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REVIEW

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Neurological applications of focused ultrasound: an introduction and update on clinical and research trends

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Abstract

Background Focused ultrasound has emerged as a non-invasive technology with potential for treating various medical conditions, particularly neurological diseases. This article aims to explore recent advancements in the utilization of focused ultrasound for treating neurological conditions.

Results A comprehensive literature review was conducted to explore current clinical applications and investigational uses of focused ultrasound, aiming to provide an up-todate overview of the field's progress. By employing different combinations of intensity and frequency, focused ultrasound can induce diverse interactions with soft tissues, including tissue ablation, cavitation, and mechanical effects. High-intensity focused ultrasound is utilized for tissue ablation and has received FDA approval for treating medication-refractory essential tremor. Conversely, low-intensity focused ultrasound is employed for neuromodulation and opening the blood–brain barrier, facilitating enhanced drug delivery for treating brain tumors and other neurological conditions. This article reviews ongoing clinical trials investigating focused ultrasound's role in neurological condition treatment.

Conclusion Focused ultrasound holds significant promise for managing and treating various neurologic conditions. Whether employed for tissue ablation or transiently opening the blood–brain barrier to enhance drug delivery, numerous potential applications exist. Further research is necessary to evaluate its safe implementation and compare clinical outcomes with standard-of-care therapies.

Background

Ever since clinical ultrasound was first introduced in the 1930s, its clinical and diagnostic use has advanced rapidly. Early in ultrasound's development, it was primarily used as a diagnostic tool for the imaging of body tumors [1]. Shortly thereafter, Lynn et al. started exploring the therapeutic applications of ultrasound through high Intensity focused ultrasound (HIFU), which utilizes significantly higher intensities compared to that of a diagnostic ultrasound. While these first attempts ultimately resulted in severe side effects such as small brain lesions and paralysis, it led to important discoveries of its future uses in tumor ablation [2]. In the 1980s, when the technology of medical imaging and ultrasound transducers had advanced, the U.S.

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Food and Drug Administration approved the first official therapeutic use of focused ultrasound (FUS): glaucoma. The indications have since expanded and currently, focused ultrasound is used for treatment of uterine fibroids, prostate cancer, and painful osseous metastasis, among other clinical applications [1].

The main setback towards the progression of focused ultrasound as a therapeutic tool was the lack of effective imaging. For example, precise targeting of a tumor is essential to avoid unnecessary off-target damage to surrounding structures. Additionally, the temperature must be closely monitored in real time, a feat that is highly challenging for diagnostic ultrasound. The relatively recent development of MRI has helped to overcome these barriers and is now used in conjunction with focused ultrasound [3]. Currently, focused ultrasound has many potential applications that are being studied in clinical trials. Our objective in this literature review is to specifically explore the recent and potential applications in neurology, including treatment of essential tremors, Alzheimer disease, Neuromodulation and opening of the Blood Brain Barrier (BBB).

Types and technique of focused ultrasound

Two main parameters determine the type of focused ultrasound and consequent interaction with soft tissues: *Intensity* and *Frequency*. With the appropriate intensity and frequency, focused ultrasound can have various therapeutic effects within the realm of neurologic pathologies. Low intensity ultrasound (<3 W/cm^2), especially when combined with low frequency (20–200 kHz), can be used for neuromodulation purposes. Models of FUS have shown that energy delivered through FUS results in oscillations of the intermembrane space and can generate either neuronal excitation or inhibition through changes in membrane capacitance to drive a current, ion flux from opening of the lipid bilayer, or activation of mechanosensitive ion channels [4]. This effect provides the base for investigating the use of FUS as a reversible neural activity modulator for treatment of pain with promising initial results [5].

On the other hand, high intensity ultrasound (≥ 3 W/CM^2) produces a high-pressure wave upon interaction with soft tissues at the focus resulting in thermal, mechanical and cavitational effects (Figs. 1 and 2). This allows for non-invasive, precise tissue targeting with different effects on soft tissue according to the parameters

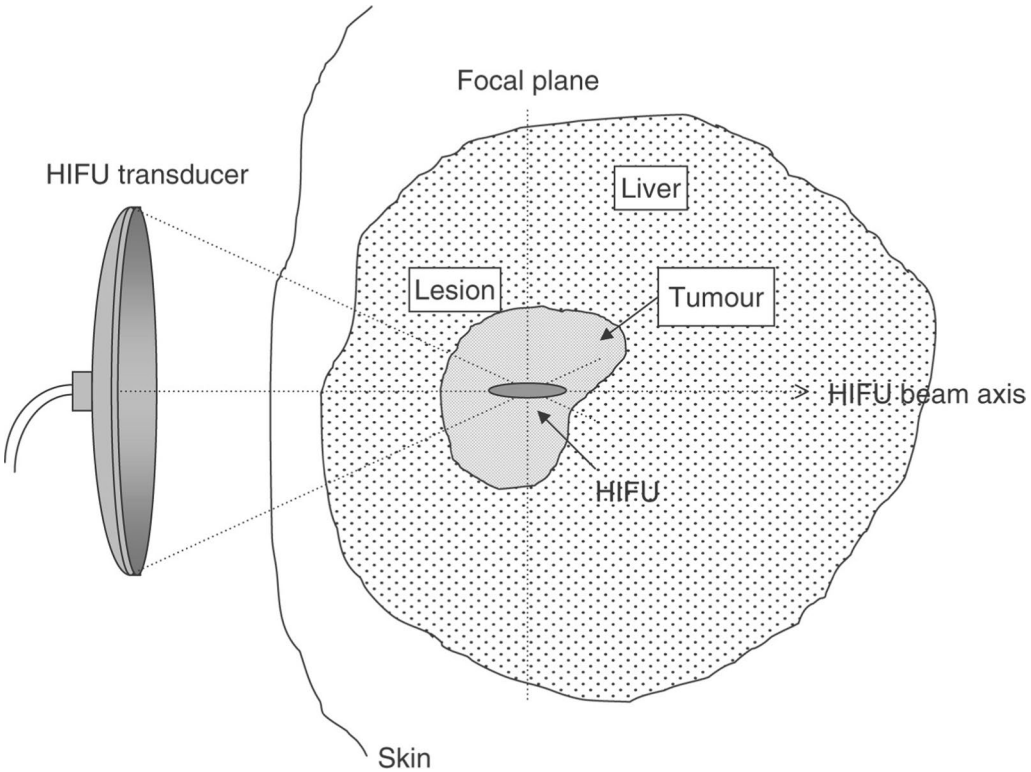

Fig. 1 Diagram showing the interaction of HIFU with soft tissue. HIFU beams intersect in a small, focused area which results in precise tissue ablation at the focus. This provides accurate targeting of tumor tissue without damage to the surrounding healthy soft tissue. (Reused with permission from ter Haar & Coussios 2007 & Taylor & Francis Ltd, www.tandfonline.com [8])

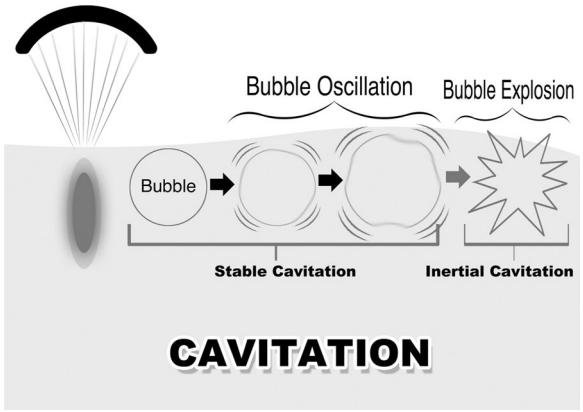

Fig. 2 An illustrative representation of the cavitation effect of focused ultrasound. Upon interaction with soft tissues, focused ultrasound excites microbubbles to oscillate in a steady pattern. This stable cavitation induces shear forces which can disrupt the tight endothelial cell junctions, opening blood brain barrier and facilitating drug delivery. Above a specific cavitation threshold, bubbles collapse vigorously, known as inertial cavitation, resulting in a strong pressure wave which can destroy soft tissues. (Reprinted with permission from [9])

Fig. 3 Image of ExAblate FUS machine used for treatment of essential tremor. Shown is the FUS transducer and MRI machine used during the procedure. (Reprinted with permission from Insightec Inc, Tirat Carmel, Israel)

selected [6–9]. Examples include tissue ablation and transient disruption of the blood–brain barrier.

The technique for focused ultrasound varies based on the clinical application; however, in the setting of neurologic conditions, real-time imaging feedback is crucial to avoid any undesired side effects and to monitor key variables such as temperature. As such, MRI imaging is used in conjunction with focused ultrasound for neurologic conditions. One example is the ExAblate platform (Insightec Inc, Tirat Carmel, Israel) used for the treatment of essential tremor (Fig. 3). First, a stereotactic frame is placed on the patient's head, which is surrounded with a bag of cooled degassed water to help prevent ultrasound-induced heating injury to the scalp. Then, the patient undergoes proper alignment with the MRI and ultrasound array. This then enables for the precise targeting of the desired tissue in the brain for FUS treatment [10]. While the indications for the use of FUS vary based on the pathology, contraindications of MRI guided FUS include patients with a pacemaker or those with other contraindications to MRI, those with a increased skull thickness, and patients who have undergone previous brain surgery [11].

Neurologic applications of focused ultrasound

Focused Ultrasound (FUS) applications in neurology have gained interest in recent years due to its wide range of utility. Its biological effect on tissue varies greatly based on the tissue type (ex. soft tissue vs blood vessels), the method of delivery (intermittent vs. consistent), and the intensity and frequency used [12, 13]. For this reason, there are ongoing clinical trials for a variety of clinical applications in different fields [5, 14]. In their literature review, Bretsztajn & Gedroyc outlined some of the potential uses of FUS in neurology, including essential tremor, Parkinson's disease, chronic neuropathic pain, obsessive compulsive disorder, depression, brain tumors, epilepsy, Alzheimer's, as well as opening the blood brain barrier and neuromodulation [15]. While only one of these (essential tremor) is currently FDA approved for clinical use, each of the other applications has supportive evidence and ongoing clinical trials that show promise for future use [15, 16]. In this review, we will focus on the main clinical applications of FUS in neurology including the treatment of essential tremor & Alzheimer's, as well as the investigational use for opening the blood brain barrier and neuromodulation.

Essential tremor

Essential tremor (ET) is characterized by involuntary rhythmic trembling, or shaking, of the hands or feet. It normally presents later in life, and while it does not affect life expectancy, it poses a significant hindrance in performing everyday tasks [17]. As the most common movement disorder, ET is a condition which still lacks a definitive treatment [18]. It is estimated that approximately 25%-55% of individuals with ET cannot be treated with medications alone and require additional interventions to alleviate their symptoms. Focused ultrasound can be used to target specific responsible location in the brain, which current studies have identified as the ventral intermediate nucleus of the thalamus [13, 19].

In 2016, Elias et al. performed a clinical study in which they enrolled 76 patients to a randomized FUS unilateral thalamotomy or sham procedure. Only patients who

were unresponsive to multiple medical treatment options were included, and the outcome measured was the standardized Clinical Rating Scale for Tremor (CRST) score. Upon completion of the trial, there was a significant improvement in hand tremors at 3 months and 12 months, with an increased ability to perform daily tasks such as drinking and writing. There were no severe side effects such as intracranial hemorrhage, but about 40% of patients experienced sensory or gait disturbances which persisted in about 10% after 12 months [18]. Two years after this study, Mohammed et al. conducted a meta-analysis including a total of nine studies with 160 patients with ET. In this study, FUS significantly improved the tremor scores and the quality of life [19]. Importantly, there were no severe side effects; however, ataxia was reported in 32.8% and paresthesia in 25.1%, both of which improved to about half at the 12-month mark. One limitation that Mohammed et al. addressed was the limited data on long term effects past 1 year [19]. In an effort to address this limitation, Park et al. obtained a four-year follow up on patients who were treated with MRI guided focused ultrasound (MRgFUS) thalamotomy for ET. Of the 15 patients enrolled, 12 completed the 4-year follow up. They found that all quality of life and tremor improvements remained statistically significant after the four years, and there were no sustained adverse effects [17].

Similar trends have been consistently found in recent studies. One research group summarized a 1-year follow up on 45 medication resistant essential tremor patients treated with MRgFUS; using forms that measure hand tremor scores and mental quality of life. All of these patients were treated with a unilateral thalamotomy. Results of the study showed an 82% improvement in the hand tremor score, with a significant decrease in depressive symptoms. The side effect profile consisted of some symptoms including paresthesias, gait disturbances & taste disturbances (78%), with 62% of these symptoms being transient [20].

MRI guided thalamotomywith FUS as a treatment for ET is currently the only FDA approved treatment within the realm of neurological pathologies, with a recent expansion to include treating debilitating symptoms of those with Parkinson's. FUS treatment shows promise for patients with ET as an alternative to the current medical and surgical (aka Deep Brain Stimulation) therapies. One review article compared outcomes in two separate clinical trials for treatment of ET with FUS or Deep Brain Stimulation (DBS), shown in (Fig. 4) [21]. Future studies should evaluate a longer follow up post treatment with FUS to determine its long-term efficacy. Additionally, a randomized control trial should be performed to determine if there is a significant difference between treatment with Deep Brain Stimulation vs Focused Ultrasound. Most ongoing clinical trials are seeking to understand the effects of a bilateral thalamotomy in the treatment of bilateral ET and ensuring there are no lasting adverse effects (NCT04112381, NCT03465761).

Opening the blood brain barrier (BBB)

One of the most exciting applications of FUS is its ability to increase vascular permeability in the BBB and facilitate drug delivery to the brain. When used at a lower intensity and pulsed rather than continuous mode, FUS can create a temporary mechanical effect on vasculature. Through this pulsating low intensity "dose", microbubbles are created which oscillate within the vasculature and create a shearing effect which stretches the endothelial tight junctions and increases permeability [15]. A myriad of studies focused on finding the optimal intensity and pulse frequency in animal models which will be helpful in using it in a safe and efficient way [22–25]. Because the effects are transient, it is being considered for several conditions that require temporary increased permeability of the BBB to allow for delivery of high concentration of medications into the brain (Fig. 5). Fishman & Frenkel outlined the pertinent diseases that are currently being studied, namely brain tumors, Alzheimer's disease, and Parkinson's disease [13]. Other attempts at opening the BBB have been made using intraarterial Mannitol, electroporation or ultrashort-pulsed laser. However, all of these methods are more invasive than FUS and each have specific limitations. The use of mannitol, for example, has a diffuse effect and is unable to target a specific region of the brain to induce increased BBB permeability [26].

Treatment of brain tumors has been the most studied application of BBB manipulation. While direct tumor ablation with HIFU is another area of study, opening the BBB to allow for easier delivery of chemotherapy is also undergoing clinical trials [13]. In a 2018 clinical trial including 5 patients with high-grade gliomas, Mainprize et al. showed a 15–50% increase in contrast enhancement on MRI following FUS application, suggesting the BBB opened effectively. Additionally, there were no adverse reactions, and all the patients tolerated the treatment well [27]. While there are limitations to this study, such as population size, this suggests that FUS can safely open the BBB and facilitate the delivery of chemotherapeutic agents to brain tumors. A recent preclinical study used mice models to observe the effects of FUS on chemotherapeutic delivery through a transiently disrupted BBB. Results showed a successful opening of the BBB, a decrease in tumor growth by 45%, and an increased survival rate of 30% [28].

In a review of current studies on the topic, Arsiwala et al. stated that many preclinical trials have proved

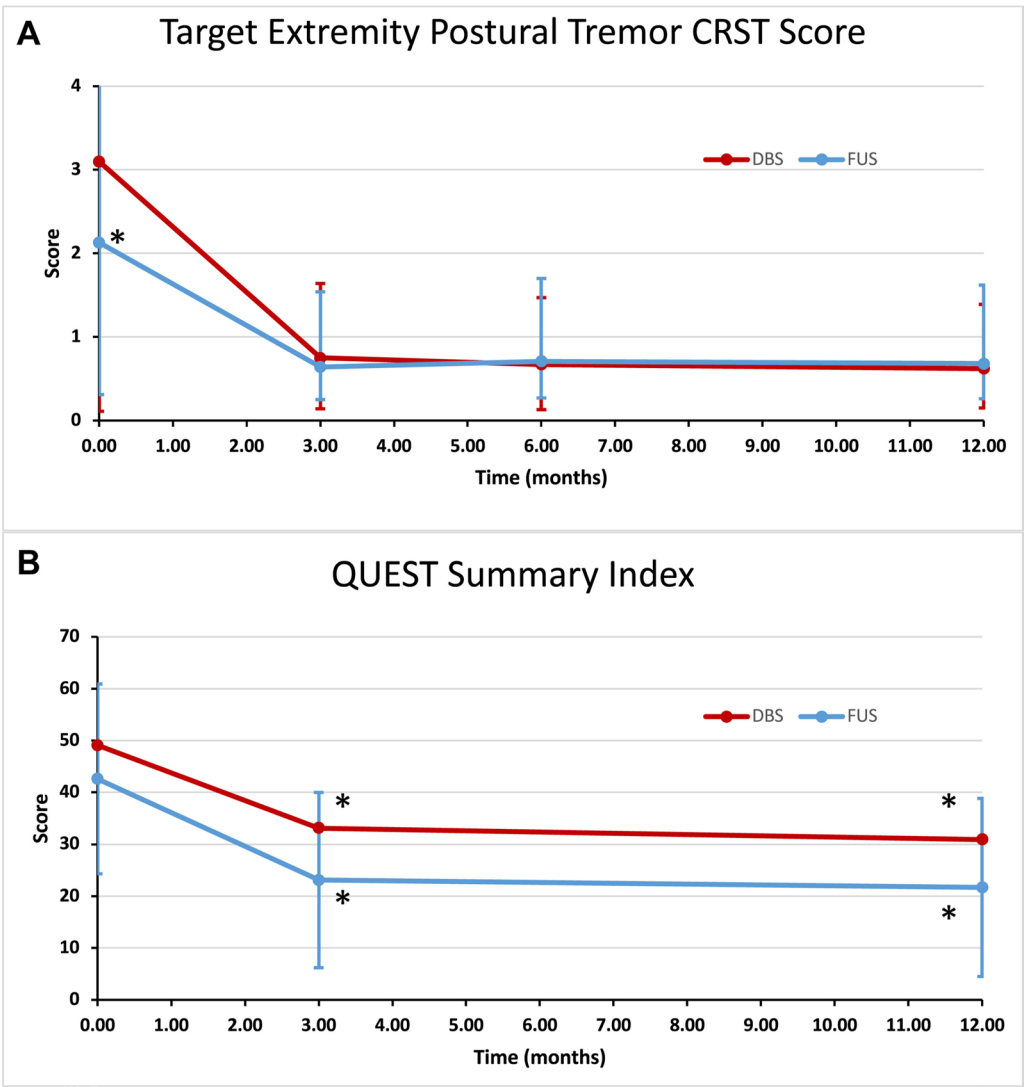

Fig. 4 Comparison between results of DPS and FUS **A** Tremor scores for DPS versus FUS over a 12 month period. There was significant improvement in tremor scores in both trials that lasted for 12 month. When comparing these two studies results against each other, there was no statistical significant difference in tremors between DBS and FUS. **B** Quality of life scores after treatment over a 12 month period are shown. Both treatments result in an improvement in quality of life. The clinical trial with DBS did not include standard deviation for this data, as such, it cannot be statistically compared to that of FUS. (Reused with permission from [21])

the effectiveness of FUS in opening the BBB, but that there were too few clinical trials with enough power to affirm FUS as an option for treatment of brain tumors in humans [29]. To date, there are a number of clinical trials ongoing to determine if this proposed mechanism of increasing chemotherapeutic delivery to brain tumors through FUS-mediated BBB disruption is effective and safe. One of these clinical trials is evaluating the ability of FUS to deliver albumin-bound paclitaxel in a study with an estimated 57 glioma patients (NCT04528680). Another clinical trial is looking to do the same, but with intravenous carboplatin in an estimated 50 participants (NCT04440358). These are just two examples of the relevant clinical trials that are in progress. While there seems to be promise, the results of these future studies will need to be evaluated to make the claim that FUS is a viable treatment option in humans.

Neuromodulation

Neuromodulation is defined as the manipulation of neurons to either inhibit or activate neural activity. This can have many implications, such as stimulating muscle movements or inhibiting pain signals. Through a low intensity FUS, many of these neuromodulation effects

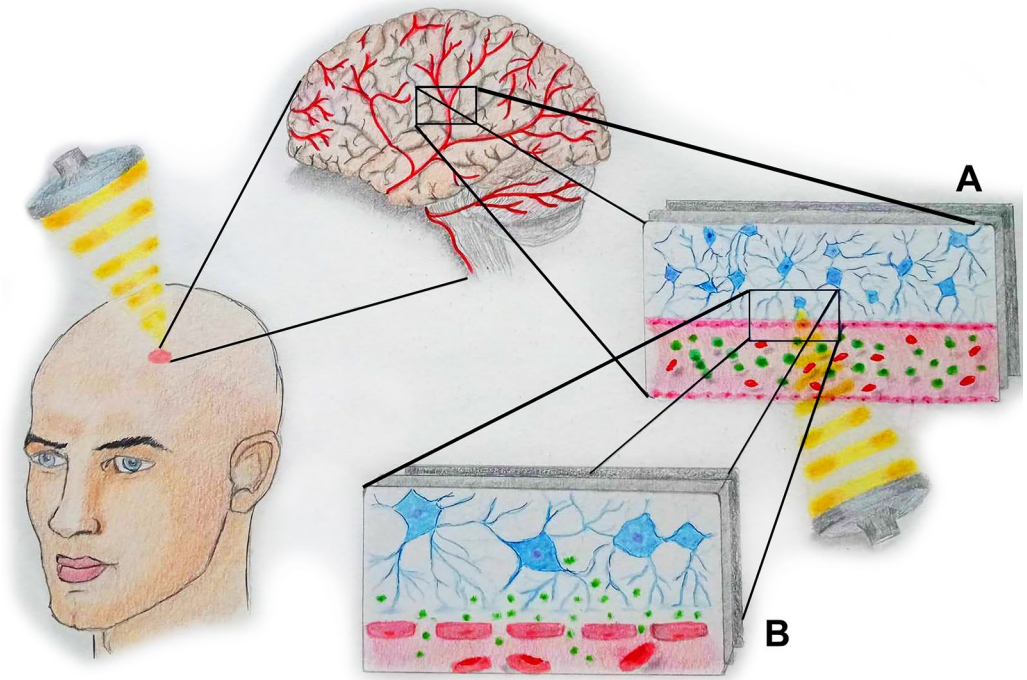

Fig. 5 Illustration of Blood-Brain Barrier (BBB) Opening with Focused Ultrasound (FUS). Focused ultrasound (FUS) offers a non-invasive transcranial approach to precisely target deep intracranial structures in a safe and precise manner. **A** The BBB, composed of tightly adherent endothelial cells lining brain blood vessels, acts as a protective barrier, limiting the permeation of microorganisms into the brain. However, it also restricts the penetration of high medication doses, reducing the efficacy of intravenous systemic medications. **B** Focused ultrasound, often combined with microbubble contrast agents, induces steady stable cavitation, disrupting the tight junctions in between the endothelial cells. This allows therapeutic agents (green beads), such as chemotherapy or immunotherapy, to diffuse into brain tissue at higher concentrations, potentially leading to improved therapeutic outcomes. BBB opening is temporary and occurs without significant damage to adjacent brain tissues

can be implemented. For example, animal studies have shown the capability of FUS to stimulate specific muscle contraction or the inhibition of epileptic attacks [13]. Using FUS for pain management, however, is currently the most popular area of study. In a study involving swine with induced neuropathic pain, FUS was utilized to treat that pain. In all the swine enrolled in the study, each stopped exhibiting pain guarding behavior after treatment, suggesting effective treatment of the neuropathic pain. Additionally, there was no evidence of histological damage after treatment [30]. While this and many other animal studies have been successful, very few published clinical trials exist to show the necessary evidence to approve this treatment in humans.

Currently, there are approximately 21 ongoing clinical trials studying the effectiveness and safety of FUS as a treatment for pain. These trials include treatment for pain due to phantom limb, bone metastases, knee osteoarthritis, disc herniation and chronic neuropathic pain. Currently, FUS thalamotomy and ablations of bone metastasis are heavily investigated, with ablation of painful bone metastasis being FDA approved currently [5]. These ongoing clinical trials hold promise because FUS has the unique capability of non-invasively targeting deep tissue in the brain with a high accuracy [31]. However, there is still the necessity to establish the safety of FUS use for neuromodulation in humans due to potential side effects [32].

Alzheimer's

As mentioned before, opening the BBB presents a potential treatment for patients with Alzheimer's, which is the primary neurodegenerative disease in the world. While the current underlying pathogenic mechanism is not entirely understood, the main hypothesis is that the disease is caused by amyloid-beta plaque deposition and tau phosphorylation in the brain [33]. As such, opening the BBB provides an opportunity for larger immunotherapies and therapeutic agents to cross the BBB with higher concentration. In a phase I trial, Lipsman et al. successfully and safely opened the BBB in five patients with Alzheimer's disease via a purely noninvasive FUS procedure [34] (Fig. 6). This study has opened the door to then implement medication administration which will help treat this currently untreatable disease. Similarly, Liu et al. conducted a

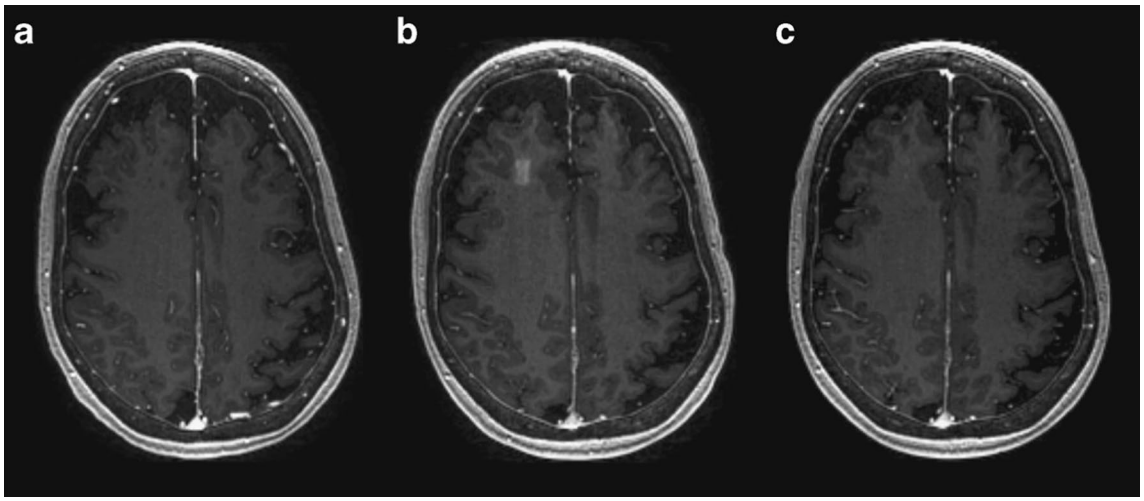

Fig. 6 MRI showing the successful opening and closure of the blood brain barrier. Image **a** is this patient's baseline, **b** is after sonication treatment resulting in contrast extravasation in the $10 \times 10 \times 7$ mm^3 area in the right frontal cortex, and **c** shows appropriate closure with resolved extravasation. This suggests transient BBB opening. (Reprinted from open access article [34])

systematic review of FUS treatment for Alzheimer's and found that FUS with infused microbubbles was safe and efficient at opening the BBB, which in turn can allow for the future implementation of medicine coadministration. They even discussed two clinical trials which showed potential benefit in cognitive ability with sustained FUS stimulation alone in Alzheimer's patients [35]. A more recent study showed 63 successful transient disruptions of the BBB in 9 different patients with Alzheimer's without any adverse effects noted [36]. There are also a few ongoing clinical trials that are observing the safe and effective BBB opening with FUS in Alzheimer's patients (NCT03739905, NCT03671889).

There are other potential benefits that FUS can have on Alzheimer's patients that are not as a result of BBB disruption enabling immunotherapy delivery. One of these was evaluated in a clinical trial performed by Jeong et al., where 8 patients with Alzheimer's received low intensity ultrasound to the right hippocampus. The study aimed to measure the effect of BBB opening, the metabolic use of glucose in the targeted area and on short-term memory. There was no sign of opening of the BBB, but there was an increase of glucose absorption and use in the right hippocampus. Additionally, the patients immediately showed improved short-term memory and recognition memory [37]. This finding of improved cognitive abilities with FUS treatment alone has been shown in preclinical studies already [38]. Currently, there are a few ongoing clinical trials to further examine the potential positive effect FUS has on the cognitive decline in Alzheimer's disease and other neurodegenerative conditions (NCT04250376, NCT03347084). If the findings continue to prove effective for cognitive improvement, then FUS will likely be an important treatment modality for many related neurodegenerative diseases.

Conclusions

FUS is an innovative, non-invasive, treatment modality that has many potential clinical applications especially in the field of neurology. Different biological effects can be achieved using high or low intensity focused ultrasound. This opens doors for unlimited opportunities to treat various diseases and disorders using different mechanisms and through a non-invasive approach. This fits very well in the current paradigm of personalized medicine and brings hope to treat many medical conditions which currently have very limited treatment options.

Abbreviations

HIFU	High intensity frequency ultrasound
FUS	Focused ultrasound
CNS	Central nervous system
ET	Essential tremor
CRST	Clinical rating scale for tremor
DBS	Deep brain stimulation
BBB	Blood brain barrier

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Author contributions

MR performed the literature review and was responsible for writing the main body of the manuscript. TH & MA contributed to the section on the types of focused ultrasound. SA contribute to the section of clinical application in

neurology. MF & MH reviewed the manuscript. **IE** was the primary editor and completed the abstract, background, and conclusion. All authors read and approved the final manuscript.

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All data supporting the findings of this study are available within the paper and its reference list.

Declarations

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References

1. Christian E, Yu C, Apuzzo MLJ (2014) Focused ultrasound: relevant history and prospects for the addition of mechanical energy to the neurosurgical armamentarium. World Neurosurg 82(3):354–365. https://doi.org/10.1016/j.wneu.2014.06.021
2. Lynn JG et al (1942) A new method for the generation and use of focused ultrasound in experimental biology. J General Physiol 26(2):179–193. https://doi.org/10.1085/jgp.26.2.179
3. Quadri SA et al (2018) High-intensity focused ultrasound: past, present, and future in neurosurgery. J Neurosurg Publishing Group (JNSPG)
4. Yoo S et al (2022) Focused ultrasound excites cortical neurons via mechanosensitive calcium accumulation and ion channel amplification. Nat Commun 13(1):493
5. di Biase L et al (2021) Focused ultrasound (FUS) for chronic pain management: approved and potential applications. Neurol Res Int 2021:1–16. https://doi.org/10.1155/2021/8438498
6. Xin Z et al (2016) Clinical applications of low-intensity pulsed ultrasound and its potential role in urology. Transl Androl Urol 5(2):255
7. Sun XL et al (2018) Multi-frequency ultrasound transducers for medical applications: a survey. Int J Intell Robot Appl 2:296–312
8. ter Haar G, Constantin Coussios (2007) High intensity focused ultrasound: physical principles and devices. Int J Hyperthermia 23(2): 89–104
9. Shehata IA (2012) Treatment with high intensity focused ultrasound: secrets revealed. Eur J Radiol 81(3):534–541
10. Fishman PS, Frenkel V (2017) Treatment of movement disorders with focused ultrasound. J Central Nervous Syst Dis 9:1179573517705670
11. Rohani M, Alfonso F (2017) Focused ultrasound for essential tremor: review of the evidence and discussion of current hurdles. Tremor and Other Hyperkinetic Movements
12 Krishna V, Francesco S, Ali R (2017) A review of the current therapies, challenges, and future directions of transcranial focused ultrasound technology: advances in diagnosis and treatment. JAMA Neurol 75(2):246–254. https://doi.org/10.1001/jamaneurol.2017.3129
13 Fishman PS, Frenkel V (2017) Focused ultrasound: an emerging therapeutic modality for neurologic disease. Neurotherapeutics 14(2):393–404. https://doi.org/10.1007/s13311-017-0515-1
14 Hectors SJCG et al (2016) MRI methods for the evaluation of high intensity focused ultrasound tumor treatment: current status and future needs. Magnet Resonance Med 75(1):302–317. https://doi.org/10.1002/mrm.25758
15 Bretsztajn L, Gedroyc W (2018) Brain-focussed ultrasound: what's the FUS all about? a review of current and emerging neurological applications. British Journal of Radiology 91(1087):20170481. https://doi.org/10.1259/bjr.20170481
16 Elhelf IAS et al (2018) High intensity focused ultrasound: the fundamentals, clinical applications and research trends. Diagnost Intervent Imag 99(6):349–359. https://doi.org/10.1016/j.diii.2018.03.001
17. Park YS et al (2019) Four-year follow-up results of magnetic resonance-guided focused ultrasound thalamotomy for essential tremor. Movement Disorders 34(5):727–734. https://doi.org/10.1002/mds.27637
18 Elias WJ et al (2016) A randomized trial of focused ultrasound thalamotomy for essential tremor. New England J Med 375(8):730–739. https://doi.org/10.1056/NEJMoa1600159
19 Mohammed N, Patra D, Nanda A (2018) A meta-analysis of outcomes and complications of magnetic resonance–guided focused ultrasound in the treatment of essential tremor. Neurosurg Focus 44(2):E4. https://doi.org/10.3171/2017.11.FOCUS17628
20 Purrer V et al (2022) Transcranial high-intensity magnetic resonance-guided focused ultrasound (tcMRgFUS)—safety and impacts on tremor severity and quality of life. Parkinsonism Related Disorders 100:6–12. https://doi.org/10.1016/j.parkreldis.2022.05.017
21. Harary M et al (2019) Unilateral thalamic deep brain stimulation versus focused ultrasound thalamotomy for essential tremor. World Neurosurg 126:e144–e152. https://doi.org/10.1016/j.wneu.2019.01.281
22 Fan CH et al (2012) Detection of intracerebral hemorrhage and transient blood-supply shortage in focused-ultrasound-induced blood–brain barrier disruption by ultrasound imaging. Ultrasound Med Biol 38(8):1372–1382
23. O'Reilly MA et al (2011) Focused-ultrasound disruption of the blood-brain barrier using closely-timed short pulses: influence of sonication parameters and injection rate. Ultrasound Med Biol 37(4):587–594. https://doi.org/10.1016/j.ultrasmedbio.2011.01.008
24 Wei KC et al (2013) Neuronavigation-guided focused ultrasound-induced blood-brain barrier opening: a preliminary study in swine. Am J Neuroradiol AJNR 34(1):115–120. https://doi.org/10.3174/ajnr.A3150
25. Wu SY et al (2014) Transcranial cavitation detection in primates during blood—brain barrier opening—a performance assessment study NIH Public Access
26. Han M et al (2017) Biological effects of blood–brain barrier disruption using a focused ultrasound. Biomed Eng Lett 7(2):115–120
27. 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.Springer Science and Business Media LLC, vol 9
28. Wei HJ et al (2021) Focused ultrasound-mediated blood-brain barrier opening increases delivery and efficacy of etoposide for glioblastoma treatment. Int J Radiat Oncol Biol Phys 110(2):539–550. https://doi.org/10.1016/j.ijrobp.2020.12.019
29 Arsiwala TA et al (2021) Ultrasound-mediated disruption of the blood tumor barrier for improved therapeutic delivery. Neoplasia 23(7):676–691. https://doi.org/10.1016/j.neo.2021.04.005
30. Hellman A et al (2020) Pilot study on the effects of low intensity focused ultrasound in a swine model of neuropathic pain. J Neurosurg. https://doi.org/10.3171/2020.9.jns202962
31 Kubanek J (2018) Neuromodulation with transcranial focused ultrasound. Neurosurg Focus 44(2):E14. https://doi.org/10.3171/2017.11.FOCUS17621
32 Bowary P, Greenberg BD (2018) Noninvasive focused ultrasound for neuromodulation. Psychiatric Clinics North Am 41(3):505–514. https://doi.org/10.1016/j.psc.2018.04.010
33. Souza RMDCE et al (2018) Focused ultrasound and alzheimer's disease a systematic review. vol. 12, FapUNIFESP (SciELO). https://doi.org/10.1590/1980-57642018dn12-040003
34. Lipsman N et al (2018) Blood–brain barrier opening in alzheimer's disease using MR-guided focused ultrasound. Springer science and business media LLC vol. 9
35. Liu X et al (2021) The applications of focused ultrasound (FUS) in alzheimer's disease treatment: a systematic review on both animal and human studies. Aging Dis 12(8): 1977–2002. https://doi.org/10.14336/AD.2021.0510
36. Epelbaum S et al (2022) Pilot study of repeated blood-brain barrier disruption in patients with mild alzheimer's disease with an implantable

ultrasound device. Springer Science and Business Media LLC, vol. 14. https://doi.org/10.1186/s13195-022-00981-1
37. Jeong H et al (2022) Short-term efficacy of transcranial focused ultrasound to the hippocampus in alzheimer's disease: a preliminary study. MDPI AG, vol. 12. https://doi.org/10.3390/jpm12020250.
38. Götz J, Richter-Stretton G, Cruz E (2021) Therapeutic ultrasound as a treatment modality for physiological and pathological ageing including alzheimer's disease. Pharmaceutics 13(7):1002

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