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A Review of the Current Therapies, Challenges, and Future Directions of Transcranial Focused Ultrasound Technology

Advances in Diagnosis and Treatment

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IMPORTANCE Magnetic resonance imaging–guided focused ultrasound ablation has been approved for the treatment of refractory essential tremor and is being studied for other neurological indications, including dyskinesias and tremor in Parkinson disease, dystonia, neuropathic pain, obsessive-compulsive disorder, epilepsy, and brain tumors.

OBJECTIVE To review the scientific foundations of FUS technology, existing neurological applications, and future advances.

EVIDENCE REVIEW PubMed was searched for the past 10 years using the terms "transcranial ultrasound," "focused ultrasound," and "neurological applications." Relevant references were selected from the author's reference collection. From the 2855 unique records, 243 publications were screened. After excluding abstracts detailing in vitro studies or non-neurological applications, 86 full texts were retrieved for qualitative review.

FINDINGS Advances in the transducer design and electronic phase correction have allowed efficient focusing of ultrasounds for transcranial treatment. The mid-frequency (650 kHz) transducer can make small (4-6 mm in diameter) and precise (accuracy of <2 mm) brain lesions. The treatment monitoring is achieved via "live" anatomical thermography imaging and clinical feedback. The initial results from its clinical application in movement disorders are encouraging. Emerging applications in epilepsy and neurobehavioral and cognitive disorders are being explored. The low-frequency (220 kHz) transducer coupled with microbubbles can potentially enable targeted drug delivery for novel applications, such as Alzheimer disease and brain tumors. Finally, neuromodulation with subthreshold sonications may allow the interrogation of brain areas previously not accessible for electrical stimulation.

CONCLUSIONS AND RELEVANCE Transcranial focused ultrasound for both ablative and nonablative applications is noninvasive, making it suitable for selected patients who are not candidates for conventional surgical options. Future advancements in imaging and sonication algorithms will improve the safety and efficacy of this technology.

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Supplemental content

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A right-handed woman in her 90s presented with essential tremor involving bilateral arms, head, and voice. The tremors started 15 years ago and progressively became disabling. She had failed propranolol hydrochloride, primidone, and gabapentin, but she had an unremarkable medical history otherwise. Her examination revealed considerable symmetric tremor, with a Clinical Rating Scale for Tremor (score range: 0-132, with the highest score indicating severe tremor) score of 88 and scores of 38 in subscale A (at rest, posture, and action), 26 in subscale B (drawing spiral, handwriting), 24 in subscale C (quality-of-life), and 26 in subscales A and B (right-side tremor). The remainder of the neurological examination results were unremarkable. Preoperative magnetic resonance imaging (MRI) revealed periventricular white-matter changes and mild age-related diffuse atrophy.

After a multidisciplinary evaluation, she was not recommended for ventral intermediate nucleus (VIM) deep brain stimulation (DBS) due to her advanced age. Instead, she was offered focused ultrasound (FUS) thalamotomy. Computed tomography imaging determined that her skull was suitable for ultrasonographic treatment; her skull homogeneity was greater than 0.4, as calculated by skull density ratio (SDR, which is the median ratio of skull density between cortical and trabecular bone; higher SDR in-

dicates more homogeneity). The preoperative diffusion tensor imaging was processed to localize pyramidal tract, sensory thalamus, medial lemniscus, and tractography-defined VIM target (**Figure 1**). She subsequently underwent FUS thalamotomy. A total of 11 sonications were performed for 2 hours, and peak temperature of 59°C was reached with 9100 J of energy. She had intraoperative tremor arrest. Her postoperative course was unremarkable without any neurological deficits (weakness, numbness, tingling, or imbalance). She was discharged home after overnight observation in the hospital. At 6 months, the patient showed marked improvements in tremor (46% improvement on the treated side and 33% improvement in total).

The US Food and Drug Administration (FDA) approved FUS ablation for the treatment of refractory essential tremor in July 2016. This technology is an approved treatment for non-neurological disorders, such as uterine fibroids and bone metastasis. It is now being actively investigated for other indications, including disabling dyskinesias in Parkinson disease (PD),[1] dystonia, tremor associated with PD or Fragile X syndrome, neuropathic pain,[2] obsessive-compulsive disorder,[3] epilepsy, and brain tumors.[4,5]

The first historical application of FUS was at the Naval Research Laboratory in Washington, DC, in 1947 and is attributed to the physicist William J. Fry and his brother Francis J. Fry.[6,7] Recent innovations in the design of the transducer, electronic phase correction, and magnetic resonance (MR) thermometry have allowed for transcranial lesioning without requiring a cranial window through burr hole or craniotomy.[8-10] In contrast to the delayed, and at times unpredictable, clinical outcomes and lesion size, as well as the use of radiation with gamma knife radiosurgery, FUS ablation can be monitored through triple feedback—immediate clinical feedback, live thermography, and anatomical imaging for visualization of the lesion. The tissue temperature can be increased to sublesion levels (less than 45°C subthreshold sonications) for inducing transient clinical reaction mirroring the intraoperative stimulation during DBS. This sublesion testing of the efficacy and adverse effects is another advantage of this technology over gamma knife. However, in contrast to the titrability of DBS, the outcomes of FUS ablation are immediate and permanent. Therefore, it is imperative to select patients well, precisely identify the therapeutic target, and carefully monitor patients intraoperatively for reduction of symptoms and development of adverse effects.

This review discusses the scientific foundation and clinical applications of FUS technology. In addition, it outlines future research and innovations to address the limitations and potentially broaden the applications of FUS ablation.

Key Points

Question What are the neurological applications of focused ultrasound technology?

Findings This review found that focused ultrasound technology can be applied for tissue ablation, neuromodulation, and opening of the blood-brain barrier. The US Food and Drug Administration has approved it for treating refractory essential tremor.

Meaning Focused ultrasound is an emerging technology that has ablative and nonablative applications for neurological and psychiatric diseases.

Clinical Features

Scientific Background

Physics of Ultrasound Transmission

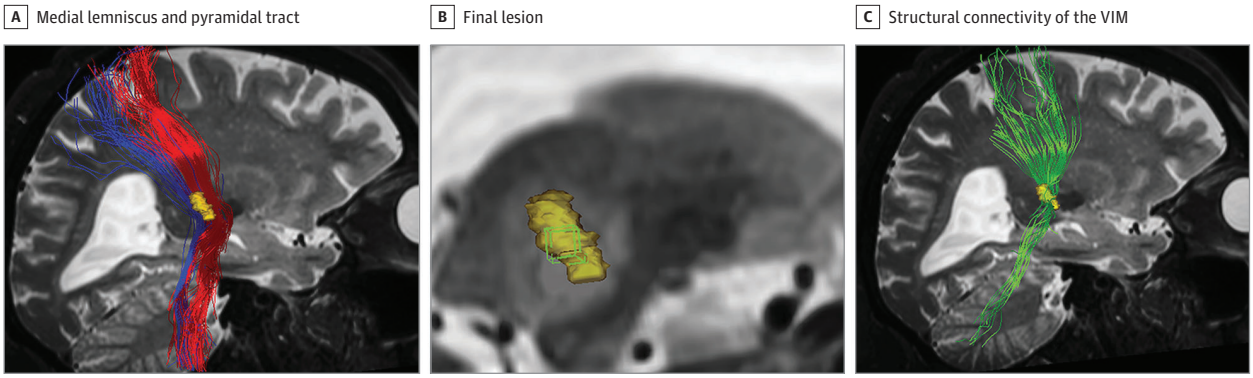
Ultrasounds are mechanical waves (with a frequency of more than 20 kHz) that travel with alternating compression and rarefaction, thereby transmitting energy by molecular movements. In contrast to diagnostic ultrasonography (with a frequency in the megahertz range), the frequencies used for the transcranial FUS are either mid-frequency (650 kHz) or low frequency (220 kHz).[11] The speed of ultrasound transmission is medium dependent[12] (eg, water and soft tissue are excellent conductors, but air and bone are not). Transmission necessitates a coupling medium (eg, degassed water) between the transducer and biological tissue. In addition, there is significant absorption and reflection of ultrasound while traveling through tissues with different "ultrasonic densities," such as layers of the skull (inner table, marrow, and outer table).[13] The extent of ultrasound reflection is also dependent on the incident angle (eg, large [25° to 30°] incident angles result in higher reflection). Besides altering the velocity, heterogeneous tissues also alter the phase of ultrasound waves.

Biological Consequences of Focused Ultrasound

The biological consequences of FUS are dependent on the intensity, frequency, and duration of exposure. At low intensity, high-frequency (2 MHz) ultrasound can produce a reversible conduction block in peripheral nerves.[14] This conduction block is associated with a mild increase in local temperature (41°C to 45°C)[14] and is mediated by the inactivation of sodium channels.[15] It can produce transient clinical results that may last for a few minutes and are particularly appealing for target localization in functional neurosurgery.[16] Under certain conditions, FUS can also reversibly open the blood-brain barrier without ablation.[17,18] Blood-brain barrier opening can be reliably achieved at subthreshold intensities with the use of microbubbles.[19] A recent proof-of-concept study demonstrated localized blood-brain barrier openings of approximately 1 cm^3 with very low sonication power (5 W and 230 kHz transducer).[20]

At high intensity, FUS creates tissue ablation, the mechanism of which is dependent on frequency. For example, the mid-frequency system (650 kHz) primarily produces thermal ablation, whereas the low-frequency system (220 kHz) achieves ablation via cavitation or histotripsy, in which ultrasound interacts with trapped gas bubbles within tissues that leads to the rapid oscillation and collapse of those bubbles.[21] Therapeutic sonications (temperature greater than 55°C) denature cellular protein and produce lesions with 3 separate zones on T2-weighted MRI: mixed-intensity core (zone 1 with necrotic center), hyperintense periphery (zone 2 with apoptosis), and surrounding vasogenic edema (zone 3).[22] The histological consequences of FUS ablation are associated with the duration of exposure (thermal dose).[23,24] The target tissue characteristics influence temperature elevation during sonication (eg, tissue perfusion may act as a heat sink, although this reaction is minimal for short-duration sonications).[25]

Figure 1. Tractography-Based Ventral Intermediate Nucleus (VIM) Targeting With Relevant Tracts Overlaid on Sagittal Projection



A, The medial lemniscus (blue) is shown in posterior relation to the lesion, and the pyramidal tract (red) is shown in lateral relation to the lesion. B, The final lesion is shown in relation to the tractography-defined VIM. C, The structural connectivity of the VIM region of interest is shown in relation to the lesion.

Critical Review of Transcranial Focused Ultrasound Technology

The technological considerations for transcranial FUS treatment are summarized in **Figure 2**.

Major Advantages

The noninvasive approach of FUS ablation is appealing to some patients. For transcranial application, 2 types of transducers are available: hemispherical[8,26] and linear.[27] The hemispherical transducers are mounted on the MRI table,[28] whereas the linear transducers are mounted on a robotic arm.[29] The FDA-approved hemispherical transducer (ExAblate 4000; Insightec Inc) circulates degassed water for coupling and provides tissue cooling.[28] The electronic phase-correction algorithms ensure an in-phase ultrasound convergence for precise lesioning.[9,30] These algorithms use a priori data on skull inhomogeneity to compensate for the estimated phase and amplitude changes of the ultrasound beams (eg, each of the 1024 elements in the hemispherical transducer has independent phase and amplitude).[28]

A unilateral VIM thalamotomy with FUS may require 10 to 15 sonications with a 2- to 4-hour total treatment time. The first several sonications are subthreshold, allowing limited physiological exploration of the sonication target. During these sonications, patients are clinically evaluated for clinical improvement and adverse effects and the targeting accuracy (sonication volume, shape, orientation, and location) is assessed. Finally, 2 or 3 therapeutic sonications are performed to create an optimal-sized lesion (4-6 mm in diameter). The intraoperative MRI guidance is crucial for monitoring brain anatomy (motion detection) and real-time temperature (thermal monitoring). The phase shift during the proton-resonant frequency imaging is used for MR thermography.[31] One study found that the accuracy of the transcranial FUS (ExAblate 4000; Insightec, Inc) was less than 2 mm,[2] which is comparable to the accuracy of gamma knife.[32] Centering the transducer focal point on the intended sonication target maximizes accuracy, although electronic steering for up to 2 mm can also be accurately performed.[2,28]

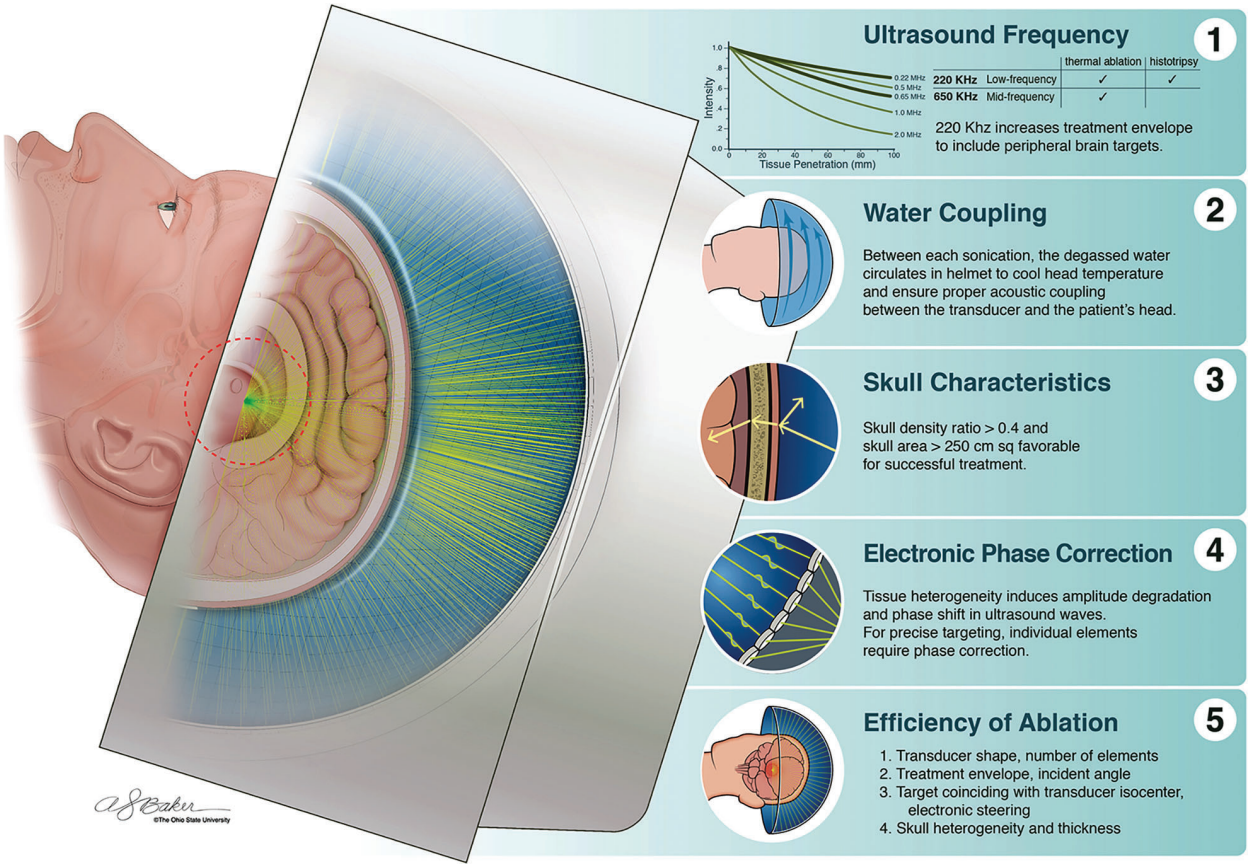
Major Disadvantages

The hemispherical mid-frequency FUS system has a limited treatment envelope (approximately 3 cm radius around the mid-commissural point). This limitation makes the FUS ideal for lesioning thalamic and basal ganglia targets that are commonly used for surgical treatment of movement disorders, chronic pain, epilepsy, and psychiatric disorders. Due to incident angle issues, the efficiency of sonication substantially decreases for brain regions close to the skull or regions outside of the treatment envelope (eg, cortical or surface targets).

High sonication pressures delivered for long duration may transmit mechanical energy to the target tissue by cavitation (ie, creating rapid compression and expansion of entrapped gas in the tissue).[33] Although cavitation may lead to nonthermal lesioning (histotripsy), random cavitation from the nonlinear conversion of acoustic energy into mechanical energy remains a safety concern regarding FUS ablation.[34] Cavitation is typically observed in areas with high tissue inhomogeneity (eg, close to blood vessels, presenting hemorrhage risk) or tissue interfaces.[21] The probability of cavitation is higher at low frequency (eg, more cavitation with 220 kHz than with 650 KHz), and the unpredictability is higher with high frequency. Therefore, in the current FUS ablation system, cavitations are monitored by analyzing the backscattering frequency. New algorithms are being developed to predict the threshold for cavitation and increase treatment safety and efficiency.[35]

The absorption of ultrasound energy at the outer table of the skull is responsible for skull heating.[36] High-energy sonications produce transient headaches and may result in necrosis of the skull, which is asymptomatic.[37] Similarly, scalp burns, although rare, have been reported at the site of head fixation pins of stereotactic frame.[38] The skull is a significant barrier to ultrasound transmission and can adversely alter temperature elevation at sonication target; in recent studies, therapeutic temperatures could not be achieved in 10% of patients.[39,40] Among all of the patient-associated factors, skull thickness and the number of ultrasonic beams with incident angles of more than 20° appear to be the most relevant.[41] In addition, lesion size may be inadequate in some patients, and the necrotic center disappears on follow-up T1- and T2-weighted MRI after 3 months.[42] The skull homogeneity quantified by SDR was found to be a significant predictor of treatment success. Therefore, the current FDA labeling includes only patients with SDR of 0.4 or higher. Other factors (eg, skull curvature) may also influence target temperature given that, in a

Figure 2. Technological Consideration for Transcranial Focused Ultrasound (FUS) Ablation Treatment



The clinically approved FUS ablation with incident frequency of 650 kHz mainly achieves lesioning via thermal ablation, but the lower-frequency system can also perform histotripsy (1). Water coupling in the transducer is critical for acoustic coupling and local cooling (2). As the ultrasound passes through the skull, a significant proportion of it is absorbed and some energy is transmitted and reflected. Therefore, skull characteristics are taken into account when evaluating the eligibility for FUS treatment (eg, the current labeling of the US Food and Drug Administration includes only patients with a skull density ratio >0.4 [3]). In addition to impeding the ultrasound transmission, the skull also induces changes in ultrasound phase. The electronic phase-correction algorithms incorporate the information about skull density in the path of individual ultrasound beams to correct for any phase shifts (4). In addition, the efficiency of FUS ablation is influenced by other factors, including the target location in relation to the treatment envelope (5). Reproduced with the permission of The Ohio State University.

pivotal randomized clinical trial, therapeutic temperature was not reached in 5 of 56 patients despite including patients with SDR higher than 0.4.[40] To extend the indications for patients with SDR lower than 0.4, the patterns of skull heating need to be better characterized with 3-D MR thermometry.[43] Future strategies may exclude skull regions with significant heterogeneity to maximize the skull area by substituting stereotactic frame with other methods for head stabilization[44] and improving the phase-correction algorithms.[45]

The neurological adverse effects of therapeutic FUS ablation can be immediate and permanent and associated with either "on-target" or "off-target" sonications. In a large randomized clinical trial, 20 patients (36%) experienced gait disturbances and 21 (38%) reported paresthesias or sensory deficits.[40] Some of these deficits can be mild and may eventually improve with the resolution of edema. In that trial, the rate of permanent gait disturbances was reduced to 9% (n = 5) and the rate of paresthesias decreased to 14% (n = 8) by 1 year.[40] These deficits are rarely seen after DBS because its trajectory can be adjusted according to thresholds of adverse effects during intraoperative testing, and postoperative stimulation can be titrated for efficacy without adverse effects.[46] In contrast, an increase in lesion size during therapeutic sonications may lead to adverse effects despite satisfactory initial testing. Sonication can also induce dizziness, nausea, and transient headaches. Finally, longer procedures often require careful positioning and generous padding at the extremities as well as deep vein thrombosis prevention from prolonged immobilization.[47]

Application in Clinical Neuroscience

Approximately 1000 patients have been treated with FUS ablation worldwide. The **Table**[1-3,40,47-55] lists the historical timeline of FUS ablation applications in clinical neuroscience, especially for movement disorders (**Figure 3**).

Essential Tremor

The VIM DBS is an FDA-approved treatment for refractory essential tremor.[56] Despite its excellent efficacy, DBS has low patient acceptability due to its invasive approach, the need for implanted hard-

Table. Summary of Focused Ultrasound Ablation Applications in Movement Disorders

Study	Participant	Clinical and Adverse Consequence	Target	Parameter
Denier,[48] 1948	3 Patients with dementia paralytica, torticollis, and Parkinson disease	NA	NA	NA
Zubiani,[49] 1951	51 Patients with various neurological disorders	NA	NA	Ultrasound cycles of between 0.6 to 1.5 W/cm
Fry et al,[50] 1958	18 Cases of Parkinsonism and 2 cases of cerebral palsy with dystonia	No intraoperative mortality; changes in deep and superficial reflexes, vibratory perception, and touch perception; changes in motor power, coordination and posture, and rigidity; changes in vital signs and responsiveness	Ansa lenticularis, medial segment of globus pallidus; substantia nigra; medial subthalamic nucleus; tegmental fields of Forel	Frequency: 980 kHz; 25 total procedures; exposure time: 1.80 to 3.00 s; series of lesions produced in each case; craniotomy needed
Meyers et al,[51] 1959	11 Patients with PD and 1 with athetoid features	Apathy (possible lesion of hypothalamus); left hemiplegia with mutism; right hemiplegia with aphasia; right conjugate ocular deviations	Ansa lenticularis (alone in 6 procedures); substantia nigra (5 procedures); ansa plus sites posterior to it (1 procedure); ansa plus medial segment of globus pallidus	Frequency: 980 kHz; exposure time: 2 to 3 s
Meyers et al,[52] 1960	3 Patients with chronic pain (1 with phantom limb pain, 1 with thalamic pain, and 1 with postherpetic pain)	NA	VPL and VPM nuclei; centromedian nucleus	Frequency: 980 kHz; exposure time: 2 to 3 s
Hasegawa et al,[53] 1964	4 Patients with agitated oligophrenia	NA	Posterior hypothalamus; amygdala	NA
Martin et al,[2] 2009	9 Patients with chronic neuropathic pain	No persistent consequences after sonications	Posterior aspect of the thalamic central nucleus; some bilateral lesions	Maximum power: 12 000 J per sonication; target temperature: Between 51°C and 60°C
Lipsman et al,[47] 2013	4 Patients with refractory ET	1 Patient with persistent paresthesias; 1 patient had DVT	VIM thalamic nucleus	Sonications of 10 to 25 s; acoustic power: 300 to 1250 W per sonication
Elias et a,[38] 2013	15 Patients with medication-refractory ET	4 Patients had persistent paresthesias; 1 patient-reported persistent dysesthesia	VIM thalamic nucleus	Final mean (SD) sonication energy: 10 320 (4537) J (range, 6500 to 20 800)
Chang et al,[54] 2015	11 Patients with refractory ET	No persistent consequences	VIM thalamic nucleus	Maximum power: 24 000 J (1200 W × 40 s)
Magara et al,[55] 2014	13 Patients with PD	None reported	Unilateral PTT (Y at AC, X = 7.5 mm lateral to the thalamo-ventricular border, Z = 1 mm above AC)	Maximum power: 1200 W; maximum applied energy: 20 to 400 J; maximum temperature: 59°C
Na et al,[1] 2015	1 Patient with PD and levodopa-induced dyskinesias	None reported	Globus pallidus internus	Maximum temperature: 59°C
Elias et al,[40] 2016	76 Patients with-refractory ET	8 Patients with persistent paresthesias; 5 patients with persistent gait impairment	VIM thalamic nucleus	Mean (SD) acoustic energy: 14 497.0 (6695.7) J (range, 3500-34 860); mean (SD) peak temperature: 55.6°C (2.3°C)

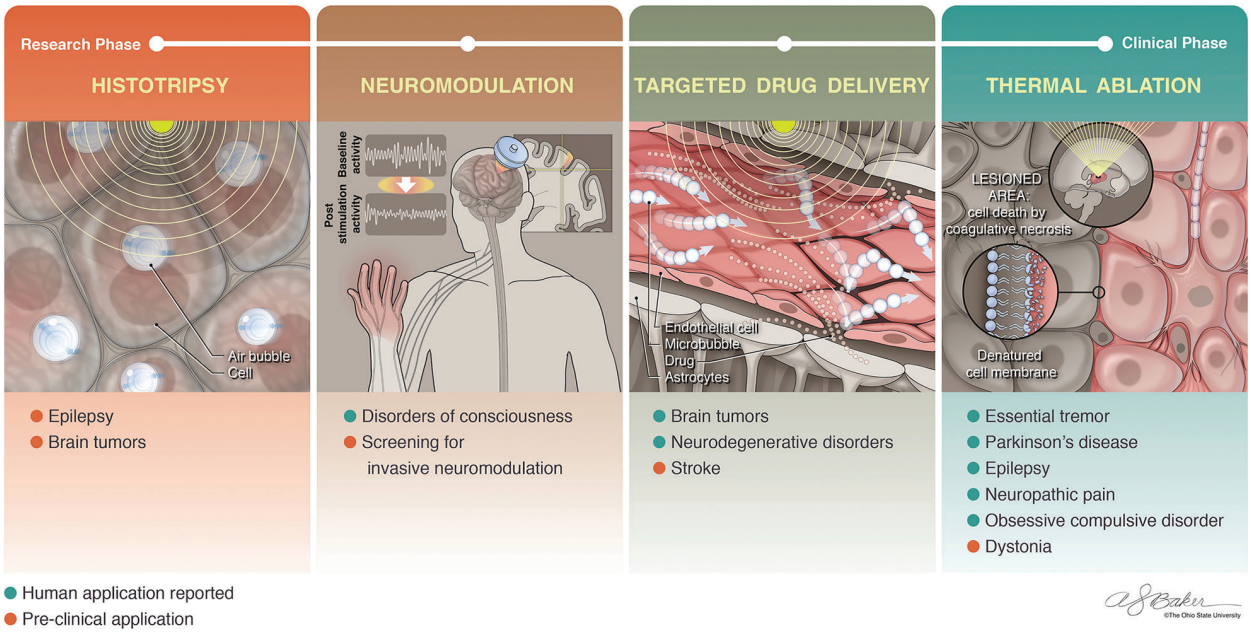
Abbreviations: ACT, anterior commissure; DVT, deep vein thrombosis; ET, essential tremor; NA, not applicable; PD, Parkinson disease; PTT, percutaneous trigeminal tractotomy; STN, subthalamic nucleus; VIM, ventral intermediate nucleus; VPL, ventral posterolateral nuclei; VPM, ventral posteromedial.

ware, and the required long-term programing and battery replacement. The FUS ablation is a treatment option for patients who either have contraindications for DBS surgery or prefer not to have a DBS implant.[22,47] Results from a randomized clinical trial showed a 47% tremor reduction at 3 months, with approximately 60% of patients showing 40% or greater improvement, although there was a rebound increase (40% improvement) in tremor at 1 year and a relatively high rate of adverse events.[40] The current safety and efficacy profiles of FUS ablation are inferior to DBS,[46] with some studies reporting 67.8% improvement in contralateral tremor (per Clinical Rating Scale for Tremor subscales A and B) at 12 months.[57] In addition to the new technology learning curve, the treating teams must understand that FUS limitations may be related to lesion location and size.

Parkinson Disease

For PD, FUS ablation of the globus pallidus internus and the subthalamic nucleus have been reported. After unilateral pallidotomy in a patient with levodopa-induced dyskinesias, the contralateral dyskinesia score declined by 53% at 1 week.[1] Magara et al[55] performed unilateral lesions of the pallidothalamic tracts in 13 patients with PD. Four patients received only 1 sonication at peak energy, whereas the remaining 9 patients underwent sonication 4 times. The 3-month outcome for the second cohort was notably better than for the first cohort (60% vs 7.3% improvement in the Unified Parkinson Disease Rating Scale). Based on these results, larger trials are under way to explore the applicability of FUS ablation in patients with advanced PD. Overall, these improvements are modest in comparison to improvements achieved in DBS[58] and radiofrequency pallidotomy.[59] The efficacy of unilateral FUS ablation may be limited for PD mainly due to lower treatment efficiency (related to a lower number of active elements in lateral globus pallidus internus target and the accuracy of FUS ablation for small subthalamic nucleus) and risk for serious adverse effects (off-target injury to the optic and pyramidal tracts and hemiballismus risk after subthalamotomy).

Figure 3. Current and Future Clinical Applications of Focused Ultrasound (FUS) Technology



The indications in preclinical stages are listed on the left and those in some clinical stages (either clinical trials or approved by the US Food and Drug Administration) are listed on the right. With thermal ablation being the most mature mechanism, several human applications have been reported for movement disorders and epilepsy. Targeted drug delivery with the 220-kHz FUS technology is being investigated for neuro-oncology and neurodegenerative conditions. Subthreshold ultrasonography can be used for neuromodulation, and the first human application was for disorders of consciousness. The use of histotripsy for microlesioning has the potential to revolutionize the treatment of epilepsy and brain tumors. Reproduced with the permission of The Ohio State University.

Obsessive-Compulsive Disorder

For obsessive-compulsive disorder (OCD), FUS ablation of the bilateral anterior limb of internal capsule was recently reported in 4 patients with refractory OCD.[3] Symptom reduction was observed in all patients at 6 months, with 2 reporting a 35% improvement on the Yale-Brown Obsessive Compulsive Scale (score range: 0-40, with the highest score indicating severe OCD). No complications were reported. Future investigations are needed to discover the tract substrates of efficacy to further refine the sonication target for this indication.

Neuro-oncology

For neuro-oncology, FUS ablation is an attractive option for the treatment of brain neoplasms, especially deep-seated tumors.[60] Ram et al[5] performed FUS ablation in 3 patients with histologically confirmed glioblastoma recurrence. Subsequently, McDannold et al[4] reported transcranial sonications in 3 patients with high-grade brain tumors. The target temperatures (higher than 55°C) could not be reached in 2 patients despite the lesions being within the treatment envelope. More recently Coluccia et al[61] reported applying FUS ablation for tumor debulking in a patient with thalamic high-grade glioma. The treatment was stopped after 4 hours due to the patient reporting "deep sensation of warmth" inside the head, resulting in a lesion volume of only 0.7 cm^3. These reports highlight the challenges associated with tumor location in relation to transducer treatment envelop, tissue heterogeneities and varying perfusion rates, and the risk for hemorrhage inside the tumor resulting in variations in temperature elevations.

Future Advances in Therapy

Because movement disorders are the most advanced clinical application for FUS ablation with the most outcome data, this section is categorized into movement disorders and novel applications. The potential advances on the horizon for nonablative indications are also discussed.

Movement Disorders

The success of FUS ablation relies on creating an optimal lesion for maximum efficacy without inducing adverse effects. The optimal lesion size and location (eg, gray matter vs white matter) for FUS ablation remain unclear. The lesion morphology experience from radiofrequency ablations may not be directly translatable to FUS ablation because its lesion size and shape are linearly correlated with electrode and current delivery.[62] Lesions for FUS ablation depend on skull and local tissue characteristics as well as incident energy and duration of exposure. Therefore, future research should address 2 critical questions: How are therapeutic targets in the brain accurately identified? and How is the treatment end point defined? The potential answers may come from neuroimaging, specifically through tractography-based targeting of and functional MRI–based real-time feedback on brain network dynamics.

The common sonication targets for FUS ablation (eg, VIM and globus pallidus internus) are not visible on the conventional 1.5T or 3T MRI.[63] Current targeting involves a combination of formulaic methods based on distance from the anterior and posterior com-

missures as well as feedback from limited physiological exploration using subthreshold sonications. However, this approach is less precise and time consuming.[38,47] Tractography-based targeting can be useful for maximizing the efficacy and minimizing the risk of adverse effects associated with off-target sonication.[64] Currently, clinical testing alone is used to determine whether sufficient lesioning has been achieved. In the absence of physiological feedback, this determination can be subjective (eg, the long-term efficacy of a number of therapeutic sonications is unknown and may be surgeon dependent). This determination can alter the consistency and durability of tremor outcomes as well as the risk of adverse effects.[65] Functional neuroimaging can be used for real-time physiological feedback during FUS ablation. These studies are increasingly being used to investigate the dysfunction within different brain networks in neurological disorders,[66] including essential tremor.[67] Initial evidence suggests that therapeutic FUS ablation decreases the pathological oscillations in the motor cortex[54] and alters the functional connectivity in the motor network.[68] These studies may provide the basis for developing functional MRI–based feedback during FUS ablation for defining the treatment end point.

The initial results of FUS ablation are encouraging. With accumulating experience and refinements in targeting techniques, the outcomes will improve, which may eventually create a clinical equipoise to justify clinical trials comparing FUS ablation with DBS. The long-term durability of FUS ablation outcomes is currently unknown. Tremor may recur with disease progression, and patients may need additional procedures (eg, FUS ablation treatments) for symptom control. Finally, all published studies have investigated only unilateral FUS ablation; therefore, the safety and feasibility of bilateral thalamotomy should be explored only in the context of research studies because of the high risk of pseudobulbar adverse effects associated with bilateral lesioning procedures.[69]

Novel Indications

Epilepsy naturally lends itself to ablation of either the epileptogenic zone or disruption of the epilepsy network. Clinical trials are under way to evaluate the outcomes of FUS ablation in patients with lesional epilepsy, specifically hypothalamic hamartoma and deeper cortical dysplasia. The role of FUS ablation in preventing secondary generalizations in patients with partial-onset refractory epilepsy is also being evaluated in a separate study. The target for sonications is the anterior thalamic nucleus. Preclinical evidence also shows that low-frequency FUS ablation can transiently inactivate the cortical seizure foci[70]; human trial is under way to assess the safety of this approach.

Monteith et al[71] have reported a proof-of-concept study of FUS ablation at the trigeminal nerve root entry zone. They performed sonications in 6 trigeminal nerves from 4 cadaver specimens using special elements and blocking techniques to avoid heating the skull base with modest temperature increase (approximately 5°C). Other novel indications may include deep-seated vascular malformations (eg, cavernomas) and hydrocephalus (eg, third ventriculostomy).

Nonablative Applications

The ability to transiently open blood-brain barrier in localized brain regions offers a promising route for targeted drug delivery (eg, chemotherapy for neuro-oncology[72]; gene and neurotrophic factors for neurodegenerative diseases[73]) (Figure 3). Two clinical trials for chemotherapy delivery are currently recruiting participants for tumor application. Plaque clearance in animal models of Alzheimer disease was recently reported.[74] Using the scanning ultrasound technique, Leinenga and Götz[74] opened cortical blood-brain barrier at multiple locations, resulting in albumin-mediated plaque clearance in the transgenic rodent model of Alzheimer disease; human trial is also under way to investigate the safety of this approach. Finally, targeted drug delivery can be an attractive option for intravascular thrombolysis (eg, in distal intracranial thrombosis where endovascular therapy has met with challenges).

The nonthermal qualities of FUS are attractive for neuromodulation.[75] Successful cortical stimulation using transcranial FUS has been reported in mice (at 650 kHz),[76] patients with chronic pain (at 8 MHz),[77] and healthy volunteers (at 500 kHz).[27] Recently, Monti et al[78] reported the case of a comatose patient with brain injury who received FUS stimulation to the entire thalamus. The patient showed some clinical improvement without major adverse effects. Finally, subthreshold sonications can be a screening tool for target selection for therapeutic interventions, especially in situations where either conventional screening (eg, levodopa challenge) provides insufficient answers (eg, subthalamic nucleus vs VIM for patients with a dual diagnosis of PD and essential tremor) or the most efficacious target for neuromodulation is unclear (eg, subthalamic nucleus vs globus pallidus internus for patients with PD). For further information on the concepts and studies mentioned in this article, see the eReferences and eFigure in the Supplement.

Conclusions

Transcranial FUS is a promising technology for both ablative and nonablative applications. Its integration with MRI allows brain anatomy monitoring, thermography, and (potentially) physiology during treatment. The noninvasive approach makes FUS suitable for an increasing number of patients who are either unable or unwilling to undergo DBS. Advances in neuroimaging and sonication algorithms may increase the safety, efficacy, and efficiency of FUS. Improvements in transducer technology will allow the interrogation of brain networks that are inaccessible by current technology and the potential treatment of challenging neurological and psychiatric disorders.

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