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Transcranial Magnetic Resonance-Guided Focused Ultrasound for Neurological Applications: Industry Challenges, Innovations, and Future Directions

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Abstract

Transcranial magnetic resonance-guided focused ultrasound (MRgFUS) represents a transformative modality in treating neurological disorders and diseases, offering precise, minimally invasive interventions for conditions such as essential tremor and Parkinson's disease. This paper presents an industry-focused perspective on the current state of MRgFUS, highlighting recent advancements, challenges, and emerging opportunities within the field. We review key clinical applications and therapeutic mechanisms, focusing on targeted ablation, while discussing technological innovations that support new indications. Current regulatory frameworks, challenges in device development, and market trends are examined to provide an understanding of the industry landscape. Additionally, we indicate some limitations in MRgFUS and suggest potential strategies for overcoming these limitations to optimize treatment outcomes. We conclude with an outlook on promising developments, including AI-enhanced targeting, low and high-field MRI integration, and multimodal imaging techniques, that could potentially drive further innovation and adoption of MRgFUS in brain therapy.

Keywords: Brain, MR-guided Focused Ultrasound, Neuromodulation, Blood-Brain Barrier, Thermal Ablation

1. Introduction

Transcranial MR-guided focused ultrasound (MRgFUS) is a minimally invasive technique that utilizes magnetic resonance imaging (MRI) combined with precisely targeted ultrasound waves to stimulate or ablate specific regions within the brain, offering immense potential for therapeutic interventions [1,2]. This technology relies on ultrasound wave propagation and tissue interaction to deliver brain-targeted therapies, such as thermal ablation [3], neuromodulation [4], and drug delivery [5]. MRgFUS presents significant advantages over standard neurosurgical procedures. Its incisionless nature minimizes the risks associated with traditional surgery, leading to shorter recovery times and reduced postoperative complications. Unlike deep brain stimulation (DBS), MRgFUS eliminates the need for implanted devices and lifelong maintenance. However, ablation is irreversible, and when unintended tissue is lesioned, it may result in long-lasting adverse effects. Compared to radiofrequency ablation (RFA), MRgFUS real-time MRI guidance and temperature monitoring provide greater precision, reducing the likelihood of unintended damage. Consequently, patients experience faster recovery, lower surgical risks, and fewer postoperative issues [6–8].

The FDA's approval for ablation of the Ventral Intermediate Nucleus (Vim) of the thalamus in 2016 (premarket approval P150038) and globus pallidus interna (GPi) in 2021 (premarket approval P150038, S014) has further prompted industry enthusiasm, facilitating progress for commercialization, insurance coverage [9], and widespread adoption in the treatment of Essential Tremor (ET) and Parkinson's disease (PD). MRgFUS thalamotomy targeting the Vim has demonstrated efficacy in reducing tremors. The Vim is a critical relay center within the thalamus that integrates and transmits motor signals from the cerebellum and basal ganglia to the motor cortex, and it is associated with the coordination of voluntary movements. Ablation of the Vim interrupts abnormal oscillations and reinstates regular thalamocortical relay function in ET [3,10] and tremor-dominant PD (TDPD) [11]. Systematic reviews and meta-analyses have comprehensively assessed complications and their long-term outcomes [12–16], including gait disturbances, paresthesia, and speech difficulties, which vary in severity and persistence among patients. The five-year follow-up data from unilateral thalamotomy reveals sustained and significant tremor relief, alongside an overall improvement in quality-of-life measures and the absence of any progressive or delayed complications [17,18]. Real-world data shows that the treatment is safe and well-tolerated and supports the use of MRgFUS-thalamotomy in patients with ET [19]. Additionally, staged, bilateral MRgFUS thalamotomy, which refers to the second-side treatment after at least 9 months interval of the first treatment, has shown a significant decrease in tremor severity and improvements in functional disability with mostly mild and temporary adverse events (AE) affecting speech, swallowing, and balance [20]. While Vim remains the primary MRgFUS target for ET, recent studies have explored lesioning of the posterior subthalamic area (PSA) [21,22] and the cerebellothalamic tract (CTT) [23–25] as alternative or adjunctive targets. These targets may benefit specific patient populations, particularly those with tremor subtypes that do not fully respond to Vim ablation.

Patients with PD experiencing dyskinesias demonstrated improved motor function after unilateral GPi ablation [26,27]. In addition, several other targets have been identified for FUS treatment, each with distinct mechanisms of action for symptom relief. The Pallidothalamic Tract (PTT) is a key component of the cortico-basal ganglia-thalamo-cortical loop that plays a crucial role in transmitting signals from the GPi to the thalamus, which in turn sends signals back to the cortex. This loop is involved in regulating movement. Ablation of PTT has been shown to disrupt hyperactive neural activity within the loop, addressing motor symptoms such as tremor, dystonia, rigidity, and bradykinesia [28–31]. Ablation or modulation of the Subthalamic Nucleus (STN) offers another avenue, normalizing abnormal firing patterns within the basal ganglia-thalamo-cortical circuit and improving motor function [32–36]. More recently, dual targeting of Vim and PTT has been reported to relieve combined PD symptoms [37,38]. Additionally, advanced clinical trials and case reports show the feasibility of treating a wide array of other brain diseases and conditions with MRgFUS ablation, including neuropathic pain [39–42], Epilepsy [43–47], status dystonicus [48], psychiatric disorders like depression and obsessive-compulsive disorder (OCD) [49–52], and range of indications for pediatric patients [53,54]. Table 1 presents a summary of MRgFUS ablation targets, indications, and findings.

The exponential growth of FUS studies since the 1990s [55], accelerating particularly over the past decade, highlights the field's remarkable evolution and its expanding impact across ablation, neuromodulation, and controlled passage of molecules through the BBB [56] in a wide range of therapeutic and diagnostic applications. With an increasing understanding of FUS's ability to precisely target and modulate brain regions, collaborations between academic institutions and industry leaders are exploring novel FUS applications in treating a spectrum of brain diseases and disorders, such as drug delivery, neuromodulation [4,57] and sonodynamic therapy (SDT) [58] with a great potential to revolutionize neurological care.

Here, we present an industry landscape surrounding FUS brain therapy, with a specific focus on identifying challenges, opportunities, and future directions. Through a review of existing literature, regulatory frameworks, and market trends, we aim to provide insights into the current state of MRgFUS ablation technology and briefly discuss emerging applications within the field of neurological care. By evaluating barriers to widespread implementation involving technological limitations, we also delineate strategic opportunities for overcoming these challenges, optimizing FUS's therapeutic potential, and exploring evolving research paradigms and innovative treatment modalities shaping the future trajectory of FUS in brain therapy.

2. Fundamentals of MRgFUS

MRgFUS combines the principles of FUS physics and MRI integration to enable minimally invasive neurosurgical treatments. Understanding how these elements interact is essential to optimizing treatment safety, precision, and clinical efficacy. This section provides an overview of MRgFUS physics, detailing the mechanisms of ultrasound wave propagation, absorption, energy deposition, and imaging (subsection 2.1). It then explores the system requirements for MRgFUS implementation, including transducer design, MRI interface, hardware, and software tools (subsection 2.2). Finally, a step-by-step breakdown of a typical MRgFUS brain ablation treatment workflow is presented, demonstrating how these concepts are applied in clinical practice (subsection 2.3).

Table 1. Overview of single and dual-target MRgFUS ablation strategies, and their associated neurological and psychiatric indications, and notable clinical findings, including efficacy, safety, and emerging research insights.

Target(s)	Indication	Findings	References
Ventral Intermediate Nucleus (Vim)	ET	FDA-approved for ET and TDPD, with postural tremor improvement of 73.1% sustained over 5 years. Adverse effects, mostly transient, occur in 20–30% of cases.	Elias *et al.,* 2016 [10], Fishman *et al.*, 2018 [12] Cosgrove *et al.,* 2023 [17]
Vim (bilateral)	ET	Approved second-side at least 9 months after treating the first side. The mean tremor/motor function scores improved by 66% at 3 months and persisted during follow-up. AE at 6 months included paresthesia (16%), dysarthria (14%), ataxia (14%), and dysgeusia (6%).	Kaplitt *et al.,* 2024 [20]
Vim	TDPD	Tremor in the on-medication state improved by 62% at 3 months. Most AE (71%) were transient. Two serious AE included one temporary ataxia and one hemiparesis.	Bond *et al*., 2016 [11], Bond *et al*., 2017 [59]
Globus Pallidus Internus (GPi)	PD	FDA-approved for PD, with a trial showing about 70% of patients (n=69) having improved symptoms. AEs were mild to moderate and included dysarthria, gait disturbance, and loss of taste in two patients each and visual disturbance and facial weakness in one patient.	Eisenberg *et al.,* 2021 [26], Krishna *et al.,* 2023 [27]
Pallidothalamic Tract (PTT)	PD	The PTT is explored unilaterally and bilaterally for PD (n=56), showing improvements of 84% for tremor, 70% for rigidity, and 73% for distal hypobradykinesia. The main AE included dysarthria in six patients.	Magara *et al.,* 2014 [28], Gallay *et al.,* 2019 [29], Gallay *et al.,* 2020 [30]
Cerebellothalamic Tract (CTT)	ET	Promising results (n=21) unilaterally and bilaterally, with 40-92% improvement at different tremor function subscores. AE included gait instability in 5 patients.	Gallay *et al.,* 2016 [24]
Subthalamic Nucleus (STN)	PD	Explored unilaterally and bilaterally with 30-60% improvement in tremor, bradykinesia, and rigidity. AE included dysarthria, gait disturbance, facial asymmetry, and paresthesia, all mild.	Rodriguez-Rojas *et al.,* 2020 [32], Armengou-Garcia *et al.,* 2024 [33], Martinez-Fernandez *et al.,* 2024 [34] Rodriguez-Rojas *et al.,* 2024 [35] Campins-Romeu *et al.,* 2024 [36]
Anterior Limb of the Internal Capsule (ALIC)	OCD, MDD	30-60% symptom reduction in patients with OCD and MDD.	Davidson *et al.,* 2020 [49], Chang *et al.,* 2021 [50], Germann *et al.,* 2021 [51], Hamani *et al.,* 2024 [52]
Hippocampus	Epilepsy	A case report of sonications for mesial temporal lobe epilepsy showed a patient almost seizure-free at 12 months postoperatively, although no lesion was observed on a 1-month follow-up MRI.	Monteith *et al.,* 2016 [43] Abe *et al.,* 2020 [44],
Hypothalamic hamartomas (HH)	Benign tumors	Case reports and trials have shown significant to complete resolution of Gelastic seizures and improvement of other symptoms in adolescents and young adults.	Yamaguchi *et al.,* 2020 [45], Tierney *et al.,* 2022 [46], Ricciardi *et al.,* 2025 [47]
Central Lateral Nucleus of the Thalamus (CL)	Neuropathic Pain	Explored for chronic and therapy-resistant neuropathic pain, lesioning unilaterally and bilaterally, this target results in ≥50% pain reduction in 51% of patients (n=63). One patient developed a somatosensory deficit in the trigeminal area.	Jeanmonod *et al.*, 2012 [39] Gallay *et al.,* 2023 [40]
GPi (bilateral)	Status Dystonicus	Simultaneous bilateral GPi lesioning led to a significant reduction in dystonic spasms in two patients. AEs included facial palsy due to perilesional edema formation.	Levi *et al.,* 2024 [48]
Vim + PTT	PD	Stepwise dual-lesion targeting of Vim and PTT showed 72-83% suppression of resting/postural/kinetic tremors and rigidity. AE included transient headache, pain, and dizziness.	Chen *et al.,* 2023 [37], Chen *et al.,* 2024 [38]
Vim + PSA	ET	Following Vim lesioning, on average, an additional 34% improvement in spiral rating was observed after targeting the PSA. Long-term AEs included gait disturbance in 35% of the cases.	Jameel *et al.,* 2022 [21], Kyle *et al.,* 2024 [22]

2.1 MRgFUS Physics

FUS uses sound waves, typically in the range of 220-710 kHz, for human brain applications. Ultrasound waves propagate through biological tissues, creating a sequence of compressional and rarefactional phases that shape their interactions with surrounding media [60]. During the compressional phase, ultrasound waves displace tissue particles and fluid molecules, creating an elastic restoring force as the tissue and fluids return to their original configurations in the rarefaction phase. This propagation produces an acoustic radiation force, with part of the ultrasound energy stored in tissue as elastic deformation and part dissipated as heat due to viscous frictional forces [61,62]. As ultrasound waves propagate through biological tissues, they encounter changes in acoustic impedance - for example, at boundaries between different tissue types (e.g., skin, bone, calcifications, brain). These impedance discontinuities result in the transmission, reflection, and refraction of parts of the ultrasound wave. The scattered waves can be reabsorbed by tissue or continue scattering, creating additional thermal effects over time. As ultrasound propagates in the tissue, the intensity *I* will decay over a distance *z* following [63]

$$I(z) = I(0)e^{-2(\alpha_s+\alpha_a)z} \quad (1)$$

where *I(0)* is the initial intensity at z=0, α_s and α_a are the scattering and absorption amplitude attenuation coefficients, respectively. The attenuation is frequency-dependent, with higher frequencies causing greater energy loss. A good approximation for the frequency dependence of the sum of scattering and absorption coefficients amplitude attenuation α is given by [63]

$$\alpha = \alpha_0 f^n \quad (2)$$

where α_0 is the attenuation factor, f is the ultrasound frequency, and n is the power law exponent for the attenuation coefficient. Typical n values for skull bone are from 0.9 to 2.1, and for adult brain 1.1 [63].

A trade-off in frequency selection must be carefully managed to optimize targeting accuracy while ensuring sufficient energy delivery through the skull. In the context of FUS, spatial resolution refers to the size of the focal spot, which directly relates to wavelength and f-number (ratio between focal length and transducer aperture). Therefore, the frequency cannot be inadvertently lowered to allow better skull transmission, as the focus size will also increase with the wavelength λ ($\lambda = c/f$, where c is the speed of sound). Typically, 220 kHz is utilized for MRgFUS BBB opening [64–66] and neuromodulation [57] protocols, and 650 kHz is utilized for transcranial MRgFUS thermal ablation and, although less commonly, also for neuromodulation in the context of ET [67]. The focus size for a concave transducer can be estimated by [63]

$$Lateral\ size \approx 1.22\lambda \frac{Focal\ length}{Transducer\ Aperture} \quad (3)$$

$$Longitudinal\ size \approx 1.22\lambda \left(\frac{Focal\ length}{Transducer\ Aperture}\right)^2 \quad (4)$$

As explored in several studies, the skull density ratio (SDR) represents a crucial metric in MRgFUS. This parameter quantifies the ratio of cancellous to cortical bone densities, serving as a predictive factor for the attenuation of ultrasound energy during transcranial FUS procedures [68]. Unlike compact cortical bone, cancellous bone is composed of a honeycomb-like structure filled with fat and bone marrow, forming a high-attenuation medium for ultrasound. The skull's attenuation varies based on SDR [68], with low SDRs (<0.4) indicating a larger trabecular (less dense) bone presence and thicker skulls causing greater scattering and absorption [69]. In addition, some studies have suggested incorporating the information on the skewness measures of the asymmetry of the SDR distribution [70] and SDR kurtosis [71], indicating that the tail weight can enhance the predictability of ultrasound energy transmission through the skull.

As ultrasound propagates through the skull, a portion of its energy is lost in transit, diminishing the thermal effect on the targeted brain tissue. In addition to energy loss affecting target efficiency, a significant portion of ultrasound energy is absorbed by the skull, leading to potential skull heating [72,73]. To mitigate this, MRgFUS systems employ active cooling mechanisms, such as circulating degassed water around the transducer and patient's head, real-time MR thermometry to monitor and regulate temperature elevation, and "cooling" period between energy delivery, to ensure non-targeted tissues return to body temperature and do not accumulate heat. The use of long sonication durations can partially compensate for this energy loss to achieve the desired thermal dose, measured in cumulative equivalent minutes at 43°C (CEM43), necessary for tissue ablation [74–77]. The CEM43 is defined as [78,79]

$$CEM43 = \int_0^t R^{(43-T)}dt,\ R = \begin{cases} 0.25, & T \le 43°C \\ 0.50, & T > 43°C \end{cases} \quad (5)$$

where T is the applied temperature over a time t. However, high-intensity ultrasound can alter the skull's acoustic properties, which may affect transmission efficiency over time due to skull changes [72,73].

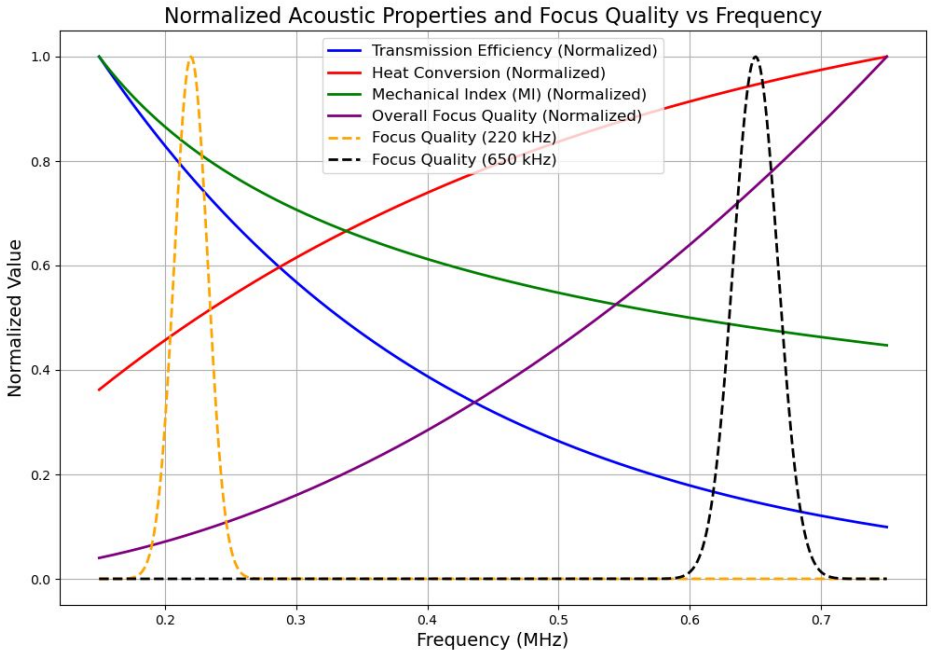

Figure 1. Normalized frequency-dependent trade-offs for two ultrasound transducers centered at 220 kHz and 670 kHz. Parameters include skull transmission efficiency, cavitation risk (mechanical index), heat conversion (absorption), and focus quality. Focus quality, derived from the combined lateral and longitudinal beam dimensions, is modeled with Gaussian profiles centered at the respective transducer frequencies, peaking at 1 and decreasing to 50% at the bandwidth edges. The plots highlight the relationship between frequency, focus sharpness, and acoustic properties, illustrating the balance between skull penetration, heating efficiency, cavitation safety, and beam focusing. This analysis provides insights into the optimization of transducer frequencies for targeted ultrasound applications.

Once passed the skull, the brain tissue partially absorbs the ultrasound energy, where the energy is converted to heat. The temperature in the brain can be estimated using Pennes' bioheat transfer equation for perfused tissues [80–82]

$$\rho_{br}C_{br}\frac{\partial T(\boldsymbol{r},t)}{\partial t} = k_t\nabla^2 T(\boldsymbol{r},t) + V\rho_b C_b(T_b - T(\boldsymbol{r},t)) + Q(\boldsymbol{r},t) \quad (6)$$

where ρ_{br} is the brain tissue density, C_{br} is the specific heat of brain tissue, T is the brain temperature at a spatial coordinate $\boldsymbol{r}$ and time t, k_{br} is the brain tissue thermal conductivity. The perfusion coefficients V,ρ_b,C_b,T_b are, respectively, the perfusion rate per unit volume of brain tissue, the blood density, the blood-specific heat, and the blood temperature. Finally, $Q(\boldsymbol{r},t) = 2\alpha I$ is the volume rate of heat deposition.

MRgFUS ablation integrates MR imaging to guide and monitor the treatment. Real-time MR thermometry is central to this process, offering temperature updates every 3 seconds to ensure precise thermal control. This process ensures that only the targeted tissue within the brain reaches therapeutic temperatures while the surrounding tissue remains unaffected [83,84]. Proton resonance frequency (PRF) shift is the primary MR thermometry method due to its fast acquisition and sensitivity. Temperature increase induces changes in the shielding constant and magnetic susceptibility of the tissue, causing phase changes in MR images and temperature changes ΔT that can be estimated as follows [85]

$$\Delta T = \frac{\phi(T) - \phi(T_0)}{\gamma\alpha B_0 TE} \quad (7)$$

where $\phi(T)$ is the current phase image, $\phi(T_0)$ is the baseline phase image, γ is the gyromagnetic ratio, α is the temperature-sensitive coefficient, B_0 is the main magnetic field, and TE is the echo time.

Head motion leads to phase errors in the PRF temperature calculation, given that a pixel-by-pixel phase subtraction measurement is performed relative to a baseline acquisition. Therefore, head stability using a headframe and imaging confirmation prior to sonication is not only important to avoid off-target sonications but also critical to avoid MR

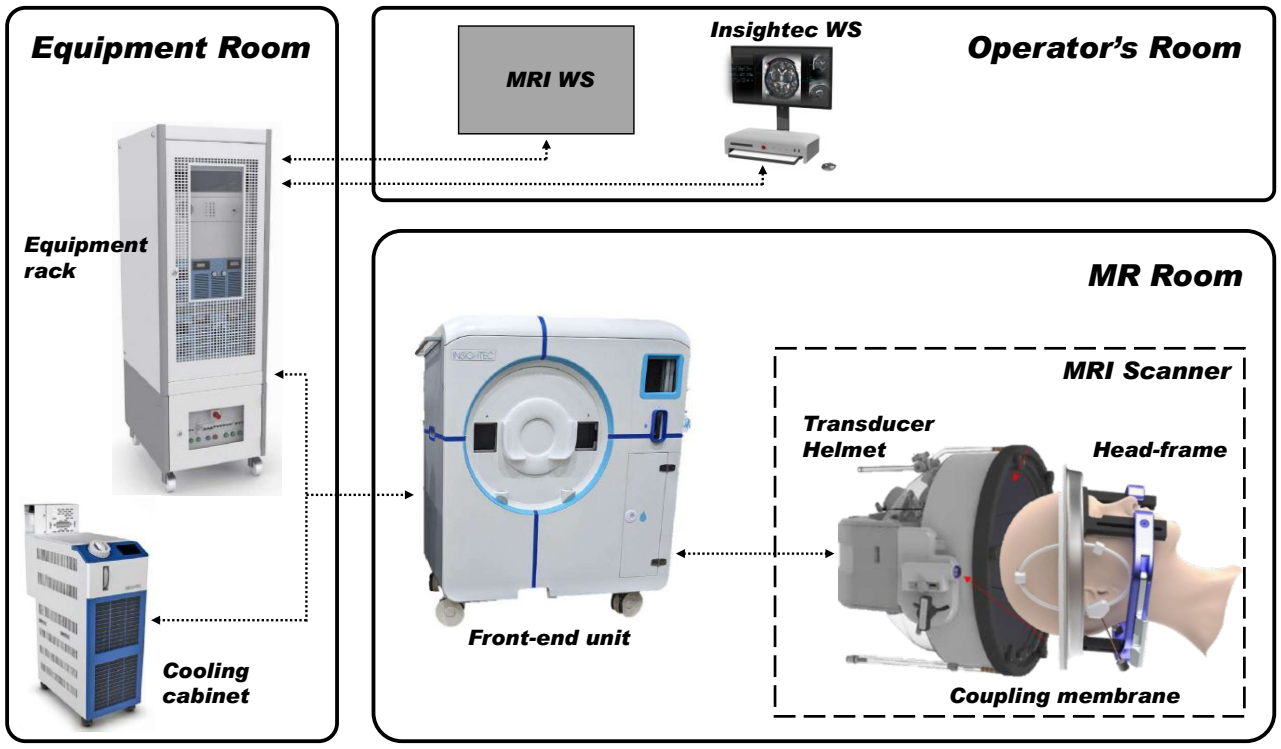

Figure 2. Schematic representation of the Insightec Exablate Neuro MRgFUS system hardware, illustrating the distribution of components across the MRI equipment room, operator's room, and MRI room. The equipment room (on the left) houses the equipment cabinet and cooling system responsible for power management and thermal regulation. The workstation console is positioned alongside the MRI workstation in the operator's room (top right), allowing clinicians to control and monitor treatments. The Front End Unit (FE) and helmet transducer system are located in the MRI room (bottom right). The helmet transducer, mounted on the MRI table, consists of a half-hemisphere phased-array transducer with 1024 independently controlled elements, enabling precise beam focusing through phase adjustments. During treatment, the MRI table moves into the bore, and real-time MR thermometry and thermal dose estimations guide safe and controlled ablation.

thermometry errors. MRgFUS systems employ movement-detection algorithms that verify the patient's position before each sonication [86]. In addition, real-time anatomical images are continuously acquired concurrently with MR thermometry during sonications, providing visual feedback to the physician. These imaging safeguards ensure that the focal point remains aligned and the MR thermometry remains reliable throughout the procedure.

The formation of bubbles in tissue during the rarefaction phase, also known as cavitation, can lead to uncontrolled mechanical stress and tissue damage if not carefully managed. MRgFUS systems include a closed-loop control feature to monitor for cavitation and prevent unintended effects. Acoustic signals emitted from tissue are analyzed in real-time with passive acoustic detectors, and if a certain threshold is surpassed, the system can adjust the ultrasound intensity (e.g., by reducing the energy delivery) or halt the treatment. In addition, the user can increase the driving frequency to reduce the mechanical index *MI*, therefore, the likelihood of inducing cavitation. *MI* is defined as

$$MI = \frac{PNP}{\sqrt{f}} \tag{8}$$

where *PNP* is the peak-negative-pressure in MPa and *f* is the driving frequency in MHz. Figure 1 illustrates the trade-offs associated with frequency-dependent parameters for two ultrasound transducers centered at 220 and 670 kHz. The normalized parameters, including skull penetration, cavitation risk (mechanical index), heat conversion (absorption), and focus quality, show the relationship among these factors with frequency. The focus size, calculated as a function of transducer f-number [63], is also shown, demonstrating how beam width varies with frequency. This analysis provides a general guide on the optimal frequencies for balancing penetration, cavitation risk, heating efficiency, and focus sharpness for each transducer. For accurate estimations, comprehensive simulations incorporating specific tissue properties and multi-physics considerations are required.

2.2 MRgFUS Hardware Overview

The MRgFUS systems comprise a FUS transducer, cavitation control system, water system, MRI interface system, and operation system. (Figure 2). The FUS transducer consists of a half-hemisphere phased-array transducer helmet with multiple independently controlled elements, allowing for phase adjustments of each element to correct for skull refraction and focus the energy on the brain. The transducer is mounted to the MRI table and includes a fixation system for head stabilization and a mechanical positioning system that enables transducer movement. The cavitation control system includes detectors integrated into the transducer, enabling real-time cavitation signal acquisition and monitoring during treatment. The passive acoustic detectors capture signals from bubble activity and mechanical interactions between the ultrasound waves and tissue [87] and use a closed-loop modulation to lower power delivery automatically when cavitation is detected. A water system circulates, degasses, and cools water to ensure acoustic coupling between the transducer and the patient's head and skull heat dissipation. The MRI interface system is designed to run the synchronized MRI scans required for the treatment (e.g., real-time MR thermometry and anatomy images) and collect, analyze, and present the imaging information. It works with various MRI scanner vendors, accommodating different magnet types (e.g., 1.5 or 3T) and software configurations. The system operation includes the algorithms used for accurate focusing, thermal dose calculations, and treatment monitoring. It also serves as a user interface, enabling the treating team to define the treatment target and parameters. More details on commercial systems can be found at [88].

2.3 Typical MRgFUS Brain Treatment Workflow

The thermal ablation treatment workflow involves several key stages in MRgFUS brain procedures, as illustrated in Figure 3. First, patients are screened based on the treatment eligibility criteria (such as MR screening, SDR levels (Figure 3a), and medical history). Those who qualify need to undergo preparation, such as head shave (to avoid energy absorption or reflection) and head fixation (to avoid movements during the procedure). The treatment begins with fixating the patient's head inside the transducer helmet (Figure 2) using a headframe and a membrane to hold water as the propagation medium for ultrasound. Once inside the MRI, the treatment planning begins with acquisitions of MR planning and movement detection baseline scans co-registered with the patient's CT, where acoustic properties are obtained (Figure 3b,c) [89,90]. The treating physician defines the target location to be treated with different targeting methods (Figure 3d) [91,92]. Indirect targeting registers a stereotactic brain atlas to the patient's brain MRI, while direct targeting methods attempt to either visualize the target on the patient's MRI or use anatomic landmarks to generate image-based coordinates for the target. Non-pass regions (NPRs) are marked at regions where ultrasound is poorly transmitted, such as calcifications in the brain (Figure 3d), sinuses, air gaps between the transducer and the patient's head, membrane folds, as well as at foreign bodies, and craniotomies (Figure 3e). This step ensures that transducer elements over these areas are suppressed, preventing unwanted ultrasound scattering.

The treatment itself is conducted in three distinct sonication stages to ensure precision and patient safety. The first stage, known as the "Align" stage, raises the target temperature to 40-45°C. This initial stage does not produce tremor relief or side effects. Instead, it confirms the spot shape and alignment with the intended target. If needed, spot adjustments can be applied for target refinement. Once the spot location is confirmed, the treatment moves to the "Verify" stage, where temperatures are increased to 46–50°C. At this point, the patient may begin to experience tremor relief. If any side effects occur or tremor relief is insufficient, the physician can adjust the target location to optimize outcomes. Multiple "Verify" sonications may be performed at this temperature range, as effects remain transient. Once the target is confirmed, the physician proceeds to the "Treat" stage, where temperatures are elevated to 54°C or higher, leading to cell death via coagulative necrosis and sustained therapeutic effects. Temperature monitoring tracks the thermal dose in CEM43, which generates thermal maps and dose estimates (Figure 3f-h). Throughout the treatment, movement detection scans confirm the patient's position before each sonication, and real-time MRI provides continuous anatomical imaging (Figure 3d). The treatment workflow also includes passive cavitation detection (Figure 3i) to identify any cavitation events that might occur, allowing for closed-loop power adjustments to maintain a controlled thermal ablation regime.

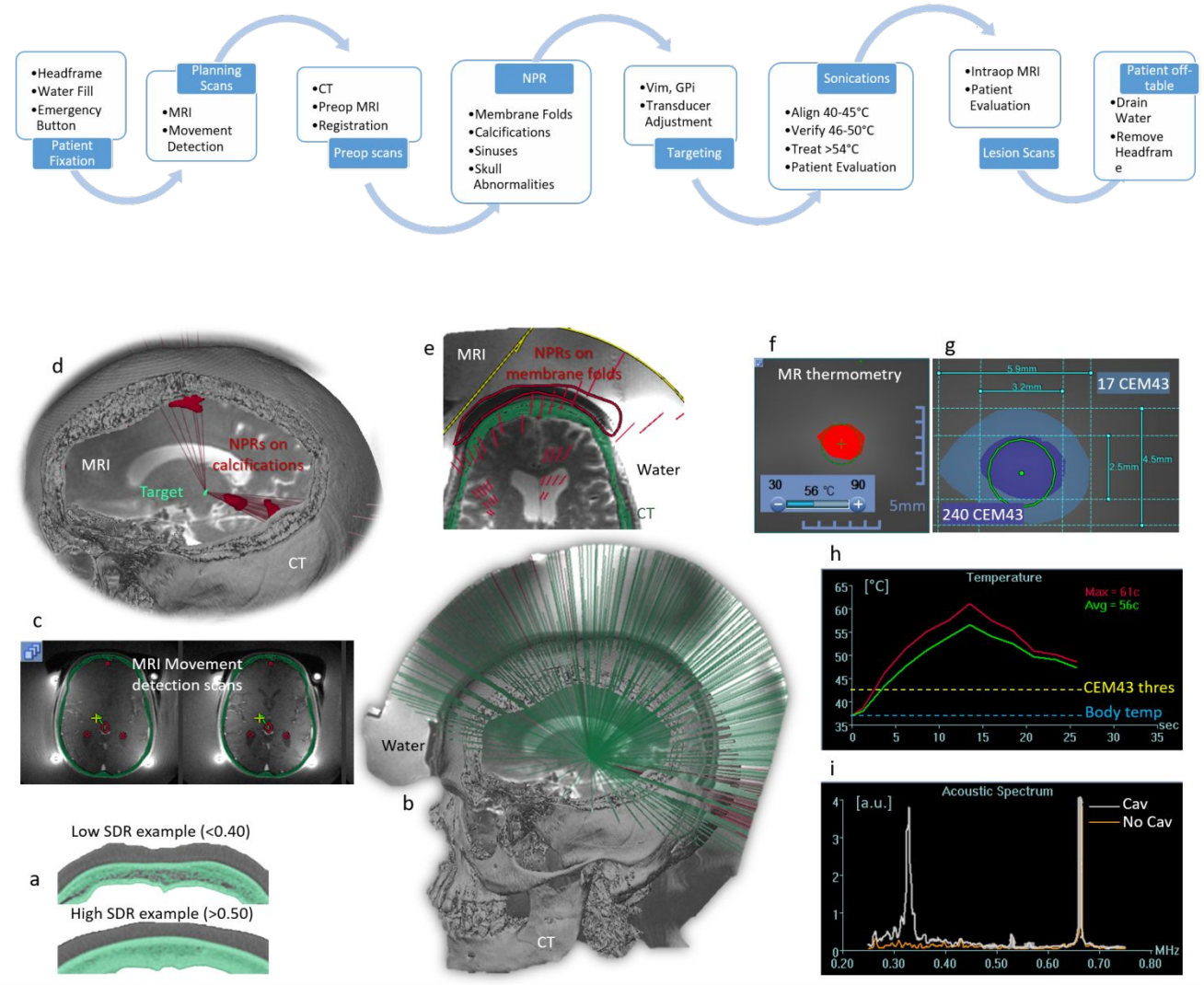

Figure 3. (Top) Thermal ablation treatment workflow. The process of MRgFUS treatment includes: patient fixation with a headframe and water coupling on the MRI table, acquisition of MRI planning scans (T1, T2, FIESTA) and baseline movement scans, co-registration of preoperative CT (mandatory) and preoperative MRI (optional) with planning images, marking of NPR (membrane folds, calcifications, sinuses, skull abnormalities), and targeting. The sonications are performed incrementally, starting with low- (40–45°C) and mid-temperature (46–50°C) sonications with patient feedback guiding adjustments. Following that lesional sonications (≥54°C) are performed and lesions are confirmed with intraoperative MRI. After treatment completion, water is drained, the patient is removed from the table and the the headframe removed from the patient's head. (Bottom) The figure illustrates the process of MRgFUS treatment, beginning with a) patient screening including Skull Density Ratio (SDR) to determine eligibility for therapy. b) Patient fixation with a headframe and water fill. This picture shows the patient's CT merged with MRI acquired during planning, highlighting active (green) and inactive (red) transducer elements, guided by non-passing regions (NPRs) and incidence angles. Water is used as a coupling medium between the transducer helmet and the patient's head. c) Reference planning and movement detection scans. The movement detection scans are later repeated prior to each sonication to confirm patient stability, while real-time MRI provides continuous anatomical imaging during treatment. The treatment planning involves marking NPRs on d) calcifications in the brain and e) membrane folds to disable transducer elements over these areas and prevent ultrasound scattering. f) Real-time thermal maps and g) thermal dose estimates are derated from h) MR thermometry. i) Passive cavitation detection identifies potential cavitation events, enabling closed-loop power adjustments to maintain a controlled thermal ablation regime.

3. Industry Landscape

According to the *State of the Field Report 2024* by the Focused Ultrasound Foundation, reporting data from 2023, 105 FUS companies and 1203 treatment sites were globally, representing only 10% of the projected market size [93]. The market was valued US$ 223.5 million in 2024 with an expected compound annual growth rate of 10.1%, reaching a valuation of US$ 585.7 million by 2034 [94]. Recently, noteworthy investments from the pharmaceutical sector, particularly aimed at advancing FUS in new therapies have been observed. Examples of companies receiving significant investments include Insightec (Tirat Carmel, Israel), which secured $150 million from Fidelity Management & Research Company, Nexus Neurotech Ventures, and Ally Bridge Group [95]. In addition, Histosonics (Plymouth, MN, USA) reported $105 million received from Alpha Wave Ventures, Amzak Health, and HealthQuest Capital [96], and CarThera secured €42 million in funding in 2023 from VC, Unorthodox Ventures, Supernova Invest, Saint-Genys and Bouscas Med [97]. While precise figures are elusive, the combined data suggests a prosperous investment landscape in FUS research and development, marked by increased venture capital funding and strategic partnerships, indicating a financially robust environment for the development of FUS technology. Concurrently, the current landscape of FUS technology and applications reflects a dynamic and rapidly evolving field marked by significant growth in device adoption, with over 22,000 MRgFUS treatments performed worldwide and many new indications explored in clinical trials, as the Focused Ultrasound Foundation reported. Particularly noteworthy is the emphasis on neurological applications, exemplified by the exploration of FUS for treating conditions such as ET, Alzheimer's disease, PD, brain tumors, and other different types of neurological disorders.

3.1 Industry Ecosystem and Regulatory Landscape

In 2022, the average cost to develop a therapeutic complex medical device in the U.S. was $54 million, increasing to $522 million when accounting for failed studies and the cost of capital [98]. The development and approval of MRgFUS is a multifaceted process, requiring close collaboration between industry, regulatory agencies, and academia to ensure both safety and efficacy before reaching widespread clinical use. Industry investment drives the execution of clinical trials in compliance with regulatory requirements to enable regulatory approvals to bring the product to market. Academic institutions contribute by conducting early-stage and pre-clinical research, identifying new clinical applications, and validating treatment outcomes and product efficacy independently. Government and private-sector funding further accelerate clinical translation, expanding MRgFUS implementation by health care providers.

As a Class III medical device, MRgFUS is subject to the Premarket Approval (PMA) process [99], the FDA's most stringent regulatory pathway, due to its high-risk nature, particularly in neurosurgical applications where precise energy delivery is critical to prevent complications. The regulatory pathway begins with bench testing, preclinical studies, and clinical trials, generating the necessary safety and efficacy data. The IDE (Investigational Device Exemption) process [100] allows manufacturers to conduct these trials under FDA oversight before submitting a comprehensive PMA application, which includes technical specifications, clinical data, and risk assessments. If prior regulatory precedent is unavailable, collaboration with regulatory agencies becomes essential to define evaluation criteria and safety standards. After approval, post-market surveillance is required, including continued long-term follow-up on patients from the clinical trials and collection of AE from commercial treatments. PMA Supplements and Amendments [101] allow manufacturers to introduce improvements, expand indications, and refine treatment protocols without requiring a full resubmission (but may require additional clinical trials). Proactive engagement with key opinion leaders and academic stakeholders can help refine treatment protocols, thus reducing trial inefficiencies and accelerating data collection.

The clinical trial NCT01827904, which supported InSightec's Exablate Neuro system PMA approval (P150038) for unilateral thalamotomy in ET took more than 3 years from the clinical trial start (05/2013) to PMA approval (07/2016), followed by 36 PMA supplements (last approved in 10/2024) to include post-market surveillance, hardware improvements, and expansion to new indications, highlighting the complexity of bringing new neurosurgical devices to market. Typical turnover times for supplement approval by the FDA were less than 30 days for Process Change (Manufacturer/ Sterilizer/ Packager/ Supplier), up to 272 days for Change (Design/ Components/ Specifications/ Material), and up to 284 days for labeling change. FDA indication expansions included unilateral thalamotomy treatment of TDPD (targeting the Vim, clinical trial: NCT01772693, PMA: P150038/S006, 2018), unilateral pallidotomy treatment of PD (targeting the GPi, clinical trial: NCT03319485, PMA: P150038/S014, 2021) [26,27], and bilateral thalamotomy treatment of ET (targeting the Vim, clinical trial: NCT04112381, PMA: P150038/S022, 2022) [20]. Other notable changes included hardware and software modifications for compatibility with additional MRI vendors GE, Siemens, and Philips (PMA: P150038/S036, 2024), and changes to the prescribers' labeling to include the 5-year follow-up post-approval study results indicating long-term durability of the treatment clinical trial (NCT01827904, PMA: P150038/S015, 2023) [17]. More

details on the PMA and supplements are available at https://www.accessdata.fda.gov/.

Following regulatory approval and compliance, the successful commercialization of MRgFUS relies on market adoption, which can occur with proper collaboration between industry, academic, regulatory, and governmental bodies. For example, to help the medical community adopt this new technology, academia should publish data to show the benefits of the technology over alternative solutions and provide a comprehensive review of its safety and efficacy. In addition, reimbursement is a key factor in patient-wide technology adoption, and the technology should show a good cost-benefit ratio. Controlled clinical trials comparing MRgFUS with established clinical solutions might be required. By integrating proactive industry engagement with academia and medical institutes (e.g., through scientific conventions and medical advisory boards), stakeholders can expand indications and drive faster, safer, and more efficient adoption of MRgFUS technology in clinical practice.

4. Clinical and Technological Challenges

Despite its numerous advantages, FUS technology encounters several limitations in precisely targeting brain regions. One significant challenge arises from the heterogeneous skull's attenuation and distortion of ultrasound waves, leading to reduced energy delivery and suboptimal focusing [60]. Current commercial clinical treatment planning based on skull data obtained from CT imaging is sensitive to the scan parameters (such as the CT vendor and the filter used) and the registration accuracy between the CT and MR images. Small inconsistencies or inaccuracies may deteriorate focusing quality. Robust algorithms are required to retain skull data and perform accurate registrations to ensure high focusing quality. While pseudo-CT offers a promising alternative to CT-based skull correction [102,103], it is not immune to vendor and sequence dependencies. Standardization efforts and cross-vendor validation will be crucial for clinical adoption. Alternatively, new studies are exploring the use of ultrasound-based measurements to directly derate attenuation by scalp and acoustic coupling and compensate for these effects prior to performing treatment [104].

The transcranial MRgFUS system uses an array of transducer elements to generate FUS beams. The algorithm calculates the optimal parameters of the ultrasound waves for each transducer element (i.e., phase and amplitude) to generate constructive interference at the target and destructive interference elsewhere, creating a small, high-intensity focal point [105,106]. In some cases, the focusing is less efficient due to the skull characteristics and may result in inhomogeneous, tilted, or elongated thermal heating. Designing optimal parameters for each transducer element may help assure the generation of uniform heating, enabling the high accuracy required for brain procedures. In some cases, conformal shaping of the heating may be required based on morphological contours or anatomical structures, which could perhaps be achieved by optimizing transducer detectors [107].

Skull characteristics are also crucial in their correlation with the acoustic energy required to achieve a temperature increase. This measure provides insights into the efficiency of ultrasound transmission through the skull, ultimately leading to different treatment strategies for optimum results [108–113]. Although SDR is currently considered the best predictive variable for temperature in the target (and therefore plays a role in patient selection), it is imperative to consider other skull parameters, such as skull thickness, incidence angles, and skull shape, as they also influence ultrasound propagation and treatment outcomes. Skull shape and incidence angle variations impact the spatial distribution and focal intensity of ultrasound energy within the brain. Moreover, skull thickness can alter the degree of skull heating and energy deposition, necessitating precise treatment planning and optimization to ensure safe and effective therapy.

For ET thalamotomy, studies and comprehensive safety analysis show it as an acceptable approach to medically refractory patients with ET, with most AEs rated as mild or moderate in severity and transient [12]. However, neurological deficits, such as gait disturbances, ataxia, weakness, speech or language disturbances, may arise from damage to critical structures surrounding the Vim. The Vim is a specific region within the thalamus associated with motor control, particularly in conditions like ET and TDPD. Referring to the homunculus map, which illustrates the somatotopic organization of motor and sensory functions in the brain, the Vim is situated adjacent to regions representing the hand, arm, legs, and face. Therefore, structures such as the internal capsule, which contains motor fibers projecting to and from the hand, arm, and face regions, must be carefully monitored to prevent damage that could lead to motor deficits. Additionally, the surrounding white matter tracts, including the corticospinal tract, should be avoided to minimize the risk of sensory disturbances. Accurate targeting is critical in MRgFUS procedures to mitigate potential AE and optimize treatment outcomes. A diverse array of targeting techniques is under investigation, ranging from atlas-based targeting to direct targeting and diffusion tensor imaging tractography [114–121]. This multiplicity highlights the nuanced nature of MRgFUS applications, suggesting that the optimal targeting approach may vary depending on the specific clinical context.

In addition, real-time imaging monitoring of temperature changes and head movements is essential for ensuring the safety and efficacy of MRgFUS therapy while preserving neighboring neurological functions. Real-time monitoring enables clinicians to dynamically assess the effects of

ultrasound energy delivery on target tissues and surrounding structures, allowing for adjustments to treatment parameters to optimize therapeutic outcomes and minimize AE. MRI thermometry enables the identification of the heating location and shape in real-time. Currently, thermometry is limited to a single orientation, with a temporal resolution of about 3 seconds. Volumetric thermometry could help in understanding the 3-dimensional shape of the heating, assuring it is confined to the targeted region and has adequate safety margins from sensitive areas. However, volumetric MR thermometry faces increased temporal constraints due to the need for acquiring multiple imaging planes (acquisitions spaced more than 3 seconds apart), depending on the number of slices, spatial resolution, and MR sequence optimizations. Parallel imaging and model-based reconstruction techniques may improve speed. Advancements in image quality can also help, such as improving the signal-to-noise ratio (e.g., development of improved head MRI coils) or reducing the noise and artifacts that FUS may induce.

Advanced imaging modalities, such as MRI or ultrasound, coupled with real-time feedback systems, can provide invaluable insights into tissue temperature changes, cavitation dynamics, and acoustic energy distribution during treatment. This enables clinicians to precisely control and tailor the therapy in response to dynamic tissue responses. Additionally, improved treatment planning tools are essential for developing patient-specific treatment strategies that account for anatomical variations and treatment goals. Sophisticated treatment planning software incorporating patient imaging data, computational modeling algorithms, and predictive analytics can facilitate the optimization of treatment parameters, dosage, and spatial targeting, thereby maximizing treatment efficacy while minimizing the risk of collateral tissue damage [122].

The cavitation detection mechanism helps maintain ablation treatments within a thermal regime. However, cavitation signals may also originate from outside the brain, for example, within the coupling water between the transducer and the patient's head. Typically, cavitation in the water does not represent a risk to the patient, but unnecessary power reduction may hinder the continuation of treatment. Precise cavitation localization can help to reduce potential false detection (cavitation not in the brain) by accurately identifying the source and location of cavitation during procedures.

Finally, vertigo and nausea sometimes experienced during MRgFUS could be partially attributed to the direct effects of either ultrasound vibrations [123–125] and/or magnetic field [126,127] on otolithic receptors that are structures associated with balance. Some patients report the sensation of turning backward, indicating the stimulation of structures within the vestibular system [128]. The phenomenon is thought to involve the cerebellothalamic and vestibulothalamic pathways, particularly when higher sonication power and more inferior targets are used. These findings are consistent with previous reports in DBS research, where stimulation of similar thalamic and vestibulothalamic pathways also produced vestibular illusions [129]. In addition, FUS can generate heat in the scalp and other tissues through the absorption of ultrasound energy, activating sensory nerves, including branches of the trigeminal nerve responsible for transmitting sensory information from the face and scalp to the brain. These sensations are more likely to occur when higher energy levels are required to reach adequate temperatures. Patient cooperation is crucial for a successful treatment. In more challenging scenarios, it is ultimately the patient's choice to continue with the treatment since sedation is not advised as tremor assessment is highly affected by anesthesia. Further research integrating neuroimaging, physiological measurements, and patient-reported outcomes is needed to understand the underlying mechanisms better and optimize treatment protocols for patient comfort.

Overcoming these technical challenges can help advance FUS technology. First, there is a need to accelerate MRgFUS treatment times to improve patient comfort and enhance clinical workflow. Shaveless treatment options would also increase patient convenience. Moreover, frameless treatments using acoustic feedback for registration could potentially offer a promising route to simplify setup and reduce the burden on patients. Achieving full-brain coverage, particularly in deep or sensitive areas, also presents a hurdle in thermal ablation applications. To expand treatment capabilities, bubble-enhanced therapies and histotripsy can be explored for their potential to safely target regions beyond thermal ablation, offering controlled mechanical disruption for a wider array of brain targets. Addressing these challenges through ongoing innovation and collaboration will be critical to enhancing FUS treatment safety, effectiveness, and accessibility.

5. Opportunities

5.1 Artificial Intelligence

Big tech companies are collectively investing staggering sums into artificial intelligence (AI) development. According to recent estimates by Goldman Sachs, the top players, including Microsoft, Alphabet (Google), Meta, and Amazon, are projected to spend over $1 trillion on AI over the next five years [130]. Similarly, the healthcare industry is increasingly adopting AI in predictive analytics and patient care. AI holds immense promise in FUS therapy, especially when big data plays a role. More than 22,000 MRgFUS procedures have been done globally. AI can help enhance targeting accuracy, treatment planning prediction, and real-time monitoring by utilizing the technical data from these treatments. By integrating machine learning techniques with anatomical atlases and patient-specific MRI and CT, AI can assist clinicians in delineating optimal treatment targets while

avoiding adjacent sensitive areas, thereby improving targeting accuracy and reducing the risk of unintended damage. Moreover, AI-driven algorithms can help predict optimal treatment parameters for accurate temperature response or develop measures for predicting patient suitability for treatment. Such measures could utilize multiple characteristics of the skull, brain, and etiology, resulting in higher sensitivity and specificity than the current SDR parameter for patient screening. In addition, more robust AI-driven measures could potentially be less sensitive to factors such as the CT vendor and filter or even rely solely on MRI data. Furthermore, during FUS therapy, AI-powered monitoring tools could analyze real-time feedback data and automatically adjust treatment parameters in response to thermal dose, providing on-the-fly treatment optimization and enhanced treatment safety and efficacy.

5.2 From portable systems to ultra-high field MRI

The potential advantages of portable MRI [131] over regular MRI for facilitating FUS procedures and treatment monitoring are significant and address several critical challenges conventional MRI systems face. Recent advancements in AI-powered image reconstruction have also enabled the development of cost-effective low-field MRI systems, such as 0.55T scanners, which deliver performance comparable to 1.5T or 3T systems. Integrating a portable MRI with a FUS device could offer flexibility and accessibility, allowing clinicians to perform treatments in remote healthcare facilities. This approach could eliminate the need for patient transportation to centralized imaging centers, reducing logistical challenges, improving accessibility for elderly or critically ill patients, and streamlining workflows for MRgFUS procedures. The compact size and mobility of portable MRI units make them well-suited for use in settings with limited space or infrastructure, such as rural clinics, field hospitals, and low-resource areas in developing countries [132–134]. These low-field MRIs provide a viable and affordable platform for integrating FUS systems, making the technology more accessible while addressing scheduling constraints and limited access to conventional MRI facilities. This innovation can potentially drive the global expansion of MRgFUS and improve access to care in underserved regions.

On the other side, high-field MRI, such as 7T systems, offers enhanced anatomical and functional imaging capabilities that could improve MRgFUS by providing finer detail in targeting and monitoring, especially in areas with small or complex brain structures, as suggested by recent advances in high-field MRI research [135]. Ultra-high field MRI (UHF MRI), such as 11.7T scanners [136], offers an opportunity to advance MRgFUS research by deepening our understanding of brain mechanisms and diseases. With its superior spatial resolution and sensitivity, UHF MRI can reveal intricate brain structures and microvascular details, aiding in understanding the cellular and circuit-level effects of FUS and potentially identifying biomarkers for treatment efficacy and safety. While current costs remain prohibitive for widespread clinical adoption, UHF MRI could serve in research settings, pushing the field forward and enabling advances in low-field MRI.

5.3 Emerging FUS Systems: Portable, Implantable, and Conformal Arrays

Portable FUS systems can integrate optical tracking to co-register MRI with CT scans, providing offline guidance for ultrasound beam targeting [137–139] with several advantages in convenience and affordability. Reduced precision compared to MRgFUS is a limiting factor that poses challenges for procedures requiring highly accurate targeting, such as thermal ablation. However, portable FUS systems can be well-suited for applications like neuromodulation and BBB disruption, where target precision requirements are less stringent, particularly for larger brain volumes in neurogenerative diseases and brain tumors.

Similarly, implantable solutions provide distinct advantages over MRgFUS, especially for repeated and diffuse BBB opening, which can facilitate drug delivery in conditions such as glioblastoma [140]. Because the ultrasound transducer is implanted within the skull, skull distortion and energy absorption issues are minimized, leading to a more efficient and consistent BBB opening. Though, this invasive approach carries an increased risk of complications associated with craniotomy and less flexibility in target adjustments, such as in portable FUS or MRgFUS.

In addition, skull-conformal phased arrays represent an innovative approach to transcranial FUS therapy [141]. These arrays are designed using patient-specific CT and MRI data to create a customized helmet-like structure that optimally positions reusable transducer modules. This technique aims to enhance treatment efficiency and patient comfort, particularly for applications such as BBB opening and neuromodulation, where precise yet flexible targeting is beneficial.

Finally, integrating scalp-mounted sensors into the 10–20 EEG system enables simultaneous recording of acoustic emissions and EEG during transcranial FUS. This solution may provide spatially consistent monitoring of ultrasound bioeffects and neural activity to enhance treatment guidance for neuromodulation, BBB opening, and epilepsy therapy [142].

These FUS innovations present promising and cost-effective alternatives for a variety of brain indications. While they may not match the precision and real-time monitoring capabilities of MRgFUS, their affordability, accessibility, and flexibility make them valuable tools for neuromodulation and BBB disruption.

5.4 Portable accessories for patient evaluation

Inertial sensors, such as gyroscopes and accelerometers, integrated into devices like smartwatches and wristbands have been studied for assessing tremor. Post-procedure patient monitoring using these devices in daily activities can also overcome the examination bias and help collect data from thousands of patients, which could be used to understand additional factors for treatment success and generate data registries for the long-term durability of the treatment. These devices measure tremor frequency, amplitude, and patterns, providing real-time data [143,144] with automatic quantification of tremor severity. If integrated inside the MRI during the treatment, these tools may provide physicians with standardized and continuous feedback on treatment efficacy, reducing the subjective tremor evaluation between sonications. In addition, if monitored during sonications, they can serve as real-time feedback, which the system can automatically use to optimize its parameters for efficiency, in addition to safety measurements such as temperature and cavitation.

5.5 Advanced imaging

MR spectroscopy (MRS) of the brain [145] has the potential to significantly enhance real-time monitoring and assessment during FUS therapy, particularly in detecting lesion formation. MRS in stroke research has enabled the examination of the dynamic metabolism within brain cells during cerebral ischemia [146]. However, in clinical settings, MRS scans often take several minutes to acquire spectra from a single region of interest. Conversely, advancements in MRI hardware, pulse sequence design, and AI-based data processing techniques have enabled faster spectroscopy acquisitions in research settings [147]. With hardware and processing advancements, MRS could potentially assess the presence or absence of a lesion formation in a single location within a short timeframe. By focusing on specific metabolites or markers associated with lesion formation, it may be possible to rapidly assess whether a lesion has formed in a particular region of interest. This approach requires careful consideration of factors like signal-to-noise ratio and spectral interpretation to ensure accuracy and reliability, especially since the coupling water used with the FUS transducer has a high proton density that may produce strong MR signals, potentially saturating the signals of interest. Although technical limitations currently restrict this idea, the prospect of employing it could potentially replace MR thermometry as an index for lesion development or allow a two-channel closed-loop control for lesion confirmation in parallel with MR thermometry.

Another potential idea involving cavitation mapping with MRI was recently described in a proof-of-concept study using phantoms [148]. By synchronizing FUS pulses with an accelerated Half-Fourier Acquisition Single Shot Turbo Spin-Echo (HASTE) sequence, the researchers achieved a 1-Hz refresh rate, allowing a precise mapping of cavitation on MR images. The technique relies on the principle that the proportion of gas-filled space in a region exposed to FUS alters the magnetic susceptibility of the surrounding area, which affects MR signal intensity. Essentially, as the bubbles grow larger with higher pressure, the MR signal drops due to these susceptibility effects. This idea is particularly valuable because cavitation control is important for the efficacy and safety of several FUS-based therapies.

In addition, innovations in real-time imaging techniques, such as functional magnetic resonance imaging (fMRI), present a promising avenue for enhancing the precision and efficacy of FUS procedures. Drawing from studies based on real-time fMRI to guide the placement of DBS electrodes [149] and laser interstitial thermal therapy (LITT) [150], FUS procedures could also benefit from real-time fMRI guidance. Similarly, functional ultrasound imaging (fUS) offers real-time visualization of cerebral blood flow dynamics and functional connectivity patterns within the brain [151–153]. By integrating real-time fMRI and/or fUS feedback with FUS procedures, clinicians could potentially optimize targeting accuracy, tailor treatment parameters based on dynamic neural responses, and ensure the safe and effective delivery of FUS therapy for various neurological conditions, for example, during FUS neuromodulation or targeting verification stage prior to MRgFUS ablation.

Finally, combining EEG, fMRI, and ultrasonic neuromodulation opens new avenues for localizing epileptic foci within an MRI environment [4]. This multimodal approach enables real-time monitoring and precise targeting within the brain, potentially allowing clinicians to identify seizure-prone regions more effectively and tailor interventions.

5.6 Ultrasound neuromodulation

Ultrasound neuromodulation is a technique that uses FUS waves to non-invasively modulate neuronal activity in targeted nerve and brain regions [4,154,155]. It is hypothesized to work through either a mechanical mechanism, where acoustic pressure waves alter ion channel states and thus membrane potentials [156,157], or a thermal mechanism, where minimal temperature changes affect cellular behavior [82,158,159]. Another hypothesis suggests that ultrasound may directly activate ion channels and synaptic transmission by promoting neurotransmitter release [160]. Clinically, ultrasound neuromodulation has been shown to create transient tremor relief in ET treatments [67] and holds promise for treating a range of neurological disorders, such as PD [161], epilepsy [162], chronic pain [163], major depressive disorder [164,165], and substance use disorder [57] given its ability to selectively stimulate [166–168] or inhibit neuronal

activity [169] with high spatial precision. However, a major barrier to its clinical and commercial application is the limited understanding of its long-term results. Additionally, achieving consistent and controlled outcomes in patients, especially regarding dosage and targeting, remains challenging, and further research is essential to address these uncertainties and translate ultrasound neuromodulation into routine therapeutic practice.

5.7 BBB Disruption

FUS has also been demonstrated to open the BBB temporarily, thereby facilitating the delivery of therapeutic agents to the brain. By utilizing targeted sound waves, FUS can induce microbubble cavitation and acoustic streaming, which temporarily disrupt the BBB structure, allowing drugs to pass through. This approach offers several advantages, including its minimal invasiveness, targeted nature, and transient effects, minimizing risks and unwanted substance entry into the brain. Studies have demonstrated improved targeting via neuronavigation [137,138,170,171], real-time safety monitoring [87,172], advancements in cavitation control [173], advancements in microbubble design [174], and applications in targeted drug delivery [175,176]. Recent studies have shown feasibility with promising safety results in patients with Alzheimer's disease [66,177]. FUS-BBB opening enabled targeted delivery of anti-amyloid antibody aducanumab, reducing cerebral amyloid-beta (Aβ) load in a specific brain side. Additionally, systematic reviews of clinical trials highlight ongoing efforts to optimize MRgFUS for brain tumor therapy through BBB permeability enhancement and targeted drug delivery strategies [178]. However, challenges such as optimizing FUS parameters, the impact the procedure on large brain volumes, and understanding long-term effects remain.

Furthermore, FUS with BBB disruption offers a promising approach for both therapeutic and diagnostic applications in brain tumors. Therapeutically, FUS can deliver medications directly to the tumor site. Studies have shown the potential of FUS to deliver chemotherapeutics, gene therapies, and nanoparticles directly to brain tumors, potentially improving treatment efficacy and reducing systemic AE [64]. Diagnostically, FUS-mediated BBB disruption can facilitate liquid biopsy by allowing tumor-derived biomarkers, such as circulating tumor DNA (ctDNA) or proteins, to enter the bloodstream [179–183]. These biomarkers can then be detected in a simple blood draw, providing valuable information about the tumor's biology and potentially enabling earlier diagnosis, treatment monitoring, and personalized medicine approaches.

5.8 Sonodynamic Therapy (SDT)

SDT presents a novel approach to treating brain tumors, leveraging the principles of sonosensitization and FUS technology [184]. In this therapeutic strategy, a sonosensitizer, potentially delivered via minimally invasive methods such as convection-enhanced delivery or intratumoral injection, is targeted directly to the tumor cells within the brain [185]. Once the sonosensitizer reaches the tumor, low-intensity ultrasound waves are directed at the targeted brain tumor. Upon exposure to ultrasound, the sonosensitizer activates within the tumor cells, generating reactive oxygen species that induce cellular damage and subsequent cell death. This approach offers several potential advantages for brain tumor treatment, including its minimally invasive nature, targeted therapy that minimizes damage to healthy brain tissue, and the possibility of transiently disrupting the BBB to enhance therapeutic agent penetration. However, challenges such as the specificity of sonosensitizers, and treatment optimization remain areas of active research. Despite these challenges, SDT shows promise as a complementary or synergistic treatment modality for brain tumors, with ongoing efforts focused on refining protocols, improving sonosensitizers, and validating safety and efficacy through further research.

6. Closing remarks

As highlighted by recent studies, the field of FUS for movement disorders is gaining traction, though challenges remain in both treatment efficacy and awareness of broader applications beyond tremor control. MRgFUS has proven the ability to target the Vim in the thalamus and provide significant symptom relief. However, while Vim targeting is well-established for tremor, broader applications for addressing other Parkinsonian symptoms via GPi, PTT, and STN targeting face limited regulatory approval in different regions of the globe.

Advanced therapies like BBB modulation via FUS also hold promise for managing neurodegenerative indications, such as Alzheimer’s and Parkinson's, and neurooncology indications, such as glioblastomas, potentially allowing for targeted drug delivery. There are many additional fields of interest, such as liquid biopsies to monitor glioma biomarkers. Collectively, these innovations reflect a growing interest in expanding FUS’s therapeutic applications and aligning the technique with personalized medicine approaches.

The evolving landscape of FUS therapy presents both challenges and opportunities. Future directions for FUS in movement disorders include integrating AI and wearable technologies to enhance symptom monitoring, refine treatment planning, and increase precision in real-time assessments during treatment. Advancements such as AI could also be used for targeting, and sophisticated imaging techniques offer promising avenues to address skull

attenuation and targeting challenges. Additionally, integrating novel technologies like drug design and theranostic agents combined with FUS-induced BBB opening and SDT signals a shift towards personalized medicine, expanding clinical indications. Collaboration among industry, academia, healthcare providers, and regulators is important for utilizing these opportunities. Collaborative efforts can drive advancements that may redefine medical imaging and therapy, accelerate innovation, ensure regulatory compliance, and deliver transformative solutions to meet the evolving needs of patients worldwide.

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Conflicts of Interest

The authors declare no conflicts of interest related to this work. No financial, commercial, or personal relationships influenced this manuscript's research, analysis, or conclusions. This study was conducted independently, and all findings reflect the authors' unbiased scientific interpretation.

References

[1] Harary M, Segar D J, Huang K T, Tafel I J, Valdes P A and Cosgrove G R 2018 Focused ultrasound in neurosurgery: a historical perspective *Neurosurg. Focus* **44** E2

[2] Bader K B, Padilla F, Haworth K J, Ellens N, Dalecki D, Miller D L, Wear K A, and Bioeffects Committee of the American Institute of Ultrasound in Medicine 2024 Overview of Therapeutic Ultrasound Applications and Safety Considerations: 2024 Update *J. Ultrasound Med.* jum.16611

[3] Elias W J, *et al.* 2013 A Pilot Study of Focused Ultrasound Thalamotomy for Essential Tremor *N. Engl. J. Med.* **369** 640–8

[4] Kamimura H A S, Conti A, Toschi N and Konofagou E E 2020 Ultrasound Neuromodulation: Mechanisms and the Potential of Multimodal Stimulation for Neuronal Function Assessment *Front. Phys.* **8** 150

[5] O'Reilly M A 2024 Exploiting the mechanical effects of ultrasound for noninvasive therapy *Science* **385** eadp7206

[6] Dallapiazza R F, Lee D J, De Vloo P, Fomenko A, Hamani C, Hodaie M, Kalia S K, Fasano A and Lozano A M 2019 Outcomes from stereotactic surgery for essential tremor. *J. Neurol. Neurosurg. Psychiatry* **90** 474–82

[7] Giordano M, Caccavella V M, Zaed I, Foglia Manzillo L, Montano N, Olivi A and Polli F M 2020 Comparison between deep brain stimulation and magnetic resonance-guided focused ultrasound in the treatment of essential tremor: a systematic review and pooled analysis of functional outcomes. *J. Neurol. Neurosurg. Psychiatry* **91** 1270–8

[8] Ferreira Felloni Borges Y, Cheyuo C, Lozano A M and Fasano A 2023 Essential Tremor – Deep Brain Stimulation vs. Focused Ultrasound *Expert Rev. Neurother.* **23** 603–19

[9] Insightec Ltd. 2024 Insightec Focused Ultrasound Now Covered For Parkinson's Disease Pallidotomy in US, https://www.prnewswire.com/news-releases/insightec-focused-ultrasound-now-covered-for-parkinsons-disease-pallidotomy-in-us-302071089.html

[10] Elias W J, *et al.* 2016 A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. *N. Engl. J. Med.* **375** 730–9

[11] Bond A E, Dallapiazza R, Huss D, Warren A L, Sperling S, Gwinn R, Shah B B and Elias W J 2016 132 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**

[12] Fishman P S, *et al.* 2018 Neurological adverse event profile of magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor. *Mov. Disord. Off. J. Mov. Disord. Soc.* **33** 843–7

[13] Halpern C H, *et al.* 2019 Three-year follow-up of prospective trial of focused ultrasound thalamotomy for essential tremor. *Neurology* **93** e2284–93

[14] Agrawal M, Garg K, Samala R, Rajan R, Naik V and Singh M 2021 Outcome and Complications of MR Guided Focused Ultrasound for Essential Tremor: A Systematic Review and Meta-Analysis. *Front. Neurol.* **12** 654711

[15] Miller W K, Becker K N, Caras A J, Mansour T R, Mays M T, Rashid M and Schwalb J 2022 Magnetic resonance-guided focused ultrasound treatment for essential tremor shows sustained efficacy: a meta-analysis *Neurosurg. Rev.* **45** 533–44

[16] Mortezaei A, Essibayi M A, Mirahmadi Eraghi M, Alizadeh M, Taghlabi K M, Eskandar E N and Faraji A H 2024 Magnetic resonance–guided focused ultrasound in the treatment of refractory essential tremor: a systematic review and meta-analysis *Neurosurg. Focus* **57** E2

[17] Cosgrove G R, *et al.* 2023 Magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor: 5-year follow-up results. *J. Neurosurg.* **138** 1028–33

[18] Ito H, Yamamoto K, Fukutake S, Kamei T, Yamaguchi T and Taira T 2024 Long-term outcome following magnetic resonance imaging-guided focused ultrasound unilateral thalamotomy for medication-refractory essential tremor *Neurol. Clin. Neurosci.* **12** 233–8

[19] Schiff G, Sokolov A, Dhawan N, Frazzetta G and Gant K 2024 Real-world Experience of the Safety of Magnetic Resonance Imaging–guided Focused Ultrasound (MRgFUS)-thalamotomy for Essential Tremor (P3-3.008) *Neurology* **102** 5114

[20] Kaplitt M G, *et al.* 2024 Safety and Efficacy of Staged, Bilateral Focused Ultrasound Thalamotomy in Essential Tremor: An Open-Label Clinical Trial. *JAMA Neurol.* **81** 939–46

[21] Jameel A, Gedroyc W, Nandi D, Jones B, Kirmi O, Molloy S, Tai Y, Charlesworth G and Bain P 2022 Double lesion MRgFUS treatment of essential tremor targeting the thalamus and posterior

sub-thalamic area: preliminary study with two year follow-up. *Br. J. Neurosurg.* **36** 241–50

[22] Kyle K, Peters J, Jonker B, Barnett Y, Maamary J, Barnett M, Maller J, Wang C and Tisch S 2024 Magnetic Resonance-Guided Focused Ultrasound for Treatment of Essential Tremor: Ventral Intermediate Nucleus Ablation Alone or Additional Posterior Subthalamic Area Lesioning? *Mov. Disord. Clin. Pract.* **11** 504–14

[23] Schreglmann S R, Bauer R, Hägele-Link S, Bhatia K P, Natchev P, Wegener N, Lebeda A, Werner B, Martin E and Kägi G 2017 Unilateral cerebellothalamic tract ablation in essential tremor by MRI-guided focused ultrasound. *Neurology* **88** 1329–33

[24] Gallay M N, Moser D, Rossi F, Pourtehrani P, Magara A E, Kowalski M, Arnold A and Jeanmonod D 2016 Incisionless transcranial MR-guided focused ultrasound in essential tremor: cerebellothalamic tractotomy. *J. Ther. Ultrasound* **4** 5

[25] Gallay M N, Moser D and Jeanmonod D 2021 MR-guided focused ultrasound cerebellothalamic tractotomy for chronic therapy-resistant essential tremor: anatomical target reappraisal and clinical results. *J. Neurosurg.* **134** 376–85

[26] Eisenberg H M, Krishna V, Elias W J, Cosgrove G R, Gandhi D, Aldrich C E and Fishman P S 2021 MR-guided focused ultrasound pallidotomy for Parkinson's disease: safety and feasibility. *J. Neurosurg.* **135** 792–8

[27] Krishna Vibhor, *et al.* 2023 Trial of Globus Pallidus Focused Ultrasound Ablation in Parkinson's Disease *N. Engl. J. Med.* **388** 683–93

[28] Magara A, Bühler R, Moser D, Kowalski M, Pourtehrani P and Jeanmonod D 2014 First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease *J. Ther. Ultrasound* **2** 11

[29] Gallay M N, Moser D, Federau C and Jeanmonod D 2019 Anatomical and Technical Reappraisal of the Pallidothalamic Tractotomy With the Incisionless Transcranial MR-Guided Focused Ultrasound. A Technical Note *Front. Surg.* **6** 2

[30] Gallay M N, *et al.* 2020 MRgFUS Pallidothalamic Tractotomy for Chronic Therapy-Resistant Parkinson's Disease in 51 Consecutive Patients: Single Center Experience *Front. Surg.* **6** 76

[31] Gallay M N, Moser D, Magara A E, Haufler F and Jeanmonod D 2021 Bilateral MR-Guided Focused Ultrasound Pallidothalamic Tractotomy for Parkinson's Disease With 1-Year Follow-Up. *Front. Neurol.* **12** 601153

[32] Rodriguez-Rojas R, Pineda-Pardo J A, Martinez-Fernandez R, Kogan R V, Sanchez-Catasus C A, Del Alamo M, Hernández F, García-Cañamaque L, Leenders K L and Obeso J A 2020 Functional impact of subthalamotomy by magnetic resonance-guided focused ultrasound in Parkinson's disease: a hybrid PET/MR study of resting-state brain metabolism. *Eur. J. Nucl. Med. Mol. Imaging* **47** 425–36

[33] Armengou-Garcia L, Sanchez-Catasus C A, Aviles-Olmos I, Jiménez-Huete A, Montoya-Murillo G, Gorospe A, Martin-Bastida A, Gonzalez-Quarante L H, Guridi J and Rodriguez-Oroz M C 2024 Unilateral Magnetic Resonance-Guided Focused Ultrasound Lesion of the Subthalamic Nucleus in Parkinson's Disease: A Prospective Study. *Mov. Disord. Off. J. Mov. Disord. Soc.*

[34] Martínez-Fernández R, *et al.* 2024 Staged Bilateral MRI-Guided Focused Ultrasound Subthalamotomy for Parkinson Disease. *JAMA Neurol.* **81** 638–44

[35] Rodriguez-Rojas R, Máñez-Miró J U, Pineda-Pardo J A, Del Álamo M, Martínez-Fernández R and Obeso J A 2024 Functional anatomy of the subthalamic nucleus and the pathophysiology of cardinal features of Parkinson's disease unraveled by focused ultrasound ablation *Sci. Adv.* **10** eadr9891

[36] Campins-Romeu M, *et al.* 2024 MRgFUS subthalamotomy in Parkinson's disease: an approach aimed at minimizing Lesion Volume *Npj Park. Dis.* **10** 230

[37] Chen J-C, Lu M-K, Chen C-M and Tsai C-H 2023 Stepwise Dual-Target Magnetic Resonance-Guided Focused Ultrasound in Tremor-Dominant Parkinson Disease: A Feasibility Study. *World Neurosurg.* **171** e464–70

[38] Chen J-C, Chen C-M, Aoh Y, Lu M-K and Tsai C-H 2024 Stepwise dual-target magnetic resonance-guided focused ultrasound in tremor-dominant Parkinson disease: One-year follow-up. *Eur. J. Neurol.* e16468

[39] Jeanmonod D, Werner B, Morel A, Michels L, Zadicario E, Schiff G and Martin E 2012 Transcranial magnetic resonance imaging–guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain *Neurosurg. Focus FOC* **32** E1

[40] Gallay M N, Magara A E, Moser D, Kowalski M, Kaeser M and Jeanmonod D 2023 Magnetic resonance-guided focused ultrasound central lateral thalamotomy against chronic and therapy-resistant neuropathic pain: retrospective long-term follow-up analysis of 63 interventions. *J. Neurosurg.* **139** 615–24

[41] Ahmed A-K, *et al.* 2024 Focused Ultrasound Central Lateral Thalamotomy for the Treatment of Refractory Neuropathic Pain: Phase I Trial. *Neurosurgery* **94** 690–9

[42] Colasurdo M, Ahmed A-K and Gandhi D 2024 MR-guided Focused Ultrasound Thalamotomy for Chronic Pain. *Magn. Reson. Imaging Clin. N. Am.* **32** 661–72

[43] Monteith S, Snell J, Eames M, Kassell N F, Kelly E and Gwinn R 2016 Transcranial magnetic resonance–guided focused ultrasound for temporal lobe epilepsy: a laboratory feasibility study *J. Neurosurg.* **125** 1557–64

[44] Abe K, Yamaguchi T, Hori H, Sumi M, Horisawa S, Taira T and Hori T 2020 Magnetic resonance-guided focused ultrasound for mesial temporal lobe epilepsy: a case report *BMC Neurol.* **20** 160

[45] Yamaguchi T, Hori T, Hori H, Takasaki M, Abe K, Taira T, Ishii K and Watanabe K 2020 Magnetic resonance–guided focused ultrasound ablation of hypothalamic hamartoma as a disconnection surgery: a case report *Acta Neurochir. (Wien)* **162** 2513–7

[46] Tierney T S, *et al.* 2022 Initial experience with magnetic resonance–guided focused ultrasound stereotactic surgery for central brain lesions in young adults *J. Neurosurg.* **137** 760–7

[47] Ricciardi G K, *et al.* 2025 MRgFUS disconnection surgery for hypothalamic hamartoma-related epilepsy: case report and literature review *Neurol. Sci.* **46** 1399–404

[48] Levi V, *et al.* 2024 Bilateral Simultaneous Magnetic Resonance-Guided Focused Ultrasound Pallidotomy for Life-Threatening

Status Dystonicus. *Mov. Disord. Off. J. Mov. Disord. Soc.* **39** 1408–12

[49] Davidson B, *et al.* 2020 Magnetic resonance-guided focused ultrasound capsulotomy for refractory obsessive compulsive disorder and major depressive disorder: clinical and imaging results from two phase I trials. *Mol. Psychiatry* **25** 1946–57

[50] Chang K W, Jung H H and Chang J W 2021 Magnetic Resonance-Guided Focused Ultrasound Surgery for Obsessive-Compulsive Disorders: Potential for use as a Novel Ablative Surgical Technique. *Front. Psychiatry* **12** 640832

[51] Germann J, *et al.* 2021 Potential optimization of focused ultrasound capsulotomy for obsessive compulsive disorder. *Brain J. Neurol.* **144** 3529–40

[52] Hamani C, *et al.* 2024 Long-Term Safety and Efficacy of Focused Ultrasound Capsulotomy for Obsessive-Compulsive Disorder and Major Depressive Disorder. *Biol. Psychiatry* S0006-3223(24)01548-8

[53] Keating G F, *et al.* 2024 MR-guided focused ultrasound in pediatric neurosurgery: current insights, technical challenges, and lessons learned from 45 treatments at Children's National Hospital *Neurosurg. Focus* **57** E6

[54] Chesney K M, *et al.* 2024 The role of focused ultrasound for pediatric brain tumors: current insights and future implications on treatment strategies *Childs Nerv. Syst.* **40** 2333–44

[55] Meng Y, Hynynen K and Lipsman N 2021 Applications of focused ultrasound in the brain: from thermoablation to drug delivery *Nat. Rev. Neurol.* **17** 7–22

[56] Hynynen K, McDannold N, Vykhodtseva N and Jolesz F A 2001 Noninvasive MR Imaging–guided Focal Opening of the Blood-Brain Barrier in Rabbits *Radiology* **220** 640–6

[57] Mahoney J J, *et al.* 2023 Low-intensity focused ultrasound targeting the nucleus accumbens as a potential treatment for substance use disorder: safety and feasibility clinical trial *Front. Psychiatry* **14** 1211566

[58] Yoshida M, *et al.* 2019 Sonodynamic Therapy for Malignant Glioma Using 220-kHz Transcranial Magnetic Resonance Imaging-Guided Focused Ultrasound and 5-Aminolevulinic acid *Ultrasound Med. Biol.* **45** 526–38

[59] Bond A E, *et al.* 2017 Safety and Efficacy of Focused Ultrasound Thalamotomy for Patients With Medication-Refractory, Tremor-Dominant Parkinson Disease: A Randomized Clinical Trial. *JAMA Neurol.* **74** 1412–8

[60] Pinton G, Aubry J-F, Bossy E, Muller M, Pernot M and Tanter M 2011 Attenuation, scattering, and absorption of ultrasound in the skull bone: Absorption of ultrasound in the skull bone *Med. Phys.* **39** 299–307

[61] O'Brien W D 2007 Ultrasound–biophysics mechanisms *Prog. Biophys. Mol. Biol.* **93** 212–55

[62] Hamilton M F and Blackstock D T 2024 *Nonlinear Acoustics* (Cham: Springer Nature Switzerland)

[63] Cobbold R 2006 *Foundations of biomedical ultrasound* (Oxford University Press)

[64] Mainprize T, *et al.* 2019 Blood-Brain Barrier Opening in Primary Brain Tumors with Non-invasive MR-Guided Focused Ultrasound: A Clinical Safety and Feasibility Study *Sci. Rep.* **9** 321

[65] D'Haese P-F, *et al.* 2020 β-Amyloid Plaque Reduction in the Hippocampus After Focused Ultrasound-Induced Blood–Brain Barrier Opening in Alzheimer's Disease *Front. Hum. Neurosci.* **14** 593672

[66] Rezai A R, *et al.* 2024 Ultrasound Blood–Brain Barrier Opening and Aducanumab in Alzheimer's Disease *N. Engl. J. Med.* **390** 55–62

[67] Bancel T, *et al.* 2024 Sustained reduction of essential tremor with low-power non-thermal transcranial focused ultrasound stimulations in humans. *Brain Stimulat.* **17** 636–47

[68] Tsai K W-K, Chen J-C, Lai H-C, Chang W-C, Taira T, Chang J W and Wei C-Y 2021 The Distribution of Skull Score and Skull Density Ratio in Tremor Patients for MR-Guided Focused Ultrasound Thalamotomy *Front. Neurosci.* **15** 612940

[69] Yuen J, Miller K J, Klassen B T, Lehman V T, Lee K H and Kaufmann T J 2022 Hyperostosis in Combination With Low Skull Density Ratio: A Potential Contraindication for Magnetic Resonance Imaging-Guided Focused Ultrasound Thalamotomy. *Mayo Clin. Proc. Innov. Qual. Outcomes* **6** 10–5

[70] Iijima K, *et al.* 2022 Predictors of thermal increase in magnetic resonance-guided focused ultrasound treatment for essential tremor: histogram analysis of skull density ratio values for 1024 elements. *J. Neurosurg.* **136** 1381–6

[71] Kyle K, Maamary J, Jonker B, Peters J, Barnett Y, Barnett M, D'Souza A, Maller J, Wang C and Tisch S 2024 Consistency is key: influence of skull density ratio distribution on the formation of clinically effective lesions and long-term tremor suppression following treatment with MR-guided focused ultrasound. *J. Neurosurg.* **140** 648–56

[72] Schwartz M L, Yeung R, Huang Y, Lipsman N, Krishna V, Jain J D, Chapman M G, Lozano A M and Hynynen K 2019 Skull bone marrow injury caused by MR-guided focused ultrasound for cerebral functional procedures. *J. Neurosurg.* **130** 758–62

[73] McDannold N, White P J and Cosgrove R 2020 Predicting Bone Marrow Damage in the Skull After Clinical Transcranial MRI-Guided Focused Ultrasound With Acoustic and Thermal Simulations *IEEE Trans. Med. Imaging* **39** 3231–9

[74] Bond A E and Elias W J 2018 Predicting lesion size during focused ultrasound thalamotomy: a review of 63 lesions over 3 clinical trials. *Neurosurg. Focus* **44** E5

[75] Huang Y, Lipsman N, Schwartz M L, Krishna V, Sammartino F, Lozano A M and Hynynen K 2018 Predicting lesion size by accumulated thermal dose in MR-guided focused ultrasound for essential tremor. *Med. Phys.* **45** 4704–10

[76] Jones R M, Kamps S, Huang Y, Scantlebury N, Lipsman N, Schwartz M L and Hynynen K 2020 Accumulated thermal dose in MRI-guided focused ultrasound for essential tremor: repeated sonications with low focal temperatures *J. Neurosurg.* **132** 1802–9

[77] McDannold N, Jason White P and Rees Cosgrove G 2020 MRI-based thermal dosimetry based on single-slice imaging during focused ultrasound thalamotomy. *Phys. Med. Biol.* **65** 235018

[78] Sapareto S A and Dewey W C 1984 Thermal dose determination in cancer therapy *Int. J. Radiat. Oncol.* **10** 787–800

[79] Van Rhoon G C 2016 Is CEM43 still a relevant thermal dose parameter for hyperthermia treatment monitoring? *Int. J. Hyperthermia* **32** 50–62

[80] Pennes H H 1948 Analysis of Tissue and Arterial Blood Temperatures in the Resting Human Forearm *J. Appl. Physiol.* **1** 93–122

[81] W L Nyborg 1988 Solutions of the bio-heat transfer equation *Phys. Med. Biol.* **33** 785

[82] H. A. S. Kamimura, C. Aurup, E. V. Bendau, N. Saharkhiz, M. G. Kim, and E. E. Konofagou 2020 Iterative Curve Fitting of the Bioheat Transfer Equation for Thermocouple-Based Temperature Estimation $In~ Vitro$ and $In~ Vivo$ *IEEE Trans. Ultrason. Ferroelectr. Freq. Control* **67** 70–80

[83] Chung A H, Jolesz F A and Hynynen K 1999 Thermal dosimetry of a focused ultrasound beam *in vivo* by magnetic resonance imaging *Med. Phys.* **26** 2017–26

[84] McDannold N, King R L and Hynynen K 2004 MRI monitoring of heating produced by ultrasound absorption in the skull: In vivo study in pigs *Magn. Reson. Med.* **51** 1061–5

[85] Mattay R R, Kim K, Shah L, Shah B, Sugrue L, Safoora F, Ozhinsky E and Narsinh K H 2024 MR Thermometry during Transcranial MR Imaging–Guided Focused Ultrasound Procedures: A Review *Am. J. Neuroradiol.* **45** 1–8

[86] Wang T R, Bond A E, Dallapiazza R F, Blanke A, Tilden D, Huerta T E, Moosa S, Prada F U and Elias W J 2018 Transcranial magnetic resonance imaging–guided focused ultrasound thalamotomy for tremor: technical note *Neurosurg. Focus* **44** E3

[87] Kamimura H A, Flament J, Valette J, Cafarelli A, Aron Badin R, Hantraye P and Larrat B 2019 Feedback control of microbubble cavitation for ultrasound-mediated blood–brain barrier disruption in non-human primates under magnetic resonance guidance *J. Cereb. Blood Flow Metab.* **39** 1191–203

[88] Insightec Ltd 2024 Exablate Neuro Documentation, https://documentation.insightec.com/ *Exablate Neuro Doc.*

[89] Schneider U, Pedroni E and Lomax A 1996 The calibration of CT Hounsfield units for radiotherapy treatment planning *Phys. Med. Biol.* **41** 111–24

[90] Mast T D 2000 Empirical relationships between acoustic parameters in human soft tissues *Acoust. Res. Lett. Online* **1** 37–42

[91] Shah B R, *et al.* 2020 Advanced MRI techniques for transcranial high intensity focused ultrasound targeting. *Brain J. Neurol.* **143** 2664–72

[92] Shah B R, *et al.* 2024 State of Practice on Transcranial MR-Guided Focused Ultrasound: A Report from the ASNR Standards and Guidelines Committee and ACR Commission on Neuroradiology Workgroup *Am. J. Neuroradiol.* ajnr;ajnr.A8405v1

[93] Focused Ultrasound Foundation 2024 *State of the Field Report 2024, Focused Ultrasound Foundation (2024), https://www.fusfoundation.org/the-foundation/foundation-reports/state-of-the-field-report-2024/*

[94] GlobeNewswire 2024 MRI-guided Focused Ultrasound Device Market is expected to see Rapid Growth of US$ 585.7 million with a CAGR of 10.1% by 2034: Fact.MR Reports, https://www.globenewswire.com/news-release/2024/04/02/2856169/0/en/MRI-guided-Focused-Ultrasound-Device-Market-is-expected-to-see-Rapid-Growth-of-US-585-7-million-with-a-CAGR-of-10-1-by-2034-Fact-MR-Reports.html *GlobeNewswire*

[95] Insightec Ltd. 2024 Fidelity Management & Research Company Leads Financing; Nexus Neurotech Ventures and Ally Bridge Group Co-Lead Robust Investor Syndicate, https://insightec.com/news/insightec-announces-150m-financing-to-fund-continued-growth/

[96] Businesswire 2024 HistoSonics Announces Oversubscribed $102 Million Series D Financing to Scale Launch of Non-Invasive Histotripsy Platform, https://www.businesswire.com/news/home/20240815865405/en/ *Businesswire*

[97] Carthera 2024 Carthera brings Series B round to €42M with additional €4.5M funding, https://carthera.eu/wp-content/uploads/2024/01/231211-Carthera-Series-B-additional-funding-EN.pdf

[98] Sertkaya A, DeVries R, Jessup A and Beleche T 2022 Estimated Cost of Developing a Therapeutic Complex Medical Device in the US *JAMA Netw. Open* **5** e2231609–e2231609

[99] U.S. Food and Drug Administration (FDA) 2022 Premarket Approval (PMA), https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-approval-pma

[100] U.S. Food and Drug Administration (FDA) 2024 Investigational Device Exemption (IDE), https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/investigational-device-exemption-ide

[101] U.S. Food and Drug Administration (FDA) 2019 PMA Supplements and Amendments, https://www.fda.gov/medical-devices/premarket-approval-pma/pma-supplements-and-amendments

[102] Leung S A, Moore D, Gilbo Y, Snell J, Webb T D, Meyer C H, Miller G W, Ghanouni P and Butts Pauly K 2022 Comparison between MR and CT imaging used to correct for skull-induced phase aberrations during transcranial focused ultrasound *Sci. Rep.* **12** 13407

[103] Yaakub S N, White T A, Kerfoot E, Verhagen L, Hammers A and Fouragnan E F 2023 Pseudo-CTs from T1-weighted MRI for planning of low-intensity transcranial focused ultrasound neuromodulation: An open-source tool *Brain Stimul. Basic Transl. Clin. Res. Neuromodulation* **16** 75–8

[104] Riis T, Feldman D, Mickey B and Kubanek J 2024 Controlled noninvasive modulation of deep brain regions in humans *Commun. Eng.* **3** 13

[105] Clement G T and Hynynen K 2002 A non-invasive method for focusing ultrasound through the human skull *Phys. Med. Biol.* **47** 1219–36

[106] Aubry J-F, Tanter M, Pernot M, Thomas J-L and Fink M 2003 Experimental demonstration of noninvasive transskull adaptive focusing based on prior computed tomography scans *J. Acoust. Soc. Am.* **113** 84–93

[107] Crake C, Brinker S T, Coviello C M, Livingstone M S and McDannold N J 2018 A dual-mode hemispherical sparse array for 3D passive acoustic mapping and skull localization within a clinical MRI guided focused ultrasound device *Phys. Med. Biol.* **63** 065008

[108] Nishida N, *et al.* 2024 Minimum and early high-energy sonication protocol of MR-guided focused ultrasound thalamotomy for low-skull density ratio patients with essential tremor and Parkinson's disease. *Neurosurg. Focus* **57** E4

[109] Vetkas A, *et al.* 2024 Successful magnetic resonance–guided focused ultrasound treatment of tremor in patients with a skull density ratio of 0.4 or less *J. Neurosurg.* **140** 639–47

[110] Hino S, *et al.* 2024 Effectiveness and safety of MR-guided focused ultrasound thalamotomy in patients with essential tremor and low skull density ratio: a study of 101 cases. *J. Neurosurg.* **141** 212–20

[111] Ng P R, Blitz S E, Chua M M J and Cosgrove G R 2024 Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor patients with low skull density ratio: a case-matched analysis *Front. Neurol.* **15** 1370574

[112] D'Souza M, *et al.* 2020 Impact of skull density ratio on efficacy and safety of magnetic resonance–guided focused ultrasound treatment of essential tremor *J. Neurosurg. JNS* **132** 1392–7

[113] Chowdhury E A, Sivan V, Kumar R P, Ruzicka Iv F F and Azmi H 2024 Delayed clinical response to focused ultrasound thalamotomy in essential tremor in a patient with suboptimal skull density ratio – A case report *Surg. Neurol. Int.* **15** 406

[114] Tian Q, *et al.* 2018 Diffusion MRI tractography for improved transcranial MRI-guided focused ultrasound thalamotomy targeting for essential tremor. *NeuroImage Clin.* **19** 572–80

[115] Buch V P, *et al.* 2020 Focused Ultrasound Thalamotomy with Dentato-Rubro-Thalamic Tractography in Patients with Spinal Cord Stimulators and Cardiac Pacemakers. *Stereotact. Funct. Neurosurg.* **98** 263–9

[116] Bruno F, *et al.* 2021 Comparative evaluation of tractography-based direct targeting and atlas-based indirect targeting of the ventral intermediate (Vim) nucleus in MRgFUS thalamotomy. *Sci. Rep.* **11** 13538

[117] Feltrin F S, Chopra R, Pouratian N, Elkurd M, El-Nazer R, Lanford L, Dauer W and Shah B R 2022 Focused ultrasound using a novel targeting method four-tract tractography for magnetic resonance-guided high-intensity focused ultrasound targeting. *Brain Commun.* **4** fcac273

[118] Ghielmetti F, *et al.* 2024 Quantitative Tractography-Based Evaluations in Essential Tremor Patients after MRgFUS Thalamotomy. *Mov. Disord. Clin. Pract.*

[119] Jameel A, Akgun S, Yousif N, Smith J, Jones B, Nandi D, Bain P and Gedroyc W 2024 The evolution of ventral intermediate nucleus targeting in MRI-guided focused ultrasound thalamotomy for essential tremor: an international multi-center evaluation. *Front. Neurol.* **15** 1345873

[120] Chua M M J, LeBlang S, Powlovich L, Gilbertson T, Krishna V, Guttmann C R G, Eames M D C, Poulsen F R and Cosgrove G R 2024 Brain targeting for focused ultrasound essential tremor ablation: proceedings from the 2023 Focused Ultrasound Foundation workshop. *Neurosurg. Focus* **57** E3

[121] Goedemans T, *et al.* 2024 FAT1 weighted MRI: Diffusion meets anatomical imaging and application in thalamic surgery for tremor *Imaging Neurosci.* **2** 1–15

[122] Miller T R, Guo S, Melhem E R, Eisenberg H M, Zhuo J, Kelm N, Dayan M, Gullapalli R P and Gandhi D 2021 Predicting final lesion characteristics during MR-guided focused ultrasound pallidotomy for treatment of Parkinson's disease. *J. Neurosurg.* **134** 1083–90

[123] Lackner J and Graybiel A 1974 Elicitation of vestibular side effects by regional vibration of the head *Aerosp. Med.* **45** 1267–72

[124] Dumas G, Curthoys I S, Lion A, Perrin P and Schmerber S 2017 The Skull Vibration-Induced Nystagmus Test of Vestibular Function—A Review *Front. Neurol.* **8**

[125] Salahshoor H, Shapiro M G and Ortiz M 2020 Transcranial focused ultrasound generates skull-conducted shear waves: Computational model and implications for neuromodulation *Appl. Phys. Lett.* **117** 033702

[126] Mian O S, Li Y, Antunes A, Glover P M and Day B L 2013 On the Vertigo Due to Static Magnetic Fields ed G Foffani *PLoS ONE* **8** e78748

[127] Mian O S, Li Y, Antunes A, Glover P M and Day B L 2016 Effect of head pitch and roll orientations on magnetically induced vertigo *J. Physiol.* **594** 1051–67

[128] Ciocca M, *et al.* 2024 Illusions of Self-Motion during Magnetic Resonance-Guided Focused Ultrasound Thalamotomy for Tremor. *Ann. Neurol.* **96** 121–32

[129] Shaikh A G, Straumann D and Palla A 2017 Motion Illusion—Evidence towards Human Vestibulo-Thalamic Projections *The Cerebellum* **16** 656–63

[130] Goldman Sachs 2024 GEN AI: TOO MUCH SPEND, TOO LITTLE BENEFIT?, https://www.goldmansachs.com/images/migrated/insights/pages/gs-research/gen-ai--too-much-spend%2C-too-little-benefit-/TOM_AI%202.0_ForRedaction.pdf *Goldman Sachs*

[131] Zhao Y, Ding Y, Lau V, Man C, Su S, Xiao L, Leong A T L and Wu E X 2024 Whole-body magnetic resonance imaging at 0.05 Tesla *Science* **384** eadm7168

[132] Asija S, Pahwa B, Agarwal A, Patil Y and Chaurasia B 2024 Status of functional neurosurgery in lower middle-income countries (LMICs): A multinational cross sectional survey based analysis of exposure, utilization and perceived barriers *Clin. Neurol. Neurosurg.* **245** 108411

[133] Guan Y, Liao J and Yue L 2024 Barriers to conducting magnetic resonance-guided focused ultrasound program for treating movement disorders in the resource-limited setting *Neurosurg. Rev.* **47** 767

[134] Khu K J O, Jamora R D G, Aguilar J A, Pascual J S G, Chan K I P, Espenido T M R, Mata J L, Nievera A M P and Legaspi G D 2024 Establishing and developing a magnetic resonance-guided focused ultrasound program in a resource-limited setting: the Philippine experience. *Neurosurg. Rev.* **47** 372

[135] Purrer V, Upadhyay N, Borger V, Pieper C C, Kindler C, Grötz S, Keil V C, Stöcker T, Boecker H and Wüllner U 2021 Lesions of the cerebello-thalamic tract rather than the ventral intermediate nucleus determine the outcome of focused ultrasound therapy in essential tremor: A 3T and 7T MRI-study. *Parkinsonism Relat. Disord.* **91** 105–8

[136] Boulant N, *et al.* 2024 In vivo imaging of the human brain with the Iseult 11.7-T MRI scanner *Nat. Methods*

[137] Pouliopoulos A N, Wu S-Y, Burgess M T, Karakatsani M E, Kamimura H A S and Konofagou E E 2020 A Clinical System for Non-invasive Blood–Brain Barrier Opening Using a Neuronavigation-Guided Single-Element Focused Ultrasound Transducer *Ultrasound Med. Biol.* **46** 73–89

[138] Pouliopoulos A N, *et al.* 2021 Safety evaluation of a clinical focused ultrasound system for neuronavigation guided blood-brain barrier opening in non-human primates *Sci. Rep.* **11** 15043

[139] Peng X, Connolly D J, Sutton F, Robinson J, Baker-Vogel B, Short E B and Badran B W 2024 Non-invasive suppression of the human nucleus accumbens (NAc) with transcranial focused ultrasound (tFUS) modulates the reward network: a pilot study *Front. Hum. Neurosci.* **18**

[140] Carpentier A, *et al.* 2016 Clinical trial of blood-brain barrier disruption by pulsed ultrasound *Sci. Transl. Med.* **8** 343re2-343re2

[141] C. Adams, R. M. Jones, S. D. Yang, W. M. Kan, K. Leung, Y. Zhou, K. U. Lee, Y. Huang, and K. Hynynen 2021 Implementation of a Skull-Conformal Phased Array for Transcranial Focused Ultrasound Therapy *IEEE Trans. Biomed. Eng.* **68** 3457–68

[142] Brinker S T, Crake C, Ives J R, Bubrick E J and McDannold N J 2018 Scalp sensor for simultaneous acoustic emission detection and electroencephalography during transcranial ultrasound *Phys. Med. Biol.* **63** 155017

[143] Zheng X, Vieira Campos A, Ordieres-Meré J, Balseiro J, Labrador Marcos S and Aladro Y 2017 Continuous Monitoring of Essential Tremor Using a Portable System Based on Smartwatch *Front. Neurol.* **8**

[144] Vescio B, Quattrone A, Nisticò R, Crasà M and Quattrone A 2021 Wearable Devices for Assessment of Tremor *Front. Neurol.* **12** 680011

[145] Jansen J F A, Backes W H, Nicolay K and Kooi M E 2006 1H MR Spectroscopy of the Brain: Absolute Quantification of Metabolites *Radiology* **240** 318–32

[146] Welch K M A, Levine S R, Martin G, Ordidge R, Vande Linde A M Q and Helpern J A 1992 Magnetic Resonance Spectroscopy In Cerebral Ischemia *Cereb. Ischemia Treat. Prev.* **10** 1–29

[147] Manu V S, Olivieri C and Veglia G 2023 AI-designed NMR spectroscopy RF pulses for fast acquisition at high and ultra-high magnetic fields *Nat. Commun.* **14** 4144

[148] Ishak O, Breton E, Cabras P, Dumont E, Mondou P, Novell A, Larrat B and Vappou J 2024 Magnetic resonance cavitation imaging for the monitoring of ultrasound therapies *Phys. Med. Biol.* **69** 215018

[149] Zhao S, *et al.* 2020 Full activation pattern mapping by simultaneous deep brain stimulation and fMRI with graphene fiber electrodes *Nat. Commun.* **11** 1788

[150] Rifi Z, Harary M, Walshaw P D, Frew A J, Everson R G, Fallah A, Salamon N and Kim W 2024 Functional magnetic resonance imaging (fMRI) as adjunct for planning laser interstitial thermal therapy (LITT) near eloquent structures *Acta Neurochir. (Wien)* **166** 66

[151] Imbault M, Chauvet D, Gennisson J-L, Capelle L and Tanter M 2017 Intraoperative Functional Ultrasound Imaging of Human Brain Activity *Sci. Rep.* **7** 7304

[152] Lee S A, Kamimura H A S, Smith M and Konofagou E E 2024 Functional Cerebral Neurovascular Mapping During Focused Ultrasound Peripheral Neuromodulation of Neuropathic Pain *IEEE Trans. Biomed. Eng.* **71** 1770–9

[153] Aurup C, Bendig J, Blackman S G, McCune E P, Bae S, Jimenez-Gambin S, Ji R and Konofagou E E 2024 Transcranial Functional Ultrasound Imaging Detects Focused Ultrasound Neuromodulation Induced Hemodynamic Changes in Mouse and Nonhuman Primate Brains *In Vivo*

[154] Kim M G, Kamimura H A S, Lee S A, Aurup C, Kwon N and Konofagou E E 2020 Image-guided focused ultrasound modulates electrically evoked motor neuronal activity in the mouse peripheral nervous system *in vivo J. Neural Eng.* **17** 026026

[155] McCune E P, Kamimura H A S, Bendau E V, Lee S A and Konofagou E E 2022 Modulation of Somatosensory Evoked Potentials Via Focused Ultrasound Median Nerve Stimulation *2022 IEEE International Ultrasonics Symposium (IUS)* 2022 IEEE International Ultrasonics Symposium (IUS) (Venice, Italy: IEEE) pp 1–4

[156] Chen H, Garcia-Gonzalez D and Jérusalem A 2019 Computational model of the mechanoelectrophysiological coupling in axons with application to neuromodulation *Phys. Rev. E* **99** 032406

[157] Plaksin M, Shoham S and Kimmel E 2014 Intramembrane Cavitation as a Predictive Bio-Piezoelectric Mechanism for Ultrasonic Brain Stimulation *Phys. Rev. X* **4** 011004

[158] Plaksin M, Shapira E, Kimmel E and Shoham S 2018 Thermal Transients Excite Neurons through Universal Intramembrane Mechanoelectrical Effects *Phys. Rev. X* **8** 011043

[159] Kamimura H A S, Saharkhiz N, Lee S A and Konofagou E E 2021 Synchronous Temperature Variation Monitoring During Ultrasound Imaging and/or Treatment Pulse Application: A Phantom Study *IEEE Open J. Ultrason. Ferroelectr. Freq. Control* **1** 1–10

[160] Song M, Zhang M, He S, Li L and Hu H 2023 Ultrasonic neuromodulation mediated by mechanosensitive ion channels: current and future *Front. Neurosci.* **17** 1232308

[161] Grippe T, *et al.* 2024 Plasticity-Induced Effects of Theta Burst Transcranial Ultrasound Stimulation in Parkinson's Disease *Mov. Disord.* **39** 1364–74

[162] Bubrick E J, McDannold N J, Orozco J, Mariano T Y, Rigolo L, Golby A J, Tie Y and White P J 2024 Transcranial ultrasound neuromodulation for epilepsy: A pilot safety trial *Brain Stimulat.* **17** 7–9

[163] Riis T S, Feldman D A, Losser A J, Okifuji A and Kubanek J 2024 Noninvasive targeted modulation of pain circuits with focused ultrasonic waves *Pain*

[164] Oh J, Ryu J S, Kim J, Kim S, Jeong H S, Kim K R, Kim H-C, Yoo S-S and Seok J-H 2024 Effect of Low-Intensity Transcranial Focused Ultrasound Stimulation in Patients With Major Depressive Disorder: A Randomized, Double-Blind, Sham-Controlled Clinical Trial *Psychiatry Investig.* **21** 885–96

[165] Riis T S, Feldman D A, Kwon S S, Vonesh L C, Koppelmans V, Brown J R, Solzbacher D, Kubanek J and Mickey B J 2024 Noninvasive modulation of subcallosal cingulate and depression with focused ultrasonic waves *Biol. Psychiatry*

[166] Kamimura H A S, Wang S, Chen H, Wang Q, Aurup C, Acosta C, Carneiro A A O and Konofagou E E 2016 Focused ultrasound neuromodulation of cortical and subcortical brain structures using 1.9 MHz *Med. Phys.* **43** 5730–5

[167] Aurup C, Kamimura H A S and Konofagou E E 2021 High-Resolution Focused Ultrasound Neuromodulation Induces Limb-Specific Motor Responses in Mice in Vivo *Ultrasound Med. Biol.* **47** 998–1013

[168] Bendau E V, McCune E P, Blackman S G, Kamimura H A S, Aurup C and Konofagou E E 2024 Modulation of cardio-respiratory activity in mice via transcranial focused ultrasound. *Ultrasound Med. Biol.* **50** 332–40

[169] Ennasr A, Isaac G, Strohman A and Legon W 2024 Examination of the interaction of parameters for low-intensity focused ultrasound of the human motor cortex *Brain Stimulat.* S1935861X2400189X

[170] Wu S-Y, Aurup C, Sanchez C S, Grondin J, Zheng W, Kamimura H, Ferrera V P and Konofagou E E Efficient Blood-Brain Barrier Opening in Primates with Neuronavigation-Guided Ultrasound and Real-Time Monitoring

[171] Chen K-T, *et al.* 2021 Neuronavigation-guided focused ultrasound for transcranial blood-brain barrier opening and immunostimulation in brain tumors *Sci. Adv.* **7** eabd0772

[172] Novell A, *et al.* 2020 A new safety index based on intrapulse monitoring of ultra-harmonic cavitation during ultrasound-induced blood-brain barrier opening procedures *Sci. Rep.* **10** 10088

[173] Kamimura H A S, Wang S, Wu S-Y, Karakatsani M E, Acosta C, Carneiro A A O and Konofagou E E 2015 Chirp- and random-based coded ultrasonic excitation for localized blood-brain barrier opening *Phys. Med. Biol.* **60** 7695–712

[174] Dauba A, Delalande A, Kamimura H A S, Conti A, Larrat B, Tsapis N and Novell A 2020 Recent Advances on Ultrasound Contrast Agents for Blood-Brain Barrier Opening with Focused Ultrasound *Pharmaceutics* **12** 1125

[175] Karakatsani M E, *et al.* 2019 Amelioration of the nigrostriatal pathway facilitated by ultrasound-mediated neurotrophic delivery in early Parkinson's disease *J. Controlled Release* **303** 289–301

[176] Schoen S, Kilinc M S, Lee H, Guo Y, Degertekin F L, Woodworth G F and Arvanitis C 2022 Towards controlled drug delivery in brain tumors with microbubble-enhanced focused ultrasound *Adv. Drug Deliv. Rev.* **180** 114043

[177] Bae S, *et al.* 2024 Transcranial blood-brain barrier opening in Alzheimer's disease patients using a portable focused ultrasound system with real-time 2-D cavitation mapping *Theranostics* **14** 4519–35

[178] Zhu H, Allwin C, Bassous M G and Pouliopoulos A N 2024 Focused ultrasound-mediated enhancement of blood–brain barrier permeability for brain tumor treatment: a systematic review of clinical trials *J. Neurooncol.* **170** 235–52

[179] Chevillet J R, Khokhlova T D, Giraldez M D, Schade G R, Starr F, Wang Y-N, Gallichotte E N, Wang K, Hwang J H and Tewari M 2017 Release of Cell-free MicroRNA Tumor Biomarkers into the Blood Circulation with Pulsed Focused Ultrasound: A Noninvasive, Anatomically Localized, Molecular Liquid Biopsy *Radiology* **283** 158–67

[180] Meng Y, *et al.* 2021 MR-guided focused ultrasound liquid biopsy enriches circulating biomarkers in patients with brain tumors *Neuro-Oncol.* **23** 1789–97

[181] Pacia C P, Zhu L, Yang Y, Yue Y, Nazeri A, Michael Gach H, Talcott M R, Leuthardt E C and Chen H 2020 Feasibility and safety of focused ultrasound-enabled liquid biopsy in the brain of a porcine model *Sci. Rep.* **10** 7449

[182] Rincon-Torroella J, Khela H, Bettegowda A and Bettegowda C 2022 Biomarkers and focused ultrasound: the future of liquid biopsy for brain tumor patients *J. Neurooncol.* **156** 33–48

[183] Zhu L, *et al.* 2018 Focused Ultrasound-enabled Brain Tumor Liquid Biopsy *Sci. Rep.* **8** 6553

[184] Hutton D L, Burns T C and Hossain-Ibrahim K 2024 A review of sonodynamic therapy for brain tumors *Neurosurg. Focus* **57** E7

[185] Syed H R, Kilburn L, Fonseca A, Nazarian J, Oluigbo C, Myseros J S, Packer R J and Keating R F 2023 First-in-human sonodynamic therapy with ALA for pediatric diffuse intrinsic pontine glioma: a phase 1/2 study using low-intensity focused ultrasound: Technical communication *J. Neurooncol.* **162** 449–51