HigH-intensity focused ultrasound is a genuine challenge in current approaches to noninvasive brain therapy.14 With the development of MR thermometric monitoring,7,24 MRgHIFU now offers real-time monitoring of the thermal ablation, ensuring a crucial control for treatment safety. As opposed to extracerebral applications (uterine fibroids,28,33 liver,3,31 prostate,8,27), brain HIFU has restrictions with regard to the cranial vault, which creates strong aberrations when ultrasonic waves pass through.30 To correct these defocusing effects, simulation-based noninvasive adaptive techniques have been developed using phase conjugation5,12,13 or time reversal.1

One of the main parameters influencing transcranial HIFU treatments is the ultrasonic frequency. As investigated by Fry and Barger9 for frequencies ranging from 250 kHz to 2.2 MHz, the aberrating effect of the skull...
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increases with the frequency, both in terms of dephasing and absorption of the wave front. Thus, low frequencies are less affected by the skull bones. Nevertheless, the half width of the focal spot (which represents the size of the therapeutic beam at focus) is proportional to the wavelength; that is to say, inversely proportional to the frequency. Thus, a compromise needs to be made in the choice of operating frequency. Multielement arrays of transducers have been developed at various frequencies: 220 kHz,21,22 660 kHz,6,12 and 1 MHz.26 Recently, clinical trials on neuropathic pain20 and glioblastoma21 have been performed in vivo in a prototype has been developed and tested. Previously, transcranial ablation has been performed with a 660-kHz system developed by Insight Tech.

In this study, an MR-compatible 1-MHz-frequency prototype has been developed and tested. Previously, transcranial ablation has been performed in vivo in sheep25 and monkeys29 at the same frequency. Nevertheless, because the morphometric structure of the human skull is unique and nonreproducible, in this study we propose a fresh human cadaver model to investigate the accuracy of transcranial MRgHIFU brain therapy at 1 MHz. As a target, we have chosen a part of the thalamic VIM. This deep-seated region is implicated in essential tremor, which is the most frequent movement disorder (median crude prevalence 6.3%) among the population older than 60 years.17

Methods

Cadaver Model

We removed heads from 18 fresh human cadavers at the Institut d’Anatomie UFR Biomédicale des Saints-Pères, Université René Descartes, Paris. All the specimens fulfilled the Centre du Don des Corps criteria, and the donors had given their informed consent before death. We obtained a special dispensation to work as soon as possible after death (24–48 hours), sooner than the classic serology delay that typically ranges between 4 and 6 days. The bodies and the detached heads were maintained in a cold environment (4°C).

To prevent air penetration (which constitutes an ultrasonic barrier) into the intracranial compartment, a specific protocol has been developed as follows. The face of the specimen is hidden with a sutured plastic patch to maintain anonymity. The scalp is totally shaved using an electric razor and depilatory cream, thus eliminating air bubbles trapped in the hair. A Leksell stereotactic frame is affixed to the head in a conventional position, with 4 ceramic tips that have been specifically created to minimize MRI artifacts. The head is placed inclined downward and the dissection begins with a skin flap preparation, using a U-shaped large cervicotomy. Both jugular and carotid vessels are ligatured (carotid artery and jugular vein separately). The larynx is separated between the hyoid bone and the thyroid cartilage. The esophagus is cut and the cervical vertebral bodies are disconnected between the C2–3 or C3–4 levels. The dural sac is ligatured to prevent air introduction into the subarachnoid spaces and then cut. The dissection ends with a cutaneous closure performed using the cervical flap. The entire procedure and the storage are performed with the head inclined downward.

The HIFU System

The aim of the HIFU system is to provide an accurate focused energy beam at the target. To achieve this, the position and orientation of the probe relative to the stereotactic frame have to be known precisely. The specially designed HIFU system consists of a head holder on which the stereotactic frame is fixed and a probe holder (Fig. 1). The constitutive elements are all nonmagnetic to be integrated into a clinical MR environment. The probe and head are manually positioned to predefined discrete positions offering 6 degrees of freedom: 2 translational and 1 rotational for the head holder, as well as 1 translational and 2 rotational for the probe holder. The probe is a 512-element phased-array transducer operating at 1 MHz. Each transducer (6-mm diameter) can deliver up to 20 W/cm² of acoustic intensity and can work separately. The device is driven by a 512-channel electronic system developed by SuperSonic Imagine. The total acoustic power of the system can reach 2900 W. The ultrasound coupling between the probe and the head is mediated by a latex membrane filled with degassed water plus conventional ultrasound coupling gel.

Imaging and Target Planning

Imaging. Two cerebral imaging studies are performed on each head: a CT scan for the time reversal process and an MR image for brain targeting. Both are made under the same stereotactic conditions.

The CT Scan. A bone stereotactic 3D CT scan is performed using a Somatom Sensation 16 imager (Siemens) from the Groupe Hospitalier Pitié-Salpêtrière. It is a dynamically timed helical multidetector row CT. The following parameters are used: resolution 0.46 × 0.46 × 0.39 mm³; helix 0.75; pitch 0.45; image reconstruction 0.75 mm with a 0.4-mm overlap in the axial direction; and filter H70. The field of view is set to encompass the skull and the whole stereotactic frame at minimum.

Fig. 1. Photograph showing the ultrasonic 512-element array with head holder. A dry skull is placed for illustration.
The MR Image. The MR imager is a 1.5-T Philips Achieva scanner installed at the Centre Inter-Établissements de Résonance Magnétique, Université Paris-Sud, Hôpital de Bicêtre. A T1-weighted 3D sequence is performed to choose the target (resolution 0.89 × 0.89 × 0.8 mm³, FOV 23 × 23 cm, matrix 256 × 256, TE 4.6 msec, TR 30 msec, flip angle 30°, bandwidth 14.4 kHz), using 1 SENSE flex medium coil (composed of two 14 × 17–cm elliptical elements) and 1 SENSE flex small coil (composed of an 11-cm circular coil pair) surrounding the head.

Targeting. The thalamic VIM was chosen as the target of the transcranial HIFU for 2 reasons: its location and its pathological implication. First, this thalamic nucleus, belonging to the basal ganglia, is a deep gray matter structure that constitutes an ideal target for a stereotactic noninvasive treatment such as HIFU. Indeed, this deep-seated region naturally lies at an ideal location for the ultrasound beams because the large distance from the outer skull surface allows a sufficient antenna gain between the focus and the skull. Second, the VIM is involved in the physiopathology of essential tremor. Its mediocaudal portion, defined by the brain stereotactic atlas, is already used as the target of deep brain stimulation. On the T1-weighted MR images, targeting is performed using the Guiot atlas that refers to the anterior commissure-posterior commissure line. The VIM coordinates obtained in anterior commissure-posterior commissure marks are turned into Leksell coordinates. The VIM side is arbitrarily chosen.

Treatment Planning. Dedicated software has been developed by SuperSonic Imagine for HIFU brain therapy in patients (Fig. 2). The CT and MR data are integrated in the software and then matched together with recognition of the Leksell frame. Anatomical verification is then performed by a neurosurgeon to make sure the image fusion has been successful. The Leksell coordinates of the VIM are defined in the software. The optimal treatment position for the therapeutic probe is numerically calculated to direct the ultrasonic beams perpendicularly to the skull surface. Specifically, the software proposes several probe positions to the physician, ranked by increasing mean angles. Each position provides a probe focus near the target, included within a 2-cm sphere centered on the target. The neurosurgeon determines the best probe position that is a compromise between the ultrasonic angles, the nearest focal point to the target, and the overall beam path.

The HIFU system offers 1 million different discrete positions, so that the software can determine geometrical focal points as close as possible to the target. Thus, its accuracy is assessed here only for a heating point at the probe focus near the target. Additional steering of the ultrasound beam can be performed electronically but was not used in this study. Indeed, the software can electronically move the acoustic focal point by adjusting additional delays when the probe emits the ultrasonic signal. Once the position is selected, the software computes the propagation of the ultrasonic wave from the probe focus to the transducer’s locations. Propagation through the skull is computed from a 3D finite-difference time domain simulation of the heterogeneous acoustic wave equation, with a 2-hour simulation time. The target coordinates in the MR frame are saved as a reference for accuracy assessment.

Treatment and Accuracy: Real-Time MR Monitoring During Treatment

The probe is placed in the calculated position and the head is fixed to the Leksell frame support. The set (head and frame) is inserted in the magnet bore (Fig. 3). The simulated ultrasound signals are time reversed and emitted during 10 seconds. A spoiled 3D gradient echo–based echo planar imaging sequence with echo train length 9 is used for MR thermometry. Five contiguous slices in the axial plane with a 3-mm thickness are acquired (resolution 1.5 × 1.5 × 3 mm³, FOV 16 × 7 cm, matrix 256 × 256, TE 20 msec, TR 100 msec, flip angle 20°, bandwidth 14.4 kHz), leading to an acquisition time of 2.5 seconds.
No additional phase shifts are added to the time-reversed simulation signals: the purpose of the MR temperature monitoring is to locate the maximum temperature elevation obtained with the simulation-based correction alone. Temperature elevation maps are computed as the difference between temperature images after HIFU heating and a reference temperature image obtained before heating. The ultrasound emissions are triggered based on the MR images to obtain reproducible synchronization for all heads.

**Ultrasonic Parameters**

The MR temperature variance in the absence of ultrasonic sonication was found to be 0.05°C. Consequently, the target temperature was chosen to be higher than 5°C to ensure accurate measurement of the location of the maximum temperature elevation. The acoustic emission consisted of a continuous 10-second sonication. Acoustic power ranged between 900 and 1600 acoustic W to reach a temperature above target.

**Accuracy Assessment**

Temperature elevation images are interpolated to fit the resolution of the MR anatomical images used in the treatment planning. The position of the maximum temperature elevation in 5 slices is automatically and blindly determined by a Matlab program, and its coordinates in the imaging slices are saved. These coordinates are converted to the MR reference axes by using information in the DICOM files. For each head the location of the maximum temperature elevation is then compared with the theoretical target location previously computed during treatment planning. The mean shift and standard deviation to the reference are calculated for the 3 directions.

**Results**

**Imaging and MR Monitoring**

The average temperature elevation observed in the 12 sonicated heads was 7.9°C ± 3°C; minimal and maximal elevations were 3°C and 13°C, respectively. Typical temperature elevation maps are displayed in Fig. 4.

The head dissections were performed without any technical difficulties. The average total time of dissection was approximately 60 minutes per cadaver. No significant air penetration was observed on cerebral CT and MR scans. After the CT scan, 6 of the 18 heads were found to have unexpected internal skull thickening (Fig. 5). These heads were excluded from the study and thus were not sonicated.

**Accuracy Assessment From MR Data**

The shift between the targeted position and the actual position of the maximum temperature elevation was calculated for each of the 12 sonicated cadaver heads: 0.4 ± 1 mm in the right/left direction, 0.7 ± 1.2 mm in the dorsal/lateral direction, and 0.5 ± 2.4 mm in the rostral/caudal direction. This has to be compared with the MRI temperature sequence voxel size: 1.5 × 1.5 × 3 mm³. The mean error demonstrates that the location of the maximum temperature location is not biased by a global shift. The standard deviation is smaller than the imaging voxel. More precisely, beyond the average data, one can specify

![Fig. 3. Sagittal (left) and coronal (right) views of the treatment setup (T1-weighted MR images).](image)

![Fig. 4. Typical MR temperature elevation in a view of the full head (left) and in the VIM (inset and right). deg = degrees.](image)

![Fig. 5. Examples of calcifications on the inner skull surface. Upper: Coronal and sagittal views of the CT data. Lower: Photograph of the inner surface of the corresponding extracted skull bone.](image)
that each individual sonication had a maximum temperature elevation located either in the targeted voxel or in the adjacent voxel. No sonication was observed at a greater distance from the target.

**Discussion**

The results show that a millimetric accuracy has been achieved and that the precision of the targeting is equivalent to the size of the imaging voxel. This supports the belief that the global MRgHIFU methodology, treatment planning, and HIFU system used are accurate enough to ensure future clinical applications. In addition, aberration correction is sufficiently precise to ensure adequate location of the treatment zone: the shifting induced by the skull has been corrected. Any refinement in the simulation model or in stereotactic positioning would have a negligible impact on treatment accuracy. Nevertheless, any refinement in the simulation model could improve both the efficiency and safety of the treatment. The aberrations induced by the skull are indeed 2-fold. On the one hand, a shift in the position of the maximum pressure amplitude can be induced. It has been demonstrated in this paper that such an effect can be successfully corrected for in cadaver heads. It confirms previous in vitro results obtained in ape and human skulls.18 On the other hand, defocusing of the main lobe can also be induced by skull bones, leading to a decrease in pressure amplitude at the focus.

Previous in vitro studies11,19 have shown that more than 80% of the pressure amplitude can be restored with the same simulations used in this study. In such an experiment, 100% corresponds to a time-reversal correction achieved with a real hydrophone implanted at the targeted position. This means there is still room for a 20% improvement in the pressure amplitude at focus for a given energy emitted by the therapeutic array. A 20% gain in pressure amplitude corresponds to a 40% gain in heating at the focus. Such an additional gain would enable lowering the total energy emitted by the therapeutic array without affecting the temperature elevation at the focus. With such an efficacy, the safety of the treatment would be improved. Tissues located in the near field would be less subject to possible side effects like unwanted heating or edema. This is the reason why ongoing research is currently aimed at recovering full pressure amplitude at the focus.10,16

No lesioning was achieved in this study: moderate heating has been chosen to assess the precision of the targeting for 2 reasons. First, the expected temperature for lesion production in a living patient’s brain is 55°C.13 This corresponds to an 18°C increase, compared with a 51°C increase in our cadaver experiments because the heads were kept at 4°C to prevent denaturation before treatment. Because it was designed for a typical 25°C temperature elevation, our system doesn’t allow such a high temperature rise in cadavers. Second, moderate heating or low-energy pulses are often used to check the treatment targeting. Such moderate heating has been used in preclinical applications for blood-brain barrier opening in nonhuman primates20 or for drug delivery.23 In clinical applications mild temperature elevation has been achieved before ablation for neuropathic pain treatment19 and essential tremor. Nevertheless, the temperature elevations were not high enough to induce noticeable temperature changes near the skull, given the signal of our MRI sequences. Such axial images only indicate that the temperature increase is below the noise level outside the main focal point. Further investigations with increased power are needed to assess if the temperature elevation close to the bone is low enough to allow repetitive sonications for large treatments. It should nonetheless be acceptable for localized treatments such as the one for essential tremor.

The use of cadaver heads, as presented in this paper, enabled us to test these clinical prototypes with a realistic model before in vivo use. Aside from the absence of blood flow and a lower temperature, cadaver heads are similar to patient heads. Treatment planning could be performed using the 3D anatomical T1-weighted images. In addition to the study, blind examination by 3 neuroradiologists of the T1 images obtained in cadaver heads revealed that no one suspected that the images were of dead tissues: only signs of aging in scans of elderly patients were pointed out, such as calcifications on the cerebral falx and at the inner surface of the frontal bone (Fig. 5), or cerebral atrophy. No significant air bubbles were seen in the images, and the ultrasonic beam was not noticeably affected by the presence of air. Because the delay after death and the time between dissection and treatment totaled less than 48 hours, we assume that the cerebral tissue was not altered by gas.

In the future, a comparison with the first treatments performed in patients with the same device will be particularly useful for fully assessing the validity of the cadaver model and discussing possible differences. Internal skull thickening of variable size and shape was observed in 6 of the 18 heads involved in the study (Fig. 5). This corresponds to hyperostosis frontalis interna.11 The statistical evaluation of accuracy was thus performed in only 12 heads. Such a high prevalence of hyperostosis (33%) in the population studied in this paper is still under investigation but could be linked to the age at death. Such skull morphologies could increase the aberration and decrease the ultrasonic beam focalization with a standard skull anatomy. The overall structure of the skulls with hyperostosis was so different from what has been studied in the past decades in aberration correction studies3,5,6 that such skulls have been excluded from the study. Nevertheless, because some patients might have such hyperostosis in the future, the skulls have been kept intact and transcranial focusing with noninvasive and invasive time reversal is currently under evaluation to quantify the additional effect of hyperostosis and to correct it if needed. The choice of cadavers was based on the date of death, and due to ethical rules we did not have access to the clinical histories of the donors. The only possible bias in the cadaver selection is related to the fact that only people...
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who had given their informed consent before death could be included in the study. The specimens involved in the study were quite old (mean 86 years old). Nevertheless, old patients are expected to be included in future clinical trials, both for multiple metastasis and essential tremors.

Conclusions

Use of MRgHIFU for brain therapy represents a promising option in neurosurgical strategies. To ensure a safe ultrasonic treatment, every step from in vitro to in vivo models has to be rigorously conducted. In this study, the millimetric accuracy of a 1-MHz HIFU system has been assessed in a fresh human cadaver model. Indeed, prior to clinical trials neurosurgeons need to train on such practical models. Moreover, the model could be helpful in validating the accuracy of new devices in a setup as close as possible to a living patient. With the cadaver model introduced here, the anatomy and positioning are optimally reproduced, but without blood flow or living cells. Nevertheless, it is probably the best model available to date and must be seen as a complementary approach to previous work performed at the same frequency in living animal models.

Disclosure

This study was partially funded by Fond d’Études et de Recherche du Corps Médical (FERCM), Fondation des Gueules Cassées, and Agence Nationale de la Recherche (TUCICRM project). Dr. Tanter owns stock in and is a cofounder of SuperSonic Imagine. Dr. Fink is a cofounder of and consultant to SuperSonic Imagine. Dr. Marsac is an employee of SuperSonic Imagine. Dr. Aubry was a consultant for SuperSonic Imagine from 2007 to 2010.

Author contributions to the study and manuscript preparation include the following. Conception and design: Aubry, Chauvet, Pernot, Boch. Acquisition of data: Aubry, Chauvet, Marsac. Analysis and interpretation of data: Aubry, Chauvet, Marsac, Pernot. Drafting the article: Chauvet, Marsac. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Chauvet, Marsac. Study supervision: Boch, Aubry, Tanter.

Acknowledgments

The authors thank Bruno Quesson for his help on implementation of the 3D real-time MR temperature monitoring, and the team of the Centre Inter-Etablissements de Résonance Magnétique (CIERM) for their support with the 1.5-T MRI platform. The authors also thank the FERCIM and the Fondation des Gueules Cassées for their assistance.

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Accepted January 22, 2013.
Please include this information when citing this paper: published online March 1, 2012; DOI: 10.3171/2013.1.JNS12559.
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