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Magnetic resonance-guided focused ultrasound in intracranial diseases: Clinical applications and future directions

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ABSTRACT

Magnetic resonance-guided focused ultrasound (MRgFUS) is a non-invasive technique for neuroregulation that offers several advantages, including non-invasiveness, no need for general anesthesia requirement, real-time target localization, and real-time temperature monitoring. Currently, the U.S. Food and Drug Administration has approved this technology for the treatment of essential tremor and Parkinson's disease, and its indications are continually expanding to encompass various intracranial diseases. In this article, we summarize clinical trials of high-intensity FUS in the treatment of intracranial diseases. Next, we introduce the preclinical and clinical studies on low-intensity FUS-induced blood-brain barrier opening and neuromodulation. Finally, we discuss the challenges and future directions of this technology. This review aims to guide future clinical trials and provide new perspectives for investigating the neural mechanisms of MRgFUS.

1. Introduction

Magnetic resonance-guided focused ultrasound (MRgFUS) is an emerging non-invasive technique used in functional neurosurgery for neuroregulation. In 1942, Lynn and colleagues successfully induced localized ablation in deep, fresh liver tissue using a focused ultrasound generator, with minimal impact on the surface and no effect on the intermediate tissue.[1] However, the use of focused ultrasound in the treatment of intracranial diseases is limited due to the need for skull removal to prevent energy absorption and reflection at the bone interface.[2] To address this challenge, Clement and colleagues developed a phased array transducer in 2000.[3] This hemispherical transducer has 1024 ultrasound elements that can reduce the heating deposition on patients's scalp and correct the phase aberrations induced by the skull, allowing the ultrasound to pass through the skull safely and focus on the target area accurately. Additionally, magnetic resonance imaging (MRI) technology provides real-time target localization and temperature monitoring, which enhances the precision of the surgery.[4,5] The combination of improved focused ultrasound transducer and MRI technology enables the ultrasound beam to pass through the intact skull, precisely ablating deep brain target tissue without harming the surrounding normal tissue. Intensity plays a key role in determining the action of ultrasound. High-intensity focused ultrasound (HIFUS) allows for precise brain ablation with sub-millimeter accuracy.[6] Low-intensity focused ultrasound (LIFUS) can modulate neuron activity.[7] When combined with microbubble injection, LIFUS can reversibly open the blood-brain barrier (BBB).[8] In this review, we focus on the latest clinical applications of MRgFUS in intracranial diseases, and we discuss current challenges and future directions.

2. Methods

This review searched the PubMed, Embase, and Web of Science databases from January 1, 2013, to November 1, 2023, using the following search terms: “MRgFUS,” or “MRI-guided Focused Ultrasound,” or “magnetic resonance imaging-guided focused ultrasound,” or “magnetic resonance-guided focused ultrasound.” A total of 4492 articles were retrieved. The inclusion criteria for literature screening encompassed clinical trials of MRgFUS in intracranial applications, utilizing one of the mechanisms of focused ultrasound, including thermoablation, BBB opening, and neuromodulation. At the same time, these clinical trials reported changes in patients' symptoms after MRgFUS. Exclusion criteria include 1) non-central nervous system diseases, such as uterine fibroids, prostate cancer and bone metastases; 2) review or meta-analyses or other literature types without original data; 3) equipment technology and functional imaging. Additionally, preclinical studies, case reports, and case series were also excluded for data eligibility. After the initial literature screening, we identified several current intracranial applications of

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magnetic resonance-guided high-intensity focused ultrasound, which encompass “essential tremor,” "Parkinson's disease," “obsessive-compulsive disorder,” “major depressive disorder,” “neuropathic pain,” and “focal dystonia”. We conducted further searches in three databases using the keyword “MRgFUS” combined with specific diseases mentioned above to include comprehensive clinical trials. For the study of LIFUS, we used the keywords “MRgFUS” and “blood-brain barrier”, “MRgFUS” and “neuromodulation” for further searches. After further searching, thirteen articles were included. Two researchers independently screened the retrieved articles. In the end, this study included 67 clinical articles (Fig. 1).

3. HIFUS-induced thermoablation

HIFUS generates frictional heat in tissues by causing molecular vibration. This process can enhance the sensitivity of tumor radiotherapy and facilitate the release of drugs from heat-sensitive liposomes when the temperature reaches a moderate range of 40–45 °C.[9,10] Temperatures exceeding 56 °C induce tissue denaturation and coagulative necrosis[11,12] (Fig. 2). The biological effects of ultrasonic thermal ablation have prompted numerous clinical trials. This technique is used to treat intracranial diseases by lesioning target tissues and suppressing pathological pathways. The currently published clinical studies are listed in the supplementary table.

3.1. Essential tremor

Essential tremor (ET) is a common movement disorder that affects millions of people worldwide. ET is primarily characterized by motor symptoms, such as postural and action tremors.[13] However, non-motor symptoms, including cognitive impairment and neuropsychiatric symptoms, may also occur.[14] Functional neurosurgery, which involves the stimulation or lesioning of specific targets, can be used to treat medication-refractory ET.[15] Currently, the ventral intermediate nucleus (VIM) and the cerebello-thalamic tract (CTT) are the most common targets for these procedures. VIM is an intermediate nucleus in the cerebello-thalamo-cortical pathway that is associated with the pathological mechanism of ET. Therefore, lesioning this target can effectively suppress tremor.[16] In 2013, Elias and colleagues conducted an open-label, non-controlled clinical study using unilateral MRgFUS thalamotomy of the ventral intermediate nucleus (VIM-MRgFUS) to treat medication-refractory ET.[17] This study included 15 patients and demonstrated improvements in tremor control and overall quality of life following treatment.[17] Nevertheless, the procedure had adverse effects, including transient sensory, cerebellar, motor, and speech abnormalities, and four patients experienced persistent sensory abnormalities.[17] In 2016, the same team conducted a multicenter randomized double-blind controlled clinical trial, and they proved the safety and efficacy of unilateral VIM-MRgFUS.[6] The results showed an average improvement of 47% in patients' hand tremor scores and a 46% improvement in their quality of life, as assessed by the quality of life in the essential tremor questionnaire score.[6] The study found that patients commonly experienced sensory and gait disturbances as side effects, but most patients reported relief within 12 months of treatment.[6] This study presents compelling scientific evidence that supports the formal FDA approval of MRgFUS for treating ET. Subsequent clinical trials have also confirmed the safety and efficacy of unilateral VIM-MRgFUS, with most of the procedure's side effects being mild and transient.[18–22] Two 5-year follow-up studies showed that unilateral VIM-MRgFUS can improve tremor and quality of life in ET patients over the long term.[23,24] A recent study demonstrated that staged bilateral VIM-MRgFUS was safe.[25] Despite mild to moderate adverse effects, ET patients experienced further improvements in function and quality of life after the second treatment.[25] The CTT is a neural pathway that connects the cerebellum and the thalamus, playing a crucial role in motor coordination. In a study conducted by Schreglmann and colleagues, unilateral MRgFUS cerebellothalamic tractotomy (CTT-MRgFUS) effectively reduced tremors in the treated hand without affecting fine motor function and dexterity during a 6-month follow-up.[26] Additionally, Gallay et al. demonstrated that CTT-MRgFUS is an effective therapeutic option for the treatment of ET, with patients experiencing a mean tremor remission of 93% at 1 year postoperatively.[27] No bleeding or infection occurred and no dysarthria was reported, although three patients had persistent gait dysfunction.[27] Another study indicated that bilateral CTT-MRgFUS significantly alleviated tremors in both hands of ET patients.[28]

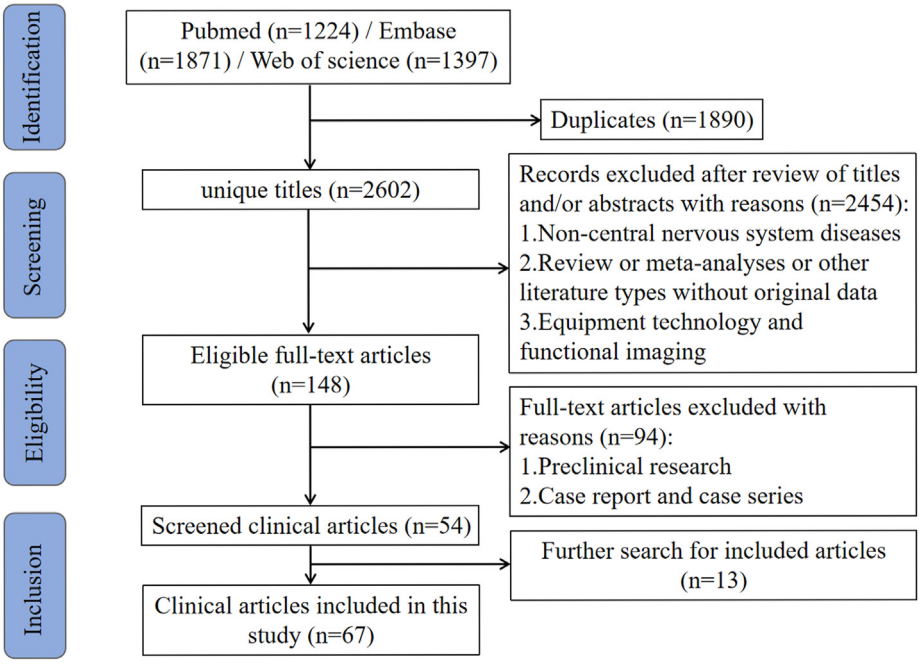

Fig. 1. The flowchart of the systematic search and selection process.

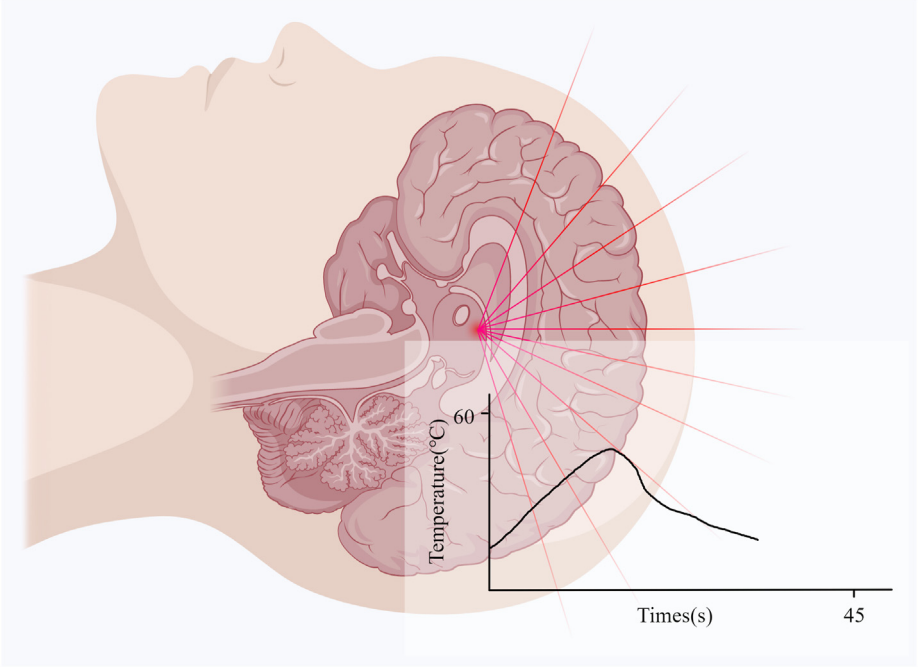

Fig. 2. The mechanism of magnetic resonance-guided high-intensity focused ultrasound-induced thermoablation. High-intensity focused ultrasound enables sub-millimeter precision brain ablation.

3.2. Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder that presents clinical symptoms such as bradykinesia, resting tremors, rigidity, and motor dysfunction.[29] The first-line treatment for PD is levodopa.[30] Deep brain stimulation or MRgFUS can be used to treat patients who do not respond to medication.[31] MRgFUS, as an emerging non-invasive neuroregulation technique, is a promising option for PD patients who are unwilling or unable to undergo implant surgery. The current treatment targets include VIM, subthalamic nucleus (STN), internal globus pallidus (GPi), and pallidothalamic tract (PTT).

VIM is a target for treating tremor-dominant PD (TDPD). Lesioning this target can effectively ameliorate patients' tremor. A randomized controlled clinical study demonstrated the safety and efficacy of unilateral VIM-MRgFUS for TDPD.[32] After treatment, the median improvement in tremor scores during medication in 27 patients was 62%.[32] Persistent adverse events included mild hemiparesis due to internal capsule heating, orofacial paresthesia, finger paresthesia, and ataxia.[32] Recent studies have shown that VIM-MRgFUS is an effective treatment for sustained tremor control in TDPD patients, with mild side effects.[33,34] Furthermore, the study found that unilateral VIM-MRgFUS did not have any negative effects on short-term cognitive, emotional, or non-motor outcomes in TDPD.[35] Additionally, a 5-year follow-up study conducted by Sinai et al. demonstrated that unilateral VIM-MRgFUS can provide long-term relief for the majority of TDPD patients.[36] Both the median Clinical Rating Scale for Tremor (CRST) and median Unified Parkinson's Disease Rating Scale (UPDRS) scores showed a significant decrease in patients overall and those treated hemibody when compared to the baseline.[36] STN is a commonly used target for alleviating motor symptoms in PD. Abnormally sustained beta-frequency synchronization between the motor cortex and the STN is involved in the pathophysiology of PD.[37] A prospective, open-label pilot study indicated that unilateral MRgFUS subthalamotomy (STN-MRgFUS) can improve motor features in PD patients with asymmetric signs.[38] The average Movement Disorder Society-UPDRS (MDS-UPDRS) III score on the treated side increased by 53% from baseline to 6 months in the off-medication state and by 47% in the on-medication state.[38] The most frequent adverse events were transient gait ataxia, transient pinpoint head pain, and transient hypertension.[38] Subsequent randomized controlled trials have shown that STN-MRgFUS improves motor features in PD patients with asymmetric signs.[39] However, adverse events such as speech and gait disturbances, weakness on the treated side, and dyskinesia have been reported.[39] The study conducted by Martínez-Fernández and their team indicated that the benefits of unilateral STN-MRgFUS on motor function in PD were sustained over the long term.[40]

The motor thalamus connects the GPi to the cortex.[41] Motor dysfunction in patients with PD is believed to be caused by hyperactivity within the GPi.[42,43] Targeting the GPi has been shown to effectively and continuously improve tremors, motor fluctuations, and levodopa-induced motor disturbances in PD patients.[44] The initial clinical trial showed that unilateral MRgFUS pallidotomy (GPi-MRgFUS) effectively improved dyskinesia in patients, with significant improvements in “medication-off” UPDRS part III scores of 39.1% and Unified Dyskinesia Rating Scale (UDysRS) of 42.7% at the 1-year follow-up.[45] No patients experienced persistent adverse effects.[45] A multicenter open-label clinical trial indicated that unilateral GPi-MRgFUS is a feasible and effective treatment for alleviating motor fluctuations in PD patients.[46] The study also found that treatment-related adverse events were mild and transient.[46] The most recent randomized controlled study suggested that unilateral GPi-MRgFUS reduced dyskinesia in PD patients.[47] In the treatment group, 69% of patients experienced symptom relief, compared to only 32% in the control group.[47] However, the treatment group experienced adverse events related to the procedure, such as dysarthria, gait disturbance, loss of taste, visual disturbance, and facial weakness.[47] The PTT connects the GPi with the thalamus, primarily involving the ventral anterior nucleus and the ventral lateral nucleus.[48] The PTT has been investigated as a target for MRgFUS to address motor symptoms and motor complications in PD patients. A study conducted by Gallay and colleagues demonstrated that unilateral MRgFUS pallidothalamic tractotomy (PTT-MRgFUS) was a safe and effective intervention for PD patients.[49] The results of the trial showed an average improvement of 84% in tremor, 70% in rigidity, and 73% in distal bradykinesia in patients following treatment, with no significant change in cognitive function.[49] The team's further research revealed that bilateral PTT-MRgFUS was effective in managing tremors, distal rigidity, distal bradykinesia, motor disturbances, muscle tone disorders, and pain

compared to the best baseline medication therapy.[50] However, speech difficulties were reported as a side effect.[50] Chen and colleagues recently conducted a stepwise dual-targeted therapy to ablate VIM and PTT, which effectively and safely improved the severity of tremors and motor deficits in PD patients.[51] No adverse effects were reported during treatment, except for temporary headaches and dizziness.[51]

3.3. Psychiatric disorders

Obsessive-compulsive disorder (OCD) is a chronic and disabling condition that significantly impairs quality of life.[52] Individuals with OCD often feel compelled to perform repetitive behaviors according to strict rules, leading to anxiety and impacting their daily lives.[52] OCD may be mediated by the cortico-striato-thalamo-cortical (CSTC) circuits, which involve sensory, motor, cognitive, emotional, and motivational processes.[52] Cognitive-behavioral therapy and selective serotonin reuptake inhibitors are the recommended first-line treatments for OCD.[53] Recently, MRgFUS capsulotomy has been proven effective in treating refractory OCD. The procedure targets the bilateral anterior limbs of the internal capsule (ALIC) for treatment. Lesioning these areas disrupts connections between the orbitofrontal cortex, dorsal anterior cingulate cortex from the ventral striatum, and thalamus, thus interrupting the CSTC circuit.[53] Major depressive disorder (MDD) is a prevalent mental illness that significantly overlaps with other psychiatric disorders, such as OCD, affecting millions of people worldwide.[54] Despite medication and psychotherapy, only half of the patients respond to the initial medication trials, and only one-third achieve relief.[55] Additionally, stimulating or lesioning the ALIC is effective for medication-resistant depression.[56] A preliminary study by Jung and colleagues suggested that bilateral MRgFUS capsulotomy (ALIC-MRgFUS) may be an effective treatment for refractory OCD.[57] Patients experienced an average reduction of 61.1% in depression and an average improvement of 69.4% in anxiety during the 6-month follow-up period after treatment, and no side effects related to the procedure were reported.[57] In a 2-year follow-up study, Kim and colleagues demonstrated that bilateral ALIC-MRgFUS was effective in improving the symptoms of obsession, depression, and anxiety in patients with refractory OCD, without any serious adverse effects.[58] Another study found that bilateral ALIC-MRgFUS did not cause cognitive decline in OCD and MDD patients.[59] Bilateral ALIC-MRgFUS can lead to targeted and widespread changes in the neural activity of OCD and MDD, in addition to relieving their symptoms.[60] This suggests that neuroimaging can be used to monitor changes in neural activity in patients after MRgFUS.

3.4. Other intracranial diseases

MRgFUS can effectively treat neuropathic pain (NP) and focal dystonia, as well as common movement disorders and psychiatric disorders. NP is a chronic pain caused by damage to the somatosensory nervous system, which can lead to long-term physical and psychological distress for patients.[61] The posterior part of the central lateral thalamus regulates the sensory, cognitive, and emotional components of chronic NP.[62] MRgFUS central lateral thalamotomy (CLT-MRgFUS) is thought to enhance the inhibition of GABAergic interneurons within thalamic cortical modules, resulting in decreased high-frequency signals within various cortical regions responsible for pain.[62] A study conducted by Gallay and colleagues at a single center provided initial evidence for the safety and effectiveness of bilateral CLT-MRgFUS.[63] The pain relief rates for patients were 51% at 3 months, 71% at 1 year, and 78% at the longest follow-up period.[63] Additionally, there were no serious adverse events associated with this treatment.[63] In the latest non-randomized, single-arm phase I trial, CLT-MRgFUS was proven to be a safe and effective treatment for refractory NP without serious adverse effects.[64] This procedure not only relieved patients' pain but also reduced medication use.[64] Treatment reactivated connections between default mode network (DMN) nodes compared to the disruption of DMN at baseline.[64] Another study demonstrated the stability of CLT-MRgFUS for NP.[65] The mean follow-up was 55 months, the mean pain relief rate was 42%, and more than half of the patients reported at least 50% pain relief.[65]

The ventral oral (Vo) nucleus receives pallidothalamic projections that are involved in dystonia. Lesioning of the Vo nucleus is an effective treatment for focal dystonia.[66] A preliminary study indicated that MRgFUS thalamotomy of the Vo nucleus (Vo-MRgFUS) significantly improved symptoms of focal hand dystonia (FHD).[67] Throughout the study, patients' scores on the Writer's Cramp Rating Scale, Tubiana Musician's Dystonia Scale, and Arm Dystonia Disability Scale significantly improved from baseline, changing from 6.3 ± 2.7, 1.4 ± 0.5, and $58.7\% \pm 14.3\%$ to 1.6 ± 3.1, 5.0 ± 0, and $81.6\% \pm 22.9\%$.[67] One case of long-term dysarthria was reported at 12 months after surgery.[67] Further large-scale, multicenter clinical trials are required to confirm the safety and efficacy of this procedure.

In conclusion, therapeutic targets are selected based on the pathogenesis of the disease. For diseases with multiple therapeutic targets, such as PD, clinicians should choose the optimal target based on the patient's clinical characteristics. Multiple target staging can also be attempted to treat patients with overlapping symptoms. It is worth noting that MRgFUS is effective in relieving patients' symptoms, but some studies have reported transient or persistent adverse effects. Therefore, future studies should focus on conducting larger randomized controlled trials to explore the efficacy and safety of this treatment.

4. LIFUS-induced BBB opening

Cavitation refers to the oscillation of bubbles in response to pressure waves. Inertial cavitation specifically denotes the formation and violent collapse of microbubbles within an ultrasonic field. LIFUS can induce oscillations in microbubbles injected intravenously without causing collapse, which is referred to as stable cavitation. The mechanical effects generated by microbubble oscillations cause the transient and reversible disruption of the BBB's tight junctions[68] (Fig. 3A).

The BBB is composed of brain microvascular endothelial cells, astrocyte end-feet, pericytes, tight junctions between endothelial cells, and the basal membrane. Its main function is to regulate the entry and exit of circulating substances to maintain homeostasis in the brain. Although the BBB prevents harmful substances from entering the brain parenchyma, it also hinders the effective delivery of drugs. Notably, the use of LIFUS in combination with microbubbles allows for safe and reversible BBB opening. Several preclinical studies have shown that LIFUS-induced BBB opening (LIFUS-BBBO) can effectively enhance drug delivery, improving the therapeutic efficacy in animal models of brain tumors, brain metastases, PD, Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS).[69–73] LIFUS-BBBO can also non-invasively transport gene vectors for the treatment of neurological disorders, enabling gene therapy and gene editing.[74,75] Furthermore, LIFUS-mediated liquid biopsy can release substances such as phosphorylated tau proteins, neurofilament light chain, and brain tumor biomarkers into the bloodstream. This can facilitate the diagnosis and monitoring of neurodegenerative diseases and brain tumors.[76,77] Multidrug-resistant efflux transporters act as functional barriers, impeding the transportation of numerous drugs across the BBB to the brain parenchyma. P-glycoprotein (P-gp) is the primary efflux transporter. Several studies have suggested that LIFUS-BBBO can induce downregulation of P-gp expression.[78,79] Interestingly, LIFUS-BBBO has been found to modulate the neuroimmune system. Firstly, it reduces amyloid plaques and excessively phosphorylated tau proteins in the brains of AD animal models, thereby improving the disease's pathological state.[80] A study has suggested that LIFUS-BBBO activates microglial cells, prompting them to phagocytose amyloid plaques.[81] Secondly, LIFUS-BBBO increases neurogenesis in the hippocampus and improves spatial memory in AD animal models.[82] Endogenous neural stem cells can be activated to induce adult neurogenesis.[83] Additionally, LIFUS-BBBO can also activate monocyte homing and differentiation in glioma models, leading to a shift towards a more

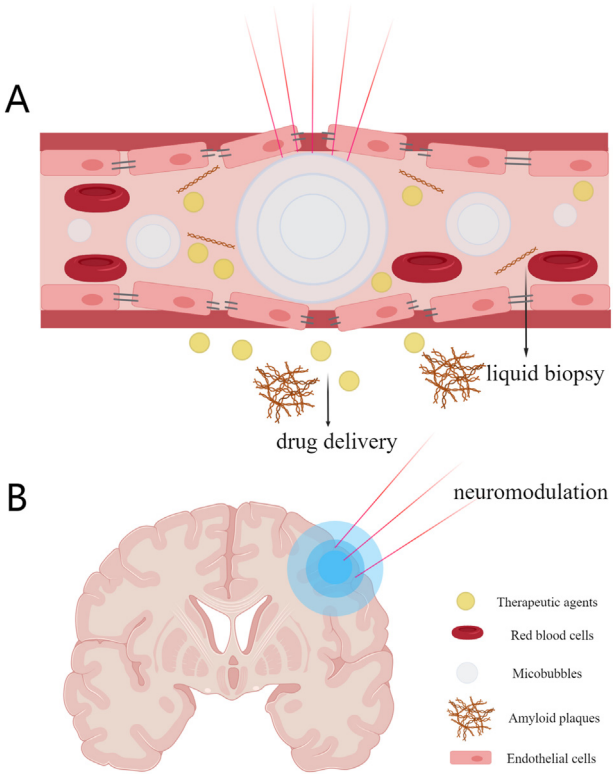

Fig. 3. The mechanisms of low-intensity focused ultrasound-induced BBB opening (A) and neuromodulation (B). A: The tight junctions of the BBB can be transiently and reversibly disrupted by the mechanical effects generated by microbubble oscillations. B: Low-intensity focused ultrasound modulates cortical function in humans and induces brain plasticity.

pro-inflammatory immune environment.[84] Furthermore, LIFUS-BBBO recruits central nervous system-related macrophages and proliferating microglial cells, thereby remodeling the immune landscape.[85] The neuroimmune regulation associated with this technique is highly complex. To investigate the mechanisms of focused ultrasound-induced immunity at the molecular level, it is recommended that more multi-omics studies should be conducted in the future. However, it should be noted that a previous study found that LIFUS-BBBO resulted in elevated levels of heat shock protein 70, IL-1, IL-18, and TNFα, indicating a sterile inflammatory response in the brain parenchyma.[86] McMahon et al. demonstrated that FUS can induce a transient inflammatory response in the microvasculature.[87] The increase in pro-inflammatory cytokine gene transcription is mostly restored within 24 h.[87] Previous studies have shown that optimizing FUS parameters or administering dexamethasone after ultrasound treatment can reduce the risk of inflammation-induced tissue damage.[88,89] Therefore, further preclinical studies are needed to validate the safety of LIFUS-BBBO, which will contribute to the wider implementation of clinical trials.

Several investigators have conducted clinical trials to confirm the safety, feasibility, and reproducibility of MRgFUS-induced BBB opening (MRgFUS-BBBO) in diseases such as ALS, AD, PD, and brain cancer, building on preclinical studies.[8,90–95] Additionally, MRgFUS has been shown to enhance signals from circulating brain-derived biomarkers, which can aid in the early diagnosis and monitoring of neurological disorders.[96] Furthermore, MRgFUS-BBBO has made it possible to safely and effectively administer drugs, including chemotherapy for brain tumors, recombinant GCase for PD, and monoclonal antibodies for Her2-positive breast cancer brain metastasis.[97–100] Previous studies have consistently shown the presence of perivenous enhancement both during and after the acute phase of MRgFUS-BBO, indicating the existence of a perivenous immune healing response downstream of the target site.[101,102] Published clinical trials of MRgFUS-BBBO have demonstrated that the treatment is feasible and well-tolerated, with no serious adverse events related to the procedure.[103–105] On the one hand, preclinical studies have demonstrated that the inflammation produced by FUS-induced BBB opening is transient, which explains the absence of adverse effects in the clinical trials. On the other hand, it should be noted that the current clinical trial was small. Therefore, future studies should focus on conducting larger randomized controlled trials to validate the safety and potential clinical value of this technique.

5. LIFUS-induced neuromodulation

LIFUS can induce neuromodulation in target areas with high spatial resolution, in addition to mediating reversible BBB opening[106] (Fig. 3B). This is achieved through various mechanisms, such as enhancing membrane permeability by inducing intramembrane cavitation effects,[107] triggering neuronal excitation through the activation of mechanosensitive ion channels or voltage-gated ion channels, and ultimately achieving neural modulation.[108,109] Table 1 summarizes published clinical studies on MRgFUS-BBO and neuromodulation.

LIFUS-induced neuromodulation is a complex phenomenon that has been extensively studied in preclinical research to understand its mechanisms. Firstly, LIFUS can be used to modulate neuronal activity. A study has suggested that LIFUS can alter the kinetics and spatial patterns of neuronal activity at the acoustic focus in the primary somatosensory cortex.[110] LIFUS affects not only cortical neural activity but also deeper brain regions.[111] When applied to specific brain areas, LIFUS can either inhibit or enhance their excitability based on sound intensity and energy deposition rates.[112] Additionally, LIFUS induces persistent changes in the synaptic connectivity of the rat hippocampus.[113] A resting-state functional MRI study suggested that applying LIFUS to deep brain structures alters functional connectivity in the default and frontotemporal networks.[114] Thirdly, LIFUS accelerated remyelination in a mouse model of multiple sclerosis.[115] Dysregulation in myelin formation can lead to neurodegenerative and neuropsychiatric disorders. Therefore, promoting remyelination contributes to improving various neurological disorders. Finally, LIFUS was effective in improving disease pathology, including controlling seizures, alleviating depression, and reversing social avoidance behavior.[116–118] Previous studies have demonstrated that LIFUS-induced neuromodulation is safe and noninvasive, without causing any FUS-related tissue damage.[106,119] These preclinical studies provide a theoretical foundation for subsequent clinical studies. However, the specific biological mechanism of neuromodulation induced by LIFUS is not yet clear. Therefore, further studies are required to explore the underlying mechanisms in the future.

Multiple clinical studies have indicated that LIFUS can be used to locally modulate human cortical function and induce brain plasticity.[120–122] Furthermore, this technique can not only modulate functional connectivity in the human brain but also induce changes in deep cortical neurochemistry.[7,123] Multiple studies indicated that neuronavigation-guided LIFUS can safely and effectively reduce the frequency of seizures in patients, improve symptoms in individuals with neurodegenerative diseases, and alleviate neuropathic pain.[124–126] As an emerging therapeutic technique, the latest clinical study indicated that MRgFUS-induced neuromodulation can continuously reduce substance craving in patients with substance use disorder (SUD) by targeting the bilateral nucleus accumbens.[127] Multiple studies have demonstrated that subjects did not experience any adverse effects during ultrasound treatment.[125,126,128] Further studies are required to explore the potential clinical value of LIFUS-induced neuromodulation.

6. Challenges and future directions

MRgFUS is a non-invasive technique for neuroregulation, but it faces several challenges. One of the main challenges is the exclusion of patients with low skull density ratio (SDR) values. Lower SDR values in the skull

Table 1
The published clinical studies on MRgFUS-induced BBBO and neuromodulation.

Author, years	Disease	Number of patients	Mechanism	Conclusion
Lipsman et al., 2018[8]	Alzheimer's disease	5	BBBO	MRgFUS-BBBO is safe, reversible, and reproducible.
Abrahao et al., 2019[90]	Amyotrophic lateral sclerosis	4	BBBO	MRgFUS-BBBO is safe, feasible, and reversible.
Mainprize et al., 2019[97]	Primary brain tumors	5	BBBO	MRgFUS-BBBO enables chemotherapeutic drug delivery.
Park et al., 2020[100]	Glioblastoma	6	BBBO	MRgFUS-BBBO enables chemotherapeutic drug delivery.
Rezai et al., 2020[104]	Alzheimer's disease	6	BBBO	MRgFUS can safely, noninvasively, transiently, reproducibly, and focally mediate BBB opening in the hippocampus/entorhinal cortex.
Anastasiadis et al., 2021[92]	Gliomas	4	BBBO	MRgFUS enables safe, localized, controlled opening of the BBB and highlights the potential of this technology to improve the surgical and pharmacologic treatment of brain tumors.
Gasca-Salas et al., 2021[91]	Parkinson's disease dementia	5	BBBO	MRgFUS-BBBO is safe, reversible, and reproducible.
Mehta et al., 2021[101]	Alzheimer's disease	3	BBBO	MRgFUS-BBBO elicits meningeal venous permeability.
Meng et al., 2021[96]	Brain tumors	9	BBBO	MRgFUS-BBBO enriches the signal of circulating brain-derived biomarkers.
Meng et al., 2021[99]	Her2-positive breast cancer and brain metastases	4	BBBO	MRgFUS-BBBO enables targeted monoclonal antibody delivery.
Park SH et al., 2021[94]	Alzheimer's disease	5	BBBO	MRgFUS-BBBO is safe and feasible.
Huang et al., 2022[105]	Parkinson's disease	4	BBBO	The cavitation emissions-based feedback controller was effective in modulating acoustic power levels.
Meng et al., 2022[98]	Parkinson's disease	4	BBBO	MRgFUS-BBBO enables recombinant GCase delivery.
Rezai et al., 2022[103]	Alzheimer's disease	10	BBBO	MRgFUS-BBBO is safe, reversible, and reproducible, with concomitant reduction of β-amyloid.
Pineda-Pardo JA et al., 2022[95]	Parkinson's disease	7	BBBO	MRgFUS-mediated striatal BBB opening is safe and feasible.
Mehta et al.,2023[102]	Alzheimer's disease	8	BBBO	MRgFUS-BBBO uncovers an intracerebral perivenous fluid network in persons with Alzheimer's disease.
Meng et al., 2023[93]	Alzheimer's disease	9	BBBO	MRgFUS-BBBO is safe in neurodegeneration.
Mahoney et al., 2023[127]	Substance use disorder	4	Neuromodulation	LIFUS targeting the bilateral NAc is safe and acutely reduces substance craving.

Note: BBBO: Blood-brain barrier opening; LIFUS: Low intensity focused ultrasound; MRgFUS-BBBO: Magnetic resonance-guided focused ultrasound-induced BBBO; NAc: Nucleus accumbens.

are considered to impede the transmission of acoustic energy. However, Chang and colleagues proposed an autofocusing echo imaging lesioning method that effectively expands the range of indications for MRgFUS, including patients with lower SDR values.[129] To expand the indications for MRgFUS in the future, innovative research is necessary. Currently, clinicians locate and ablate the target using indirect coordinates, rather than directly observing the target. Selecting the appropriate ablation target and deciding whether to perform bilateral or dual-target ablation are also challenging. Therefore, advanced neuroimaging studies are required for personalized target localization and visualization to improve the precision of MRgFUS. In clinical practice, it is crucial to conduct more clinical trials to investigate the therapeutic value of targeting different or multiple targets. Finally, the neurobiological effects of MRgFUS-mediated treatment remain unclear. Previous studies have explored the effects of HIFUS or LIFUS on brain structure and function.[130–134] Future neuroimaging studies are needed to investigate the potential neurobiological effects of MRgFUS.

7. Conclusion

MRgFUS has emerged as a novel therapeutic approach in functional neurosurgery. HIFUS is a safe and effective treatment for various intracranial diseases. However, the neurobiological effects of LIFUS-BBBO and neuromodulation are not fully understood. Therefore, further preclinical and clinical studies are required to explore these effects. Neuroimaging is essential for localizing targets and exploring potential neurobiological effects in MRgFUS.

Authorship Statement

Haoxuan Lu: Writing – original draft, Visualization, Methodology, Investigation. **Yujue Zhong:** Writing – original draft, Methodology, Investigation. **Yongqin Xiong:** Writing – review & editing, Methodology, Investigation. **Xiaoyu Wang:** Writing – review & editing, Methodology, Investigation. **Jiayu Huang:** Validation, Methodology, Investigation. **Yan Li:** Validation, Methodology, Investigation. **Xin Lou:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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