APPLICATIONS OF TRANSCRANIAL FOCUSED ULTRASOUND SURGERY

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Introduction to transcranial focused ultrasound

Focused ultrasound is capable of delivering energy into tissue, non-invasively and without the use of ionizing radiation.[1] The ability of focused ultrasound to generate heat in tissue was demonstrated in the brain decades ago, with the creation of lesions in the mammalian central nervous system.[2] A spherically focused ultrasonic transducer causes emitted ultrasound waves to superimpose constructively at a focus, leading to very high energy deposition within a small volume, of a size proportional to the wavelength. Focused ultrasound is an emerging non-invasive alternative to surgery and an alternative to radiation therapy. This has led to the use of ultrasound in non-invasive hyperthermia and ablative applications, such as the treatment of uterine fibroids.[3]

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Hurdles preventing the use of focused ultrasound in the skull

For many years, the brain remained an elusive target and it was believed that ultrasonic brain therapy could only be accomplished through a cranial window.[1] The increased speed of sound in the skull results in severe distortion of the ultrasonic focus, the large impedance mismatch between water and bone results in much of the acoustic energy being reflected away from the skull, and the high attenuation of ultrasound in bone greatly reduces the intensity of the acoustic wave after it passes through the skull.[4,5] Furthermore, with standard transducers, the high absorption of ultrasound in bone meant that undesired heating of the skull could occur before sufficient heating of the underlying tissue would be achieved.[6] These issues were not reasonably addressed until the 1990s, with the development of large aperture phased arrays,[7,8] illustrated in Fig. 1. This enabled the incident ultrasonic energy to be spread over a large surface area producing large gains, which were sufficient for safe heating. The use of a multi-element phased array allows one to electronically correct for the skull's distortion to restore a strong focus within the brain (Fig. 2).

Development of computer tomography (CT) -based correction

Phased arrays are composed of many small transducer elements, each connected to independent driving amplifiers, which can emit ultrasound waves with independently set phases and amplitudes. Phased arrays can be used to electronically steer an ultrasound focus within a volume by applying appropriate delays to the RF-signals driving the transducer elements. With *a priori* knowledge of the transmission delay faced along each beam path, phases of the RF-signals driving each of the transducer elements can be set to ensure that emitted waves all arrive coherently at the focus. There are a number of techniques for measuring the phase corrections or time delays required for transcranial focusing. These include placing a hydrophone at the intended focus and emitting from each element independently[4] or placing an acoustic point source at the focus and measuring the received signal at each array element.[9] Although potentially less invasive than a full craniotomy, these techniques still require some form of surgery to achieve the measurements required for transcranial focusing.

It was not until the development of CT-based correction techniques that completely non-invasive transcranial focused ultrasound became possible. CT-based phase correction models rely on spatially varying skull thickness and density information derived from CT images, which can be used to estimate both the speed of sound and attenuation along each beam path.[10,11] Similarly, inverse calculations using time-reversal methods have been proposed for precise through-skull focusing.[10] Transcranial therapy has been further refined through the use of amplitude correction, which can be optimized to either maintain a spatially uniform focus or minimize localized hotspots on the skull.[12]

Treatment monitoring

Although CT imaging enables non-invasive focusing in theory, in practice, difficulties related to image registration have lead to targeting inaccuracies, making open-loop treatments risky. It was not until the adoption of magnetic resonance (MR) imaging and thermometry for the guidance of focused ultrasound that transcranial focused ultrasound surgery became a clinical reality. With the addition of image guidance and feedback, focused ultrasound grew into a safe and potentially viable treatment alternative.[13] These systems relied first on MR imaging to register previously acquired CT data to patient position and determine the proper phase correction values required for transcranial focusing. Second,

they utilized real-time MR thermometry to confirm focal size and location during treatment, as well as monitor temperature increases.

As well as being able to generate heat, ultrasound is capable of inducing mechanical bioeffects within tissue. Ultrasonic cavitation refers to either stable cavitation, which is the periodic oscillation of a microbubble under an oscillating pressure field, or inertial cavitation, which is the formation and violent collapse of a cavity under very high acoustic pressures. Inertial cavitation is capable of causing tissue vaporization.[14] Stable cavitation is associated with sub-harmonic and ultra-harmonic acoustic emissions and inertia cavitation is associated with the emission of acoustic broadband noise. Passive cavitation detection has been adopted to measure the spectrum and intensity of an acoustic signal to assess whether any desirable or undesirable cavitation events are occurring.[15,16]

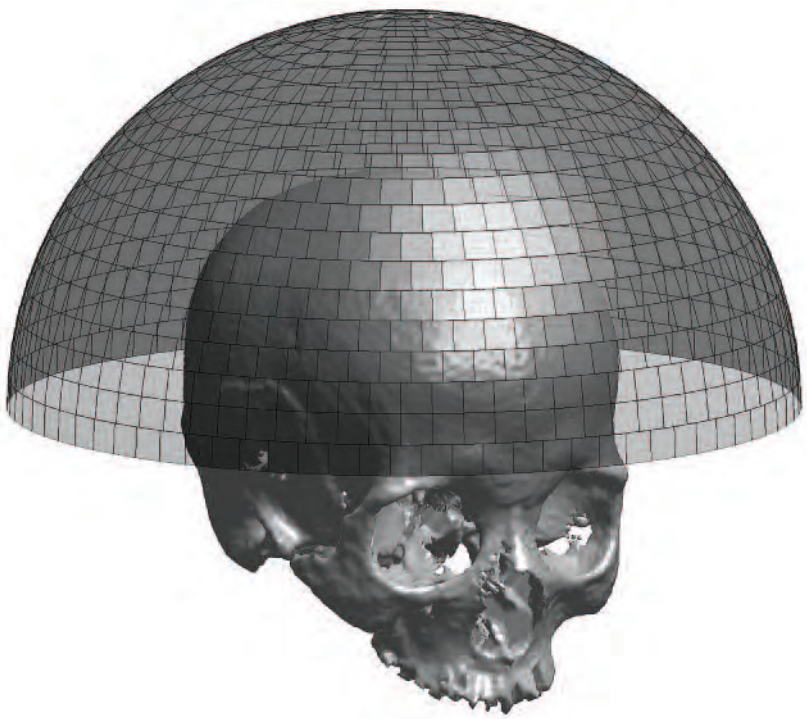

Fig. 1. Rendering of hemispherical phased array and skull, illustrating their relative locations during sonication. Virtual array shown contains approximately 1,000 elements.

Development of transcranial arrays

Modern transcranial transducer arrays take the form of a large hemisphere composed of a large number of high power transducer elements. Choice of frequency is an important consideration when designing a transcranial phased array. Ultrasound at lower frequencies suffers less attenuation and distortion through the skull.[4] Higher frequencies result in tighter focusing, higher pressure amplitudes, but also greater attenuation and focal distortion. Furthermore, element sizes required for steering are proportional to the wavelength, meaning that higher frequencies require a larger number of smaller elements to populate an entire array, to achieve adequate focusing and avoid grating lobes. It has been determined that optimal transcranial focusing for thermal treatments occurs at 600-700 kHz.[6,17] However, lower frequency phased arrays could be used to perform transcranial treatments without the need for phase correction.[18]

The first MR-guided clinical transcranial hemispherical phased array system was the Exablate 3000 developed by Insightec (Haifa, Israel). It had a diameter of 30 cm and consisted of 512 elements operating at 670 kHz that were coupled to a 512-channel driving system capable of producing 800 W of acoustic power.[19] The system also implemented treatment planning, MR feedback control, and a water cooling system to reduce skull heating. The resulting half power focus size was 2 mm by 4 mm.

Dividing the hemispherical array into a larger number of smaller transducer elements increases the ability of the phased array to steer and to correct for skull distortion.[6] However, increasing the number of elements greatly increases the technical complexity, as it not only requires additional transducer elements, but also independent driving amplifiers and matching circuitry. The use of lateral mode transducer ele-

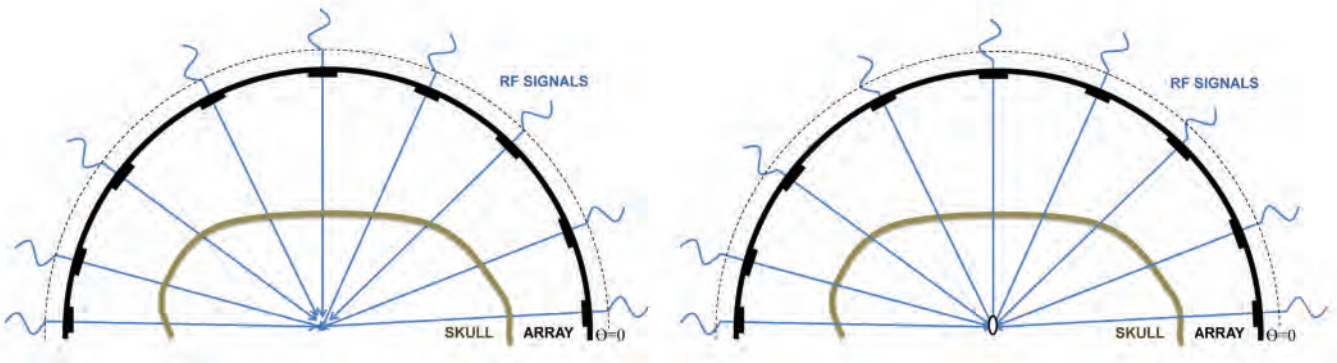

Fig. 2. Phased arrays utilize phase correction to focus through a skull. The image on the left demonstrates how phase aberration caused by the skull causes the transmitted waves to not arrive coherently at the target and results in focal distortion. For the image on the right, phase delays are applied to regain a strong focus at the target.

ments has potential in simplifying array design, as the elements have reduced electrical impedance, which enables the construction of phased arrays without matching circuits. A prototype hemispherical array was constructed in this fashion, consisting of 1372 hollowed out cylindrical elements that are capable of operating at 306 kHz or 840 kHz.[20]

The current clinical prototypes (Exablate 4000; Insightec, Haifa, Israel) operate at nominal frequencies of 230 kHz and 650 kHz. The higher frequency system has been used to treat patients with giloblastomas,[19] chronic neuropathic pain,[21] and essential tremor[22-24] currently at the clinical trial stage.

Applications under clinical investigation—thermal tumor therapy

The first procedures undertaken using a clinical prototype have been for the treatment of glioblastoma patients.[19] These procedures incorporated patient-specific treatment planning and MR thermometry feedback control, and so demonstrated the clinical feasibility of MR-guided transcranial focused ultrasound surgery. Each patient received multiple sonications, with focal heating viewable through real-time MR images. Limited by device power available at the time, thermal coagulation was not definitely demonstrated. However, extrapolation of the temperature measurements suggested that thermal ablation would be possible with this device, demonstrating a potential alternative to surgical resection.

Applications under clinical investigation—chronic neuropathic pain

The use of high intensity focused ultrasound (HIFU) for non-invasive neurosurgical procedures has shown great initial promise, with the chronic neuropathic pain being the first treated pathology.[21] Focused ultrasound was used to perform noninvasive central lateral thalamotomies in 12 patients.[25] The ablations were 3-4 mm in diameter and achieved peak temperatures of 51–64°C. Treatments could be visualized and guided in real-time through MR thermometry and the lesions were clearly visible on follow-up imaging. At 3 months, patients had a mean pain relief of 49% and 6 patients experienced immediate and persisting improvements. Within this initial trial, there was one complication, a bleed at the target and ischemia in thalamus. This lead to the establishment of two safety parameters: the implementation of passive cavitation detection and ensuring the peak temperature remained below 60°C. For the remaining patients, the treatments have been well tolerated, producing no side effects or neurological deficits.

Applications under clinical investigation—essential tremor

Treatment of essential tremor, a common movement disorder in adults, with focused ultrasound involves the ablation of the ventralis intermedius of the thalamus and represents a non-invasive alternative to deep brain stimulation.[22] Treatment outcomes can be quite dramatic, giving patients the use of a once uncontrollably shaking hand, after a single same-day procedure.[23] There are currently ongoing clinical trials at the University of Virginia in the US, Sunnybrook Health Sciences Centre in Canada, the Center of Ultrasound Functional Neurosurgery in Switzerland, and at Yonsei University Medical Centre in Korea to investigate the full potential of this treatment.

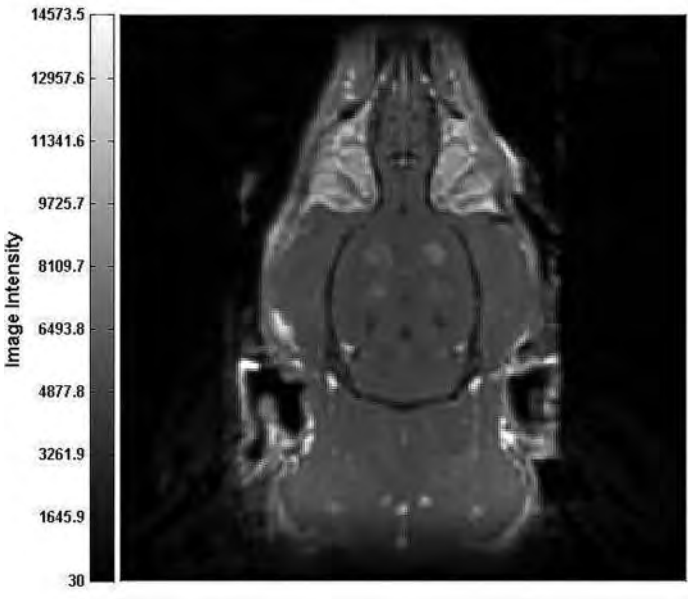

Fig. 3. Visible enhancement regions in the above magnetic resonance (MR) image indicate blood brain disruption of the rat brain induced by focused ultrasound. (Image courtesy of Meaghan O'Reilly)

Future applications of focused ultrasound—blood brain barrier disruption

The ability to disrupt the blood brain barrier (BBB) allows therapeutic agents that would normally be too large for delivery to the brain to be delivered using a method that is localized and non-invasive. It has been demonstrated that, in conjunction with injected microbubbles, ultrasound is capable of disrupting the BBB.[26] With microbubbles, the energy required to cause disruption is roughly two orders of magnitude smaller than with ultrasound alone allowing the blood brain barrier to be disrupted without causing harm to the surrounding tissue. Following sonication, it has been shown that the barrier is naturally restored 24 hours following treatment. BBB disruption within a rat brain is shown in Fig. 3. Preclinically, Herceptin,[27] D4-receptor antibodies,[28] doxorubicin,[29] and methotrexate[30] for cancer treatment; anti-amyloid-beta antibodies for Alzheimer's;[31] and stem cells for neuronal regeneration[32] have been delivered through the BBB using focused ultrasound. Figure 4 demonstrates delivery of neural stem cells through the BBB have ultrasound-induced disruption. With the goal of eventual clinical use, transcranial BBB disruption studies have recently been completed on non-human primates, using a single element transducer at 500 kHz[33] and the Exablate 4000 clinical prototype at 230 kHz.[34] Cognitive testing did not show any negative effects following treatment. Furthermore, with a goal of optimizing safe disruption, control algorithms have been developed that utilize passively received acoustic signals to adjust sonication power levels.[35] BBB disruption is an exciting area of active

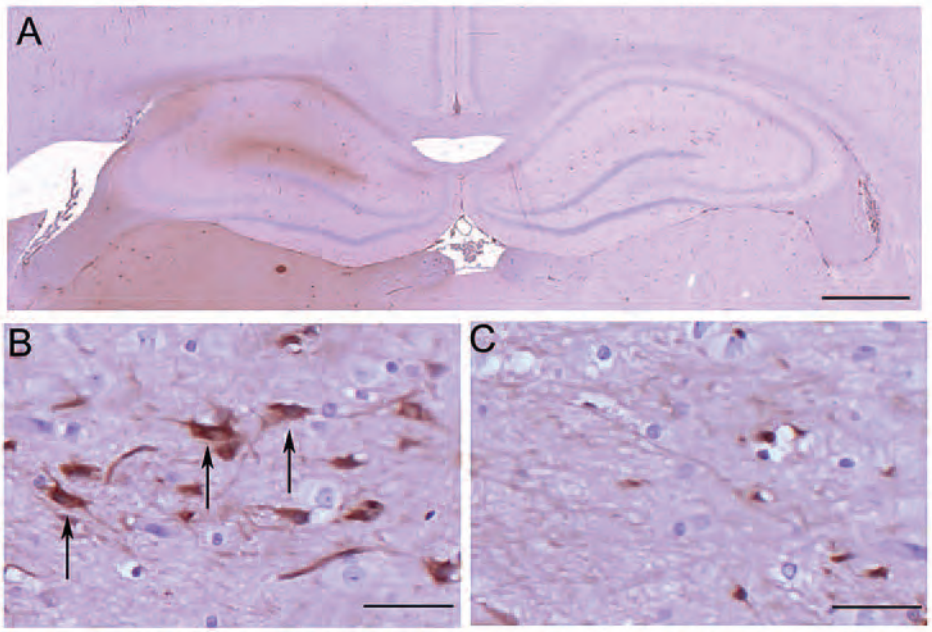

Fig. 4. Neural stem cells, tagged with green fluorescent protein (GFP), were delivered to the left hippocampus of the rat using focused ultrasound. A) Post-mortem GFP-immunohistochemistry confirms that stem cells are only present in the left (targeted) hemisphere. B) At 40x, the GFP-positive cells clearly exhibit a neuronal phenotype (arrows). C) No cells were detected in the non-sonicated hemisphere. Scale bars: A=500 μm, B,C=50 μm[32]

research with many possible applications and the potential to have a significant clinical impact.

Future applications of focused ultrasound—sonothrombolysis

Sonothrombolysis generally refers to the breaking apart of a blood clot using ultrasound. The use of transcranial low intensity ultrasound to enhance the efficacy of thrombolytic drugs in the treatment of ischemic stroke is being explored through clinical trials, both with[36] and without microbubbles. Results have demonstrated enhanced recanalization, but have also been met with increased risks of hemorrhaging.[37,38] Sonothrombolysis has been demonstrated using microbubbles in the absence of thrombolytics, as well.[39]

HIFU is capable of mechanically breaking apart a blood clot in less than 30 seconds without the use of thrombolytics or microbubbles.[40,41] These procedures require very high pressure amplitudes, as they only occur after inertial cavitation has occurred. Preclinically, HIFU sonothrombolysis has been demonstrated in animal femoral models using an acoustic power of 300 W[42,43] and in an embolic middle cerebral artery (MCA) model using an acoustic power of 450 W.[44] In Fig. 5, fluoroscopy images of a rabbit model pre-stroke, post-stroke, and post-treatment demonstrate blocking and recanalization of the MCA. HIFU thrombolysis has the potential to enable faster recanalization and it may provide a treatment option for patients contraindicated to thrombolytics—approximately 97%.[45] Due to the high pressures and relatively high frequencies required for safe sonothrombolysis, studies conducted thus far have required a surgical craniotomy, however numerical simulations have shown that the application of this technique transcranially is feasible,[46] though it may require the development of new multi-element phased arrays consisting of an order of magnitude more elements and the corresponding high power multi-element driving technology.

Summary

Transcranial focused ultrasound is an emerging non-invasive treatment modality with many potential applications. Ultrasound is unique in that it has the capability to initiate either

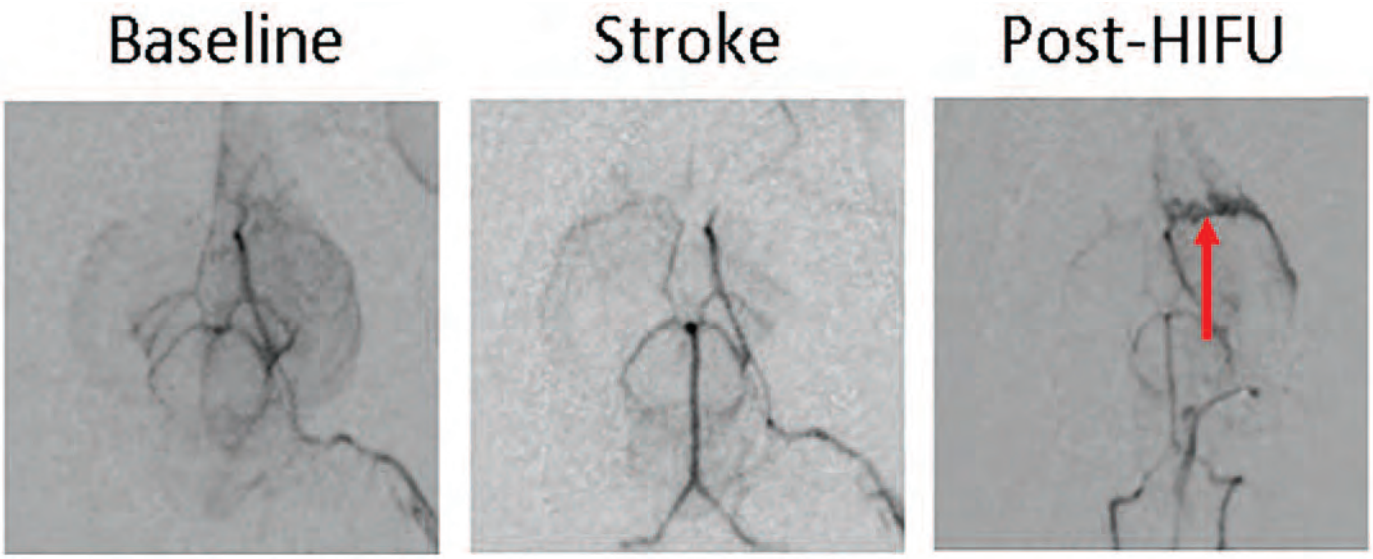

Fig. 5. Two-dimensional projection images of the rabbit cerebral vasculature are displayed. Normal perfusion of the middle cerebral artery (MCA) is observed in the baseline images. The blockage of the MCA is confirmed following injection of an embolism through a 20g catheter in the internal carotid artery. Following high intensity focused ultrasound (HIFU) treatment, restoration of flow in the MCA is demonstrated (red arrow).[44]

mechanical or thermal bioeffects. The addition of MR guidance and feedback control, in particular, have resulted in a complete system that is capable of depositing energy into the skull in a manner that is both non-ionizing and non-invasive. The developments over the last decade have culminated in clinical trials for chronic neuropathic pain, essential tremor, and the treatment of brain metastasis. For neurosurgical procedures in particular, focused ultrasound enables a same-day alternative to surgery, making potential risky procedures now viable. Furthermore, the use of ultrasound in conjunction with therapeutic agents could potentially allow safe, localised, targeted delivery to the brain. Finally, with the development of more advanced correction algorithms, phased arrays, and multi-channel driving systems, devices will gain an increased ability to precisely target locations within larger steerable volumes and with more power. Continued development will continue to unveil new applications and enable new therapies for the treatment of brain metastasis and central nervous system (CNS) diseases.AT

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