stereotactic approach (Figure 1B).²² A study of 14 ET patients treated with MRgFUS using highly sensitive white matter nulled the three-dimension magnetization-prepared rapid gradient-echo sequence associated with improved clinical outcomes.

MRgFUS-pallidothalamic tractotomy

The pallidothalamic tract connects the globus pallidus internus (GPi) and ventrolateral portion of the thalamus, and ablation of the pallidothalamic tract (pallidothalamic tractotomy [PTT]) using MRgFUS has been performed since 2011 and has been shown to be a safe and effective intervention for PD.²³

CLINICAL TRIALS OF MRgFUS

MRgFUS in ET

To date, several open-label, prospective, and retrospective studies have demonstrated that MRgFUS leads to clinically significant and statistically robust improvements in patients with ET

(Table 1).

Although studies date back to the early 19th century, foundational research²⁴ highlighted that 20 patients receiving sham treatment under a double-blind protocol for 3 months showed a tremor score improvement of 41% in the treated group, with a 47% improvement in contralateral hand tremor scores. Importantly, disability, as measured by Part C of the Tremor Scale, improved by 62%.

Following the initial pilot studies by Elias et al.⁸ and Lipsman et al.,⁹ a comprehensive pivotal study involving 56 patients who underwent MRgFUS (Elias et al.¹⁰) revealed clinically significant and statistically robust improvements in tremor scores. Additional studies from the early 20th century²⁵⁻²⁷ indicated a 46% improvement in disease-related quality of life scores for ETs (using the Quality of Life in Essential Tremor Questionnaire [QUEST]), although the following adverse events were frequently reported at both 3 and 12 months: paresthesia (9%–36%), gait disturbances (9%–36%), limb dysmetria (4%–12%), weakness (2%–4%), dysarthria (up to 2%), and dysphagia (up to 2%), with many of these events resolved by the 12 months. A follow-up study by Chang et al.²⁸ involving 67 patients treated with MRgFUS over 2 years revealed sustained improvements, with 55% reduction in contralateral hand tremor scores at 6 months, 53% at 1 year, and 56% at 2 years, indicating that the treatment response remained remarkably stable. Initially, 91% of the cohort exhibited a postural tremor with an amplitude exceeding 1 cm, and 97% had an action tremor greater than 1 cm. By 2 years post-treatment, only 7% of the patients displayed a postural tremor, whereas 14% presented with an action tremor larger than 2 cm. Notably, no new complications were reported between the 1- and 2-year follow-ups. Several uncontrolled studies and clinical experience have shown consistent findings with controlled data regarding tremor management interventions. Five-year data indicated a minor yet not statistically significant decline in tremor efficacy, similar to that observed with VIM-DBS. The improvement in quality of life, measured

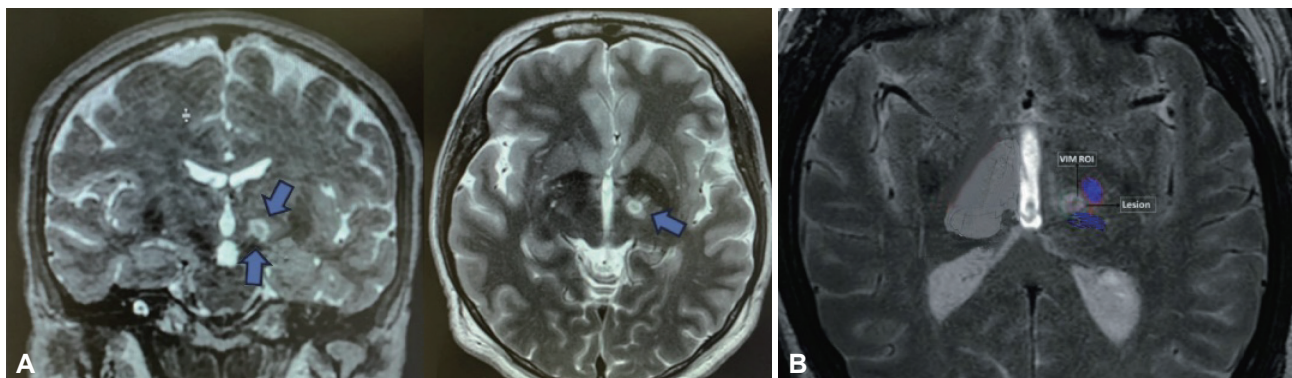


Figure 1. MRgFUS target of thalamotomy and VIM. A: MRgFUS target of thalamotomy. B: MRgFUS VIM. Arrows indicate the site of lesion in each cases. MRgFUS, magnetic resonance-guided focused ultrasound; VIM, ventral intermediate nucleus; ROI, region of interest.

Table 1. Clinical trials for MRgFUS for ET

Author, year	Type of study	Design	Conclusion
Tröster et al., ⁸⁶ 1999	Prospective study	ET patients after thalamic stimulation	Unilateral thalamic DBS was associated with significant improvements in tremor and dominant-hand fine visuomotor coordination
Elias et al., ⁸ 2013	An open-label, uncontrolled study	Unilateral VIM of the thalamus in 15 patients with severe, medication-refractory ET	In this pilot study, ET improved in 15 patients treated with MRgFUS thalamotomy. Large, randomized, controlled trials will be required to assess the procedure's efficacy and safety
Lipsman et al., ⁹ 2013	Prospective study	4 patients with chronic and medication-resistant ET were treated with MRgFUS	Patients showed immediate and sustained improvements mean reduction in tremor score of the treated hand was 89.4% at 1 month and 81.3% at 3 months
Gallay et al., ³¹ 2016	Prospective study	21 consecutive patients suffering from chronic, therapy-resistant ET were treated with MRgFUS	The mean ETRS score for all patients was 57.6±13.2 at baseline and 25.8±17.6 at 1 year (n=10). The HF 16 score reduction was 92% global tremor relief after CTT was 92%
Elias et al., ¹⁰ 2016	Randomized prospective case control study	76 patients with moderate-to-severe ET that had not responded to at least two trials of medical therapy and randomly assigned them in a 3:1 ratio to undergo unilateral FUS thalamotomy or a sham procedure	MRgFUS thalamotomy reduced hand tremor in patients with ET. Side effects included sensory and gait disturbances (Funded by InSightec and others; ClinicalTrials.gov number, NCT01827904)
Hopfner et al., ²⁶ 2016	Observational-cross sectional study	138 ET cases were diagnosed according to the tremor investigation group criteria and carried out assessments including Archimedes spirals rating, EQ-5D, Beck Depression Inventory and QUEST German version	A neuropathology consortium is suggested to standardize postmortem analyses and enhance the characterization of neuropathological findings, particularly in the cerebellum
Federau et al., ³⁰ 2018	Retrospective study	8 patients with medication-refractory ET treated by amended to MRgFUS system at 3T	The correlations between thermal dose, lesion volume posttreatment and at 1 year, and outcomes after 1 year were very promising
Zaaroor et al., ⁴⁰ 2018	Prospective study	Patients with severe medication-resistant tremor who underwent unilateral VIM thalamotomy using MRgFUS	MRgFUS created a lesion at the planned target in all patients, resulting in cessation of tremor in the treated hand immediately following treatment, and UPDRS decreased (24.9±8.0 to 13.4±9.2) months after treatment
Kovács et al., ²⁷ 2017		133 consecutive patients fulfilling the criteria for either definite or probable ET were enrolled	Patient-reported outcomes and self-completed questionnaires are crucial for patient assessments and clinical decision-making in both clinical practice and research. The study reports that the Hungarian version of the QUEST scale has satisfactory clinimetric properties, consistent with the original research
Iacopino et al., ³⁶ 2018	Prospective study	Study of results of toMRgFUS VIM thalamic ablation in a sample of patients with ET and with PD	All the ET and PD treated patients who completed the procedure showed an immediate amelioration of tremor severity, with no intra- or posttreatment severe permanent side effects
Chang et al., ²⁸ 2018	Randomized study	76 patients with moderate-to-severe ET, who had not responded to at least two trials of medical therapy following unilateral thalamotomy	Mean hand tremor score at baseline improved by 55% at 6 months disability score at baseline improved by 64% at 6 months
Harary et al., ³⁴ 2019	Two controlled trials	Studies that evaluated DBS and MRgFUS for the unilateral treatment of refractory ET were compared	Both DBS- and MRgFUS-treated patients had significant tremor improvement that was sustained for 1-year and significant improvement in QOL. The MRgFUS cohort had higher rates of persistent neurologic AE, whereas the DBS group had higher rates of surgery- and hardware-related AEs, including intracranial haemorrhage
Halpern et al., ³³ 2019	A controlled multicenter prospective trial	3-year follow-up of a controlled multicenter prospective trial	Measured scores remained improved from baseline to 36 months on CRST. Range of improvement from baseline was 38%–50% in hand tremor, 43%–56% in disability, 50%–75% in postural tremor, and 27%–42% in QOL

Table 1. Clinical trials for MRgFUS for ET (continued)

Author, year	Type of study	Design	Conclusion
Park et al., ³⁸ 2019	Retrospective study	Intractable ET tremor patients treated with MRgFUS thalamotomy for ET	4 years postoperatively, improvement of the hand tremor score was 56%, disability score was 63%, postural score was 70%, and action score was 63%. There was no permanent adverse effect throughout the 4-year follow-up period
Sinai et al., ³⁹ 2020	Prospective study	44 ET patients treated with unilateral MRgFUS VIM thalamotomy over 5 years	Tremor was significantly improved immediately following MRgFUS in all patients. CRST scores in the treated hand improved by a median of 23 at 5 years. QUEST scores showed significant improvement, with median change of 28 points at 5 years
Paschen et al., ⁸⁷ 2019	Prospective study	20 patients with ET with DBS	VIM-DBS improved the TRS in the short term and long term significantly. Long-term worsening of the TRS was more profound during stim-ON than in the stim-OFF condition, indicating habituation to stimulation
Gallay et al., ⁶¹ 2020	Prospective study	Unilateral MRgFUS on ten chronic therapy-resistant ET patients	Reduction in CRST score at 3 months. No bleeding or infection. No dysarthria
Martínez-Fernández et al., ⁵⁴ 2020	Retrospective study	9 patients with refractory ET and previously treated with unilateral FUS thalamotomy at least 5 months before underwent bilateral treatment	9 patients were treated. No permanent AEs. CRST score improved by 71%, reduction in head and voice tremor was 66%
Ito et al., ³⁷ 2020	Prospective study	10 ET patients who underwent MRgFUS left-sided VIM thalamotomy	60% decrease in the average CRST score of the right hand persisted until 2 years. CRST score of the left hand and the average QUEST score showed no improvement. Headache was the most common AE no delayed AEs
Iorio-Morin et al., ⁸⁸ 2021	Prospective, single-arm, single-blinded phase two trial of second-side magnetic resonance	Guided FUS thalamotomy in patients with ET	Improvement in QOL at 3 months. Tremor significantly improved in all patients
Fukutome et al., ⁸⁴ 2022	Retrospectively study	Study of efficacy and safety of staged bilateral VIM thalamotomy for refractory ET	Progressive reduction of CRST total scores from baseline to second postop review
Cosgrove et al., ²³ 2023	Prospective, controlled, multicenter clinical trial	The long-term safety and efficacy of unilateral MRgFUS thalamotomy for medication-refractory ET in a cohort of patients	CRST scores for postural tremor (Part A) for the treated hand remained significantly improved. Combined hand tremor/motor scores (Parts A and B) also improved by 49.5% and 40.4%
Kaplitt et al., ⁸⁹ 2024	Prospective, open-label study	Bilateral FUS thalamotomy on ET	Tremor/motor score improved from 17.4 to 6.4. Significant improvement in mean (SD) postural tremor and mean (SD) disability score 12 developed- ataxia, 6 persisted at 12 months
Hino et al., ³⁵ 2024	Retrospective study	Real-world data from 101 patients who underwent MRgFUS between July 2019 and March 2022 at a single institution were analyzed	MRgFUS significantly improved total CRST and tremor score across all SDR subgroups. Additionally, there were no significant differences in the improvement rates among the 4 subgroups
Saporito et al., ⁹⁰ 2024	Prospective evaluation	Cognitive and neurobehavioral profile of patients with ET or PD related tremor undergoing MRgFUS thalamotomy at 1 year-follow-up following the treatment	Significant improvement was detected at the 1 year-follow-up assessment in anxiety and mood feelings (Hamilton Anxiety rating scale). Beck depression Inventory II score

MRgFUS, magnetic resonance-guided focused ultrasound; ET, essential tremor; DBS, deep brain stimulation; ETRS, essential tremor rating score; CCT, cerebellothalamic tractotomy; HF, hand function; FUS, focused ultrasound; EQ-5D, EuroQol-5 dimension; VIM, ventral intermediate nucleus; UPDRS, Unified Parkinson's Disease Rating Scale; QUEST, Quality of Life in Essential Tremor Questionnaire; PD, Parkinson's disease; QOL, quality of life; AE, adverse event; CRST, Clinical Rating Scale for Tremor; TRS, tremor rating scale; SD, standard deviation; SDR, skull density ratio.

by the QUEST, significantly increased by approximately 60% at 1 year, decreased to 50% at 3 years, and further declined to 30% at 5 years. This decline was anticipated despite a smaller reduction in the unilateral motor response, and cognitive function remained stable, with no significant changes observed.²⁹⁻³⁵ Numerous open cohort studies have focused on larger patient groups, with one study reporting a 60% improvement in tremor scores at 6 months and another showing an 85% improvement. Additional research highlighted sustained quality-of-life improvements for up to 2 years post-intervention. The adverse events reported were comparable to those reported in a pivotal study.³⁶⁻⁴¹

Clinical trials of MRgFUS in PD

The first successful unilateral MRgFUS pallidotomy was conducted in 2015 in a 55-year-old woman with PD (Table 2).⁴² Following the procedure, the patient experienced significant reductions in both levodopa-induced dyskinesia and cardinal motor symptoms. In the same year, a prospective study of MRgFUS thalamotomy by Schlesinger et al.⁴³ also showed promising results in a patient with PD suffering from severe refractory tremors. The first randomized controlled trial (RCT) conducted by Bond et al.⁴⁴ in 2017 demonstrated improvements in the Clinical Rating Scale of Tremors A and B subscores, motor function, and quality of life, with no reported cognitive impairments or negative effects on mood. The most common adverse events following treatment include mild or transient finger paresthesia, ataxia, and orofacial paresthesia. The persistent adverse effects noted included mild hemiparesis (two incidents, 8% early on), orofacial paresthesia (four incidents, 20%), finger paresthesia (one incident, 5%), and ataxia (one incident, 5%).^{40,45} Based on this study, the Food and Drug Administration (USA) granted approval for the treatment of tremor-dominant Parkinson's disease (TDPD) in December 2018. A few nonrandomized controlled trials have also highlighted the benefits of VIM-MRgFUS for patients with ET or TDPD. Yamamoto et al.⁴⁶ reported that the improvements were sustained over a 1-year follow-up period. Furthermore, Sinai et al.⁴¹ observed only a few instances of complete ($n=2$) or partial ($n=8$) recurrence during follow-up of 1–5 years in a cohort of 26 patients with TDPD who underwent VIM-MRgFUS for tremor control.

The subthalamic nucleus (STN) has emerged as a key target for the treatment of PD because of its hyperactivity and resulting excessive inhibition of thalamocortical projections. Previous animal and clinical studies have demonstrated that stereotactic radiofrequency (RF) ablation can significantly alleviate motor symptoms in PD patients.⁴⁷⁻⁵²

An open-label pilot study conducted in 2018 by Martínez-Fernández et al.⁵³ assessed the efficacy of MRgFUS subthalamotomy in patients with asymmetric PD. Reported adverse

events included transient gait ataxia, pin-site pain, increased blood pressure, facial asymmetry, and moderate impulsivity. Another RCT by the same research group in 2020 showed a significant reduction in the mean Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III score in the treatment group. Notable adverse effects include dyskinesias, weakness on the treated side, speech disorders, facial weakness, and gait disturbances.^{53,54} More recently, Armengou Garcia et al.⁵⁵ reported improved motor and nonmotor outcomes following unilateral MRgFUS subthalamotomy for the treatment of asymmetric PD, with enhancements in visual memory and a reduction in cognitive problems.

In 2023, Martínez-Fernández et al.⁵⁶ demonstrated a 23% improvement in total motor scores in the OFF-medication state. Additionally, in 2024, Martínez-Fernández et al.⁵⁷ reported a unilateral STN-FUS study involving 10 patients with early-stage PD, revealing effects and side effects similar to those observed in more advanced cases, which may serve as a pilot trial for MRgFUS in early PD.

The GPi is the output nucleus of the basal ganglia that processes motor information from the striatum, external pallidum, and STN. Jung et al.⁵⁸ conducted a prospective nonrandomized controlled trial on unilateral MRgFUS pallidotomy for treating Parkinsonian dyskinesia and reported significant improvements in motor function and reductions in dyskinesias in eight out of ten patients. Earlier, Eisenberg et al.⁵⁹ conducted a 1-year multicenter open-label trial of unilateral MRgFUS pallidotomy in patients with PD, demonstrating consistent benefits, particularly a 45% improvement in the lateralized motor score and 59% improvement in the total dyskinesia scale (the primary outcome). Moderate side effects were noted in both the short and long term, including visual field deficits (1 incident), cognitive disturbances (1 incident), dysarthria (4 incidents, 2 persistent), fine motor deficits (2 incidents), and balance difficulties (1 incident), which is consistent with findings in other studies, resulting in more favorable overall outcomes.

The PTT is an efferent motor pathway linking the GPi and thalamus and is a target for surgical ablation in PD patients. The most recent RCT on unilateral MRgFUS pallidotomy for PD by Krishna et al.⁶⁰ in 2023 randomized 69 patients to undergo ultrasound ablation of the internal globus pallidus, with 25 patients receiving sham procedures. Compared with 32% in the sham group, 69% of the responders in the treatment group died. The overall incidence of adverse events, both short- and long-term (7 days/12 months), included dysarthria (2/1), gait disturbances (2/0), loss of taste (2/0), visual disturbances (1/0), imbalance (2/2), and nonmotor symptoms (4/2), all of which were lower than those observed with STN-FUS.⁶⁰ In 2020, Galloway et al.⁶¹ performed unilateral MRgFUS pallidotomy, and the same

Table 2. Clinical trials for MRgFUS for PD

Author, year	Type of study	Design	Conclusion
Mitchell et al., ⁹¹ 1989	Animal case control study	Induced generalized parkinsonism vs. unilateral parkinsonism studied on monkeys	The central importance of the STN in all three conditions is proposed, and supportive evidence for the excitatory nature of subthalamic efferent fibres is adduced
Bergman et al., ⁴⁹ 1990	Experimental animal study	Artificially induced parkinsonism studied on monkeys	Significant role of excessive activity in the STN in PD
Guridi et al., ⁵⁰ 1996	Experimental animal case control study	9 monkeys treated with MPTP in which the STN was unilaterally lesioned by kainic acid injection	Significant role in role of STN hyperactivity in the pathophysiology of parkinsonism and may have surgical implications
Alvarez et al., ⁵⁰ 2005	Open label pilot study	Patients with staged subthalamotomy compared to 11 patients received bilateral simultaneous subthalamotomy	Bilateral subthalamotomy may induce a significant and long-lasting improvement of advanced PD
Alvarez et al., ⁵¹ 2009	Prospective study	89 patients with PD were treated with unilateral subthalamotomy and followed up	Unilateral subthalamotomy was associated with significant and sustained motor benefit
Na et al., ⁴² 2015	Case report	Study of unilateral MRgFUS pallidotomy in a patient with PD	Unilateral MRgFUS controls levodopa-induced dyskinesia and cardinal motor symptoms
Schlesinger et al., ⁴³ 2015	Prospective study	7 PD patients, with severe refractory tremor, underwent VIM thalamotomy using MRgFUS	Thalamotomy using MRgFUS is safe and effective in PD patients
Bond et al., ⁴⁴ 2017	Randomized controlled study	53 patients underwent FUS thalamotomy or a sham procedure at 2 centers from October 18, 2012, to January 8, 2015 were studied	FUS thalamotomy for patients with TDPD demonstrated improvements in medication-refractory tremor by CRST assessments
Zaaroor et al., ⁴⁰ 2018	Prospective study	Patients with severe medication-resistant tremor who underwent unilateral VIM thalamotomy using MRgFUS	MRgFUS created a lesion at the planned target in all patients, resulting in significant relief of symptoms
Martínez-Fernández et al., ⁵³ 2018	Prospective, open-label pilot study	10 patients with asymmetric parkinsonism underwent FUS unilateral subthalamotomy	MRgFUS unilateral subthalamotomy was well tolerated and improved motor features
Jung et al., ⁵⁸ 2019	Prospective, nonrandomized, single-arm clinical trial	10 patients with medication-refractory, dyskinesia-dominant PD underwent unilateral MRgFUS pallidotomy using the Exablate 4,000 device	Demonstrated the efficacy of pallidal lesioning using MRgFUS and certain limitations that are unavoidably associated with incomplete thermal lesioning due to technical issues
Eisenberg et al., ⁵⁹ 2021	Multicentre open-label study	20 patients with PD and L-dopa responsiveness, asymmetrical motor signs, and motor fluctuations, including dyskinesias, underwent unilateral MRgFUS ablation of the globus pallidus internus	MRgFUS pallidotomy is feasible and effective in the treatment of patients with PD and motor fluctuations, including dyskinesias
Polyakova et al., ⁴⁸ 2020	Experimental animal study	2 male Japanese monkeys were studied for recording of STN neuronal activity was performed 2 or 3 d/week for several months	The STN, receives cortical inputs through the cortico-STN direct and cortico-striato-external pallido-STN indirect pathways

Table 2. Clinical trials for MRgFUS for PD (continued)

Author, year	Type of study	Design	Conclusion
Martínez-Fernández et al., ⁵⁴ 2020	Randomized control study	40 enrolled patients, 27 were assigned to FUS subthalamotomy (active treatment) and 13 to the sham procedure (control)	FUS subthalamotomy in one hemisphere improved motor features of PD
Gallay et al., ⁶¹ 2020	Case series	52 interventions in 47 patients	Significant reduction in UPDRS
Gallay et al., ²³ 2021	Prospective study	10 patients suffering from chronic and therapy-resistant PD having received bilateral PTT were followed for 1 year after operation of the second side	UPDRS reduced by 52%. Gait and postural instability unchanged. Speech difficulties increased
Armengou Garcia et al., ⁵⁵ 2021	Prospective study	14 patients underwent unilateral MRgFUS subthalamotomy were studied	MRgFUS is safe and that the benefits on PD motor features are similar to what was previously reported
Yamamoto et al., ⁴⁶ 2021	Prospective study	1-year outcomes of VIM thalamotomy with FUS in patients with medication resistant TDPD	VIM-FUS thalamotomy can be safely and effectively used to treat patients with TDPD
Sinai et al., ⁴¹ 2022	Retrospective study	Outcome of FUS thalamotomy in TDPD patients with 1–5 years of follow-up	CRST score, median UPDRS score, decreased significantly
Krishna et al., ⁶⁰ 2023	Randomized controlled study	94 patients, 69 on active treatment were studied	Adverse events were mild Unilateral pallidal ultrasound ablation improved motor function or reduced dyskinesia

MRgFUS, magnetic resonance-guided focused ultrasound; PD, Parkinson's disease; STN, subthalamic nucleus; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; FUS, focused ultrasound; TDPD, tremor-dominant Parkinson's disease; CRST, Clinical Rating Scale for Tremor; VIM, ventral intermediate nucleus; UPDRS, Unified Parkinson's Disease Rating Scale.

group conducted bilateral PTT procedures in 2021. Unilateral PTT lesions in 51 patients led to a 38% reduction in the UPDRS III score in the OFF-medication state, along with significant decreases in tremor and rigidity and fewer treatment complications. Bilateral PTT treatment in 10 patients resulted in a 52% reduction in the UPDRS III score and notable enhancements across all major symptoms. Adverse events were related primarily to speech difficulties, with seven of the 10 patients requiring speech therapy after 1 year. One patient experienced hiccups for 10 months, whereas the other experienced episodes of uncontrollable laughter. These findings indicate that further validation of these interventions is required.^{23,61}

MRgFUS–OTHER INDICATIONS

DT

Two patients with DT and one patient with tremor associated with dystonia gene mutations were successfully treated using VIM-MRgFUS.⁶² Horisawa et al.⁶³ demonstrated significant improvement in a patient suffering from action-induced guitarist cramp following MRgFUS lesioning of the thalamic ventro-oral nuclei. A subsequent study was conducted involving 10 patients with various forms of action-induced focal hand dystonia, all of whom underwent MRgFUS targeting the ventro-oral nucleus of the thalamus. On average, participants experienced 59% improvement on the Tubiana Musician's Dystonia Scale and 82% improvement on the Arm Dystonia Disability Scale. Notably, one patient continued to experience dysarthria even after 12 months.⁶³

A study by Peters et al.⁶⁴ involved 63 patients, including those with ET, DT, and PD tremor, to assess the effectiveness of unilateral MRgFUS thalamotomy. Results showed that both ET and DT patients experienced a 61% improvement in hand tremor scores and significant improvements in quality of life after 24 months. The study explored various surgical targets for tremor treatment and found that while targeting the GPi may reduce dystonia, focusing on the VIM offers better tremor relief. There is ongoing debate about the best surgical approach for DT, with some experts suggesting dual-target strategies; however, the findings confirm that unilateral MRgFUS thalamotomy is an effective treatment option for DT.

MRgFUS–FUTURE DIRECTIONS

Neuropsychiatric disorders

Neuropsychiatric disorders such as Obsessive-Compulsive Disorder (OCD), Tourette syndrome, and major depressive disorder arise from abnormal neural circuits involving limbic re-

gions, including the anterior limb of the internal capsule, anterior cingulate cortex, subgenual cingulate cortex, and ventral striatum. Jung et al.⁶⁵ conducted a study in which they performed bilateral capsulotomy via MRgFUS in patients with medically refractory OCD. They reported a significant improvement of over 33% in the Yale-Brown Obsessive-Compulsive Scale score after 6 months of follow-up (Figure 2).^{65,66}

Neurocognitive disorders

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder, and the amyloid cascade hypothesis suggests that the deposition of amyloid-beta is a critical initial step in the pathogenesis of AD. One significant challenge in treating this disease is the BBB, which poses major obstacles to the effective delivery of therapeutic compounds to the brain. The BBB imposes size and biochemical restrictions on the passage of molecules. In a study by Lipsman et al.,⁶⁷ a FUS device featuring 1,024 individual transducers operating at a frequency of 220 kHz was used, and a power ramp test was conducted following the initial injection of microbubbles. A gadolinium-enhanced T1-weighted sequence was subsequently performed to provide definitive evidence of BBB opening. The success of the barrier opening and its subsequent restoration were verified, aligning with findings from animal models.^{67,68}

Neuro-oncology (brain tumors)

Although resection is the main treatment for brain tumors, a clinical trial using MRgFUS to target brain tumors (NCT 01473485) has recently been completed, and the results will be available soon.

Epilepsy syndromes

Epilepsy syndromes represent another promising area for the application of MRgFUS surgery. A clinical trial (NCT02804230) is currently underway to evaluate the feasibility and safety of MRgFUS ablation for epilepsy associated with subcortical visible pathologies, such as hypothalamic hamartomas and tuberous sclerosis. In addition to its ablation capabilities, MRgFUS can also be employed to reduce cortical excitability and suppress epileptogenic discharges. This is due to the mechanical effects of acoustic waves, which can alter the properties of cellular membranes. Furthermore, a trial is ongoing to investigate the neuromodulatory effects of low-frequency FUS (NCT02151175).

Neuro-vascular

Stroke is one of the leading causes of long-term morbidity and mortality worldwide. The concept of sonothrombolysis utilizing MRgFUS has emerged as a viable alternative or neoadjuvant therapy for patients with stroke who are unable to benefit from conventional treatment options. This innovative therapy leverages the piezoelectric effect to generate acoustic waves, which induce inertial cavitation, ultimately leading to the disintegration of blood clots.^{69,70}

Chronic pain syndromes

Chronic neuropathic pain that does not respond to standard medical treatments, including sodium channel blockers, anti-convulsants, and interventional nerve blocks, presents a significant challenge for modern medicine. Some countries have officially approved MRgFUS ablation for chronic pain management. In the United States, a phase I clinical trial (NCT03111277) is currently recruiting participants with uncontrolled chronic pain.

Indication	Targets	Future directions
Essential tremor	Ventral intermediate nucleus or posterior subthalamic area	Neuro-psychiatric disorders Example: OCD, MDD
Tremor dominant Parkinson's disease	Pallidothalamic tract, subthalamic nucleus, other targets GP, GP externa, GP interna, internal capsule, left, mammillothalamic tract, putamen	Neuro-cognitive disorders Example: Alzheimer's disease
Dystonic tremor	Ventral intermediate nucleus, ventral lateral nucleus of thalamus	Neuro-oncology disorders Example: brain tumors
		Neuro-vascular disorders Example: stroke
		Epilepsy syndromes Example: refractory temporal lobe epilepsy
		Chronic pain syndromes Example: refractory neuropathic pain

Figure 2. A summary of indication, targets, and potential future directions for use of MRgFUS. OCD, obsessive-compulsive disorder; MDD, major depressive disorder; GP, globus pallidus; MRgFUS, magnetic resonance-guided focused ultrasound.

who are willing to undergo MRgFUS ablation. Comprehensive clinical outcomes from large-scale studies on MRgFUS thalamotomy for pain relief will be available in the near future.

DBS VS. MRgFUS SURGERY FOR PD

The two primary targets for DBS in PD patients are the STN and GPi. In addition, the thalamic VIM and pedunculopontine nucleus can be specifically targeted for tremor management. Numerous RCTs⁶³ have confirmed the therapeutic effects of DBS, recommending its use to alleviate both motor and nonmotor fluctuations, as well as dyskinesias and refractory tremors. The clinical application of DBS predates the development of MRgFUS over several decades.⁷¹⁻⁷⁴

DBS and MRgFUS fundamentally differ in their neural modulation mechanisms. DBS employs electrical currents to either inhibit or stimulate specific target nuclei and can also influence adjacent white matter areas, alleviating symptoms such as tremors; it utilizes adjustable electrodes, allowing for personalized therapeutic effects, although optimizing the treatment can be complex and time-consuming. In contrast, MRgFUS completely ablates the targeted areas to eliminate neural activity.^{62,75-77}

DBS requires frequent hospital visits for programming and may result in long-term complications, such as device malfunction or infection, with a notable percentage of patients needing revision surgery. In contrast, MRgFUS focuses on lesioning and is most beneficial in the early stages of the disease, with its efficacy gradually decreasing as the disease progresses. MRgFUS does not require an extensive programming period, which is particularly advantageous for patients who have difficulty visiting hospitals.^{77,78} Other limitations of DBS include its unsuitability for patients with dementia or severe systemic diseases, whereas MRgFUS surgery may be a viable alternative for those contraindicated for DBS.⁷⁹ However, factors such as skull density can influence the appropriateness of MRgFUS, particularly among Asian patients, and certain implants may disqualify others from undergoing the procedure.^{80,81} Unlike established protocols for DBS, MRgFUS remains an emerging treatment that requires further research, particularly regarding its application in PD. Various studies have demonstrated improvements with both DBS and MRgFUS, with DBS generally yielding more significant outcomes based on established data, whereas MRgFUS has shown promising but comparatively fewer improvements in small-scale trials. The text highlights the need for comprehensive reviews and larger studies to better understand and compare these interventions for PD. Compared with DBS, MRgFUS is less invasive, more cost-effective, and associated with fewer surgical risks, as it does not require hardware implantation. How-

ever, the decision for optimal outcomes should also involve patients and their caregivers.

DISCUSSION

MRgFUS is an innovative treatment that employs a promising technique to create precise stereotactic lesions in the brain, a process that could previously only be accomplished through open stereotactic surgery or RF lesioning and incisionless radiosurgery, although less established. One main drawback of MRgFUS is its lesional nature compared with that of DBS, although the effects can be evaluated beforehand. Similar to DBS, MRgFUS requires complete immobilization of a patient's shaved head. However, unlike DBS, it does not require skull opening, and the treatment is conducted within an MRI environment without the need for anesthesia. Thus, MRgFUS is particularly suitable for elderly or frail patients despite the lesional nature of the treatment, and many patients perceive it as significantly less invasive than DBS, which warrants detailed discussion with patients, especially given that lower limb tremor-dominant subtypes are common among Emirati females, as indicated by the EmPark study conducted by Metta et al.⁸² Currently, MRgFUS is being evaluated for various movement disorders. Furthermore, a promising but unapproved application of MRgFUS involves reversible and localized opening of the BBB, which could facilitate targeted pharmacological or molecular treatments. For patients with ET who have not responded to standard pharmacological treatments or those with drug-resistant refractory ETs, unilateral treatment has demonstrated effectiveness, providing results comparable to the current standard of DBS. However, long-term data for this treatment are available for only up to 5 years, in contrast to the 15–20 years of data available for VIM-DBS. Although adverse events occur more frequently with this treatment than with DBS, they are generally less severe and mostly reversible. Common complications include ataxia and balance issues, which are not always entirely resolved. Importantly, there have been no reported instances of bleeding or infections associated with this treatment. The use of bilateral MRgFUS for ET is less established and unclear; however, few studies by Scantlebury et al.⁸³ and Fukutome et al.⁸⁴ have demonstrated that bilateral staged MRgFUS is efficacious for the treatment of bilateral ETs with sufficient intervals (>1 year) between procedures, and it remains uncertain whether axial tremor symptoms are sufficiently addressed. Cognitive and emotional side effects have been examined to a limited degree; however, thus far, there is no evidence of long-term deterioration. For severely affected elderly patients unable to undergo DBS, this treatment often represents the only viable option with adequate efficacy (Figure 3).

In PD, VIM-FUS effectively alleviates drug-resistant tremors with short-term success comparable to that observed in patients with ET. This treatment specifically improves tremors associated with PD; however, it does not significantly address akinesia, rigidity, postural disturbances, or other symptoms sensitive to dopamine levels. Further testing with larger cohorts and additional long-term data is necessary. Evidence suggests that long-term deterioration may limit its efficacy. Nonetheless, drawing from our experience with VIM-DBS, new targets that hold promise for mitigating this issue are being tested. The adverse event profile appeared to be similar to that of MRgFUS in patients with ET. While STN-FUS has demonstrated expected results across a broad range of motor symptoms and improvements in quality of life, the outcomes for Gpi-FUS have been less convincing thus far. The effects on dyskinesia were comparable; however, quality of life assessments were not performed. Further research is necessary to evaluate the efficacy of Gpi-MRgFUS. Additionally, the potential of bilateral treatment has not been published for either intervention, or long-term data will ultimately guide the future of these therapies. Despite numerous uncertainties, this innovation represents a significant advancement in the treatment of advanced PD while preserving dopaminergic sensitivity.

DBS has a well-established role in the treatment of PD, supported by numerous RCTs that have demonstrated its effectiveness in reducing motor fluctuations, dyskinesia, and tremors. The STN and GPi are primary DBS targets, whereas the thalamic VIM and pedunculopontine nucleus may also be considered for tremor and gait issues. DBS modulates brain activity through adjustable electrical currents but can involve adjacent brain matter and presents challenges in optimizing therapy and managing side effects, requiring frequent hospital visits and potential complications. Conversely, MRgFUS works by ablating target areas to eliminate neural activity, providing benefits primarily in early-stage PD with limited flexibility for postoperative adjustments. MRgFUS does not require extensive programming and is easier for patients who struggle with frequent hospital visits. However, certain anatomical considerations and implant limitations may disqualify patients with MRgFUS. DBS is typically bilateral, whereas MRgFUS treatment is usually unilateral. Pallidotomy is a potential target for MRgFUS; however, it presents specific challenges, including the difficulty of focusing ultrasound rays on the target, identifying the precise area within the pallidum to treat, and the close proximity of the optic nerve. Currently, it is uncertain which target is optimal for alleviating PD symptoms or if different targets are needed for different pa-

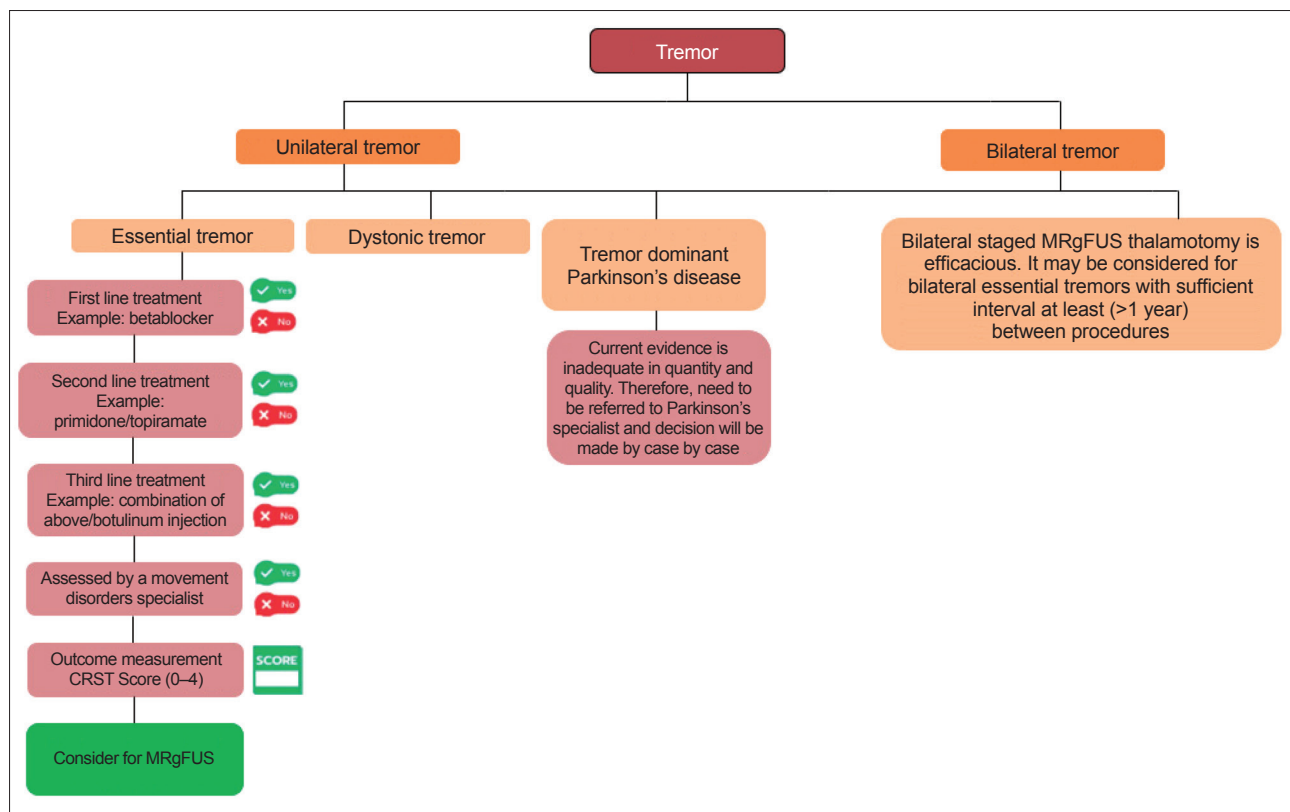


Figure 3. Proposed pathway for use of MRgFUS in unilateral or bilateral tremor. MRgFUS, magnetic resonance-guided focused ultrasound; CRST, Clinical Rating Scale for Tremor.

tients. Additionally, the feasibility of performing bilateral treatments remains unclear, as the existing procedures are unilateral to minimize serious adverse events. Recent reports from a multicenter trial on FUS thalamotomy for ET highlighted adverse effects, such as gait disturbances and persistent numbness, suggesting that this treatment should be conducted at specialized centers with experience. MRgFUS has been approved for the treatment of medication-resistant PD symptoms in regions such as Israel, Europe, Korea, and Russia; however, further research is required to refine patient selection and determine appropriate treatment targets. The clinical landscape shows that while DBS protocols are well defined, MRgFUS remains an emerging intervention for PD. The aim of this study⁸⁵ was to compile data on the efficacy and safety of both treatments rather than directly comparing them, highlighting the need for further studies to better understand the role of MRgFUS in PD management.

PTT, pallidotomy, and subthalamotomy are three promising MRgFUS lesioning treatments that effectively address tremors in addition to other cardinal symptoms of PD. In addition to MRgFUS thalamotomy, two additional lesioning procedures for tremors include RF thalamotomy and gamma knife radiosurgical (GKRS) thalamotomy. Thalamotomy for ET and TDPD is now well established. The use of MR thermometry for lesion prediction and the provision of real-time clinical feedback regarding intraprocedural tremor control are notable advantages. These features render MRgFUS thalamotomy superior to both RF and GKRS thalamotomy in most cases.⁸⁵

CONCLUSION

MRgFUS is a promising treatment for patients with PD who experience medication-resistant symptoms, particularly tremors and motor complications. Patients generally show significant benefits with few transient side effects. Different treatment centers have targeted various brain areas, such as the pallidothalamic tract, thalamus, and pallidum. However, the target that yields the best results for specific symptoms remains unclear. The lack of uniform outcome measures complicates comparisons between studies. Despite this, the findings indicated similar improvements in motor scores between the different treatment targets. Long-term efficacy poses challenges, as symptom recurrence has been noted, particularly in patients with a history of ET; this highlights that MRgFUS might not be ideal for certain PD patients with a background of ET. Collaboration between neurologists and neurosurgeons in patient selection and treatment planning is crucial for successful MRgFUS and clinical outcomes. Further research on staged bilateral MRgFUS targeting areas outside the basal ganglia, as well as the potential for multiple simul-

taneous lesions in patients with PD, could be valuable.

Conflicts of Interest

The authors have no financial conflicts of interest.

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