Incisionless Brain Surgery: Overcoming the Skull with Focused Ultrasound

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A "Focus" on the Brain

The brain is the command center for all our thoughts and actions and can be considered the essence of who we are, housing our personalities and the lifetime of memories that define us. For that reason, brain diseases and disorders are frightening in a way unlike those impacting other parts of the body because we risk losing what makes us, us. What do you do when faced with one of these conditions? When it is necessary to operate, exposing and cutting into the brain, the treatment can seem as daunting as the illness. It is not hard to see why the idea of incisionless brain surgery, where a patient can be surgically treated for a brain disorder, precisely interrupting the problematic brain region with millimeter precision without even piercing the skin, is incredibly appealing. But is this vision for the future just science fiction?

Treating the Brain

Let's take the example of essential tremor, a motion disorder that results in uncontrollable shaking that can make even basic tasks such as putting pen to paper or drinking from a cup impossible. In addition to the practical challenges faced by these patients due to their impaired motor function, the social impact is significant. Embarrassment about the condition, which cannot easily be hidden, can result in social withdrawal. Treatments for severe tremor cases can include invasive approaches such as radiofrequency ablation or deep brain stimulation, both of which involve opening a hole in the skull and penetrating the brain tissue with a probe or electrode. Radiosurgery provides a noninvasive treatment alternative but exposes the brain to damaging ionizing radiation. Certainly, given the very real risk of damage to the healthy brain tissue, none of these interventions seem ideal. Enter focused ultrasound.

Focused Ultrasound

Focused ultrasound (FUS; not to be confused with functional ultrasound [fUS]) is a noninvasive treatment approach that can be directed through the intact skull without the use of harmful radiation. Instead, it uses large aperture ultrasound devices that can focus energy to millimeter-scale focal volumes with high focal gain. This highly focused beam can generate targeted bioeffects deep within the body. Bioeffects is a catch-all term that refers to temporary or permanent changes or responses by biological tissues exposed to ultrasound. At high powers, the ultrasound energy absorbed by the tissue at the focus causes rapid heating, tens of degrees Celsius, in under one minute (Jones et al., 2019). This energy destroys the targeted tissue by effectively cooking it.

It is this thermal destruction (termed "thermal ablation") that is the key to its use in essential tremor. The ultrasound energy is focused through the intact skull bone and then precisely to a specific deep brain target where it thermally destroys a small volume of brain tissue, interrupting the tremor. Outside the focal volume, the ultrasound waves undergo destructive interference, meaning that they cancel each other out due to phase mismatch. This destructive interference means that there is no damage caused to the intervening healthy brain tissue.

A simple internet search for "essential tremor" and "FUS" will return several remarkable videos (see youtu.be/6BR94G5tRLY). We can see patients before and immediately after FUS treatment, and observe a miraculous normalization of motor function on the treated side. Although there are many emerging applications for focused ultrasound in the brain (see **Beyond Thermal Ablation** and **Future Directions**), its use in treating essential tremor

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provides some of the most compelling visual evidence of the power of this technology, and it was the first brain application to receive regulatory approval. First tested in tremor patients in the early 2010s (Elias et al., 2013), by 2016 the device, InSightec's Exablate Neuro, had received approval from both the US Food and Drug Administration and Health Canada for the treatment of essential tremor. Since then, this procedure has also become reimbursable, meaning that the costs are partially or fully covered by government or private health coverage, an even more important milestone for the ultimate longevity of a medical technology.

Many people have never heard of FUS and are surprised to learn that this seemingly futuristic "scalpel-less brain surgery" is an approved procedure. But what might be more surprising to those outside the field of focused ultrasound is that FUS neurosurgery was being tested in patients over 60 years ago. Brothers William and Francis Fry, considered founding fathers of the field of focused ultrasound, had a very active research program and early successes in neurosurgery patients (Fry and Fry, 1960). For more on the history of the Fry brothers, see O'Brien and Dunn (2015) and O'Brien (2018). Despite these successes, and subsequent clinical investigations in brain tumors by others through the early 1990s (Heimburger, 1985; Guthkelch et al., 1991), the technology failed to gain critical momentum, and it all came down to the skull bone.

Overcoming the Skull Problem

Until the 1990s it was considered impossible to focus therapeutic ultrasound exposures through the intact skull, the reason being twofold. First is the distorting effect due to the bone. The skull bone is irregularly shaped with spatially varying thickness, resulting in different path lengths that sound can take when traversing it (**Figure 1**).

Consider that the speed of sound in the skull bone can be double that in soft tissues (Fry and Barger, 1978) and the problem starts to take shape. Further complicating the situation is the fact that the sound speed in bone is density-dependent (Pichardo et al., 2011), and the bone density is spatially heterogeneous. Thus, due to the combination of varying path lengths and sound speeds, the skull bone acts as a complex aberrating lens, shifting and distorting the intended focus (**Figure 2**).

It is true that some regions of the skull bone, such as near the temples, have thinner, more uniform bone, enabling,

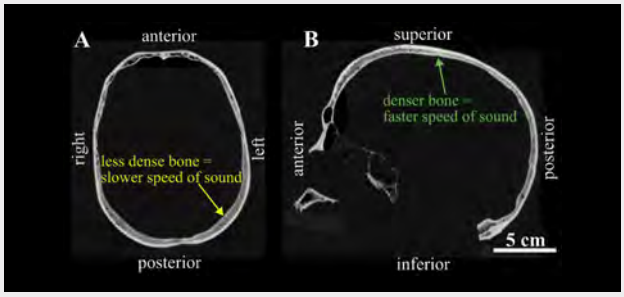

Figure 1. *X-ray computed tomography (CT) cross sections of a human skull illustrating the variability in bone thickness in a transverse view (**A**) and a sagittal view (**B**). The heterogeneity in bone density is observable in the pixel intensity, with brighter voxels reflecting denser bone and a higher speed of sound.*

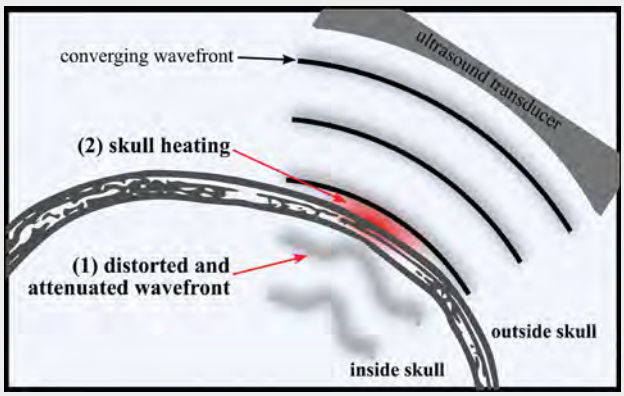

Figure 2. *Illustration of a focused ultrasound wave front passing through a section of skull bone. The spatially varying bone density and thickness result in distortion of the wave front (**1**). The strong absorption and scattering of ultrasound by bone attenuates the transmitted wave (**1**), illustrated here by a shift in the gray scale. The absorption also results in unwanted bone heating (**2**).*

for example, transcranial Doppler ultrasound imaging (Aaslid et al., 1982). Ignoring the limited field of view afforded by these acoustic windows, we are still faced with the second problem. Ultrasound absorption in the skull bone is an order of magnitude higher than in brain tissue (Pinton et al., 2012), meaning that achieving therapeutically relevant temperatures in the brain tissue runs the risk of even higher temperatures in the skull bone.

These two confounding factors, distortion and skull heating, mean that in order for the Fry brothers to conduct their groundbreaking neurosurgical studies using FUS, they needed to open a window in the skull to enable an

unimpeded path for the ultrasound beams. The need to perform an invasive craniotomy prevented FUS from outcompeting other existing and new brain interventions, and so the technology stalled.

Fortunately, this was not the end. Interest in FUS for use in the brain was revitalized through major advances in methods and in magnetic resonance imaging (MRI), which occurred in the 1990s and 2000s. Specifically, the success of FUS for treating essential tremor was realized through three specific advances: the development of large-aperture phased-array transducer technology, the associated methods for correcting the beam distortions, and MRI thermometry.

Large-Aperture Phased Arrays

Hynynen and Jolesz (1998) published a landmark study demonstrating that, contrary to existing dogma, it was indeed possible to achieve a focus through the human skull bone. It turns out that below 1 MHz, as the wavelength starts to become larger relative to the variations in bone thickness and the internal microstructure, the distortions and absorption are reduced and make generating a focus, albeit still somewhat distorted or shifted, possible. Breaking the transducer into an array of subelements further improved focusing because the timing of each element can be adjusted to compensate for the variations in skull transit time, enabling the waves from each element to arrive in phase at the intended focus (**Figure 3**).

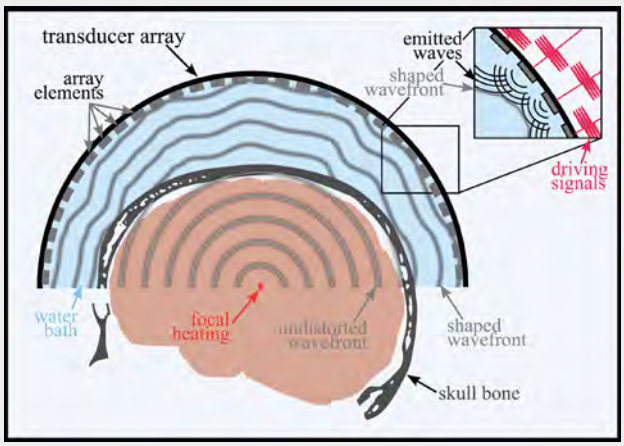

Figure 3. *Illustration of a large-aperture, hemispherical transducer array surrounding a human skull. The device is acoustically coupled to the head with a water bath.* ***Inset:*** *elements populating the surface. The timing of the electrical signals (**red waveforms**) can be adjusted to individually control the firing time of each element. For illustrative purposes, this is shown as short bursts. In practice, continuous sinusoidal waves are used for thermal ablation and the applied delays are subwavelength, adjusting the relative phase of the waves emitted by each element. The applied delays result in a shaped wave front that counteracts the skull distortions, resulting in an undistorted wave front after transmission through the bone. The large aperture also spreads the energy out over the entire skull surface, minimizing bone heating while achieving therapeutic levels of heating at the focus.*

Finally, by using a large aperture, the skull heating problem can be mostly overcome (Sun and Hynynen, 1998; Connor and Hynynen, 2004). The anatomy of the skull is conducive to the use of large hemispherical transducers (which resemble a bowl or a hairdressing helmet) that spread the ultrasound energy out over the entire skull surface (Clement et al., 2000). This reduces the absorption and associated heating experienced by a given location. Furthermore, high focal gains are achieved due to the waves emanating from a large-source surface area and all converging at the target.

Aberration Correction

With the advent of these new phased arrays, it was also critical to develop methods to non-invasively predict the time for sound to transit through different points of the skull bone. Only in doing so could the necessary delays be applied to each array element to counteract the distorting effect of the skull bone. The first model derived skull geometry from a MRI (Sun and Hynynen, 1998), but models based on X-ray computed tomography (CT) data soon followed, allowing both geometry and bone density (hence, speed of sound) information to be incorporated into the models (Clement and Hynynen, 2002; Aubry et al., 2003).

Since then, many different computational models have been proposed that aim to improve accuracy, computational efficiency, or both. A recent benchmarking study of 11 transcranial acoustic propagation models found that, at least with respect to modeling the compressional wave component of transcranial sound propagation, there was reasonably good agreement, with the median values for focal pressure varying by less than 10% across all models and the focal position varying by less than 1 mm (Aubry et al., 2022).

In short, despite varied approaches for modeling the transskull propagation, existing models perform similarly for

near-normal incidence where the main propagation mode is compressional. A caveat with this simulation-only study, however, is that it considered the skull bone to be homogenous. Yet, it has been shown separately that despite different equations determining sound speed from the bone density, the different published sound speed-bone density relationships all perform reasonably well (Bancel et al., 2021). With even the earliest computational models for calculating aberration corrections, positional errors less than 1 mm were achievable when measuring sound fields through bone samples (Clement and Hynynen, 2002), and similar results have been reported from clinical data (Moser et al., 2012).

But are these models accurate enough in practice to blindly apply them? Although the models have good positional accuracy, the restored focal pressure is more variable (Bancel et al., 2021), making it harder to predict tissue heating. Furthermore, the resulting heating depends on the local ultrasound absorption, and so heterogeneity in brain tissue can, in theory, results in the maximum pressure field not necessarily aligning perfectly with the location of maximum heating. Consequently, it is necessary to monitor the heating during the treatment, which is realized using MRI thermometry.

Magnetic Resonance Imaging Guidance

FUS was first combined with MRI guidance to enable targeting and also spatial temperature mapping in the early 1990s (Cline et al., 1992; Hynynen et al., 1996). The temperature dependence of MRI parameters enables the use of MRI to image temperature changes in the body (Ishihara et al., 1995).

MRI thermometry is sensitive enough to detect small temperature elevations during FUS exposures. This allows the location of the treatment focus to be verified using a relatively low-power exposure that does not produce permanent changes in the brain. This is done prior to the therapeutic high-power exposure to ablate the tissue.

Temperature mapping also allows the temperature rise and thermal dose (a metric of the time spent at elevated temperature) to be quantified at the treatment target to ensure sufficient heat deposition. MRI thermometry can also assess unwanted heating outside the intended target. In practice, however, only a limited number of imaging planes are captured, providing an incomplete picture of heating outside the treatment volume.

Successes and Shortcomings

Together, these technologies have enabled the success of thermal FUS in the treatment of essential tremor. Moreover, FUS thermal ablation is being used and studied clinically in other functional neurosurgery applications, including Parkinson's disease (Martínez-Fernández et al., 2018), chronic pain (Martin et al., 2009), obsessive-compulsive disorder (Jung et al., 2015), and major depressive disorder (Davidson et al., 2020). It would be safe to estimate that, worldwide, patients who have received this intervention number in the thousands (at my home institution alone, colleagues have treated over 300 tremor cases).

Indeed, by all measures, the technology appears to be a success and adoption is expected to continue to grow. But the success of FUS thermal ablation in these indications (deep brain ablation) is also because what is needed for the intervention conveniently aligns with the capabilities of FUS. That is to say, thermal ablation via FUS is ideal for generating lesions with sharp margins and in centrally located brain regions.

At the same time, once the focus moves too close to the skull, bone heating once again becomes a problem, despite the use of large apertures. Furthermore, despite early interest in using thermal ablation for treating brain tumors (McDannold et al., 2010), malignant brain tumors present the same challenges with FUS as with conventional surgery. Even after complete resection, some tumor cells remain and the tumor recurs. Add to these challenges the fact that there are many brain disorders that are diffuse and where tissue destruction would have no therapeutic role.

It is clear that high-intensity FUS thermal ablation has found an ideal niche in deep brain functional neurosurgery. However, what is also apparent is that an arsenal of other tools is needed to fully extend FUS to a broader set of brain conditions.

Beyond Thermal Ablation

Transcranial FUS is being studied preclinically and clinically for many applications, some of which have been previously described in *Acoustics Today* (Pajek and Hynynen, 2012). One application that has reached the stage of clinical investigations is the use of ultrasound for targeted drug delivery.

Targeted Drug Delivery

One of the greatest obstacles to the successful treatment of many brain conditions is the presence of the so-called "blood-brain barrier" (BBB). The BBB describes several features of brain endothelial cells (the cells that make up the walls of blood vessels) and their surroundings, which result in restricted transport of molecules from the bloodstream to the brain tissue. The purpose of the BBB is to preserve the privileged environment of the brain, warding off would-be invaders such as bacteria or viruses and ensuring a balanced chemical environment for brain cells. But a consequence of this robust natural defense system is that it also prevents most existing therapeutic drugs from getting into the brain in sufficient quantities to be useful (Pardridge, 2005).

Hynynen et al. (2001) demonstrated that FUS, in combination with diagnostic ultrasound contrast agents termed "microbubbles" (micrometer-size gas bubbles with a lipid or albumin shell to stabilize them and prevent rapid dissolution) could transiently and reversibly increase the permeability of the BBB to enable targeted drug delivery. Like the story of thermal ablation, investigations into the influence of ultrasound on the BBB actually predate this landmark study by over 40 years (Bakay et al., 1956).

However, what was critical about the 2001 study was that by employing pre-formed bubbles that could be administered intravenously and stimulated in combination with ultrasound, a reversible opening of the barrier was possible (**Figure 4**). Since then, several hundred studies have investigated and further developed this technique, and clinical investigations began in the mid-2010s.

An earlier *Acoustics Today* article (Konofagou, 2017) reported in greater detail on this approach for mediating drug delivery in the brain. A complete description is out of the scope of this article, but what is important to understand is that the mechanism by which the barrier is permeabilized is the oscillation of the bubbles in response to the ultrasound field. The vibrating bubbles stimulate the blood vessel walls through several mechanisms. This causes a transient increase in permeability as well as a suppression of the efflux mechanisms by which the barrier works to pump out unwanted molecules that do manage to find their way into the brain.

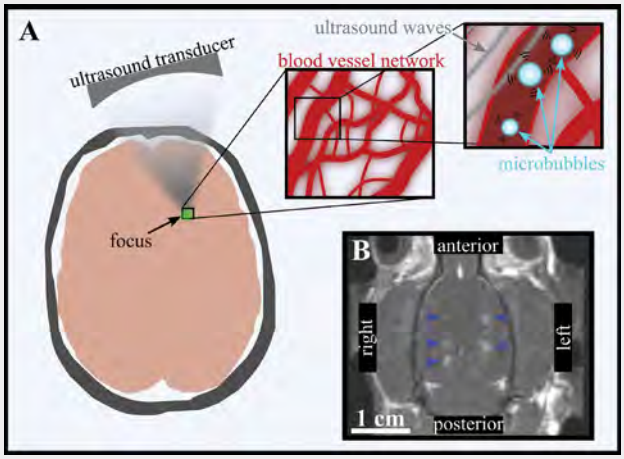

Figure 4. ***A:*** *conceptual image of ultrasound and microbubble-mediated blood-brain barrier (BBB) opening. Ultrasound is targeted to the brain (for simplicity, illustrated here using a small-aperture device). The callouts show the microvascular network. Microbubbles are injected intravenously and circulate through the vasculature. Where they interact with the ultrasound field, they oscillate, stimulating the blood vessel walls, resulting in a temporary increase in permeability of the vessels.* ***B:*** *example of a magnetic resonance imaging (MRI) image of a BBB opening in a rat brain. The bright spots within the brain (**blue arrowheads**) are discrete targets exposed to ultrasound. These are rendered visible by the local accumulation of a MRI contrast agent. The transient increase in vascular permeability caused by the ultrasound and bubbles allows the contrast agent, normally confined to the blood vessels, to reach the brain tissue.*

Technical Considerations

The power levels needed to achieve a BBB opening are several orders of magnitude lower than what is used thermally and produce no significant thermal rise (Hynynen et al., 2001). That is, it is a purely mechanical effect that, in some ways, allows more flexibility with respect to the systems for delivering this therapy.

Because the time-averaged power of FUS BBB opening exposures is so low, these treatments avoid heating the skull bone, affording a much larger treatment envelope than for thermal ablation. This also enables use of simpler devices with smaller apertures, although still substantially larger than diagnostic ultrasound probes. Furthermore, if the number of treatment targets within the brain is relatively limited, transcranial treatment

devices can be further simplified using three-dimensional (3D)-printed acoustic lenses to correct the skull distortions (Maimbourg et al., 2018). These lenses can be combined with single-element transducers, making them much more affordable and less complex than larger multielement devices.

MRI-guided interventions for FUS BBB openings are performed clinically with a system similar to that used for the thermal ablation studies (Lipsman et al., 2018). The BBB system operates at a lower frequency than the thermal ablation system (roughly 200-250 kHz vs. 600-700 kHz, depending on the specific system). The use of this lower operating frequency has several effects, including reducing the field distortion due to the skull and improving trans-skull transmission. Furthermore, the lower frequency slightly loosens the focal spot to enable opening over a larger volume for each focal location. Multielement phased arrays can be electronically steered, adjusting the firing timing of the different elements to move the focus around the brain, interleaving many spots to greatly increase the area of opening as desired.

Treatment Monitoring

However, because this is a nonthermal procedure, MRI thermometry is no longer particularly useful for treatment monitoring. Instead, it is necessary to rely on the unique signatures of the oscillating microbubbles, which reemit not just the driving frequency of the ultrasound but also the harmonics and noninteger multiples of the driving frequency (sub- and ultraharmonics) (Neppiras, 1980). Furthermore, when these bubbles are driven to the point where they overexpand and violently collapse, they emit broadband noise, a signature of so-called "inertial cavitation" (the collapse of the bubble due to the dominant inertial forces of the surrounding medium).

By recording the scattered emissions from these bubbles and examining the spectral characteristics of their vibrations, it is possible to gain insight into the regimen of bubble behavior. It has been known for some time that changes in the spectral content of bubble emissions are correlated with the opening of the BBB (McDannold et al., 2006). Furthermore, it is possible to use bubble signals as feedback mechanisms to actively modulate the ultrasound pressure to ensure that the treatments remain in a safe, effective regimen (O'Reilly and Hynynen, 2012).

Although MRI can still play a role in assessing the extent of barrier opening by visualizing the uptake of MRI contrast agents into the targeted region, the field is moving toward decoupling this technology from the treatments themselves. MRI is an expensive technology, and so by removing the need to occupy a MRI suite for the duration of the treatments, it is possible to reduce the cost to ultimately make this procedure more widely available. Therefore, in addition to studies using MRI-guided devices, neuronavigation-guided FUS is now being investigated clinically (Chen et al., 2021).

It is also worth mentioning that an implantable ultrasound device for a BBB opening exists that completely circumvents the skull bone by being surgically implanted at the time of conventional surgery to excise the tumor (Carpentier et al., 2016). However, due to the nature of it being implantable, the position of the device cannot be adjusted once it has been placed and it is suitable only for patients already undergoing surgical resection of a tumor. Thus, it lacks the flexibility afforded by transcranial devices.

A transcranial FUS BBB opening is being tested clinically for many different indications, including primary (Mainprize et al., 2019) and metastatic (Meng et al., 2021b) tumors situated in the brain, Parkinson's disease (Gasca-Salas et al., 2021), Alzheimer's disease (Lipsman et al., 2018), and amyotrophic lateral sclerosis (ALS) (Abrahao et al., 2019). These studies are expected to yield valuable clinical insight and hopefully pave the way for regulatory approvals for these treatments.

Future Directions

It is an exciting time for FUS use in the brain. The clinical successes of this technology in functional neurosurgery and the translation of FUS BBB opening to clinical studies have been enabled by robust transcranial devices and methods for focusing through the skull bone. Beyond these treatments, new therapeutic ultrasound approaches for the brain are being studied, including the use of ultrasound to very precisely mechanically destroy tissue (Sukovich et al., 2018), to stimulate or modulate brain circuits (so-called "neuromodulation") (Legon et al., 2014), and to enable noninvasive biopsy by releasing tissue biomarkers into the bloodstream to be sampled by a simple blood draw (Zhu et al., 2018; Meng et al., 2021a).

No doubt the coming decade will see more "first-in-human" testing of these technologies and exciting new discoveries. With each new application of transcranial ultrasound, there is likely to be the need to refine the delivery approach. For example, our current models perform sufficiently well for MRI-guided thermal ablation and for BBB opening. However, both procedures have imaging readouts that can enable confirmation of targeting and that sufficient energy was applied. For neuromodulation, which lacks an imaging readout, these models may not yet be sufficiently accurate. Broadly, there is also a need to continue to innovate new approaches that can reduce the costs associated with this technology and therefore improve access. Certainly, given the strength and number of researchers working in this area, the field will rise to meet these challenges.

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