High-intensity focused ultrasound: past, present, and future in neurosurgery

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Since Lynn and colleagues first described the use of focused ultrasound (FUS) waves for intracranial ablation in 1942, many strides have been made toward the treatment of several brain pathologies using this novel technology. In the modern era of minimal invasiveness, high-intensity focused ultrasound (HIFU) promises therapeutic utility for multiple neurosurgical applications, including treatment of tumors, stroke, epilepsy, and functional disorders. Although the use of HIFU as a potential therapeutic modality in the brain has been under study for several decades, relatively few neuroscientists, neurologists, or even neurosurgeons are familiar with it. In this extensive review, the authors intend to shed light on the current use of HIFU in different neurosurgical avenues and its mechanism of action, as well as provide an update on the outcome of various trials and advances expected from various preclinical studies in the near future. Although the initial technical challenges have been overcome and the technology has been improved, only very few clinical trials have thus far been carried out. The number of clinical trials related to neurological disorders is expected to increase in the coming years, as this novel therapeutic device appears to have a substantial expansive potential. There is great opportunity to expand the use of HIFU across various medical and surgical disciplines for the treatment of different pathologies. As this technology gains recognition, it will open the door for further research opportunities and innovation.

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INTEREST in sound waves dates back to Aristotle's theory of their propagation via air particles.²¹ Vitruvius proved the hypothesis in the 1st century BC by determining the mechanism of transmission of sound waves.³⁶ Ultrasonic waves are sound waves that propagate through matter, and their frequencies are above the hearing range of human ears (> 20,000 Hz). Medical use of ultrasonic imaging started in early 20th century after Paul Langevin used it for submarine detection during World War I.^{6,83} The use of ultrasound transducers for therapeutic purposes started in 1938⁶² and was later applied to the management of inflammatory muscle disorders and rheumatoid arthritis.^{34,35}

In the modern era of minimal invasiveness, high-intensity focused ultrasound (HIFU) promises therapeutic utility

for multiple neurosurgical pathologies. In the current review, we intend to shed light on the use of HIFU in different neurosurgical avenues as well as on its mechanism of action. We also provide an update on the outcomes of various trials and discuss advances expected from various preclinical studies in the future.

Historical Remarks on HIFU

The use of focused ultrasound (FUS) waves for intracerebral ablation was first described by Lynn et al. in 1942.⁵⁴ Later, the Fry brothers designed a complex device with 4 piezoelectric transducers that had the ability to focus pinpoint lesions²⁹ and used HIFU for safe ablation of intracranial tumors by performing craniectomy to create

ABBREVIATIONS AD = Alzheimer's disease; BBB = blood-brain barrier; ET = essential tremor; FUS = focused ultrasound; GBM = glioblastoma multiforme; GSR = global symptom relief; HIFU = high-intensity focused ultrasound; MRgFUS = magnetic resonance-guided FUS; MRgHIFU = magnetic resonance-guided HIFU; OCD = obsessive-compulsive disorder; PD = Parkinson's disease; PRPA = peak rarefaction pressure amplitude; tcMRgFUS = transcranial MRgFUS; tcMRgHIFU = transcranial MRgHIFU; tPA = tissue plasminogen activator; UPDRS = Unified Parkinson's Disease Rating Scale; VIM = ventral intermediate nucleus.

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a window for the transmission of acoustic waves.³⁹ Afterward, HIFU devices were used in many clinical trials for treating tumors of the prostate gland, kidney, and bladder.^{27,33,82}

Originally, HIFU was guided by diagnostic ultrasound imaging, which has limited guidance accuracy and lacks the capacity to determine the real-time temperature.^{82,84} With intraoperative MRI, the magnetic resonance–guided focused ultrasound (MRgFUS) is more precise than ultrasound or a surgeon’s direct visualization. The presonation volume target is identified by MRI, postsonication temperature is measured by proton resonance frequency shift by means of fast gradient-echo sequences, and the ablated volume is identified by means of T2-weighted fast spin-echo sequences.⁴¹

Table 1 summarizes important events in the timeline of the development of HIFU technology and current studies validating its use for various brain pathologies.

Principles and Mechanisms of Action of HIFU

In the MRgFUS procedure, a small target is heated with ultrasound rays, a technique called sonication. The area of tissue exposed to the temperature and the length of exposure to this heat define an equivalent thermal dose, which determines the extent of the thermal lesion.

In HIFU treatment, FUS is applied for local ablation therapy of various types of tumors in the body using an intensity (I_{SATA}) of 100–10,000 W/cm². The primary goal of this technique is to maximize energy accumulation at the target area to induce significant biological reactions (coagulation necrosis) without instigating harm to surrounding tissues.⁵³

For transcranial treatment, a focused piezoelectric transducer is used to converge ultrasonic energy (usually 1–3 MHz for noninvasive applications) into a target tissue and produce localized tissue destruction (Fig. 1). The “focal zone” can be defined as the area where the ultrasound intensity (energy/unit area) is high enough to create a lesion. These lesions are ellipsoidal, 8–15 mm in length, and have a diameter of 1–2 mm (Fig. 1B).

Thermal Mechanisms of Action

HIFU exposure can be either constant (thermal) or pulsed (acoustic cavitation). Ultrasound produces frictional heat by causing vibration of molecules in tissue; a temperature of > 56°C maintained for 2 seconds or more leads to coagulative necrosis.^{13,14,75}

The thermal damage leads to unplanned cell death. The targeted cells retain their outline, their proteins coagulate, and their metabolic activity halts.⁷⁴ In soft tissues, HIFU lesions demonstrate a necrotic center and a rim of functionally impaired glycogen-poor cells, which eventually fade, leaving a sharp edge between the affected and unaffected tissues 48 hours postexposure, described as an “island and moat” presentation.⁷⁸ An intense acute inflammatory response ensues, with the cells detaching from their basement membrane and from each other. This is followed by chronic inflammation and remodeling, which involves cellular regeneration, proliferation, migration, fibroblast infiltration, and removal of debris, lasting up to

TABLE 1. Timeline of the development of HIFU technology from the late 19th century to the present

Year	Description
1880	Piezoelectric effect (Curie)
1907	Electronic vacuum tube (de Forest)
1918	Sonar (Langevin)
1927	Effects on biologic tissues (Looms and Wood)
1942	HIFU effects in animals (Lynn and Putnam; Lynn et al. ⁵⁴)
1950–1969	Molecular studies on HIFU effects (Francis and William Fry; Fry and Meyers ²⁹)
1951–1960	Radiofrequency generator and electrode development (Bernard Cosman, in light of FUS developments)
1951–1967	Radiosurgery and Gamma Knife development (Lars Leksell after ultrasound investigation)
1960–1980	Clinical studies on HIFU surgery with open skull (Fry and Heimburger)
1980s–present	MRI technology
Early 1990s	Ultrasound phased arrays (Hynnen)
Mid-1990s	MR thermometry (Jolesz)
2001	The first integrated MRgFUS machine (InSightec Ltd.)
2006	Report on MRgFUS for treatment of GBM after craniotomy (Ram et al. ⁶⁹)
2009	tcMRgHIFU for chronic neuropathic pain (Martin et al. ⁵⁶)
2009	In vitro study for thrombolysis by histotripsy using HIFU (Maxwell et al. ⁵⁷)
2010	Phase I clinical trial for noninvasive tumor ablation; to prevent heating of the skull, a water cooling, circulating, and degassing was used (McDannold et al. ⁵⁸)
2011–2013	Use of tcMRgHIFU for ET (Elias et al. ²² and Lipsman et al. ⁵³)
2013–2014	In vitro and in vivo studies for sonothrombolysis of ICH (Monteith et al. ⁶⁴ and Harnof et al. ³⁸)
2014	Report on the first experience with tcMRgHIFU for PD (Magara et al. ⁵⁵)
2016	Randomized controlled trial of tcMRgFUS thalamotomy for ET (Elias et al. ²³)
2016	Preliminary report on randomized controlled trial of MRgFUS thalamotomy for PD (Bond et al.) ⁴

ICH = intracerebral hemorrhage.

3 months.^{10,77} Later these lesions become encapsulated by granulation tissue, finally leading to scar formation.⁷⁸

Nonthermal (Mechanical) Mechanisms of Action

The pulsed method of HIFU exposure can cause fast changes in the targeted tissue pressure, known as the peak rarefaction pressure amplitude (PRPA). There is a threshold for PRPA for each tissue at which acoustic cavitation (formation of gas- or liquid-filled cavities) occurs, generally at points of “weakness,” such as the interfaces between different layers of tissue or fluid-filled structures.²⁸ The cavitation occurs when the negative component of the acoustic waves causes liquid components to fail un-

FIG. 1. A: Noninvasive setup of HIFU transducer with transducer tracker, head-motion tracker, and degassed water. **B:** HIFU transducer converging noninvasive transcranial ultrasonic energy at the ellipsoidal focal zone to produce tissue lesions at depth.

der tension, consequently forming gas- and vapor-filled “cavities.”³⁴⁴ These acoustic cavitation bubbles oscillate at large displacement amplitudes and exert shear stresses on the surrounding tissue, causing mechanical tearing. The bubbles expand rapidly and collapse, disrupting the cell membrane and destroying the surrounding tissue structure by a process known as histotripsy.¹⁰

The cavitation damage caused by pulsed exposure is more random than thermally mediated cell death, as cavitation requires the existence of a nucleation site.⁴⁴

Initial Challenges With Transcranial MRgHIFU

Bone has a relatively high attenuation coefficient and absorbs and reflects considerable amounts of ultrasound energy. Its acoustic impedance is much higher than that of the soft tissues. This causes an inferior efficacy of energy transfer and unwanted heating of the skull in transcranial HIFU therapy. To overcome this low-efficiency problem, transducers with a large number of high-energy sources are employed. An external cooling system that circulates chilled water around the scalp helps avoid thermal injury to the scalp. To distribute the heat as widely as possible, the active area has been maximized through a hemispheric design, known as a piezoelectric component arrangement.

Another challenge in transcranial HIFU was the severe aberration of FUS waves. Irregularity in skull thickness and a high speed of sound waves in the bone result in the defocusing of ultrasound beams.^{11,42} A computerized multichannel hemispheric phased-array transducer (ExAblate Neuro, InSightec Ltd.) is now being used to overcome this problem. The direction of each beam from the transducer is controlled by computer calculations and adjusted over different skull thicknesses with the help of CT. Combined

with acoustic simulations, this allows for phase adjustments to focus on a small sharply margined area.⁴³

Current Applications in Neurosurgery

Magnetic resonance–guided high-intensity focused ultrasound (MRgHIFU) is rapidly gaining clinical recognition as a treatment modality that allows noninvasive tissue heating and ablation. The setup consists of a positioning system, a transducer, and a stereotactic head frame, which is placed for patient immobilization during the procedure (Fig. 2). A silicone diaphragm is fitted to the scalp, and the transducer is filled with degassed water (dissolved oxygen below 1.2 ppm). The cooled degassed water (between 15°C and 20°C) is circulated between sonications to prevent unwarranted heating and lower the skull temperature.

Tumor Thermocoagulation

Successful transmission of ultrasound waves for thermocoagulation of intracranial lesions has been described.^{29,30,39,46,47} Glioblastoma multiforme (GBM) is the most common and most aggressive of malignant primary CNS tumors³⁷ and has been the center of attention for multiple HIFU trials. In an article published in 2006, Ram et al.⁶⁹ reported on 3 patients with GBM who underwent MRgHIFU thermal ablation. The shortcomings that they faced included the need for craniectomy, performed 7–10 days before sonication, to get a bone window for the HIFU transmission, and one of the patients had an adverse outcome. The adverse outcome was caused by thermal ablation of brain parenchyma outside the target in the pathway of transmission of the ultrasound waves, leading to neurological deficits. The primary lesions responded to the MRgHIFU with immediate changes in the

FIG. 2. Schematic of tcMRgHIFU setup.

contrast enhancement in T1-, T2-, and diffusion-weighted MRI scans, in addition to thermocoagulation on histological examination.⁶⁹ In 2006, Park et al.⁶⁸ also reported the successful ablation of an anaplastic astrocytoma in a 17-year-old female patient, in whom no other therapeutic option was available. A decrease in the tumor volume and surrounding edema was noted on the 6-month follow-up imaging. In 2010, McDannold et al. reported on a Phase I clinical trial conducted at Brigham and Women's Hospital in 3 GBM patients; the tumors were treated with transcranial MRgHIFU (tcMRgHIFU) using the ExAblate 3000 (InSightec) treatment system.⁵⁸ The authors described the use of transcranial HIFU and real-time temperature measurement of target tissue with MR. This trial was limited by the low power of the HIFU device (650–800 W), which was unable to thermally ablate the focused lesion,⁵⁸ and was stopped when a fourth patient suffered a cavitation-induced intracranial hemorrhage and subsequently died.

In 2014, Coluccia et al.¹⁶ reported a case from an ongoing Phase I trial in which a 63-year-old patient was treated with tcMRgHIFU for a centrally located recurrent GBM. FUS pulses of 10–25 seconds' duration with an acoustic power of 150–950 W were transmitted to the targeted tumor. The treatment consisted of 25 sonications, and the energy was increased until it reached 19,950 J per sonication; the intraoperative MR thermometry identified 17 of the 25 sonications as capable of coagulation, with temperature peaks in the range of 55°C–65°C. Immediate postprocedural diffusion-weighted MRI identified multiple bright lesions in the targeted tumor volume. MRI at 21 days' follow-up demonstrated tumor ablation with no tumor progression. Long-term postprocedural examination showed improvement in neurological deficits.¹⁶

Ultrasound contrast agents, such as preformed microbubbles, amplify focal heating during sonication and have been used to reduce the time-averaged power needed during transcranial FUS ablation.⁷⁹ In a study on rabbits, McDannold et al.⁶⁰ demonstrated that the administration of a microbubble-based ultrasound contrast agent reduced the acoustic power needed to induce lesions to less than one-tenth of what is required to produce thermal lesions without the contrast agents.

Based on these studies, transcranial MRgFUS (tcMRgFUS) seems to be a feasible treatment option for tumor ablation; however, further investigations are necessary. According to Medel et al.,⁶¹ high-grade gliomas are not an ideal pathology for HIFU, and the technique might be more effective for well-circumscribed lesions, such as metastases or benign tumors, inaccessible to surgery. Present trials underway in the United States and Switzerland in patients with metastases and gliomas are expected to provide further data regarding treatment efficiency.

Functional Neurosurgery

Transcranial MRgHIFU now gives interventionists the capability to treat various chronic and therapeutically resistant brain diseases with precise ablation of the focused targets in the thalamus, subthalamus, or basal ganglia.² These locations are centers to many pathological conditions, namely neuropathic pain, Parkinson's disease (PD), and essential tremor (ET).

Chronic Neuropathic Pain

In 2009, Martin et al.⁵⁶ reported the first successful application of tcMRgHIFU for functional neurosurgery. They treated 9 patients with chronic neuropathic pain with

medial thalamotomies. The ablations were precisely located within a diameter of 4 mm according to MRI. There were no neurological deficits on follow-up.⁵⁶

In 2012, Jeanmonod et al.⁴⁵ also reported the use of tcMRgHIFU to perform noninvasive central lateral thalamotomies in 11 patients for chronic therapy-resistant neuropathic pain. They used a hemispheric 1024-element phased-array transducer functioning at 650 kHz to yield precise lesioning of the central lateral nucleus of the thalamus. Pain relief 48 hours postprocedure averaged 68% (range 30%–100%). One patient had a bleed at the target with ischemia in the motor thalamus. Two safety measures were introduced—detection of potential cavitation by a cavitation detector and the maintenance of sonication temperatures below 60°C.

Essential Tremor

In 2013, Elias et al.²² reported on 15 patients treated with tcMRgHIFU ablation of the unilateral ventral intermediate nucleus (VIM) of the thalamus for therapeutically resistant ET from February 2011 to December 2011 in an open-label, uncontrolled study. At 12 months' follow-up, significant improvement was noticed in hand tremors ($p = 0.001$), total tremor scores ($p = 0.001$), disability scores ($p = 0.001$), and quality of life scores ($p = 0.001$) in comparison with the preoperative scores. Adverse effects included transient sensory, motor, speech, and cerebellar abnormalities, with 4 patients developing permanent paresthesias. Lipsman et al.⁵³ treated 4 patients complaining of chronic ET resistant to medical therapy with tcMRgHIFU. These patients underwent precise ablation of the thalamic focus of the ET, with a mean reduction in tremor scores of 81.3% at 3 months compared with baseline. Gallay et al. also reported favorable results for tcMRgFUS cerebellothalamic tractotomy in 21 patients with ET.³¹

In 2016, Elias et al.²³ reported on their randomized controlled trial of tcMRgFUS thalamotomy versus a sham procedure. Hand-tremor scores improved in tcMRgFUS thalamotomy patients (from 18.1 points at baseline to 9.6 at 3 months), with a between-group difference in the mean change of 8.3 points (95% CI 5.9–10.7, $p < 0.001$).²³

Parkinson's Disease

Parkinson's disease (PD), a degenerative disorder of the CNS involving basal ganglia presenting with both motor and neuropsychiatric symptoms,⁴⁹ has been a focus of HIFU research for the last few years. In 2014, Magara et al.⁵⁵ were the first to report on the use of MRgHIFU for the treatment of PD, describing the results of pallidothalamic tractotomy in 13 patients. For assessment purposes, the Unified Parkinson's Disease Rating Scale (UPDRS) and global symptom relief (GSR) were used at follow-up. Thermal ablation was repeated up to 5 times to achieve a higher volume of thermally ablated lesions causing visible ablated lesions on T2-weighted images. These patients achieved clinical reduction in UPDRS (60.9%) and GSR (56.7%).⁵⁵

In 2015, Schlesinger et al. reported on the treatment of moderate to severe tremor in PD in 7 patients with VIM thalamotomy using MRgHIFU.⁷² The same team reported additional experience in 30 patients with PD and ET in

February 2017.⁷² This study included 18 patients with ET, 9 with PD, and 3 with ET-PD who underwent MRgFUS VIM thalamotomy to relieve medication-resistant tremor. Adverse events experienced postprocedure in some patients included gait ataxia, unsteady feeling, taste disturbances, asthenia, and hand ataxia. None of these complications lasted beyond 3 months.

Bond et al.⁴ have reported early results of their double-blind, randomized controlled trial on the effectiveness of MRgFUS thalamotomy in tremor-dominant PD. They found that MRgFUS treatment was associated with improvement in hand tremor and a clinically significant reduction in mean UPDRS scores postprocedure, but the final results of this study are still awaited.

Na et al.⁶⁶ reported the only case of pallidotomy, lesioning of the globus pallidus interna, using MRgFUS in a woman with severe levodopa-related motor complications. There are technical issues in focusing ultrasound rays to find the exact target within the pallidum. Another challenge is the proximity of the optic nerve to the globus pallidus internus. It is not clear what will be the best target for treating PD symptoms or whether different targets should be used for different patients. Another question is the safety of the bilateral procedure.

As of this writing, MRgFUS is approved for the treatment of medication-refractory PD symptoms in Israel, Europe, Korea, and Russia.⁷³

Obsessive-Compulsive Disorder and Depression

Jung et al., with their 2015 publication,⁴⁸ were the first to describe the use of MRgFUS for the treatment of medically refractory obsessive-compulsive disorder (OCD). They performed bilateral thermal anterior limb capsulotomy in 4 patients and reported favorable results. Similarly, a clinical trial of 10 patients evaluated the feasibility, safety, and initial efficacy of MRgFUS in the treatment of major depressive disorder.⁵¹ Currently, a single arm, non-randomized trial of MRgFUS targeting the anterior limb of the internal capsule for treatment-refractory OCD has just begun (NCT03156335; clinicaltrials.gov). The results of all these trials are eagerly awaited and could change the clinical management of OCD and depression.

Enhancing Drug Delivery Across the Blood-Brain Barrier

Several animal studies have demonstrated the potential of FUS to deliver chemotherapeutic agents, antibodies, growth factors, or genes to the desired area of the brain.^{52,59,80} By modifying the sonication parameters from those used for ablation, a controlled, reversible, and reproducible opening of the blood-brain barrier (BBB) can be achieved, allowing for the delivery of targeted drugs, such as liposomal doxorubicin; nanoparticles; fluorophores; and naked DNA injected systemically to locally sonicated tissue *in vivo*.⁵⁹

A preclinical study using anti-dopamine-4 (anti-D4) antibodies demonstrated a high degree of selectivity for the FUS-targeted area.⁵⁵ Targeting ligands can also be conjugated to microbubbles, enabling the microbubble complex to accumulate selectively in areas of interest. When these microbubbles are destroyed with low-frequency, high-power ultrasound, the microvessel walls

become permeable, allowing for the drugs or genes contained within microbubbles to be released into the bloodstream and then delivered to tissue by convective forces.⁴³ Preclinical studies involving chemotherapeutic agent demonstrated that anti-Her-2 antibody trastuzumab (Herceptin) was successfully delivered into the brain with a concentration gradient that matched the expected BBB disruption magnitude measured using MRI.^{3,52} This opens the possibility of estimating the actual concentration of a drug at the target location using MRI-guided BBB opening.^{3,52}

Several preclinical studies have also demonstrated the successful delivery of anti-amyloid antibodies and other disease-modifying drugs across the BBB using FUS therapy for the treatment of Alzheimer's disease (AD).^{8,12} Recently, a Phase I clinical trial to evaluate the feasibility and safety of opening the BBB in AD patients utilizing FUS has commenced (NCT02986932; clinicaltrials.gov). It is hoped that this trial will be a milestone in the path toward successful treatment of AD.

Sonothrombolysis

Ischemic Stroke

As evident from several preclinical studies, HIFU-based thrombolysis has recently emerged as a promising drug-free treatment option for ischemic stroke.^{9,17,57,67,76,85} FUS causes microbubble oscillation, leading to mechanical disruption of the ischemic clot and improving rates of recanalization.²⁰ Low-intensity ultrasound combined with systemic delivery of microbubble contrast agents has been shown to improve thrombolysis in the presence or absence of tissue plasminogen activator (tPA) in the past.^{7,19,20,24} The Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic tPA (CLOTBUST) trial and the Transcranial Low-Frequency Ultrasound-Mediated Thrombolysis in Brain Ischemia (TRUMBI) trial with unfocused, low-frequency (300 kHz) ultrasound have shown some promise, but with complications such as increased hemorrhage rates.^{1,18} HIFU as a stand-alone method for thrombolysis seems to be more advantageous, as it reduces the risk of hemorrhage by eliminating the side effects of thrombolytic drugs as well as adequately causing thrombolysis without damage to the targeted vessels.^{9,57,85} Also, HIFU reduces the treatment time from hours to minutes, which may cause significant reductions in the size of infarct and lead to better clinical outcomes in stroke patients,^{9,17,57,67,76,85} and therefore has the potential to revolutionize current treatment paradigms. Further investigations and clinical trials are warranted.

Hemorrhagic Stroke

Preclinical studies by Harnof et al.³⁸ and Monteith et al.⁶⁴ demonstrated the feasibility of HIFU for fast, efficient, and safe thrombolysis of intracranial hemorrhage in both in vitro and in vivo models without introducing tPA. MRgHIFU should provide the ability to lyse an intracerebral thrombus with a high degree of accuracy, followed by aspiration in a minimally invasive manner under immediate MRI guidance, without requiring any indwelling catheters. Clinical trials are expected to begin soon.

HIFU-Induced Immunomodulation and Antitumor Immunity

The release of tumor antigens from necrotic cells and a diverse array of endogenous signals from HIFU-damaged tumor cells can enhance an antitumor immune response.^{40,71} Several clinical studies have provided evidence that immunomodulation occurs following HIFU treatment, which could affect the patient's immune status.^{5,71} Animal studies suggest that following a FUS treatment there is a rise in CD3+ and CD4+ subsets and the CD4+/CD8+ ratio in the blood due to the activation of dendritic cells.^{40,87} HIFU might be an attractive option in situations in which a host's antitumor immunity needs to be enhanced. A HIFU-induced strong antitumor immune response could help to combat residual tumor cells at the primary lesion site and suppress metastasis.^{40,87}

Future Applications of tcMRgFUS

Trigeminal Neuralgia

A recent cadaveric model study with real-time MR thermometry and experimentation with thermocouples in a transcranial in vitro setup successfully demonstrated the capability to produce a focal rise in temperature within the trigeminal nerve without heating the bone or causing changes in the temperature of the immediate structures.⁶⁵ Although more investigation is needed in preclinical models and, eventually, in patients, this does illustrate the expansive potential of MRgFUS.

Neuromodulation and Epilepsy

In the past years, several in vitro as well as in vivo studies have demonstrated the ability of FUS to both reversibly and irreversibly block nerve conduction.^{15,25,26,70,86} Other studies have demonstrated activation of neural tissue, both peripherally and in the CNS.^{32,50,81} These effects have been postulated to occur as a result of mechanical stimuli (reversible) and thermal ablation (potentially irreversible). These techniques of modulating neural transmission also promise potential application in the treatment of epilepsy. In a murine epilepsy model, MRgFUS has been shown to decrease epileptic activity that was induced by intraperitoneal injection of pentylenetetrazol.⁶³ Although further studies are warranted, neuromodulation with MRgFUS might provide clinicians with a future potential to noninvasively target a seizure focus in the brain before its permanent ablation, if needed.

Conclusions

Several developments have occurred in the field of tcMRgFUS, and the modality seems poised to broaden the neurosurgical armamentarium. It holds the promise of providing multiple therapeutic options for various neurological diseases. Despite improvements that have overcome the initial technical challenges, only very few clinical trials have thus far been carried out. The number of trials related to neurological disorders is expected to increase in the coming years, as this novel therapeutic device appears to have substantial expansive potential. There are abundant opportunities for research on the use of this technology across various medical and neurological disciplines.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: Quadri, Waqas. Acquisition of data: Quadri. Analysis and interpretation of data: Quadri, I Khan. Drafting the article: Quadri, I Khan. Critically revising the article: Waqas, MA Khan, Suriya, Farooqui. Reviewed submitted version of manuscript: Quadri, Waqas, MA Khan, Suriya, Farooqui, Fiani. Approved the final version of the manuscript on behalf of all authors: Quadri.

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