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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 1938[62] 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 lesions[29] 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 presonication 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.

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 (Hynyen)
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.

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/cm^2. 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 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-

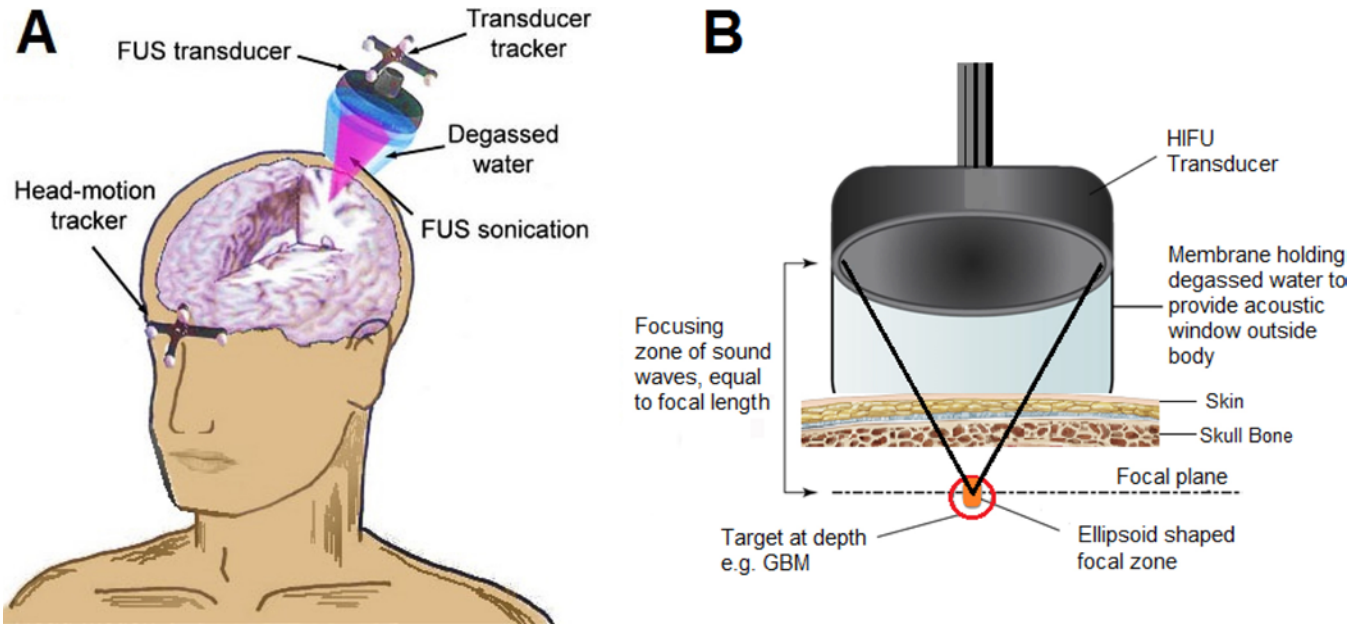

FIG. 1. A: Noninvasive setup of HIFU transducer with transducer tracker, head-motion tracker, and degassed water. **B:** HIFU transducer converging noninvasive transcranial ultrasonic energy at the ellipsoidal focal zone to produce tissue lesions at depth.

der tension, consequently forming gas- and vapor-filled "cavities."[44] 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 tumors[37] 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

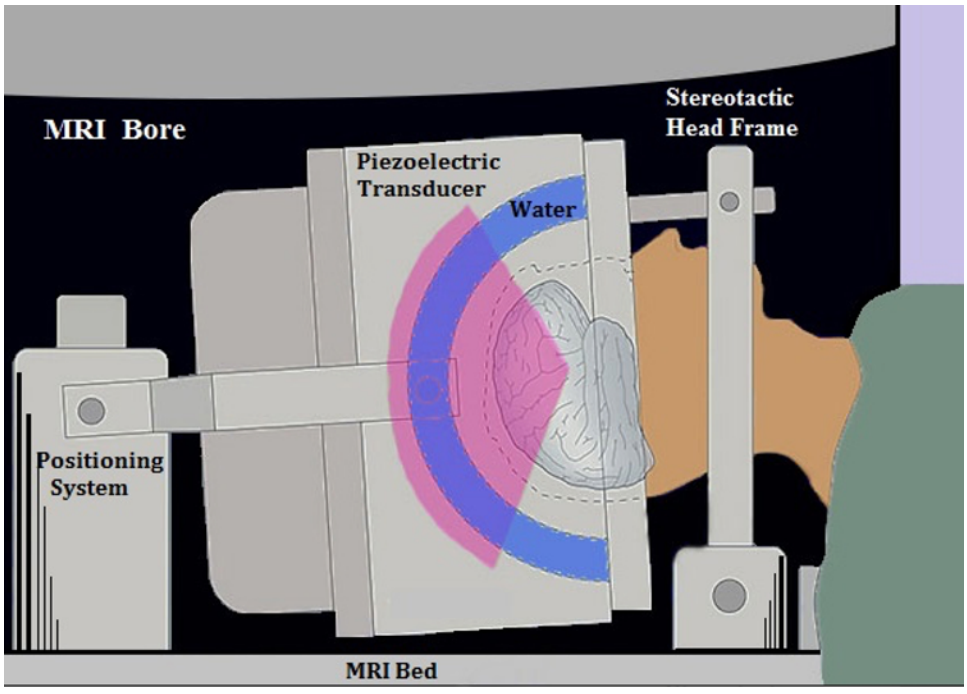

FIG. 2. Schematic of tcMRgHIFU setup.

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, nonrandomized 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.

References

1. Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, et al: Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. **N Engl J Med 351:**2170–2178, 2004
2. Bauer R, Martin E, Haegele-Link S, Kaegi G, von Specht M, Werner B: Noninvasive functional neurosurgery using transcranial MR imaging-guided focused ultrasound. **Parkinsonism Relat Disord 20 (Suppl 1):**S197–S199, 2014
3. Bendell JC, Domchek SM, Burstein HJ, Harris L, Younger J, Kuter I, et al: Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. **Cancer 97:**2972–2977, 2003
4. Bond AE, Dallapiazza R, Huss D, Warren AL, Sperling S, Gwinn R, et al: A randomized, sham-controlled trial of transcranial magnetic resonance-guided focused ultrasound thalamotomy trial for the treatment of tremor-dominant, idiopathic Parkinson disease. **Neurosurgery 63 (Suppl 1):**154–154, 2016 (Abstract)
5. Brayman AA, Coppage ML, Vaidya S, Miller MW: Transient poration and cell surface receptor removal from human lymphocytes in vitro by 1 MHz ultrasound. **Ultrasound Med Biol 25:**999–1008, 1999
6. Briquard P: Paul Langevin. **Ultrasonics 10:**213–214, 1972
7. Brown AT, Flores R, Hamilton E, Roberson PK, Borrelli MJ, Culp WC: Microbubbles improve sonothrombolysis in vitro and decrease hemorrhage in vivo in a rabbit stroke model. **Invest Radiol 46:**202–207, 2011
8. Burgess A, Dubey S, Yeung S, Hough O, Eterman N, Aubert I, et al: Alzheimer disease in a mouse model: MR imaging-guided focused ultrasound targeted to the hippocampus opens the blood-brain barrier and improves pathologic abnormalities and behavior. **Radiology 273:**736–745, 2014
9. Burgess A, Huang Y, Waspe AC, Ganguly M, Goertz DE, Hynynen K: High-intensity focused ultrasound (HIFU) for dissolution of clots in a rabbit model of embolic stroke. **PLoS One 7:**e42311, 2012
10. Burks SR, Ziadloo A, Hancock HA, Chaudhry A, Dean DD, Lewis BK, et al: Investigation of cellular and molecular responses to pulsed focused ultrasound in a mouse model. **PLoS One 6:**e24730, 2011
11. Chang WS, Jung HH, Zadicario E, Rachmilevitch I, Tlusty T, Vitek S, et al: Factors associated with successful magnetic resonance-guided focused ultrasound treatment: efficiency of acoustic energy delivery through the skull. **J Neurosurg 124:**411–416, 2016
12. Choi JJ, Wang S, Brown TR, Small SA, Duff KEK, Konofagou EE: Noninvasive and transient blood-brain barrier opening in the hippocampus of Alzheimer's double transgenic mice using focused ultrasound. **Ultrason Imaging 30:**189–200, 2008
13. Clarke RL, ter Haar GR: Temperature rise recorded during lesion formation by high-intensity focused ultrasound. **Ultrasound Med Biol 23:**299–306, 1997
14. Cline HE, Schenck JF, Hynynen K, Watkins RD, Souza SP, Jolesz FA: MR-guided focused ultrasound surgery. **J Comput Assist Tomogr 16:**956–965, 1992
15. Colucci V, Strichartz G, Jolesz F, Vykhodtseva N, Hynynen K: Focused ultrasound effects on nerve action potential in vitro. **Ultrasound Med Biol 35:**1737–1747, 2009
16. Coluccia D, Fandino J, Schwyzer L, O'Gorman R, Remonda L, Anon J, et al: First noninvasive thermal ablation of a brain tumor with MR-guided focused ultrasound. **J Ther Ultrasound 2:**17–17, 2014
17. Cui H, Yang X: Laser enhanced high-intensity focused ultrasound thrombolysis: an in vitro study. **J Acoust Soc Am 133:**EL123–EL128, 2013
18. Daffertshofer M, Gass A, Ringleb P, Sitzer M, Sliwka U, Els T, et al: Transcranial low-frequency ultrasound-mediated thrombolysis in brain ischemia: increased risk of hemorrhage with combined ultrasound and tissue plasminogen activator: results of a phase II clinical trial. **Stroke 36:**1441–1446, 2005
19. Datta S, Coussios CC, Ammi AY, Mast TD, de Courten-Myers GM, Holland CK: Ultrasound-enhanced thrombolysis using Definity as a cavitation nucleation agent. **Ultrasound Med Biol 34:**1421–1433, 2008
20. Datta S, Coussios CC, McAdory LE, Tan J, Porter T, De Courten-Myers G, et al: Correlation of cavitation with ultrasound enhancement of thrombolysis. **Ultrasound Med Biol 32:**1257–1267, 2006
21. Dunn PM: Aristotle (384–322 BC): philosopher and scientist of ancient Greece. **Arch Dis Child Fetal Neonatal Ed 91:**F75–F77, 2006
22. Elias WJ, Huss D, Voss T, Loomba J, Khaled M, Zadicario E, et al: A pilot study of focused ultrasound thalamotomy for essential tremor. **N Engl J Med 369:**640–648, 2013
23. Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W, et al: A randomized trial of focused ultrasound thalamotomy for essential tremor. **N Engl J Med 375:**730–739, 2016
24. Flores R, Hennings LJ, Lowery JD, Brown AT, Culp WC: Microbubble-augmented ultrasound sonothrombolysis decreases intracranial hemorrhage in a rabbit model of acute ischemic stroke. **Invest Radiol 46:**419–424, 2011
25. Foley JL, Little JW, Vaezy S: Effects of high-intensity focused ultrasound on nerve conduction. **Muscle Nerve 37:**241–250, 2008
26. Foley JL, Little JW, Vaezy S: Image-guided high-intensity focused ultrasound for conduction block of peripheral nerves. **Ann Biomed Eng 35:**109–119, 2007
27. Foster RS, Bihrle R, Sanghvi NT, Fry FJ, Donohue JP: High-intensity focused ultrasound in the treatment of prostatic disease. **Eur Urol 23 (Suppl 1):**29–33, 1993
28. Fry FJ, Kossoff G, Eggleton RC, Dunn F: Threshold ultrasonic dosages for structural changes in the mammalian brain. **J Acoust Soc Am 48:**2, 1413, 1970
29. Fry WJ, Meyers R: Ultrasonic method of modifying brain structures. **Confin Neurol 22:**315–327, 1962
30. Fry WJ, Mosberg WH Jr, Barnard JW, Fry FJ: Production of focal destructive lesions in the central nervous system with ultrasound. **J Neurosurg 11:**471–478, 1954
31. Gallay MN, Moser D, Rossi F, Pourtehrani P, Magara AE, Kowalski M, et al: Incisionless transcranial MR-guided focused ultrasound in essential tremor: cerebellothalamic tractotomy. **J Ther Ultrasound 4:**5, 2016
32. Gavrilov LR, Tsirulnikov EM, Davies IA: Application of focused ultrasound for the stimulation of neural structures. **Ultrasound Med Biol 22:**179–192, 1996
33. Gelet A, Chapelon JY, Margonari J, Theillère Y, Gorry F, Souchon R, et al: High-intensity focused ultrasound experimentation on human benign prostatic hypertrophy. **Eur Urol 23 (Suppl 1):**44–47, 1993
34. Gersten JW: Relation of ultrasound effects to the orientation of tendon in the ultrasound field. **Arch Phys Med Rehabil 37:**201–209, 1956
35. Gersten JW, Kawashima E: Recent advances in fundamental aspects of ultrasound and muscle. **Br J Phys Med 18:**106–109, 1955
36. Gitter AH: [A short history of hearing research. I. Antiquity.] **Laryngorhinootologie 69:**442–445, 1990 (Ger)
37. Hariri OR, Quadri SA, Farr S, Gupta R, Bieber AJ, Dyurgerova A, et al: Third ventricular glioblastoma multiforme: case report and literature review. **J Neurol Surg Rep 76:**e227–e232, 2015
38. Harnof S, Zibly Z, Hananel A, Monteith S, Grinfeld J, Schiff G, et al: Potential of magnetic resonance-guided focused ultrasound for intracranial hemorrhage: an in vivo feasibility study. **J Stroke Cerebrovasc Dis 23:**1585–1591, 2014

39. Heimburger RF: Ultrasound augmentation of central nervous system tumor therapy. **Indiana Med 78:**469–476, 1985
40. Hu Z, Yang XY, Liu Y, Sankin GN, Pua EC, Morse MA, et al: Investigation of HIFU-induced anti-tumor immunity in a murine tumor model. **J Transl Med 5:**34, 2007
41. Hynynen K, Freund WR, Cline HE, Chung AH, Watkins RD, Vetro JP, et al: A clinical, noninvasive, MR imaging-monitored ultrasound surgery method. **Radiographics 16:**185–195, 1996
42. Hynynen K, McDannold N, Clement G, Jolesz FA, Zadicario E, Killiany R, et al: Pre-clinical testing of a phased array ultrasound system for MRI-guided noninvasive surgery of the brain—a primate study. **Eur J Radiol 59:**149–156, 2006
43. Hynynen K, Pomeroy O, Smith DN, Huber PE, McDannold NJ, Kettenbach J, et al: MR imaging-guided focused ultrasound surgery of fibroadenomas in the breast: a feasibility study. **Radiology 219:**176–185, 2001
44. Jagannathan J, Sanghvi NT, Crum LA, Yen CP, Medel R, Dumont AS, et al: High-intensity focused ultrasound surgery of the brain: part 1—a historical perspective with modern applications. **Neurosurgery 64:**201–211, 2009
45. Jeanmonod D, Werner B, Morel A, Michels L, Zadicario E, Schiff G, et al: Transcranial magnetic resonance imaging-guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain. **Neurosurg Focus 32(1):**E1, 2012
46. Jolesz FA, Hynynen K: Magnetic resonance image-guided focused ultrasound surgery. **Cancer J 8 (Suppl 1):**S100–S112, 2002
47. Jolesz FA, Hynynen K, McDannold N, Tempany C: MR imaging-controlled focused ultrasound ablation: a noninvasive image-guided surgery. **Magn Reson Imaging Clin N Am 13:**545–560, 2005
48. Jung HH, Kim SJ, Roh D, Chang JG, Chang WS, Kweon EJ, et al: Bilateral thermal capsulotomy with MR-guided focused ultrasound for patients with treatment-refractory obsessive-compulsive disorder: a proof-of-concept study. **Mol Psychiatry 20:**1205–1211, 2015
49. Khan MA, Quadri SA, Tohid H: A comprehensive overview of the neuropsychiatry of Parkinson's disease: A review. **Bull Menninger Clin 81:**53–105, 2017
50. Kim H, Chiu A, Lee SD, Fischer K, Yoo SS: Focused ultrasound-mediated non-invasive brain stimulation: examination of sonication parameters. **Brain Stimul 7:**748–756, 2014
51. Kim M, Kim CH, Jung HH, Kim SJ, Chang JW: Treatment of major depressive disorder via magnetic resonance–guided focused ultrasound surgery. **Biol Psychiatry 83:**e17–e18, 2018
52. Kinoshita M, McDannold N, Jolesz FA, Hynynen K: Noninvasive localized delivery of Herceptin to the mouse brain by MRI-guided focused ultrasound-induced blood-brain barrier disruption. **Proc Natl Acad Sci U S A 103:**11719–11723, 2006
53. Lipsman N, Schwartz ML, Huang Y, Lee L, Sankar T, Chapman M, et al: MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. **Lancet Neurol 12:**462–468, 2013
54. Lynn JG, Zwemer RL, Chick AJ, Miller AE: A new method for the generation and use of focused ultrasound in experimental biology. **J Gen Physiol 26:**179–193, 1942
55. Magara A, Bühler R, Moser D, Kowalski M, Pourtehrani P, Jeanmonod D: First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease. **J Ther Ultrasound 2:**11, 2014
56. Martin E, Jeanmonod D, Morel A, Zadicario E, Werner B: High-intensity focused ultrasound for noninvasive functional neurosurgery. **Ann Neurol 66:**858–861, 2009
57. Maxwell AD, Cain CA, Duryea AP, Yuan L, Gurm HS, Xu Z: Noninvasive thrombolysis using pulsed ultrasound cavitation therapy—histotripsy. **Ultrasound Med Biol 35:**1982–1994, 2009
58. McDannold N, Clement G, Black P, Jolesz F, Hynynen K: Transcranial MRI-guided focused ultrasound surgery of brain tumors: Initial findings in three patients. **Neurosurgery 66:**323–332, 2010
59. McDannold N, Vykhodtseva N, Raymond S, Jolesz FA, Hynynen K: MRI-guided targeted blood-brain barrier disruption with focused ultrasound: histological findings in rabbits. **Ultrasound Med Biol 31:**1527–1537, 2005
60. McDannold NJ, Vykhodtseva NI, Hynynen K: Microbubble contrast agent with focused ultrasound to create brain lesions at low power levels: MR imaging and histologic study in rabbits. **Radiology 241:**95–106, 2006
61. Medel R, Monteith SJ, Elias WJ, Eames M, Snell J, Sheehan JP, et al: Magnetic resonance-guided focused ultrasound surgery: part 2: a review of current and future applications. **Neurosurgery 71:**755–763, 2012
62. Meyers R, Fry WJ, Fry FJ, Dreyer LL, Schultz DF, Noyes RF: Early experiences with ultrasonic irradiation of the pallidofugal and nigral complexes in hyperkinetic and hypertonic disorders. **J Neurosurg 16:**32–54, 1959
63. Min BK, Bystritsky A, Jung KI, Fischer K, Zhang Y, Maeng LS, et al: Focused ultrasound-mediated suppression of chemically-induced acute epileptic EEG activity. **BMC Neurosci 12:**23, 2011
64. Monteith SJ, Kassell NF, Goren O, Harnof S: Transcranial MR-guided focused ultrasound sonothrombolysis in the treatment of intracerebral hemorrhage. **Neurosurg Focus 34(5):**E14, 2013
65. Monteith SJ, Medel R, Kassell NF, Wintermark M, Eames M, Snell J, et al: Transcranial magnetic resonance-guided focused ultrasound surgery for trigeminal neuralgia: a cadaveric and laboratory feasibility study. **J Neurosurg 118:**319–328, 2013
66. Na YC, Chang WS, Jung HH, Kweon EJ, Chang JW: Unilateral magnetic resonance-guided focused ultrasound pallidotomy for Parkinson disease. **Neurology 85:**549–551, 2015
67. Pajek D, Burgess A, Huang Y, Hynynen K: High-intensity focused ultrasound sonothrombolysis: the use of perfluorocarbon droplets to achieve clot lysis at reduced acoustic power. **Ultrasound Med Biol 40:**2151–2161, 2014
68. Park JW, Jung S, Jung TY, Lee MC: Focused ultrasound surgery for the treatment of recurrent anaplastic astrocytoma: a preliminary report. **AIP Conf Proc 829:**238–240, 2006
69. Ram Z, Cohen ZR, Harnof S, Tal S, Faibel M, Nass D, et al: Magnetic resonance imaging-guided, high-intensity focused ultrasound for brain tumor therapy. **Neurosurgery 59:**949–956, 2006
70. Rinaldi PC, Jones JP, Reines F, Price LR: Modification by focused ultrasound pulses of electrically evoked responses from an in vitro hippocampal preparation. **Brain Res 558:**36–42, 1991
71. Rosberger DF, Coleman DJ, Silverman R, Woods S, Rondeau M, Cunningham-Rundles S: Immunomodulation in choroidal melanoma: reversal of inverted CD4/CD8 ratios following treatment with ultrasonic hyperthermia. **Biotechnol Ther 5:**59–68, 1994
72. Schlesinger I, Eran A, Sinai A, Erikh I, Nassar M, Goldsher D, et al: MRI guided focused ultrasound thalamotomy for moderate-to-severe tremor in Parkinsons disease. **Parkinsons Dis 2015:**219149, 2015
73. Schlesinger I, Sinai A, Zaaroor M: MRI-guided focused ultrasound in Parkinsons disease: a review. **Parkinsons Dis 2017:**8124624, 2017
74. Shaw CJ, ter Haar GR, Rivens IH, Giussani DA, Lees CC: Pathophysiological mechanisms of high-intensity focused ultrasound-mediated vascular occlusion and relevance to non-invasive fetal surgery. **J R Soc Interface 11:**20140029, 2014

75. Shi X, Martin RW, Rouseff D, Vaezy S, Crum LA: Detection of high-intensity focused ultrasound liver lesions using dynamic elastometry. **Ultrason Imaging 21:**107–126, 1999
76. Suo D, Guo S, Lin W, Jiang X, Jing Y: Thrombolysis using multi-frequency high intensity focused ultrasound at MHz range: an in vitro study. **Phys Med Biol 60:**7403–7418, 2015
77. Susani M, Madersbacher S, Kratzik C, Vingers L, Marberger M: Morphology of tissue destruction induced by focused ultrasound. **Eur Urol 23 (Suppl 1):**34–38, 1993
78. ter Haar GR, Robertson D: Tissue destruction with focused ultrasound in vivo. **Eur Urol 23 (Suppl 1):**8–11, 1993
79. Tran BC, Seo J, Hall TL, Fowlkes JB, Cain CA: Effects of contrast agent infusion rates on thresholds for tissue damage produced by single exposures of high-intensity ultrasound. **IEEE Trans Ultrason Ferroelectr Freq Control 52:**1121–1130, 2005
80. Treat LH, McDannold N, Vykhodtseva N, Zhang Y, Tam K, Hynynen K: Targeted delivery of doxorubicin to the rat brain at therapeutic levels using MRI-guided focused ultrasound. **Int J Cancer 121:**901–907, 2007
81. Tufail Y, Matyushov A, Baldwin N, Tauchmann ML, Georges J, Yoshihiro A, et al: Transcranial pulsed ultrasound stimulates intact brain circuits. **Neuron 66:**681–694, 2010
82. Vallancien G, Harouni M, Veillon B, Mombet A, Prapotnich D, Brisset J, et al: Focused extracorporeal pyrotherapy: feasibility study in man. **J Endourol 6:**173–181, 1992
83. Van Tiggelen R, Pouders E: Ultrasound and computed tomography: spin-offs of the world wars. **JBR-BTR 86:**235–241, 2003
84. Visioli AG, Rivens IH, ter Haar GR, Horwich A, Huddart RA, Moskovic E, et al: Preliminary results of a phase I dose escalation clinical trial using focused ultrasound in the treatment of localised tumours. **Eur J Ultrasound 9:**11–18, 1999
85. Wright C, Hynynen K, Goertz D: In vitro and in vivo high-intensity focused ultrasound thrombolysis. **Invest Radiol 47:**217–225, 2012
86. Yoo SS, Bystritsky A, Lee JH, Zhang Y, Fischer K, Min BK, et al: Focused ultrasound modulates region-specific brain activity. **Neuroimage 56:**1267–1275, 2011
87. Zheng H, Benjamin IJ, Basu S, Li Z: Heat shock factor 1-independent activation of dendritic cells by heat shock: implication for the uncoupling of heat-mediated immunoregulation from the heat shock response. **Eur J Immunol 33:**1754–1762, 2003

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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