

The Use of Magnetic Resonance Imaging-guided Focused Ultrasound in Movement Disorders— A Review

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The use of surgical treatments for movement disorders has been well established for several decades, with a strong focus, in the past, on ablative lesioning procedures and, more recently, deep brain stimulation. Magnetic resonance imaging (MRI)-guided focused ultrasound (MRgFUS) is emerging as a newly recognized surgical technique for the treatment of various movement disorders. The most robust data, demonstrating safety and efficacy of MRgFUS, have been published in trials directed at treatment of essential tremor (ET); however, many trials are underway to define its role in other movement disorders, such as Parkinson's disease with preliminary results echoing those from studies in ET. The full potential for use of MRgFUS, both in the field of movement disorders and beyond, is only beginning to be explored.

Keywords

Essential tremor, Parkinson's disease, tremor, thalamotomy, focused ultrasound

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Over the past few decades, the use of surgical techniques for the treatment of movement disorders has become well established. Ablative lesioning procedures, including radiofrequency ablation and gamma knife radiosurgery, were utilized in practice starting in the 1960s, and deep brain stimulation (DBS) was introduced in the 1980s. Indications for these procedures have included motor fluctuations and levodopa-induced dyskinesia in Parkinson's disease (PD), medication-refractory essential tremor (ET) or, more rarely, dystonia. Here, we review the emerging technology of magnetic resonance imaging (MRI)-guided focused ultrasound (MRgFUS) with regard to its background, current evidence for use, and potential future applications.

Introduction of technology

FUS is emerging as a newly recognized surgical option in the field of movement disorders. Though robust trials studying the clinical application of MRgFUS have only recently been carried out, its roots date back to the 1950s when the Fry brothers of Illinois described use of ultrasound energy for precise lesioning of the internal capsule of cats.¹ While this technique initially required craniectomy for accurate energy focusing, the advent of a phased array transducer has allowed for an incisionless procedure with retained precision.

The technique for use of MRgFUS has become largely standardized. A patient's head is shaved to avoid possible heat trapping between hair and scalp and a water-filled elastic cap is placed over the scalp. Lesions are targeted using 1,024 ultrasonic transducers arranged in a hemispheric orientation (*Figure 1*). The utility of MRgFUS as a lesioning technique is based on studies showing that tissue changes occur when temperatures reach 55–65°C.² In practice, initial energy pulses are applied to reach a non-ablative temperature of 40–45°C. Lesion accuracy is determined by clinical examination of the patient while temperature monitoring is provided through MRI thermometry. A series of sonications are then delivered to reach goal temperature and clinical effect. Prior studies by Jeanmonod et al. have demonstrated accuracy of this technique to within 1 mm of a target lesion.³ This precision, along with the ability to monitor treatment effect in real-time, have made MRgFUS an attractive tool for treatment of multiple movement disorders with the most robust data emerging from trials in ET.

Essential tremor

ET is one of the most common movement disorders worldwide estimated to affect almost 5% of individuals over 65 years old.⁴ The tremor is fast frequency (4–12 Hz) with postural and kinetic components; it primarily affects the arms but can involve the head, voice, trunk, and legs.⁵ While the diagnosis does not shorten a person's lifespan, the tremor can impair function, lead to disability

and diminish overall quality of life. Pharmacologic therapy includes first-line agents propranolol and primidone, and second-line agents including topiramate, gabapentin, atenolol, alprazolam, and others.⁶ While medication is effective for most patients with ET, large population studies have suggested that 25–50% of ET is refractory to medication.⁵

Stimulation and ablation of the thalamic ventral intermediate nucleus (Vim) has been shown to effectively reduce tremor in ET.⁷ Multiple trials report clinical improvement of ET following radiofrequency thalamotomy,^{8,9} gamma knife radiosurgery^{10–13} and DBS.¹⁴ Comparison studies of these varying techniques are limited. Schuurman et al.'s randomized study comparing unilateral radiofrequency thalamotomy versus bilateral DBS in patients with PD, ET, or multiple sclerosis suggests that thalamic stimulation is more effective with regard to tremor suppression than thalamotomy with a lower overall rate of adverse events; however, one mortality was reported in the stimulation group related to intracerebral hematoma.⁹ The morbidity associated with historical surgical techniques has led to exploration of additional procedural tools.

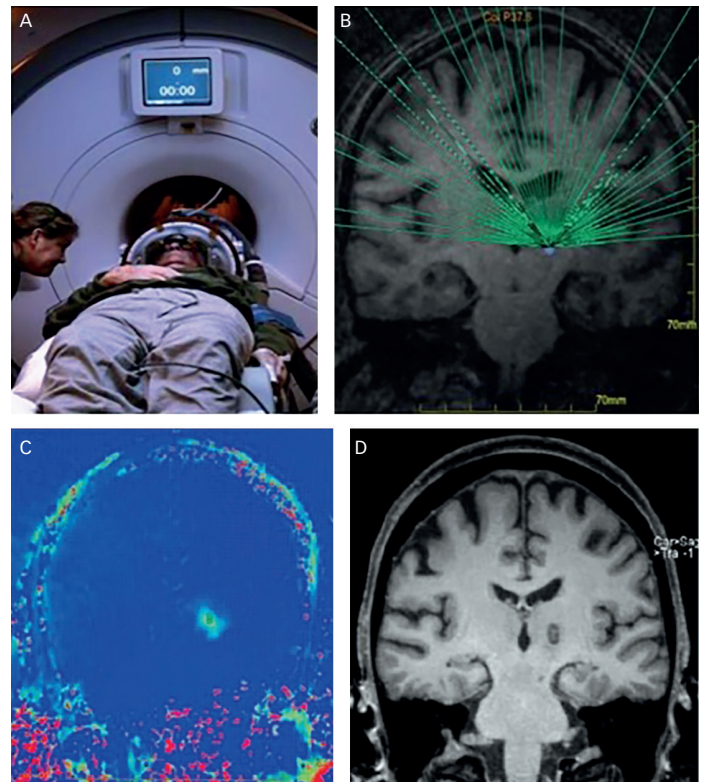
Since 2010, there has been new attention given to the use of FUS for the treatment of ET with the publication of multiple pilot trials. Lipsman et al. published a small, open-label study which included outcomes of unilateral thalamotomy in four patients, targeting the Vim. Patients were followed for 3 months with outcomes measured by scores on the Clinical Rating Scale for Tremor (CRST). An 81.3% reduction in tremor was reported at 3 months. Participants additionally reported a 45.5% improvement in fine motor tasks (writing, drawing), and 51.1% reduction in subjective functional disability at 3 months. The adverse effects included persistent finger paresthesias in one patient at 3 months, and a deep venous thromboembolism 1 week after the procedure in another patient.¹⁵

Chang et al. published a feasibility trial, in which 11 participants were recruited to undergo unilateral focused-ultrasound thalamotomy. Of the 11 participants, only eight reached therapeutic temperature. These patients were followed for 6 months at which time they reported improvement in parts A, B, and C of the CRST. Parts A and B involve clinician/investigator rating of tremor severity with a patient writing, drawing spirals, pouring water, and other physical exam tasks. Part C of the CRST relates to patient-reported disability due to tremor. Despite the participants' clinical improvement, MRI lesions disappeared after 1 month. There were minimal intra-procedural side effects reported. One patient experienced mild balance problems following the procedure, but this resolved with 1 month of steroids.¹⁶

Elias et al. published a larger, open-label study, in which 15 patients were recruited for unilateral FUS thalamotomy targeting the Vim. Follow-up extended to 12 months with outcomes measured on CRST. Patients experienced a relative reduction in contralateral tremor of 75% from baseline, at 12 months. There was also significant improvement in disability, improved quality of life, and improved physical function ($p=0.001$). Immediate adverse effects included transient contralateral paresthesias and unsteadiness. One patient developed persistent dysesthesias of a single finger.¹⁷

Building on the results of their pilot study, Elias et al. went on to publish the pivotal trial¹⁸ which led to US Food and Drug Administration (FDA) approval of MRgFUS for treatment of ET in July 2016. This multicenter, prospective,

Figure 1: Aspects of magnetic resonance imaging-guided focused ultrasound¹⁸



Included with permission of Dr Elias and reproduced from the New England Journal of Medicine.¹⁸ Panels demonstrate A: patient positioning, B: 1,024 ultrasonic transducers arranged in hemispheric orientation, C: thermometry guidance, and D: magnetic resonance imaging lesion.

randomized trial confirmed the results of prior pilot studies. Elias et al. recruited 76 patients with moderate to severe ET. Study participants were randomized 3:1 to receive ultrasound-guided thalamotomy versus sham procedure. Patients and assessors were blinded to treatment group. Hand tremor severity (based on the CRST) improved by 47% at 3 months in the treatment group, compared to 0.1% in the sham group. This effect was sustained at 12 months with a 40% improvement from baseline of tremor severity in the treatment group. In addition to tremor improvement, the individuals who underwent FUS thalamotomy had improved overall disability scores and improved quality of life (based on the Quality of Life in Essential Tremor Questionnaire [QUEST]), with the most significant improvement noted in the psychosocial domain. Adverse effects during this trial included gait disturbance in 36% and sensory disturbance in 38%; these symptoms did not persist in the majority of patients at 12 months (9% and 14%, respectively).¹⁸ This study was the first to provide robust data demonstrating the effect of MRgFUS thalamotomy, with sustained improvements noted in tremor severity, disability, and quality of life.

Though FUS has proven to be safe and effective for unilateral thalamotomy in patients with ET, further work will be required to determine durability of benefit. With this consideration, it will also be important to see if tremor re-emerges and if retreatment with MRgFUS thalamotomy has value. While lesioning procedures have typically been used for unilateral treatments only, understanding the safety and therapeutic effects of bilateral lesioning may be explored in the future. As such, comparing concurrent versus

staged procedures will be important. A study published in 2016 by Galloway et al. demonstrated, in a small number of patients with ET, that bilateral lesioning of the cerebellothalamic tract could be effectively performed in staged procedures, though with increased gait instability reported as an adverse effect.¹⁹ Additional questions include what, if any, long-term cognitive effects of FUS thalamotomy in ET may have, particularly with bilateral procedures.

Parkinson's disease

Surgical treatment for PD has been explored since the early 20th century.^{20,21} Due to high morbidity and mortality of initial open procedures, the technique of closed stereotactic functional neurosurgery was developed starting in the 1940s. With the advent of levodopa in the late 1960s, surgical treatments for PD fell out of favor and were not re-examined rigorously until the 1980s as a way to target the motor fluctuations associated with chronic levodopa use.²² DBS was developed during that time and approved by the FDA for treatment of PD in 1997. Over the course of several decades, the target for DBS in PD has shifted to preferentially include the globus pallidus interna (GPI) and subthalamic nucleus (STN). Because of the ability to modulate its effects, DBS has become the favored surgical option for treatment of PD. Thalamotomy and pallidotomy are now usually reserved for select individuals, including those with surgical contraindications, those desiring palliative treatments, and those with strong preference away from DBS. The successful use of FUS in the ET population, however, has led to further exploration of this technique for PD. Currently, data on the safety and utility of FUS lesioning in PD has been limited but is being vigorously explored.

Thalamus

The Vim of the thalamus has been a target for lesioning procedures for treatment of tremor in PD for many years. MRgFUS thalamotomy in PD has recently been explored.

Magara et al. enrolled 13 patients with treatment-resistant PD. The majority of participants suffered from tremulo-akinetic disease phenotype. The pallidothalamic tract was targeted with the first group of patients receiving a single application of ultrasound energy, and the second group receiving multiple applications of energy (four to five in total). Follow-up examinations were performed at 3 months. This study demonstrated that repeated application of energy allowed for more sustained effects with a 60.9% mean total Unified Parkinson's Disease Rating Scale (UPDRS) score reduction noted in the second group, versus 7.6% reduction in the first group at 3 months.²³ There were no procedure-related side effects reported in either group. Based on the Mini Mental Status Test and the Hospital Anxiety and Depression Scores, there was no change in mood or cognition pre and post procedure for either group.

Schlesinger et al. studied seven patients with moderate to severe Parkinson tremor, performing unilateral FUS Vim thalamotomy to the side with most severe tremor.²⁴ Patients were followed for 3–12 months. Results showed a significant improvement at 1 week on the mean UPDRS (from 37.4±12.2 points to 18.8±11.1, $p=0.007$), UPDRS Item 20 mean score (from 2.7±1.1 to 0.0±0.0, $p<0.001$) and UPDRS Item 21 mean score (from 3.0±1.0 to 0.0±0.0, $p<0.001$). Quality of life as measured by the Parkinson's Disease Questionnaire (PDQ39) also improved significantly at 1 week (42.3±16.4 to 21.6±10.8, $p=0.008$). These improvements persisted at 3 months. Side effects included hypogeusia, subjective gait instability and difficulty tandem

walking, the latter two of which resolved. The Mini Mental Status Exam scores were stable before and after the procedure.²⁴

A randomized, sham-controlled trial by Bond et al. was recently completed with enrollment of 27 subjects (in submission). The primary outcome measured tremor improvement between the procedure and sham groups at 3 months based on the CRST. Preliminary results show a 50% improvement in hand tremor at 3 months in patients undergoing FUS despite a strong placebo effect, with 22% improvement reported in the sham group. Outcome at 1 year showed a 40.6% improvement in tremor scores in the treatment group along with 32% reduction in UPDRS motor scores ($p=0.088$ and 0.033, respectively).²⁵ Subjects undergoing sham treatment also showed improvement in both measures. While there was a significant difference between active and sham groups in tremor reduction measured by CRST, the difference in UPDRS part III was not significant. Cognitive measures were not different between the groups at 3 months.

Prior studies in the PD population have suggested that cognition may be affected following thalamotomy, particularly when performed in the left hemisphere.²⁶ This risk for this effect following MRgFUS thalamotomy is currently unknown but will be important to study in the future.

Subthalamic nucleus

The anti-tremor effects of either ablation or stimulation of the STN have historically made it an attractive target for functional neurosurgery in PD. Prior reviews have suggested that unilateral subthalamotomy not only improves the cardinal features of PD in the on and off medication states, but additionally allows for a substantial decrease in the daily requirement of levodopa, thereby often leading to decreased dyskinesia. Side effects from unilateral STN ablation can include hemiballismus/hemichorea and postural instability, though these are typically transient.²⁷ The effects of FUS on the STN are unclear at this time but multiple trials are currently under way to explore this (ClinicalTrials.gov Identifiers: NCT02003248 and NCT02252380). As of yet, there are no published preliminary data from these studies available.

Globus pallidus

The GPI has been a favored target for lesioning and DBS particularly due to its effects on suppressing dyskinesia in PD, though there is also well characterized benefit in bradykinesia and rigidity. A case report from Na et al. has demonstrated safety and efficacy of FUS pallidotomy in a single patient with PD with sustained effects 6 months later. This patient experienced an 80% reduction in the UPDRS Part I score, a 51% reduction in the Part II score, and a 60% and 54% reduction in the Part III score "on" and "off" medication, respectively, by 6 months. No adverse effects of the procedure were documented.²⁸ A multicenter feasibility trial is currently underway exploring unilateral FUS-guided lesioning of the globus pallidum for medically-refractory dyskinesias in advanced PD.

Use of focused ultrasound in other movement disorders

There is limited data, at present, for the use of FUS in less common movement disorders. The safety and efficacy of MRgFUS in treatment of ET and PD would suggest that this technique could be successfully applied to other movement disorders such as chorea or dystonia. The use of DBS in dystonia is well established with the target typically the GPI, and other less studied targets including the STN or the thalamus. In 2017, researchers from Tokyo published a case report of an individual with focal hand dystonia who

was successfully treated with MRgFUS to the ventrooralis nucleus of the thalamus.²⁹ One case report demonstrated efficacy of MRgFUS in tremor associated with Fragile X tremor ataxia syndrome (FXTAS).³⁰ There are no trials published evaluating MRgFUS in the treatment of chorea.

The future of focused ultrasound

Low-intensity focused ultrasound

While high-intensity FUS lesioning has received the most recent attention, research into low-intensity FUS (LIFUS) is gaining momentum in the field of neuromodulation. Though multiple modalities for neural stimulation are currently available, they either require an invasive surgery (in the case of DBS and vagal nerve stimulation) or lack target specificity (in the case of transcranial magnetic stimulation and cranial electrotherapy stimulation). LIFUS could provide a non-invasive precise targeting technique for neuromodulation. While the exact mechanism of LIFUS is unknown, prior studies have suggested that lower power sonications can cause either inhibitory or excitatory effects which are reversible.³¹ The threshold for thermal ablation is not met with lower intensity sonications. Tufail et al. observed clinical motor contraction following stimulation of the motor cortex of mice,³² while others have described reversible suppression of visual-evoked potentials using LIFUS.³² The potential uses of LIFUS not only in neuromodulation but also brain mapping suggest that this is a novel and emerging technology; however, the efficacy and duration of effect of this technique is currently unknown.

Use of focused ultrasound in other diseases

FUS is not only under review for use in multiple movement disorders, but is being applied as a treatment for many other neurologic and

non-neurologic diseases. These include, but are not limited to, treatment of neuropathic pain,³ tumor ablation,³⁴ and sonothrombolysis for stroke therapy.³⁵ MRgFUS is also being studied as a means for drug delivery across the blood–brain barrier, which may have implications for treating brain tumors, demyelinating disorders, neuroinflammatory conditions, and other disorders where targeted therapy may be indicated.^{36,37}

Summary

Though various surgical techniques have been adopted as treatment methods for various movement disorders, the development of FUS for lesioning procedures adds a new treatment paradigm. MRI guidance intraprocedurally, phased-array transducers, and real-time clinical feedback allow for precise lesioning using FUS techniques. MRgFUS has been shown to be effective and safe. The most robust evidence for use of this technique comes from studies targeting patients with ET with reproducible effects following FUS thalamotomy including a sustained decreased tremor, decreased disability and improved quality of life. These studies led to approval of MRgFUS for the treatment of ET in 2016. Studies exploring the efficacy and safety of MRgFUS in Parkinson's patients for treatment of tremor or dyskinesias are currently under way with promising preliminary data; however, the ideal ultrasound target in this disease has been yet to be defined. There is a paucity of data regarding use of MRgFUS in rarer movement disorders though individual case reports have also been published demonstrating efficacy in FXTAS tremor.³⁸ Larger studies will be required to define, not only the role of MRgFUS for these rarer diseases and the long-term effects of unilateral versus bilateral lesioning, but also the role of this treatment vis-à-vis currently utilized and effective therapies such as DBS. □

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