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REVIEW

Focused transcranial ultrasound stimulation: a breakthrough approach to treating brain disorders

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ABSTRACT

Introduction: Focused transcranial ultrasound stimulation (fTUS) has emerged as a novel noninvasive technique with promising therapeutic potential for various neurological and psychiatric conditions. The aim of this review is to evaluate current research on fTUS, examining its mechanisms, therapeutic applications, challenges, and future potential in neurological and psychiatric disorders.

Area covered: High-intensity fTUS leads to heat-induced thermoablation, which has shown efficacy in treating essential tremor and tremor-dominant Parkinson's disease, with promising outcomes in clinical trials. fTUS has been explored for blood–brain barrier opening, facilitating drug delivery for conditions like glioblastoma and Alzheimer's disease. Low-intensity fTUS can also be used as a novel neuromodulation tool which has shown potential in alleviating chronic pain, depression, and cognitive decline.

Expert opinion: Challenges remain, including technical refinements, standardization of parameters, and optimization of therapeutic protocols. Emerging approaches like hyperthermia therapy, sonodynamic therapy, and sonothrombolysis hold promise for future applications. With ongoing research and collaboration, the next decade holds immense potential for further advancements in fTUS technology and its clinical integration.

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Focused transcranial ultrasound stimulation; thermal ablation; blood-brain barrier applications; drug delivery; neuromodulation

1. Introduction

Sound waves, in contrast to electromagnetic waves, are mechanical waves. Since the 1920s the effect of sound waves on biological tissue has been explored, with a specific interest arising in 1929 on the effect of sound on neuronal tissue [1]. However, it was not until the 1950s that reports began to emerge that indicated the reversible suppression of spontaneous neuronal spiking following exposure to ultrasound [2–4]. In 1958, a seminal paper was published showing that the lateral geniculate nucleus could be targeted using focused ultrasound [5]. Leksell also proposed that ultrasound holds promise for the treatment of psychiatric disorders [6]. However, the initial efforts to apply ultrasound to the brain necessitated a craniectomy, with sonication carried out in the operating room. A skin flap was created over the craniectomy, providing a portal for recurrent ultrasound hyperthermia treatments [7] and tumor thermal ablation [8].

Since its initial medical application, ultrasound has undergone a remarkable evolution. It has transitioned from a tool primarily used for diagnostic sensing to a versatile modality with diverse applications, enabling ultrasound to modulate the brain without a craniectomy for the treatment of specific neurological and psychiatric conditions [9]. This narrative review focuses on ultrasound stimulation as a novel treatment option with a high spatial resolution capable of targeting deep brain tissue structures [10]. We employed a narrative review of studies published between 2012 and 2025 on focused transcranial ultrasound stimulation (fTUS), synthesizing findings on its mechanisms, clinical applications, and emerging research directions.

2. Transcranial ultrasound stimulation from diagnosis to treatment

TUS can be broadly categorized into two groups of devices. A first group is comprised of fTUS, while a second group includes unfocused diagnostic ultrasound (dUS). The fundamental distinction between these modalities lies in the design of the transducer and associated hardware, which determines whether acoustic energy can be concentrated into a focal spot or dispersed across a wider field. fTUS devices employ focusing mechanisms such as concave acoustic lenses or multichannel phased arrays, which allow constructive interference of sound waves at a defined target location. In contrast, dUS devices typically use convex transducers that produce divergent wavefronts, resulting in broader, unfocused insonation of tissue. Once these physical design principles are established, differences in operational parameters naturally follow. Frequency is not the primary defining feature, but rather a parameter chosen in accordance with the hardware's focusing properties and the biological constraints of transcranial application [11,12]. Lower frequencies (≤700 kHz) are generally used in fTUS to reduce skull attenuation and achieve a smaller focal spot at depth, whereas higher frequencies (1–15 MHz)

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Article highlights

- The current iteration of fTUS technology results from decades of interdisciplinary research, combining expertise in medical physics, engineering, imaging, biology, and neuroscience.
- The past 10 years have witnessed a remarkable surge in innovation and global collaboration in low and high-intensity fTUS clinical applications.
- fTUS has showcased its safety and adaptability across various medical conditions.
- Regulatory approval has been granted for MR-guided fTUS thalamotomy in essential tremor and tremor-dominant Parkinson's disease.
- Thermal ablation has transitioned from experimental to established treatment.
- Efficacy data for low-intensity fTUS -mediated drug delivery, particularly in neuro-oncology, are eagerly anticipated within the next couple of years.
- A growing number of clinical trials are investigating fTUS neuromodulation's potential in epilepsy, Alzheimer's disease, Parkinson's disease, depression, and traumatic brain injury.
- The next decade promises deeper insights into fTUS mechanisms and broader integration with promising therapeutic avenues.
- Numerous challenges persist, necessitating ongoing collaboration and global initiatives to advance safe and efficacious treatments for complex brain disorders.

are employed in dUS to maximize resolution in superficial imaging, but at the cost of poor penetration and lack of focus through bone [13,14]. Additional differences include aperture size, which influences focal depth and energy concentration, and the spatiotemporal waveforms employed. Together, these hardware and parameter choices explain why fTUS enables precise stimulation of circumscribed brain regions, while dUS produces widespread insonation suitable for diagnostic imaging [13–15].

Equally important is the consideration of acoustic intensity, which is frequently described ambiguously in the literature. Intensity represents the time-averaged rate of acoustic energy flow through a unit area, expressed in watts per square centimeter (W/cm^2) [16]. However, several definitions exist, most notably the spatial-peak temporal-average intensity (Ispta) – the mean over the pulse repetition interval – and the spatial-peak pulse-average intensity (Isppa) – the highest intensity found at the peak of the ultrasound beam, averaged over the duration of a single pulse [16]. This distinction is fundamental, as Ispta is most relevant for assessing cumulative thermal effects and long-term safety, while Isppa better reflects peak mechanical effects such as cavitation [16].

fTUS can be applied across a broad intensity range depending on the intended application. At the higher end, intensities exceeding ~ 100 W/cm^2 (typically Isppa) can cause tissue necrosis, forming the basis of ablative therapies. At the lower end, intensities between 0.125 and 3 W/cm^2 (typically reported as Ispta) are used to induce reversible mechanical effects on neural tissue [16]. For intermediate applications, such as transient opening of the blood – brain barrier (BBB) in humans, values between ~ 0.2 and 11.5 W/cm^2 have been reported [16]. Careful specification of both the intensity metric and the exposure regime (spatial, temporal, and duty cycle parameters) is therefore essential for accurately interpreting bioeffects and ensuring reproducibility across studies [16].

An even more novel technique is Transcranial Pulse Stimulation (TPS). The TPS system produces individual ultrashort (1 µs) asymmetric ultrasound pulses with energy levels ranging from 0.2 to 0.3 mj mm^{-2} followed by a tensile wave of lower amplitude (4–5 µs), and pulse frequencies spanning 1 to 5 Hz [17]. These shockwave-like pulses feature a positive peak amplitude succeeded by a smaller negative amplitude and subsequent smaller pulses, analogous to a ripple effect. This contrasts with fTUS, which employs higher frequency symmetrical periodic oscillatory waves at 1 µs pulse width and extended sonication trains lasting several hundred of milliseconds [17]. The precise mechanism of action for TPS remains uncertain and may differ from that of fTUS. Some conjecture suggests that the TPS system could potentially minimize risks associated with brain heating and secondary stimulation maxima while enhancing skull penetrance due to the lower frequency of pulses compared to conventional fTUS [17]. However, more research is needed to confirm these suggestions.

3. The potential biological treatment effects of fTUS

Three applications are leveraging these biological impacts to explore potential treatment effects of fTUS. The section below will briefly introduce these three applications, and the subsequent sections will discuss recent research exploring the potential treatment benefits of these applications.

In a first application, ultrasound absorption by brain tissue has the potential to induce localized thermal necrosis within mere seconds [18] (see Figure 1). High-intensity fTUS can induce temperatures exceeding 56°C that typically trigger rapid necrosis [19]. Thermoablative procedures have been practised since the early days of neurosurgery for a wide range of indications with the goal of interrupting pathological brain circuits that drive troublesome symptoms [9,20].

A second application of fTUS involves inducing cavitation, which refers to the oscillations of bubbles in response to pressure waves [21] (see Figure 1). The blood–brain barrier consists of tight junctions, membrane transporters, receptors, and channels (such as ATP-binding cassette transporters) that tightly regulate the passage of substances from the systemic circulation into the brain parenchyma [22]. This barrier plays a vital role in maintaining central nervous system homeostasis by controlling interstitial fluid composition, peripheral and central signaling, and immunity. Dysfunction of the blood–brain barrier is implicated in various brain diseases, including multiple sclerosis, Alzheimer's disease, and amyotrophic lateral sclerosis [9].

Currently, low-intensity fTUS is being explored for its potential to open the blood–brain barrier. When combined with intravenously injected microbubbles, low-intensity fTUS increases blood–brain barrier permeability, resulting in enhanced intracellular and paracellular transport [21]. Mechanical forces generated by stable microbubble cavitation disrupt the structure and function of tight junctions, reduce P-glycoprotein expression, and promote caveolae formation [23]. The temperature increase resulting from the FTUS-induced blood–brain barrier opening is minimal, with the power needed for this usually process three orders of magnitude lower than that required for thermoablation [24,25]. Additionally, cerebral vessels exhibit resilience to the

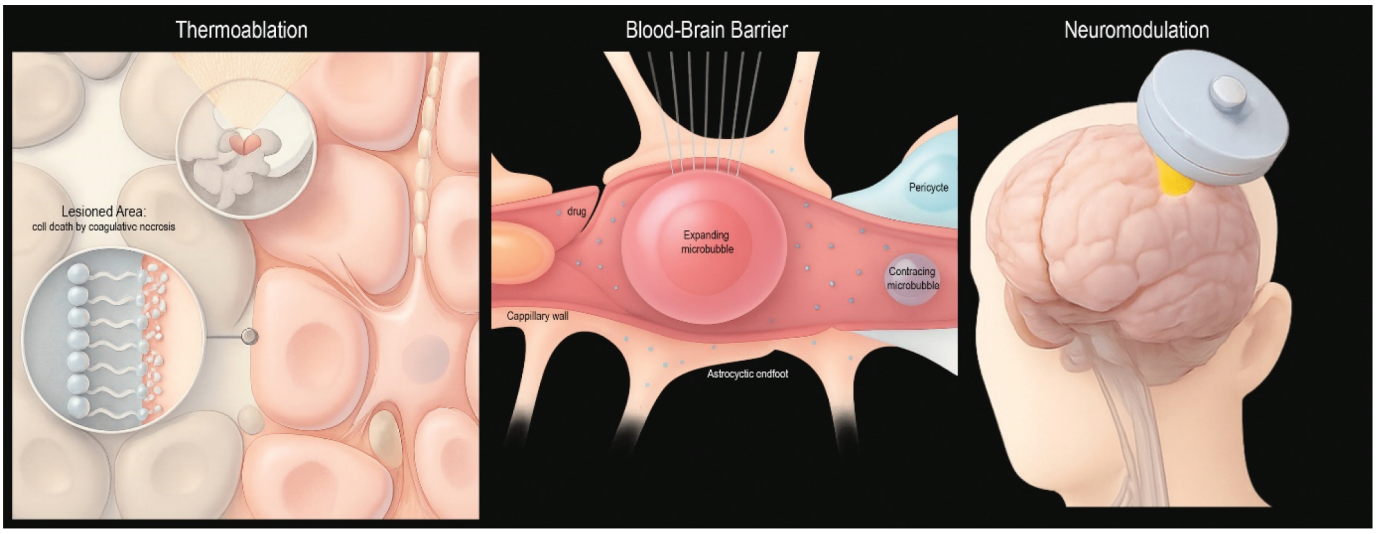

Figure 1. (Right panel) high intensity fTUS for thermoablation is magnetic resonance (MR) guided to enable real-time monitoring of the lesion and temperature during sonication, (middle panel) opening the blood-brain barrier by applying fTUS to target drug delivery, (left panel) transcranial ultrasound stimulation for neuromodulation.

mechanical stress induced by stable microbubble cavitation [26]. This resilience enables the restoration of blood-brain barrier integrity without the occurrence of hemorrhagic or ischemic complications following its opening [26].

Transient opening of the BBB permits a bidirectional flow of tissue. On the one hand, it can be used to deliver medication, chemotherapy, antibodies, stem cells or other substances across the blood–brain barrier into the brain. On the other hand, it can help remove tau protein, amyloid beta, alpha synuclein, from the brain, potentially benefiting Alzheimer's or Parkinson's disease [27]. It can also enable taking liquid biopsies from brain tumors [28]

A third application of fTUS involves neuromodulation, aiming to either restore or prevent functional decline by modulating brain circuits associated with brain disorders [11,13] (see Figure 1). Low intensity fTUS presents a host of advantages over alternative modalities. In contrast to transcranial electrical stimulation and transcranial magnetic stimulation, low-intensity fTUS boasts the ability to accurately pinpoint deeper brain structures with spatial resolution at the millimeter scale.

For a conceptual diagram for section 3.1 Thermoablation, section 3.2 blood-brain barrier applications and section 3.3 transcranial ultrasound stimulation for neuromodulation indicating the proposed mechanisms for each application and the current developmental stage see Figure 2.

3.1. Thermoablation

Typically, high intensity fTUS for thermoablation is magnetic resonance (MR) guided to enable real-time monitoring of the lesion and temperature during sonication. Initially, the sonication is performed at energies that result in transient heating of the neural tissue without tissue destruction. If this results in a clinical benefit, for example the arrest of tremor, the energy is increased to necrosis-inducing levels for permanent destruction. As such, the target can be tested before inducing a permanent lesion. To date, the neurological indications that received regulatory approval for fTUS using MR guidance are thalamotomy for essential tremors and tremor-dominant Parkinson disease (NCT01772693 and NCT01827904) [29,30]. The idea is that ablation of the ventral intermediate nucleus stops the pathological oscillations that are responsible for the essential tremor, providing clinical benefits [31]. In a pivotal, randomized, sham-controlled clinical trial, MR-guided high-intensity fTUS was applied to 76 patients with essential tremor, and significant improvements were reported (NCT01827904) [30]. Specifically, at the 3 month follow-up, a 47% tremor reduction was observed in the treated patients in comparison to the sham condition [30]. The sonication-related adverse events of headache, paresthesia and imbalance were the most common [32]. Notably, the rare serious events are lower than expected for an invasive procedure in which surgical complications, such as infections and intracranial hemorrhage, are material risks [32]. More advanced structural imaging, such as lesion mapping relative to key anatomical pathways, can help to enhance the spatial accuracy of targeting and to improve outcomes [33]. For tremor-dominant Parkinson's disease, a randomized clinical trial in 27 patients showed a 62% reduction in tremors up to 3 months later from unilateral fTUS thalamotomy, in comparison to a 22% reduction in a sham group (NCT01772693) [29]. No difference in cognitive assessment or depression scale was identified in both groups. Three severe adverse events were reported, of which two led to persistent mild hemiparesis. Based on the safety profile it was suggested that that this risk is higher in patients with more complex condition or comorbidities [29].

In Parkinson's disease, the application of MR-guided high-intensity fTUS is under investigation targeting the globus pallidus and subthalamic nucleus. In a placebo-controlled study, unilateral MR-guided high-intensity fTUS targeting the subthalamic nucleus was conducted in 40 Parkinson's patients. This study reported that patients who received the MR-guided fTUS subthalamotomy showed an approximate 50% reduction on their motor score (measured by Movement Disorder Society-Unified Parkinson's Disease Rating Scale) in

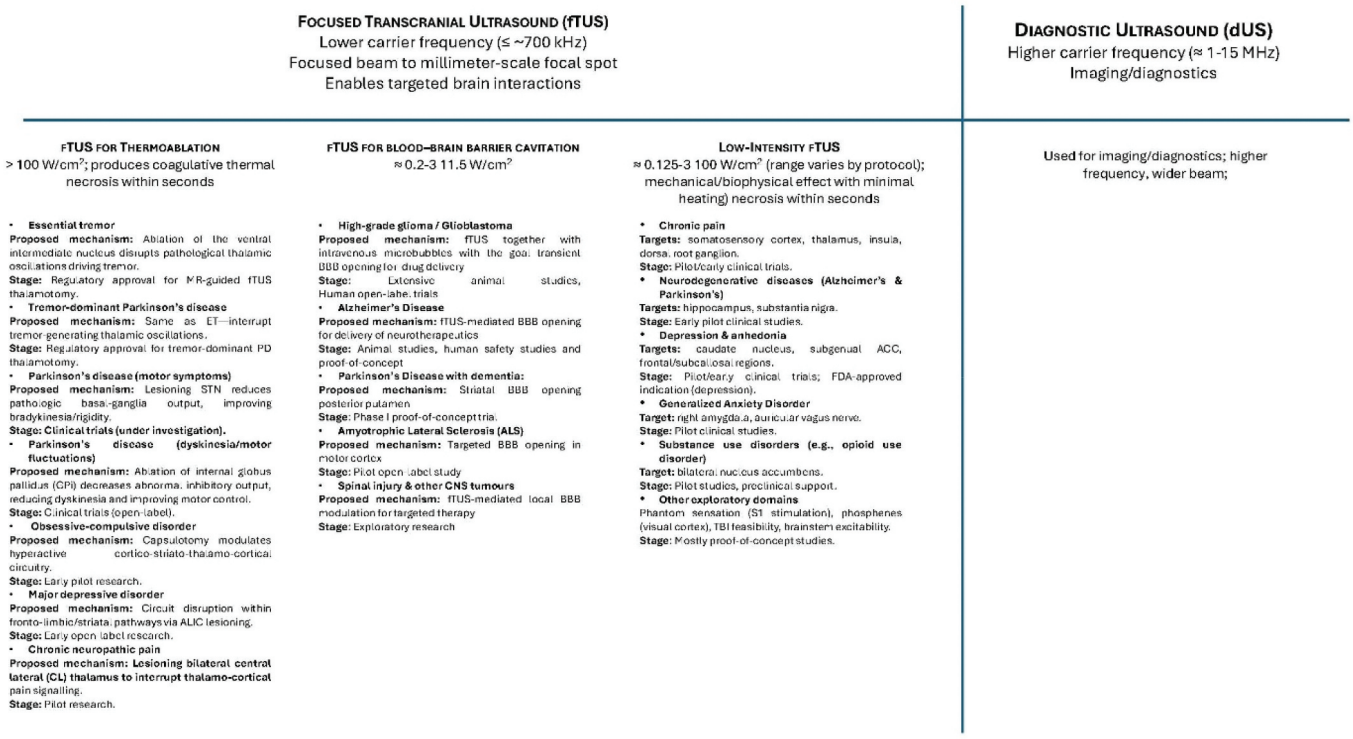

Figure 2. Conceptual diagram illustrating the overall landscape of TUS.

comparison to only an 8.5% reduction for the sham group (NCT03454425) [34]. In terms of adverse events, dyskinesia was reported in 6 patients in the off-medication state, and in 6 patients in the on-medication state. At a 4 month follow-up, these symptoms persisted in 3 and 1 patients, respectively [34]. Also, speech disturbances, facial weakness and gait disturbances were reported in some patients that persisted [34]. In a follow-up study, the benefit of unilateral MR-guided fTUS subthalamotomy on Parkinson's disease motor features was shown to sustain over three years after treatment (NCT02912871 and NCT03454425) [35].

In an open-label study in patients with Parkinson's disease and dyskinesias or motor fluctuations and motor impairment, unilateral MR-guided focused ultrasound ablation of the internal segment of globus pallidus demonstrated in the active-treatment group a response rate of 69% in comparison to 32% in the control group (NCT03319485) [36]. Of the patients who responded in the active-treatment group, 19 met the Movement Disorders Society-Unified Parkinson's Disease Rating Scale criterion only, 8 met the Unified Dyskinesia Rating Scale criterion only, and 18 met both criteria. The sustained therapeutic benefits of this protocol were evident up to 12 months later. Of the 69% of patients in the active-treatment group who responded, 57% exhibited continued response at a 3-month follow-up, and 43% at 12 months. Adverse events in the active-treatment group included dysarthria, gait disturbance, loss of taste, visual disturbance, and facial weakness.

Overall, the possibility of MR-guided fTUS might provide an alternative for individuals with comorbidities, or for those who prefer non-surgical options, live far from a specialized neuromodulation center or who do not want an implanted device [9]. Other important considerations to opt for MR-guided fTUS in comparison to deep brain stimulation might be the cost of the implant, battery replacement and associated maintenance.

Beyond its well-documented efficacy in addressing tremor and motor dysfunction in Parkinson's disease, investigations have extended to explore the potential of MR-guided high intensity fTUS in treating obsessive-compulsive disorder, major depressive disorder, and chronic pain. A pilot study involving four patients demonstrated a notable 33% improvement on the Yale-Brown Obsessive Compulsive Scale after 6 months, achieved by targeting the anterior limb of the internal capsule through fTUS [37]. Similarly, in the realm of major depression, an open-label trial utilizing MR-guided fTUS capsulotomy exhibited substantial improvement, as evidenced by a reduction from 26 to 7 on the Hamilton Depression Rating Scale, with no reported adverse events [38]. Moreover, in the domain of chronic neuropathic pain, a pilot study was initiated to assess the efficacy of MR-guided fTUS. Targeting the bilateral central lateral thalamic nuclei, the study showcased significant pain relief, with over 50% of the participants experiencing relief 1-year post-treatment [39]. In summary, while these initial findings are promising, further research is imperative to fully elucidate the potential of high-intensity fTUS in addressing a spectrum of neurological and psychiatric conditions.

Although MR-guided high-intensity fTUS has some promising results to treat specific neurological or psychiatric conditions, the introduction of deep brain stimulation (DBS) provided

a non-ablative modality distinguished by its reversibility and capacity for titration of clinical effects. For several disorders, including Parkinson's disease, DBS has become the preferred therapeutic approach over fTUS. In addition, fTUS in neuro-oncology are limited by an inability to achieve adequate intratumoral temperatures due to technical constraints. Moreover, the heterogeneous outcomes of MR-guided high-intensity fTUS for thermoablation across specific neurological conditions highlight the need for further investigation (see below – 4. Challenges). Additional limitations include reduced efficacy in peripheral brain regions, diminished utility for creating larger lesions, and suboptimal performance in patients with unfavorable skull morphology. Finally, lesions located near the skull base pose a particular risk, as adjacent neurovascular structures may be susceptible to collateral injury.

3.2. Blood-brain barrier applications

A second application aims to open the blood–brain barrier by applying fTUS. This approach has been extensively investigated in rodents and non-human primates, showing safety and efficacy [40]. After intravenous microbubbles injection, ultrasound increases the blood–brain barrier permeability locally and transiently, which enhances intracellular and paracellular transport and provides a potential strategy for drug delivery across the blood–brain barrier [21].

Using MR-guided fTUS to open the blood–brain barrier can be assisted with the delivery of multiple therapeutic agents that can potentially lead into improving their efficacy. These therapeutic agents include tumor suppressing drugs such as doxorubicin, paclitaxel and boron, neurotherapeutic drugs such as monoclonal antibodies, stem cells or gene therapies [21]. One promising approach using microbubbles together with MR-guided fTUS is for high-grade glioma, in particular glioblastoma. Numerous animal studies have demonstrated that MR-guided fTUS combined with chemotherapy drugs such as doxorubicin, paclitaxel and carmustine are successful in delivering these drugs to tumor-bearing brains, significantly enhancing the drugs' concentrations and effectively inhibiting tumor progression [41–44]. The therapeutic agents may be encapsulated by liposomes that are disrupted/opened mechanically when targeted by the fTUS beam. The fTUS can simultaneously also open the blood–brain barrier locally, thereby permitting the released therapeutic agents to enter the brain [45].

In humans, two open-label studies in glioblastoma patients investigated whether applying fTUS in conjunction with specific drugs would increase intracerebral drug concentrations and the potential efficacy of these drug treatments (NCT02343991 and NCT02253212) [46,47]. In one study, patients had a cranial ultrasound device (SonoCloud-1) implanted, and MR-guided fTUS was applied monthly to transiently disrupt the blood–brain barrier prior to intravenous administration of chemotherapy drug carboplatin [43]. In the second study, the ExAblate Neuro device was used for fTUS delivery [42]. Patients were fitted with an ultrasound helmet that enabled intraoperative imaging, and systemic temozolomide (a chemotherapy drug) was administered in timing with the expected opening of the blood–brain barrier from the fTUS [42]. Critically, both studies demonstrated that transient opening of the blood-brain barrier was safe, well-tolerated and technically feasible in patients with high-grade glioma (NCT02343991 and NCT02253212) [46,47]. In another pilot trial, neuronavigation and a manually operated frameless fTUS system were combined to treat recurrent glioblastoma patients in a dose-escalating protocol (NCT03626896) [48]. In this study, the fTUS system showed safety and feasibility, while a dose-dependent blood-brain barrier opening effect was observed, which reverted to baseline within 24 hours after treatment. No immunological response was observed clinically under the applied fTUS level in humans [48]. A second indication for BBB opening may be to take liquid biopsies of tumors, either diagnostically or as a follow-up to guide adjustments of brain tumor treatments [9]. Numerous clinical investigations combining ultrasound and chemotherapy in patients with new or recurrent primary brain tumors are ongoing, and new avenues for the treatment of spinal injury and tumors are being explored [23,49].

Another indication where MRI-guided fTUS has been proven to permeate the blood-brain barrier locally and transiently, is in Alzheimer`s disease animal models and humans (NCT02986932) [50,51]. Studies in Alzheimer`s disease animal models have demonstrated its excellent therapeutic effect through fTUS mediated blood–brain barrier opening delivering more prominent therapeutic agents, including exosomes, exogenous anti-Aβ antibodies, antitau antibodies, glycogen synthase kinase (GSK)-3, recombinant adeno-associated viruses, and nanoparticles [52–54]. A recent study in humans further demonstrated the safety and feasibility of transiently opening blood–brain barrier within the hippocampus in people with early Alzheimer's disease (NCT03671889) [55] that has led to more clinical trials. For example, one open-labeled single-arm trial investigated the feasibility of modulating BBB permeability in the default mode network and its impact on cognition, amyloid and tau pathology as well as BBB integrity (NCT03739905) [56]. The BBB permeability of the bilateral hippocampi, anterior cingulate cortex and precuneus was transiently increased without grade 3 or higher adverse events. Moreover, participants did not experience worsening trajectory of cognitive decline. PET imaging demonstrated reduction in Tau-uptake in the right parahippocampal and inferior temporal lobe [56]. However, CSF and blood biomarkers did not demonstrate any amelioration of Alzheimer's disease pathology, nor did it show persistent BBB dysfunction. In a recent proofofconcept trial involving three participants with mild Alzheimer's disease, aducanumab infusion therapy was combined with regional MR-guided focused ultrasound to transiently open the blood – brain barrier [57]. The procedure was generally well tolerated, with few adverse events (predominantly headache). Over the 6 month combinationtreatment phase, amyloidβ reduction was greater in regions treated with focused ultrasound than in homologous control regions receiving aducanumab alone, suggesting a potential synergistic effect of targeted BBB opening on antibody delivery and plaque clearance. Nevertheless, in comparison to fTUS' success

Table 1. Comparison of invasiveness, depth penetration and precision for different therapeutic neuromodulation modalities.

	Optogenetics	DBS	Pharmacology	TMS	tES	tPBM	fTUS
Invasiveness	Invasive	Invasive	Noninvasive	Noninvasive	Noninvasive	Noninvasive	Noninvasive
Depth Penetration	Deep	Deep	Variable	Shallow	Shallow	Shallow	Deep
Precision	Precise	Precise	Non-precise	Poor Precision	Poor Precision	Poor Precision	Precise

Abbreviations: DBS: Deep brain stimulation, TMS: Transcranial Magnetic Stimulation; tES: Transcranial Electrical Stimulation; fTUS: focused Transcranial Ultrasound; tPBM: Transcranial Photobiomodulation.

in glioma treatments, the challenge with its application in Alzheimer`s disease, is that it has a diffuse pathology which limits the therapeutic potential of ultrasound mediated blood–brain barrier opening approaches.

Clinical protocols for striatal transient blood–brain barrier opening using fTUS in Parkinson's disease patients are currently being explored. In a single-arm, nonrandomized, proof-of-concept, phase I clinical trial in Parkinson disease with dementia, seven Parkinson disease patients with cognitive impairment were treated with a blood–brain barrier opening in the posterior putamen [58]. This was performed in two sessions separated by 2 to 4 weeks, where the second session included bilateral putaminal opening in 3 patients. The procedure was feasible and well tolerated, with no serious adverse events. Moreover, no neurologically relevant deterioration in motor and cognitive functions (assessed via a battery of neuropsychological tests) was observed at follow-up.

The application of MRI-guided fTUS blood–brain barrier opening has also been recently explored for amyotrophic lateral sclerosis (ALS). In a single-arm open-label study, transiently opening the blood–brain barrier via ultrasound was tested in the non-dominant primary motor cortex in four ALS patients with leg or arm weakness and showed no serious adverse advents [59]. Furthermore, no acceleration of disease progression, or deterioration in functional measurements or cognitive testing was demonstrated.

Despite encouraging preclinical and early clinical results, several significant limitations and potential adverse events are associated with fTUS-mediated opening of the BBB. The use of microbubbles introduces the risk of microvascular injury, including hemorrhage, apoptotic cellular stress, and sterile inflammation – particularly when acoustic parameters exceed the safe threshold (NCT03671889 [60–64]. Frequent or excessive exposures can precipitate tissue damage or transient behavioral changes, as demonstrated in animal studies involving repeated BBB opening protocols. Even under safe settings, the inflammatory response – marked by the upregulation of cytokines and immune pathways – highlights the presence of a safe yet biologically active response that warrants monitoring [63]. Furthermore, achieving a consistent and reproducible BBB opening poses technical challenges: variability in microbubble dose, timing, and dynamic circulation can undermine safe, uniform BBB permeabilization across treatment sessions [65,66]. The closure kinetics of the BBB are generally favorable – most studies show restoration within 24–48 hours – but some investigations report delayed closure up to 3–5 days, emphasizing the need for careful timing of drug delivery and follow-up monitoring [62]. On the technical side, patient-specific differences in skull density, thickness, and geometry significantly distort and attenuate ultrasound transmission, potentially reducing targeting accuracy and complicating dose planning.

3.3. Transcranial ultrasound stimulation for neuromodulation

Low-intensity fTUS presents numerous potential benefits compared to current modalities such as transcranial electrical stimulation (tES) and transcranial magnetic stimulation (TMS), as it can target deeper brain structures with millimetric spatial resolution [67]. In other words, it has similar spatial accuracy to deep brain stimulation (DBS), albeit with lower temporal resolution, and superior spatial accuracy over TMS or tES. In comparison to optogenetics and DBS, it is also less invasive (see Table 1). Various superficial brain regions, such as the frontal lobe, motor cortex, somatosensory cortex, and visual cortex can be modulated by low-intensity fTUS, but also deeper structures such as the putamen, caudate, thalamus, nucleus accumbens and substantia nigra, can be targeted for sonication by adjusting the positioning or steering of the transducer [13,68,69]. The energy can thus be delivered focally at depths of 6 cm or deeper in the human brain. This is typically achieved by linking the low-intensity fTUS to a neuronavigation system, like what is done in surgery or other forms of non-surgical neuromodulation.

The first human low intensity fTUS study dates back to 2013 that aimed to improve pain and mood scores in chronic pain patients targeting the frontal cortex [70] and was followed by a study reporting changes in the primary somatosensory cortex using fTUS [68]. One year later, it was demonstrated that TUS targeting primary somatosensory cortex can induce phantom sensation in the hand and the induction of a specific evoked potential [71]. The same research groups also showed a visual evoked potential, and induced phosphenes by targeting the primary visual motor cortex [72]. In 2016, the first evidence was provided that fTUS could induce changes in blood oxygen level dependent signals in humans [73]. That same year a case report was published testing the feasibility and safety of thalamic fTUS in a patient with traumatic brain injury [74].

In subsequent years, further clinical trials have begun in patients with various neurodegenerative conditions. For example, the hippocampus or substantia nigra have been targeted using fTUS in patients with Alzheimer's dementia or Parkinson's disease [75]. In this study of 22 patients (11 of which had Alzheimer's and 11 with Parkinson's), 62.5% of patients had one or more improved cognitive scores, and 87% of patients had stable or improved fine motor scores after fTUS treatment [75]. In recent years, a significant increase has been observed in fTUS human studies, with more than half of the studies published after 2020. Given that most of this research has taken place so recently, it is unsurprising that new potential applications of fTUS neuromodulation continue to be explored. For example, it

has been proposed that fTUS neuromodulation could likewise hold therapeutic benefit for patients with drug-resistant epilepsy, pain, and depression as well as modulation of brainstem excitability [11]. Furthermore, low-intensity fTUS has also been applied to the spine, more specifically to the dorsal root ganglion to treat pain [76,77]. In the Focused Ultrasound (FUS) foundation report of 2023 the state of the field describes 166 clinical indications amenable to FUS, most of these 166 clinical indications are still in the preclinical phase or pilot trials are being conducted. There are three reimbursed indications (i.e. essential tremor and Parkinson tremor, neuropathic pain) and six FDA approved indications (essential tremor and Parkinson's tremor, neuropathic pain, Parkinson's dyskinesia, depression, and OCD) [78].

Furthermore, in a recent phasel safety and feasibility trial, one session of low-intensity fTUS induces positive changes in both motor sequence learning and corticospinal excitability [79].

In the domain of chronic pain, research has largely focused on targeting regions such as the somatosensory cortex, the thalamus, and insula [80]. Early experimental studies suggest that low-intensity fTUS can dampen neural responses to painful stimuli and inhibit mechanisms underlying pain sensitization with limited adverse events provide evidence that low-intensity fTUS may serve as a novel approach to modulating pain perception and potentially treating chronic pain syndromes [81–83].

In depression and anhedonia, stimulation of deep reward-related structures such as the caudate nucleus [84] and subgenual anterior cingulate cortex [85] has shown early signs of improving reward processing and mood regulation. Some others studies report reductions in depressive symptoms following stimulation of frontal [86] or subcallosal targets [87].

In generalized anxiety disorder, inhibitory low-intensity fTUS applied weekly to the right amygdala over an eight-week period produced significant symptom reduction in individuals who had not responded to conventional treatments in a pilot study [88]. Additional work has also shown reductions in worry and anxiety through repeated transcranial ultrasound stimulation sessions, as well as promising results using ultrasound stimulation of the auricular vagus nerve [89].

Perhaps, some of the most striking findings have come from early trials in substance use disorders. A pilot human study applying bilateral nucleus accumbens stimulation in individuals with opioid use disorder demonstrated that low-intensity ultrasound was safe, well-tolerated, and associated with significant reductions in cue-induced cravings [90,91]. Notably, these effects were most pronounced at higher stimulation intensities and persisted for up to 90 days following treatment. Complementary mechanistic studies in healthy participants have shown that low-intensity tFUS can reduce nucleus accumbens activity and enhance its connectivity with the medial prefrontal cortex, while preclinical work suggests it can disrupt reward-related circuitry and diminish drug-seeking behaviors [92]. Although the efficacy of neuromodulation by fTUS for many indications is apparent, the exact mechanisms of action are still unclear. The first proposed mechanism involves acoustic cavitation, which refers to the formation of microbubbles within the neuronal membrane. This phenomenon can lead to changes in the membrane capacitance or even rupture of the cell membrane [93]. While there is broad consensus that externally-administered microbubbles can induce neuromodulation through capacitance alterations, evidence supporting the notion that ultrasound can reliably induce these changes in tissue in or near cell membranes is lacking [13,94]. The second mechanism that has been suggested pertains to temperature changes induced by ultrasound. As ultrasound energy is applied, localized heating may occur, potentially influencing neuronal activity and signaling pathways [95]. However, further research is needed to clarify the extent and significance of these temperature effects on the overall therapeutic efficacy of low-intensity fTUS. A third mechanism that has recently garnered increased attention involves the mechanical interaction of fTUS waves with the lipid membrane. The rational is that mechanical force due to fTUS applied to membrane disrupts lipid rafts resulting in translocation of enzyme and increasing substrate enzymatic reactions [96]. Alternatively, the ultrasound may mechanically change the state of mechanosensitive ion channels embedded in the cellular membranes causing ion flow, depolarization and triggering of voltage-gated ion channels, resulting in action potential generation [97]. Yet currently, evidence is lacking for this latter hypothesis. However, it is important to note that these three mechanisms can operate simultaneously, and depending on the selected parameters and the target, one or more of these mechanisms may contribute to the overall effect. In addition, it is important to better understand the direct or immediate of low-intensity fTUS as well as the offline or indirect effects of low-intensity fTUS minutes to hours after the stimulation that might reflect structural and functional brain changes (see [98] for a considered review of these effects).

To support the rapid expansion of lowintensity fTUS in neuromodulation, a critical need has emerged for consistent and transparent reporting across studies. In response, the International Transcranial Ultrasonic Stimulation Safety and Standards Consortium (ITRUSST) released an expertdriven consensus guideline detailing a structured checklist for key ultrasound parameters – including the transducer and drive system specifications, drive settings, freefield acoustic metrics, pulse timing details, in situ exposure estimates within the brain, and intensity measures – to enhance reproducibility, comparability, and safety in fTUS research [99].

4. Challenges

Even with the significant strides made in fTUS over the past decade, there still exists ample room for both technical refinement and clinical advancement. Presently, high-intensity fTUS for thermoablation faces challenges with efficiency when dealing with large lesions and in patients with a low skull density ratio [100]. Additionally, there is heightened concern regarding sensitive neurovascular structures when lesions are in proximity to the skull base [101]. Anticipated technical advancements in the near future include refined ultrasound focusing and correction, personalized ultrasound arrays tailored to individual patients, and the introduction of microbubble-mediated non-thermal ablation techniques aimed at reducing heating effects and broadening treatment options near the skull base [9,101,102].

Several unanswered questions remain surrounding MR-guided fTUS opening the blood–brain barrier, including the extent of drug passage through the blood–brain barrier, the optimal therapeutic choice for specific diseases, and the safety profile of chronic blood–brain barrier opening. The immediate focus of the field is on establishing direct measures of therapeutic delivery and targets in humans. Achieving enhanced clinical outcomes requires broad interdisciplinary collaborations to acquire radiopharmaceuticals, tissue, or cerebrospinal fluid samples.

In relation to low-intensity fTUS, standardization of ultrasonic action parameters is lacking, with varied equipment and settings across studies. Focal length and size, influenced by the focusing fraction of ultrasound transducers, require uniform guidelines. Moreover, the thermal impact of ultrasound, linked to frequency, necessitates careful selection of transducers to avoid tissue damage. Additionally, fTUS encounters attenuation when passing through the skull, posing challenges for consistent energy delivery to target areas.

For low-intensity fTUS neuromodulation an important challenge is blinding of clinical studies, as participants not uncommonly (15%) perceive tactile, pressure or painful sensations when the ultrasound is delivered, which is significantly more than in sham. The clicking sound component may be mimicked, but the somatosensory component is more difficult to blind, analogous to blinding problems in, for example, TMS.

Over the next decades, advancements in fTUS delivery will hopefully address these challenges, revisiting existing pharmaceuticals and exploring novel therapies. To effect meaningful change in addressing humanity's most challenging conditions, a concerted global effort through research networks and consortia is imperative.

5. Conclusion

FTUS has rapidly progressed from a novel research concept to a versatile neuromodulatory and therapeutic tool with applications in both neurological and psychiatric disorders. High-intensity fTUS has demonstrated clinical efficacy in tremor control, Parkinson's disease, and select psychiatric conditions, while low-intensity fTUS shows promise for targeted drug delivery, blood – brain barrier modulation, and neuromodulation. Despite these advancements, critical challenges remain, including standardization of parameters, optimization of targeting, and ensuring long-term safety. The coming decade will likely see continued technical refinements, expansion of clinical trials, and integration of fTUS into multidisciplinary treatment frameworks. With sustained research and cross-specialty collaboration, fTUS has the potential to become an important pillar in noninvasive brain therapeutics, offering precision, versatility, and accessibility in treating some of the most challenging neurological and psychiatric conditions.

6. Expert opinion

6.1. High intensity fTUS

While thermoablation stands as the most extensively studied methods, possibly nearing, or already receiving regulatory approval, novel applications such as prognostic mapping, hyperthermia, sonodynamic therapy, sonothrombolysis, and histotripsy are currently undergoing investigation.

Prognostic mapping could consist of delivering sublesional doses to different targets to evaluate which target would be optimal for the individual. For example, in Parkinson's disease the subthalamic nucleus, globus pallidus interna, globus pallidus externa, motor cortex, etc., could be sonicated and the target with the optimal transient clinical benefit could be subsequently selected for permanent lesioning or insertion of DBS electrodes.

Hyperthermia fTUS therapy aims to elevate the temperature of targeted tissue to 40–45°C, potentially boosting the uptake of chemotherapy by tumor cells, increasing radiosensitivity, and enhancing immunogenicity [103,104]. However, achieving hyperthermia with fTUS poses a challenge due to the risk of excessive skull heating, particularly when treating large or off-center targets. *Sonodynamic* fTUS therapy represents a second investigational application in neuro-oncology, employing ultrasound to trigger the production of reactive oxygen species from sonosensitizers [105]. However, these reactive oxygen species are highly reactive and can cause damage to nearby cells, particularly tumor cells [105]. Other applications include *sonothrombolysis*, which utilizes ultrasound to dissolve the intravascular thrombus for the treatment of ischemic stroke [106], and *histotripsy*, which aims to fractionate tissue within seconds to minutes through cavitation induced by ultrasound pulses [107].

6.2. Low intensity fTUS

FTUS holds immense promise for treating brain disorders owing to its high spatial resolution and penetration capabilities. This noninvasive technique facilitates neuromodulation in deep brain regions, presenting significant therapeutic potential. Indeed, repetitive sonication of deep brain structures could be attempted as a treatment, in view of the long residual inhibition after single session sonication. This would be similar to noninvasive repetitive TMS or tES treatment approaches. Yet, its clinical neuromodulation application is in its infancy, facing several pressing technical hurdles.

Notably, further investigations involving both animal and human subjects are imperative if the field is to deepen our comprehension of fTUS mechanisms, ascertain its safety thresholds in human subjects, craft-efficient protocols for inducing brain plasticity, and determine the ideal fTUS parameters for specific disorders and targeted brain regions. Pilot studies should precede well-structured randomized controlled trials, to delineate the precise role of fTUS in addressing brain disorders.

Furthermore, the evolution of closed-loop brain stimulation methods like deep brain stimulation and optogenetics underscores the demand for precise, adaptive neuromodulation [108]. A closed loop fTUS system would exemplify this trend, enabling real-time modulation in epilepsy models.

6.3. Parameters

FTUS parameters are critical determinants of both the safety and therapeutic efficacy of treatment, as they influence the intensity, depth, and selectivity of acoustic energy delivery.

Table 2. Key focused ultrasound parameters and their effects.

Parameter	Definition	Effect/Consideration
Frequency	Oscillation rate of ultrasound wave (Hz)	Higher frequency → better spatial resolution, greater attenuation through skull
Intensity (ISPTA/ISPPA)	Energy delivered over time and space	Higher intensity → stronger biological effects; excessive intensity may increase heating or cavitation risk
Duration	Total time of ultrasound exposure	Longer durations may increase physiological response magnitude
Pulse Repetition Frequency (PRF)	Number of pulses per second	Influences excitatory vs. inhibitory effects depending on protocol
Duty Cycle (DC)	Ratio of pulse duration to total pulse period	Higher DC increases net energy delivery and thermal effects
Pulse Width (PW)	Duration of a single ultrasound pulse	Longer PW may enhance effect but raises heating risk
Pulse Repetition Period (PRP)	Time between consecutive pulse onsets	Determines pacing of pulses, influencing cumulative effects
Mechanical Index (MI)	Measure of cavitation potential	Higher MI increases likelihood of mechanical effects and BBB opening
Acoustic Tissue Properties	Skull thickness, density, acoustic impedance	Strongly affects transmission, focal accuracy, and required power adjustments

Key parameters include frequency, which governs spatial resolution and attenuation through the skull; intensity, often expressed as spatial peak temporal average (ISPTA) and spatial peak pulse average (ISPPA), which directly impacts tissue responses; and sonication duration, which can modulate the likelihood and magnitude of physiological effects (see Table 2). Pulsing characteristics – comprising pulse repetition frequency (PRF), pulse width (PW), duty cycle (DC), and pulse repetition period (PRP) – further shape neuromodulatory outcomes, with distinct protocols eliciting excitatory or inhibitory effects. Additional considerations include the mechanical index (MI), which reflects the cavitation potential, and patient-specific acoustic factors such as skull thickness and density, which significantly alter ultrasound transmission. Optimizing these parameters remains a key challenge, as their effects are highly interdependent and applicationspecific. Advancing mechanistic understanding, developing computational models for transmission and targeting, and accounting for individual anatomical variability will be essential to refining parameter selection and ensuring safe, effective, and personalized clinical protocols for neuromodulation and other FUS applications.

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