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Clinical applications of focused ultrasound—The brain

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Abstract
This paper provides a historic and contemporary overview of the use of focused ultrasound for treating brain disorders.

Keywords: *Transskull ultrasound, transcranial ultrasound, ultrasound therapy, HIFU, FUS, brain*

Introduction

Since the inception of ultrasound as a therapeutic tool, its potential to treat disorders throughout the brain has been explored. The objective has been to utilize ultrasound's focusing ability to target precisely within deep tissues, affecting only the interested volume while leaving all other structures unaltered. Unfortunately, ultrasound's use in the brain has been inhibited by the skull bone, as well as the inability to target and monitor treatments.

In fact, for more than 50 years it was believed that the attenuation and distortion caused by the skull was so severe that it created an impenetrable barrier, making transskull therapies impossible [1]. Contemporary work, however, has shown that focusing through the intact skull is possible. Furthermore, technological advancements have made it practical, owing to the development of high-powered transducer arrays and high-performance computers to calculate the corrections necessary to restore a focus in the brain.

Similarly, the ability to target and monitor the deposition of ultrasound energy in the brain has improved dramatically over the past half-century. Radiological developments including X-ray computed tomography (CT) followed by magnetic resonance imaging (MRI) made millimeter precision registration with brain structures possible.

This progression of improvements has led to the present state of research, where non-invasive transskull focusing for the purposes of thermal ablation has reached the early stages of clinical testing. Meanwhile, advances continue in the laboratory toward expanding both the number of treatable disorders and the mechanisms of treatment.

The purpose of this paper is to review the clinical studies that used focused ultrasound beams for brain treatments and introduce the basic concepts for the future clinical use of high intensity focused ultrasound in the brain.

Early research

Early brain studies date back to the works of Lynn et al. [1, 2] in the 1940s which targeted areas in the brains of cats, dogs and monkeys. Although they concluded that, given their configuration, it was not possible to produce permanent changes in the brain without undesired damage, they speculated that modifications such as removal of the skull bone and use of multiple focused beams could make such treatment possible. Ensuing investigations,

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performed after craniotomy, indicated the ability to produce discrete deep lesions in the brain [3–8] as well as an ability to open the blood–brain barrier [9] in a targeted region.

Inspired by the successful clinical trials by the Fry brothers, several investigators conducted animal research to establish the biological effects of ultrasound in the brain tissue. Most notably, Lele conducted a large number of experiments, many with implanted micro-thermocouples. Lele's work established that the ultrasound-induced tissue damage was caused by temperature elevation in the focus [10, 11]. He continued these animal studies related to ultrasound surgery of the brain for more than a decade, with only a few publications but a wealth of information hidden in student dissertations and summarized in conference papers. His experimental results established temperature-exposure time curves for brain tissue damage [12, 13]. He also established the threshold (at one frequency) for inertial cavitation in brain tissue [14] and observed that inertial cavitation was associated with sudden increase in the tissue temperature [15].

Later with some overlap with Lele's studies, Natalia Vykhodtseva in the Soviet Union investigated the parameters for damage in the brain [16], including the cavitation threshold, pulse shape and pulse duration.

Clinical treatments through a bone window

The early findings led the way to a 5-year clinical study beginning in 1957 at City Hospital in Iowa City, Iowa, led by brothers William J. and Francis J. Fry of the University of Illinois and Russell Meyers of the Department of Neurosurgery at the University of Iowa. The patients were treated for Parkinson's disease through a surgery that included opening the scalp, removing a section of skull bone, and delivering the ultrasound through the intact dura [17]. The sonications were performed with a transducer head that had multiple focused beams overlapping at their focal spots. The beams were aimed with the aid of a stereotactic frame based on X-ray images of bony landmarks. The work by the Illinois group provided substantial information on the ability to treat within the brain, while also establishing quantitative thresholds for inducing permanent changes in brain tissues [18, 19]. The Fry method was also tested in the treatment of malignant brain tumors by Heimburger [20]. These treatments were performed through the skin, which was placed over the ultrasound window created by surgically removing a piece of the skull bone. This series had a small number of patients and the results were inconclusive. A more advanced CT-guided system was developed later but was not clinically tested [21].

Further insight into the focusing abilities, targeting and thermal absorption in the brain became available from focused ultrasound hyperthermia treatments performed starting in 1986 [22, 23]. These treatments were performed through the skin after the removal of a portion of the skull bone; the skull being viewed as a barrier to therapeutic applications in the brain since the work of Lynn (Figure 1).

Similar through-the-skin and craniotomy sonications of brain were tested with a MRI-guided focused ultrasound system in Rhesus monkeys [24] (Figure 2). Locations up to 4.8 cm deep were targeted. Focal heating was observed in all cases with MRI-derived temperature imaging. Subthreshold heating was observed at the focus when the ultrasound beam was targeted with low power sonications, and in the ultrasound beam path during high-power exposures. Lethal temperature values and histologically confirmed tissue damage were confined to the focal zone (e.g. not in the ultrasound beam path), except when the focus was close to the bone. In that case, damage to the neighboring brain tissue was observed. Focal lesions were observed on histological examination and, in some cases, in MR images acquired immediately after the ultrasound exposures.

This method of using MRI-guided focused ultrasound (Exablate 2000, InSightec, Haifa, Israel) after craniotomy was later used in the treatment of malignant brain tumors in three patients in Israel [25]. The results demonstrated some tumor response and the ability of MRI to guide and monitor the ablation. It was also shown that brain damage outside of the focal zone can happen if the transducer and sonication parameters are not carefully designed for the treatments. Similar treatment of one patient with malignant brain tumor was also performed using an ultrasound imaging guided focused ultrasound system (Mode-JC HIFU System, Chongquing Hifu, China) in Korea. The follow-up imaging showed some evidence of tumor coagulation [26]. Despite the clinical feasibility of performing ultrasound surgery through a craniotomy, the method has not gained clinical acceptance. This is most likely due to the need of two expensive surgeries to remove and restore the skull bone.

Development of transskull ultrasound surgery

In the mid-1970s, however, work by Fry et al. [27–29] began to investigate the possibility of focusing through the skull with reduced distortion at frequencies less than 1 MHz. They [28] showed

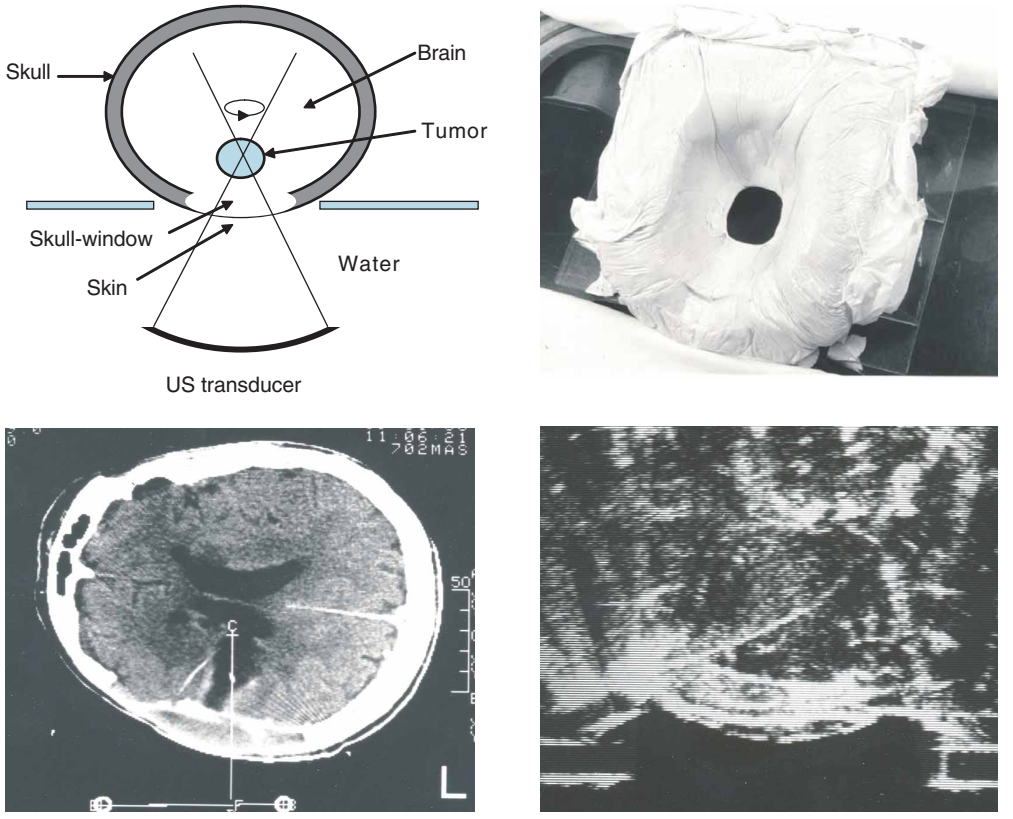

Figure 1. Ultrasound guided focused ultrasound treatment of brain tumors as described in [22]. Top, Left: A diagram of the treatment setting showing the skull window through which the beam is propagating into the tumor. Right: A foam mold made for each of the patients to allow positioning of the head. The mold has a hole through which the ultrasound is propagating in to the brain. Bottom, Left: A CT image of a patient in a treatment position in the head mold. The image shows a thermocouple probe that was inserted to monitor and guide the treatments. In this case the prior surgery had removed most of the tumor (shown as a fluid filled cavity with tumor in the enhancing rim). Right: An ultrasound image of a patient during the treatment showing a thermocouple probe and the tumor.

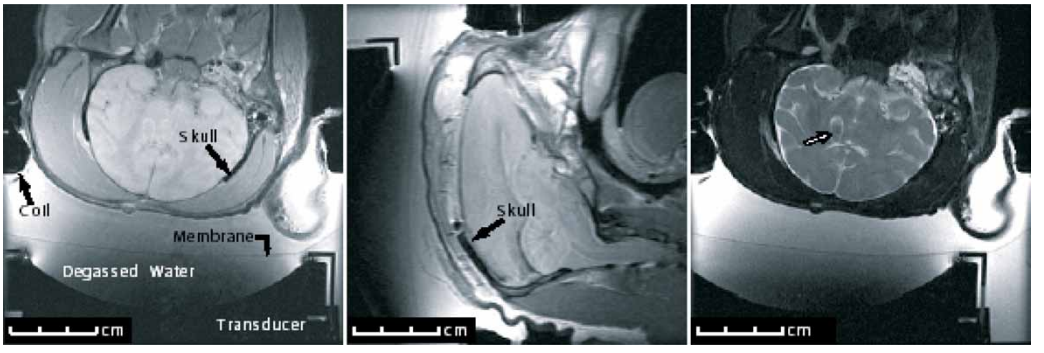

Figure 2. MRI slices, showing (left, center) the ultrasound transducer coupled via a water interface to a Rhesus monkey that has undergone a craniotomy before replacement of the skin, and an ultrasound-induced lesion (right) is enhanced following sonication (graphic courtesy of N. McDannold).

that focusing is possible, but that these foci tended to be distorted and shifted.

A means to compensate for the distortion caused by the skull was demonstrated in the late 1990s. The approach made use of the development of high-power phased ultrasound arrays [30–38] and driving systems suitable for thermal ablation [39]. It was demonstrated that a phase conjugation approach with a small transmitter inside the brain could be used to focus through a skull fragment [40]. Hynynen and Jolesz [41] then demonstrated that a focus distorted by the insertion of a human skull fragment in a water bath could be restored by simply adjusting the driving phase of each element in

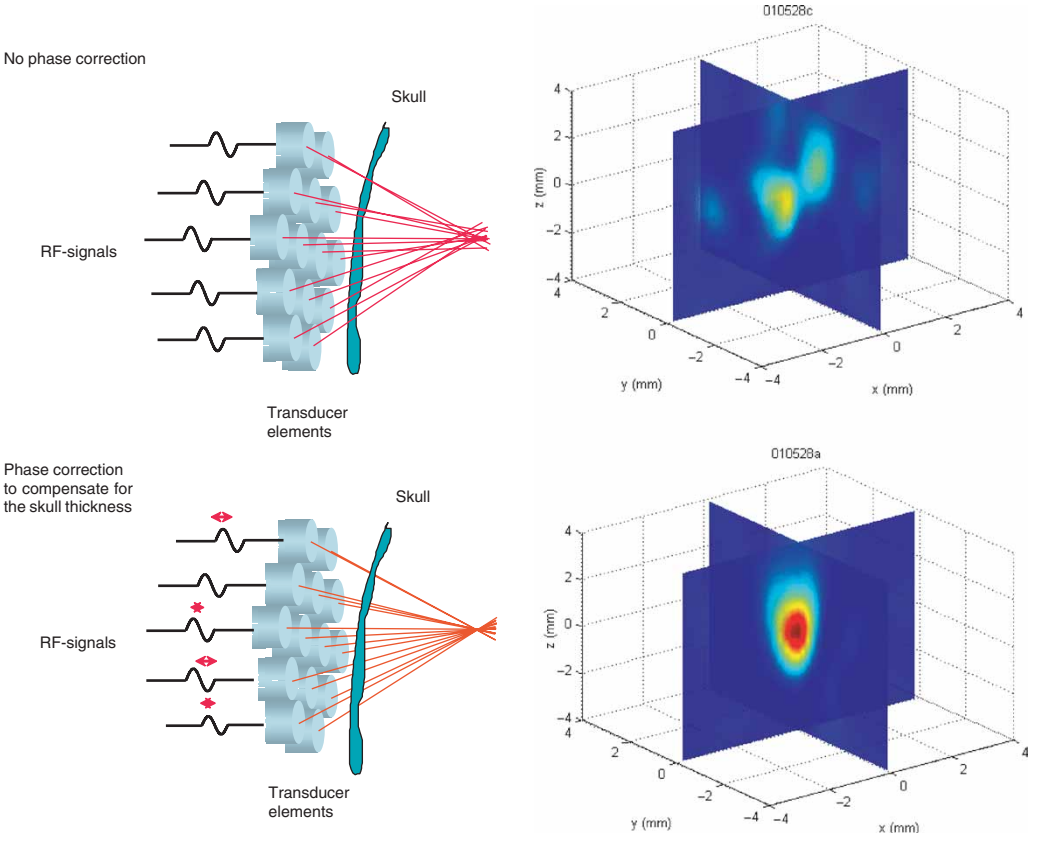

Figure 3. Top, Left: A diagram showing the wave distortion induced by a skull. Top, Right: The measured focused ultrasound field after it propagated through an *ex vivo* human skull showing the multiple foci induced. Bottom, Left: A diagram showing the adjustment of the phase of the array elements to compensate for the skull induced wave distortion. Bottom, Right: The measured ultrasound field after propagating through the *ex vivo* human skull when a CT correction algorithm was used to correct for the distortion induced by the skull [49].

a spherically curved transducer array with transducer elements large enough to make practical, high gain arrays feasible. The technique resembled an aberration correction method proposed for diagnostic ultrasound by Smith et al. [42] a decade earlier.

While the skull distorts the ultrasound field, it also absorbs ultrasound energy, causing unwanted heating in and around the skull and attenuating the beam. To attain a focus intense enough to coagulate tissues without overheating the skull, a hemispherical transducer design was devised to maximize the surface area of the skull, and thus distribute the energy [43, 44]. In numeric studies it was determined that approximately 64 elements were sufficient to focus the ultrasound after phase correction while maintaining skull temperatures below the burn threshold. A 64-element array with a 30-cm diameter was prototyped [45], constructed and tested [46], verifying the earlier numeric work.

With the feasibility of treatment verified, practical methods for reconstructing a focus were sought. One suggested method was the use of a small—perhaps catheter-inserted—receiver in the brain that would serve as a beacon to be used in conjunction with phase conjugating electronics [47], or alternatively as a receiver for phase correction [48]. However, it was the development of a model-based approach to focal restoration that made the technique completely non-invasive [49] (Figure 3). This spectral method, as well as a related finite-difference approach [50] required information from CT images in order to infer density, sound speed [49, 51, 52], and to register the transducer with the skull (Figure 3).

From simulations of ultrasound propagation into the brain [44] it was determined that a phase-corrected array on the order of 500 elements would produce a focus of about 1 mm in diameter in the brain at the array's geometric center. Thermal studies comparing the temperature rise at the focus to that on the skull surface further indicated that the optimal thermal gain between the focus in the brain and the skull surface is reached, on average, at frequencies near 0.7 MHz [46, 53]. Based on these studies a 500-element 1–3 piezocomposite MRI-compatible transducer was designed and constructed [54]. The composite material was used to allow for flexibility in the transducer bandwidth without impeding the high-power continuous-wave operation

of the array. Although this array was primarily intended to provide adequate aberration correction at the geometric focus rather than electronic steering [43], the array also allowed for limited electronic beam steering.

Equally critical to brain procedures has been the ability to target and monitor the treatment region. MR-guided focused ultrasound surgery (MRgFUS) [55–59] has demonstrated the ability to image both the tissue structure and the temperature rise throughout the region. Operation required that the ultrasound applicators were MR compatible, imposing unique design criteria for the ultrasound applicators [54, 55, 60]. MRI studies were critical to identifying potentially dangerous thermal variation over the skull surface [61], as well as methods to correct for such variation [62]. These studies also indicated the need to circulate cooled, degassed water between the array and the patient to provide skin and skull surface cooling to avoid excessive temperatures and tissue damage.

The complete 500-element MRI-guided system was tested by sonicating ultrasound phantoms and *in vivo* rabbit muscle and brain tissue using both model-based and hydrophone-based phasing through *ex vivo* human skulls [60]. These experiments showed that adequate energy can be delivered through the human skull to ablate an *in vivo* brain tissue, and that MRI can detect the focal temperature rise and tissue coagulation. It had been shown earlier with *in vivo* rabbit brains that the focal hot spots induced by subthreshold sonications could be detected with MRI thermometry [63] allowing accurate targeting prior to ablative sonications.

Separate experiments with an ultrasound-guided system and 300-element array [64] were also performed *in vivo* in sheep [65] demonstrating that transskull focal brain tissue coagulation is feasible. In these experiments, an invasive hydrophone was used to aid in the aberration correction. This work has recently been continued with *in vivo* monkey experiments that demonstrated model-based transskull brain ablation [66].

Clinical transskull ultrasound surgery procedure

Based on the culmination of brain research, a clinical brain system has been produced (ExAblate 3000, InSightec, Haifa, Israel) (Figure 4). This system was tested in the treatment of Rhesus monkeys to verify the system functionality and determine the level of temperature elevation at the skull bone surfaces [67]. These experiments also allowed the testing of the treatment planning programs. The results clearly demonstrated the importance of having a uniform ultrasound intensity at the skull surface and showed that high enough powers can be transmitted through the monkey skull to allow focal tissue coagulation in humans.

A clinical treatment series with three patients was then performed to gather feasibility information and determine clinical patient machine interface features. Briefly, the patient treatment is executed in the following manner.

Non-invasive brain procedures begin with a high-resolution CT scan of the patient's head using a bone kernel (Typical FOV 200 mm with 0.75-mm slice thickness), which is rendered into three dimensions to provide relevant acoustic input parameters. These CT images must be registered with both the reference frame of the treatment transducer as well as the MRI scanner for treatment planning. Treatment planning is performed with the patient's head rigidly affixed to the treatment array. In the initial trial this was done using a facemask. However stereotactic frames (that have been routinely used in radiosurgery) secured to the patient's head provide the most rigid support, and offer an ability for planning to be performed hours before the actual treatment.

The planning procedure numerically simulates the ultrasound beam along its path through the skull bone and into the brain in order to determine the amplitude and phase of the ultrasound when it reaches the intended focal position. While there are many possible approaches to simulating the ultrasound field, only the spectral approach [49] has been shown to repeatedly focus through the skull over a range of skull samples. The primary contribution of the planning is to determine the relative phase of the ultrasound contributed by the individual elements in the array. Once determined, the individual phases can be adjusted, so that the contributed beam from each element arrives at the focus in phase. Furthermore, the path of the ultrasound beam through the skull is identified (Figure 4a). If energy from a given element is severely attenuated or refracted in such a way that it cannot contribute appreciatively to the focus, the amplitude of this element can also be adjusted. In severe cases this element can be turned off, as it will only deposit energy in the skull or other undesired volumes. In cases of milder attenuation it may be more beneficial to increase the amplitude of the element in order to strengthen its pressure output [62].

The patient is prepared for treatment by shaving and cleaning the scalp before inserting the head into a watertight membrane that is affixed to the treatment array. The region between the array and the patient is filled with degassed water cooled to approximately 15°C in order to cool the outer surface of the skull to prevent overheating.

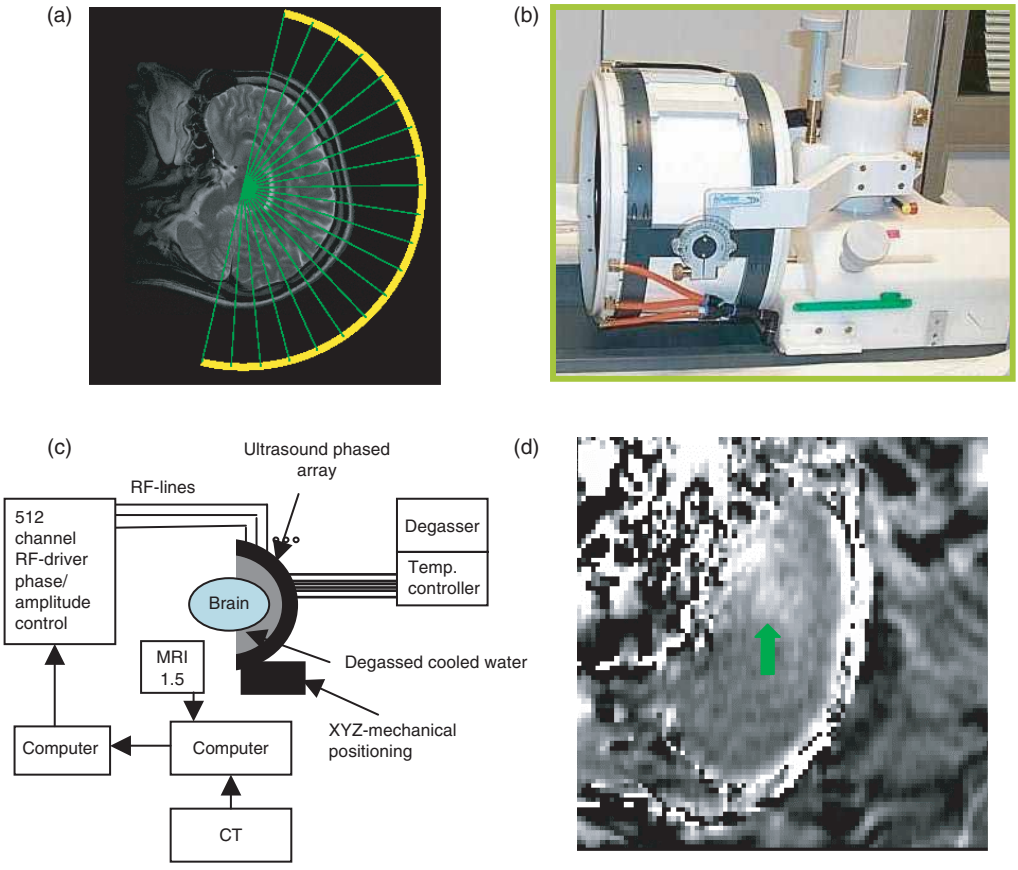

Figure 4. A clinical prototype brain treatment system (Exablate 3000, InSightec, Inc., Haifa, Israel). (a) An illustration of the treatment planning showing how each of the ultrasound beams are propagated through a section of a skull based on the CT images obtained before the treatment and co-registered with the online MR image. (b) A photograph of the 512-element array and the mechanical positioning system. (c) A block diagram of the complete system. (d) A temperature elevation image derived from the MRI thermometry information at the end of a sonication of a monkey [67]. The hotspot and the skull heating are visible in the image.

The clinical trial of treating neoplastic brain tumors is currently under way at the Brigham and Women's Hospital, Boston, MA, USA. Another study expected to start also at Univeristy Children's Hospital in Zurich, Switzerland, will initially target non-invasive functional neurosurgery starting with neurogenic pain, with plans to extend into Parkinson's disease and epilepsy. The first series in Boston treated three patients, verifying transskull focusing and the quantity of skull heating. The continuation of the trial is pending modifications to be made to the patient immobilization system.

Future applications

Although transskull thermal coagulation of tumors appears feasible, it may turn out that cavitation-enhanced heating [68–71] or mechanical tissue destruction [72] may offer benefits due to the increased focal energy absorption and thus reduced energy transmission through the skull. Owing to the reduced time, average power requirement, low-duty cycle, high-pressure amplitude sonications inducing cavitation were originally proposed as the method of choice for transskull surgery [41]. By injecting an ultrasound contrast agent with preformed micro-bubbles into the blood stream, the thermal and mechanical tissue damage methods can be combined [73]. This could results in at least an order of magnitude reduction in the required power. An example of a focal lesion that was produced with only 8 Watts of acoustic power emitted by the transducer during 20 s sonication through an *ex vivo* human skull in a living rabbit brain after a bolus injection of an ultrasound contrast agent is shown in Figure 5.

Ultrasound holds the promise of providing multiple therapeutic functions in the brain by way of coagulative necrosis, through potential reversible blocking of certain functions [74], by assisting in the delivery of thrombolytic agents [75–77], or through delivery of an agent to a targeted volume by opening of the blood–brain barrier. These methods have been suggested for the treatment of Parkinson's

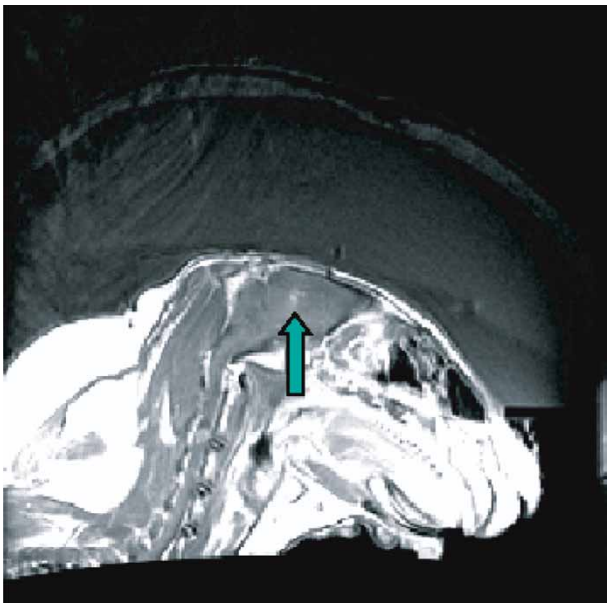

Figure 5. Bubble-enhanced tissue destruction as seen with MRI contrast enhanced imaging after the sonication. The image shows ultrasound being delivered through an *ex vivo* human calvarium and brain-mimicking phantom and into a rabbit brain *in vivo*.

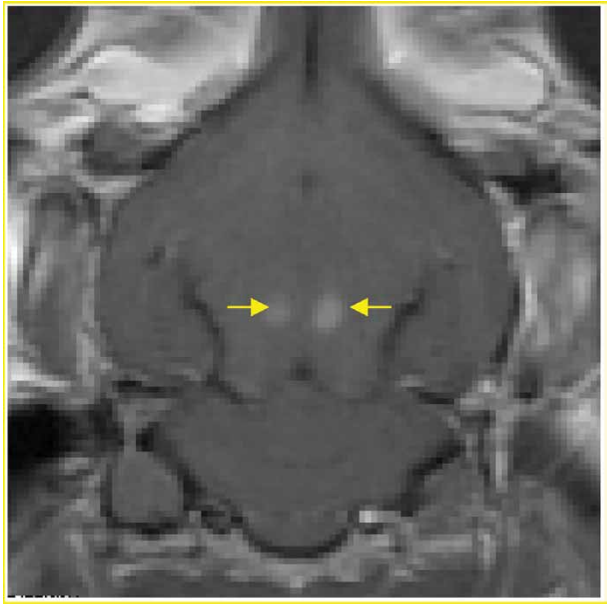

Figure 6. A T1-weighted contrast enhanced image of a rabbit brain showing two locations with disrupted blood–brain barrier [80].

disease, epilepsy and tumors and to inhibit transmission of nerve signals in the brain [74] and may be useful in targeting genetherapy [78, 79].

Significant attention has recently focused on the ability of ultrasound to temporarily open the blood–brain barrier (Figure 6), providing a means for spatially targeted and time-windowed passage of therapeutic agents into the brain. It has long been recognized that ultrasound can disrupt the blood–brain barrier [9] but the prospect of creating a controlled reversible process [80], introduces significant promise for delivering agents that currently cannot be delivered into the brain. Furthermore, the prospect of targeting may protect certain areas in the brain while providing benefit to the target. Online monitoring abilities [80–82] make the procedure especially exciting.

Much work remains to be performed for disease-specific models and drugs in order to determine clinical viability, but the body of quantitative data is increasing rapidly. A range of particle sizes has been demonstrated to pass the blood–brain barrier, including molecular weights of 961 (trypan blue), 938 (Magnevist®), 10 000 (MION) [82], 40 000 (horseradish peroxidase) [83], and 150 000 (antibodies) [84]. Recent evidence has indicated that significant concentrations of the chemotherapy drug liposomal doxorubicin can be delivered to the normal rat brain [85], and the monoclonal antibody Herceptin in mice [84].

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