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REVIEW

# Treating patients with movement disorders using MRI-guided focused ultrasound: recent developments and challenges

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**Abstract:** MRI-guided focused ultrasound (MRgFUS) is being considered in the treatment of movement disorders like essential tremor and Parkinson's disease and has shown promising preliminary results both in terms of effectiveness and safety. However, several technical challenges have come to light that must be addressed. This review examines several studies using MRgFUS to treat essential tremor and Parkinson's disease and discusses the following challenges: adequate energy delivery with brachycephalic and dense skulls, adverse events related to procedural time, the need to further understand the role of high-intensity focused ultrasound in brain mapping, and the need for multiple sonications at lesional temperatures for permanent tremor capture. Preliminary experiences reported with this technology have been promising, and the challenges discussed here can be addressed with additional data and experience. In the future, MRgFUS is likely to play an important role in the treatment of movement disorders.
**Keywords:** MRgFUS, movement disorder, essential tremor, Parkinson's disease

## Introduction

Essential tremor (ET) and Parkinson's disease (PD) are the two most common movement disorders. The prevalence of ET is approximately 0.4%–6% in the general population, while PD prevalence is much lower at approximately 0.3%–1% in people over 60 years of age.[1–3] Current medical management for ET includes propranolol, primidone, gabapentin, or benzodiazepenes, while patients with PD typically receive carbidopa-levodopa, dopamine agonists, or anticholinergics.[4–6] Over time, it is common for patients to develop medication resistance or side effects in both ET and PD, at which time surgical options are considered. Currently there are a variety of procedures to treat movement disorders. The most common is deep brain stimulation, involving placement of electrodes that emit electrical signals to regulate abnormal neuron processes.[4,5] Typically, the ventral intermediate nucleus (VIM) is targeted for ET, while either the subthalamic nucleus or globus pallidus internus is the target of choice for PD.[4–6] Thalamotomy, which involves producing an ablative lesion at the target site that causes tissue necrosis, is another common surgical technique. The ablation can either be created by radiofrequency (use of a heat probe inserted to the target site that produces heating temperatures of 80°C) or gamma-knife (radiosurgery that directs radiation produced from cobalt-60 to ablate the target location).[4,5]

MRI-guided focused ultrasound (MRgFUS) is an incision-less procedure that uses focused ultrasonic waves to create lesions at specific intracranial targets. These ablations typically occur below 60°C, as higher temperatures may cause uncontrollable tissue damage from cavitation events.[7,8] The procedure is most similar to radiofrequency

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thalamotomy, but with some exceptions. MRgFUS has been used to treat conditions including uterine fibroids, metastatic bone cancer, and, most recently, movement disorders.[9] During the earlier years of MRgFUS, the procedure required removal of a portion of skull bone to ensure adequate delivery to the brain.[10] It was not until the turn of the 21st century when the first successful transcranial MRgFUS procedure was performed that the technology began to become advantageous for treating neurological disorders.[10,11] To date, the MRgFUS has received US Food and Drug Administration approval for treatment of bone metastases and uterine fibroids. Premarket approval for the treatment of ET was granted in July 2015.

This paper explores some of the technical challenges associated with MRgFUS in the two movement disorders studied so far, ET and PD. These include treatment of brachycephalic and dense skulls, procedure time length, brain mapping, and the need for several sonications during treatment.

## Essential tremor

The use of MRgFUS for treatment of ET is relatively new and remains experimental. Nevertheless, studies evaluating the use of MRgFUS for treating ET have provided us with information pertaining to the efficacy and safety of the device.[12–14] More importantly, these studies highlight some of the technical limitations this technology must overcome in order to be considered a standard surgical intervention for tremors.

## Brachycephalic skulls

Inadequate temperature rise at a desired location due to physical characteristics of the cranium such as calcifications, shape, size, and thickness can create barriers to sonication efficacy.[11–14] Another related challenge in using MRgFUS for brain disorders is delivering adequate energy through the skull that is simultaneously efficacious and safe for the patient. Chang et al[12] showed that three out of the eleven cases treated for ET by MRgFUS failed to achieve an adequate temperature rise, resulting in poor tremor capture. Maximal temperatures achieved were below 50°C (approximately 42°C) with 24,000 J delivered. While the authors suggested inadequate heating could be caused by certain procedural elements (distance from transducer elements and patient skull) and technical aspects (angle of wave introduced into the skull), they also postulated that there is an inverse relationship between skull volume (based on measurements from above the anterior commissure–posterior commissure) and maximum temperature; data showed correlation coefficient of 0.003.[12] In other words, they suggested a large cranial volume potentially caused the failed cases. A follow-up study in which eleven patients received transcranial MRgFUS ablation of the VIM nucleus of the thalamus to treat ET took skull density into consideration by devising a ratio between skull marrow thickness and mean inner and outer cortical bone thickness. For the eleven cases treated, the ratio ranged from 0.15 to 0.71.[15] After analyzing the relationship between the calculated ratio and the maximum temperature, it was found that all cases had ratios below 0.3 with maximum temperatures below 45°C. Based on the extrapolation of data from all cases, including the three failed cases in this study, the authors suggested that skull density ratios below 0.40 had a higher probability of not producing lesional temperatures despite high energy delivery during sonication treatments. Ratios below 0.30 never achieved lesional producing temperatures (ie, temperature rises above 45°C).[15] This suggests that both skull volume and density must be taken into consideration when deciding if MRgFUS is a viable option. How do we overcome this issue? A potential solution would be a combination of increased energy delivery coupled with different phase modulation patterns of the sonication waves that will help to prevent overheating of surrounding tissue and allow for greater flexibility in generating wave patterns. However, significant challenges in engineering design need to be overcome before effective implementation of this proposed solution.[15]

## Procedural time

Another technical aspect involves reducing the risk of complications related to procedural time. Two main complications arose in the literature. The first was related to the prolonged prone position required for the procedure. Given that the procedure requires patients to remain in a fixed position for hours at a time, a common concern is the development of deep vein thrombosis (DVT).[14] A study completed in 2013 reported that one patient who underwent MRgFUS for treatment of ET developed lower limb DVT, requiring 3 months of anticoagulant treatment; this was potentially attributed to the length of the procedure.[14]

The second was related to prolonged exposure to the magnetic field. It has been established that vestibular symptoms manifesting as motion sickness (ie, dizziness, nausea, vomiting, etc) occur with patients inside a magnetic field. This is most likely because the magnetic field affects the cellular functions of the neurons controlling the vestibular system.[12] Chang et al[12] found that 50% of subjects reported symptoms of dizziness, nausea, and vomiting. Elias et al[13] also reported symptoms consistent with motion sickness, but concluded that they were "related to sonication". If prolonged procedure time is in fact the underlying reason leading to DVT and/or motion sickness, the obvious mitigation to this risk is to decrease exposure time. This can be accomplished by one or more of the following. First, increasing experience and exposure to the technology, as lack of experience tends to increase total treatment time. Second, devising strategies to decrease pause times helps prevent skull over-heating. In addition, more efficient cooling methodologies are required.

## Brain mapping

During stereotactic procedures, the neurosurgeon probes the target area to help define its boundaries. In deep brain stimulation, for example, microelectrode recordings are typically used.[6,16] Brain mapping is also necessary with use of MRgFUS to treat movement disorders. For targeting a certain brain region for MRgFUS, neurosurgeons take into consideration three different depictions of the target: 1) atlas target (established based on atlas coordinates); 2) prescribed target (position of the target based on intraoperative MR images); and 3) realized target (center of the therapeutic thermolesion).[14] Based on this, three accuracies are calculated: 1) global accuracy (difference between the atlas target and the realized target); 2) device accuracy (difference between the prescribed and realized target centers); and 3) planning accuracy (difference between the atlas and prescribed target center coordinates).[14] The three accuracies are linked as global accuracy = device accuracy + planning accuracy. These calculations help in achieving precise targeting of the brain region of interest in MRgFUS.[14]

All MRgFUS treatments begin at low-power sonication, producing sublesional temperatures and thus potentially reversible physiological effects.[17,18] This allows the subject to become acclimated to the physical demands of the procedure while providing clinicians a method to probe the potential targeting area to ensure accuracy. Given the spatial relationship between the ventroposterolateral nucleus and the VIM, clinicians monitor for paresthesia in the face and extremities.[13] MRgFUS has been shown to produce immediate, clinically significant tremor capture effects, which makes it easier for the clinicians to correlate neurological symptoms with targeting accuracy.[13] Elias et al[13] indicated that four out of the 15 patients reported intraoperative neurological symptoms, which allowed MRgFUS operators to refocus the transducer to create better tremor capture. While low-powered sonications have been shown to produce reversible physiological effects, it is not clear if there are any long-term detrimental effects solely caused by this sonication. No prior research has explored whether numerous low-powered sonications by MRgFUS for mapping in the treatment of movement disorders caused any additional long-term effects to the patient. If this technology were to show promise in this area, it could provide a nuanced approach in targeting for the field of stereotactic surgery.

## Parkinson's disease

Technical challenges have also emerged in using MRgFUS to treat PD.[18–20] The Center for Ultrasound Functional Neurosurgery in Switzerland treated 13 patients for idiopathic PD at the fasciculus thalamicus (so called "pallidothalamic tractotomy" or PTT).[19] The overall procedure was similar to MRgFUS to treat ET, with a few differences in MRI sequences and follow-up time points. The overall safety profile was consistent with the safety profile from ET studies; the most significant adverse event reported was dysarthria.[19] A key focus of this study was the exploration of how to ensure permanent tremor capture.

## Multiple sonications

It is understandable that different targets may require slightly different energy delivery profiles in order to achieve effective results, most likely due to anatomical and physiological differences. The aforementioned study divided the patient population into two groups: the first group received a single sonication (n=4) at maximum energy at the target location, while the second group received 4–5 sonications at maximum energy (n=9).[19] The results showed recurrence of Parkinsonian symptoms approximately 3 months post-MRgFUS procedure, and MRI confirmed that the lesion produced had disappeared for patients who received a single sonication. Despite an otherwise successful procedure achieving lesional temperatures at the target site, permanent tremor capture was not achieved.[19] These four patients later underwent a second treatment with several maximum-energy sonications and did achieve long-term tremor capture.[19,20] The authors attributed the lack of permanent lesion in the initial attempts to the axons of PTT, as the desired axons to be thermocoagulated were protected by myelin sheaths.[19] Extrapolating this information to a broader context, it is clear that in order to achieve permanent tremor capture, the energy delivery profile must involve numerous sonications at lesion-producing temperatures, thereby creating adequate tissue necrosis and thermocoagulation of the axon bundles. The study used 4–5 sonications.[19,20] The total number of sonications, however, is dependent upon the targeted area and anatomical makeup (ie, axons protected by myelin sheaths). Multiple sonications in this study did not produce any new neurological symptoms. In order to treat movement disorders, MRgFUS may require the clinicians to, at a minimum, consider more than one sonication during the treatment-planning phase of the procedure, while balancing the need for safe delivery of sonications.[21,22]

## Concluding remarks

MRgFUS technology is still being refined for use in the treatment of common movement disorders. The challenges fall into two main categories. The first involves how various aspects can be manipulated to better take into consideration the complex anatomy present in neurological structures (eg, skull makeup or axon anatomy). The second involves logistical issues so that the technology can deliver the desired goal (ie, effective tremor capture) in a safe and efficient manner. These challenges include the total number of sonications delivered and the duration of the procedure. Based on the current literature exploring MRgFUS for treatment of movement disorders, there is potential for the research community to develop a framework to solve many of the issues discussed.

## Future directions

Initial results of studies performed both to treat ET and PD show promising results, but certain technical challenges remain. Many of these issues may be resolved with further study and expanded use of the technology. Additional premarket studies will increase exposure of clinicians to the device, which will provide opportunities to overcome some of the technical challenges that remain for MRgFUS, particularly in optimizing for brachycephalic skulls, decreasing "on-table" time, and brain mapping. While use of focused ultrasound in treatment of movement disorders remains experimental, it continues to show great promise.

## Dedication

This paper is dedicated to the memory of Ferenc A Jolesz, MD, the B Leonard Holman Professor of Radiology, Department of Radiology, Harvard Medical School.

## Disclosure

The authors report no conflicts of interest in this work.

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