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Predicting bone marrow damage in the skull after clinical transcranial MRI-guided focused ultrasound with acoustic and thermal simulations

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Abstract

Transcranial MRI-guided focused ultrasound (TcMRgFUS) thermal ablation is a noninvasive functional neurosurgery technique. Previous reports have shown that damage in the skull bone marrow can occur at high acoustic energies. While this damage is asymptomatic, it would be desirable to avoid it. Here we examined whether acoustic and thermal simulations can predict where the thermal lesions in the marrow occurred. Post-treatment imaging was obtained at 3–15 months after 40 clinical TcMRgFUS procedures, and bone marrow lesions were observed after 16 treatments. The presence of lesions was predicted by the acoustic energy with a threshold of 18.1–21.1 kJ (maximum acoustic energy used) and 97–112 kJ (total acoustic energy applied over the whole treatment). The size of the lesions was not always predicted by the acoustic energy used during treatment alone. In contrast, the locations, sizes, and shapes of the heated regions estimated by the acoustic and thermal simulations were qualitatively similar to those of the lesions. The lesions generally appeared in areas that were predicted to have high temperatures. While more work is needed to validate the temperature estimates in and around the skull, being able to predict the locations and onset for lesions in the bone marrow could allow for better distribution of the acoustic energy over the skull. Understanding skull absorption characteristics of TcMRgFUS could also be useful in optimizing transcranial focusing.

Keywords

Bone; Brain; Image-guided treatment; Tissue modelling; Ultrasound

I. Introduction

TRANSCRANIAL MRI-guided focused ultrasound (TcMRgFUS) is a noninvasive neurosurgical method that is approved for the treatment of essential tremor and tremordominant Parkinson's disease [2, 3], and it is being investigated for other functional neurosurgery applications [4–6]. The method uses a hemispherical phased array transducer to focus ultrasound energy through the human skull to thermally ablate small volumes in central brain locations. The magnitude and phase offsets for the transducer elements are manipulated to correct for aberrations of the ultrasound field induced by the skull bone and to normalize the acoustic intensity on the skull, respectively. These offsets are determined based on the geometry and density of the skull bone that are obtained from CT scans [7,8]. The procedure is performed within an MRI scanner and guided by MR temperature imaging (MRTI) [10] and the patient's clinical response.

To avoid overheating the skull, scalp, and brain surface, a low acoustic frequency is used to minimize absorption in the bone, a hemispherical transducer design is employed to distribute the acoustic energy over a large surface area, and the head is actively cooled with chilled and circulating water. The acoustic energy needed to achieve an effective thermal dose at the focus varies substantially [12]. Furthermore, if the symptoms are not improved, sonications are repeated at different focal targets. Thus, both the peak acoustic energy as well as the total acoustic energy delivered over the course of a treatment can vary substantially. Depending on the geometry and acoustic properties of the skull, the absorbed energy can result in changes in the bone marrow. Schwartz et al. reported bone marrow changes following TcMRgFUS three months after sonication at acoustic energies of 15.5–25.8 kJ [13]. The changes were not visible in imaging acquired 24 h after sonication.

Damage to the marrow is asymptomatic and does not appear to pose a risk of harm for TcMRgFUS patients. Nevertheless, it could be desirable to avoid it and to predict where excessive heating might occur. Furthermore, observing where it occurs could improve our understanding of the acoustic propagation across the bone. This analysis could ultimately be used to optimize the aberration correction and perhaps devise new strategies to improve the size, shape, and obliquity of the focal lesion at the brain target.

The purpose of this study was to investigate the use of acoustic and thermal simulations to predict the onset and extent of bone marrow damage after TcMRgFUS thermal ablation. Bone marrow lesions were identified and segmented on T2-weighted MRI obtained 3–15 months after 40 clinical treatments and registered to a common reference frame. The locations of the lesions were then compared to the predicted heating based on acoustic simulations obtained in an earlier study [12].

II. Methods

A. TcMRgFUS

The patients were treated using the ExAblate Neuro device (InSightec, Haifa, Israel), which uses a 1024-element phased array transducer to focus ultrasound through the human skull into central locations of the brain for thermal ablation. Our transducer had 993 active elements. The elements have a central frequency of 660 kHz and are arranged in a 30 cm

diameter hemisphere. The TcMRgFUS device is integrated into a 3T MRI scanner (GE750W, GE Healthcare, Milwaukee, WI). Imaging during the treatments was performed using the body coil. The transducer location within the MRI coordinate system was found using MRI tracking coils [14]. The patient was placed in a stereotactic frame that was attached to the MRI table. The space between the scalp and the transducer face was filled with degassed water that was chilled to 15°C and circulated between sonications. A flexible membrane placed around the patient's shaved head and attached to the face of the transducer contained the water.

Over a three-year period, we treated 61 patients at our institution. Overall, 59 patients were treated for essential tremor (thalamotomy) and two for Parkinson's disease (pallidotomy). MRI was obtained 3–15 months after TcMRgFUS in 40 treatments. The transducer was positioned so that the focal point was within ± 1 mm of the target selected by the neurosurgeon; additional steering was performed electronically using the phased array. Low energy sonications were applied while acquiring MRTI to verify the focal target. Then, the energy was increased over several sonications until the focal temperature was approximately 60°C and symptoms were improved. Between sonications, the patient was evaluated for symptom improvement and side effects. The focal target was steered to different targets if necessary. Depending on the skull properties and how many sonications were needed to achieve symptom improvement, the maximum and total acoustic energy varied substantially. In our experience this energy can vary by an order of magnitude [12].

B. Imaging

Before treatment, a CT scan was obtained with a bone reconstruction kernel. On treatment day, neurosurgical planning was performed using a 3D FIESTA sequence. One day after treatment, an MRI exam was acquired on a 3T scanner at our institution. At 3–15 months after treatment, an additional MRI exam was obtained at either 3T or 1.5T. All MRI exams included an axial T2-weighted sequence, which we used to detect treatment-induced changes in the bone marrow. Details about the patients, treatment parameters, and post-FUS imaging are shown in Table S1.

C. Registration and segmentation

The transformation matrices describing the registration between the treatment planning images obtained with the patient in the TcMRgFUS device, the pre-treatment CT scan, and the reference frame of the transducer were obtained from treatment log files exported from the device. The registrations between the MRI obtained during treatment and that obtained 24 h and 3–15 months after FUS were created manually using 3D slicer (www.slicer.org). After registration, comparisons of axial T2-weighted MRI obtained at 24 h and 3–15 months later was used to identify bone marrow damage. The extent of the lesions at 315 months was manually segmented by one author (NM). Representative images covering the whole head at 24 h and 3–15 months after FUS along with the lesion segmentations for all patients are included in the Supplemental Data. The lesions were identified when obvious changes were observed between these two time points. The segmentations were completed before the thermal simulations were performed. All imaging and the segmentations were interpolated using MATLAB into the same $256 \times 256 \times 145$ element matrix, which was in the reference

frame of the phased array transducer. This matrix had dimensions of $30 \times 30 \times 17$ cm; bicubic interpolation was used.

D. Acoustic and thermal simulations

Acoustic simulations were performed in an earlier study [12] using k-Wave, an open source MATLAB toolbox [15]. The patient-specific simulations used CT scans with a bone reconstruction kernel to define the geometry of the head and to estimate the acoustic properties of the skull. The orientation of the patient and the registrations between the reference frames of the transducer, MRI and CT coordinates were obtained from the treatment log files of the TcMRgFUS system.

We simulated the pressure field in a small volume for the 993 transducer elements separately for each patient (Fig. 1a). These simulations were performed in the coordinate system of the individual elements (elemental simulation matrix size: $44 \times 44 \times 492$), and the resulting complex pressure fields were rotated and interpolated into the reference frame of the TcMRgFUS transducer and summed (Fig. 1b). In our previous study, we interpolated and summed the simulations around the focal region. Here, for the thermal simulations we interpolated to the same $256 \times 256 \times 145$ element matrix that we used for the imaging data. We assumed the individual elements were each 1 cm diameter pistons centered at the element locations provided by the manufacturer. The acoustic simulations were performed using a spatial resolution of 0.325 mm (wavelength/7). We used a perfectly matched layer with a size of 10 grid points and an attenuation of 2 Np per grid point. The acoustic simulations were ran in parallel using a computing cluster. Parameters used for the acoustic and thermal simulations are shown in Table 1. We used the relationships between the skull density and the attenuation/sound speed found in our earlier study [12].

For each treatment, we used the phase and magnitude values for the transducer elements that were employed during the sonication with the highest acoustic energy. We estimated the heating in and around the skull including the scalp with the bioheat equation [16]. For the thermal simulations, we used absorption coefficients of 20.5 and 41.0 Np/m for cortical and trabecular bone, respectively. These values were based on the study by Pinton et al., who used simulations and high-resolution microCT to estimate the longitudinal and shear absorption coefficients of the human skull [11]. We used the shear coefficient for the trabecular bone based on an assumption that the complex bony structure in the diploe had many internal interfaces with large incidence angles. We previously identified the location of the inner and outer table for each voxel in the simulations [12]. Voxels between these two points with a density of 2000 kg/m^3 or less was characterized as trabecular bone.

Because of uncertainty in absorption coefficient, the absolute temperature predicted by the thermal simulations were not expected to be precisely accurate, but instead were intended to provide a relative prediction of the pattern and severity of skull heating. The head was assumed to be at a uniform temperature of 37°C before sonication. The surrounding water was assumed to be 15°C . We did not simulate the cooling of the head before sonication due to the chilled and circulating water.

E. Data analysis

To compare the location, shape, and size of the bone marrow lesions to the simulated heating, we created maps of maximum temperature rise that were superimposed on the skull surface obtained from the CT scan. We further superimposed isosurfaces of the lesion segmentations on these maps. In addition to qualitative comparison, we compared the area of the lesions across the skull surface to that predicted by isotherms at different thresholds. For this analysis, we calculated the Dice similarity coefficient (DSC) between the lesions and isotherms as a function of threshold temperature. Receiver operator characteristic (ROC) curves were also generated. The area under the ROC curve was calculated. We then compared the volume of the lesions to the acoustic energy used during treatment and to isotherms at the temperature that had the highest DSC.

The presence (or lack) of bone marrow lesions was plotted as a function of the maximum acoustic energy used during each treatment as well as the total applied energy. We also plotted the presence or lack of a lesion as a function of the skull temperature for each point on the skull surface. These data were fit using probit regression to estimate the probability for lesions along with 95% confidence intervals. All data analyses were performed in MATLAB.

III. Results

T2-weighted MRI was obtained 3–15 months after 40 TcMRgFUS treatments in 38 patients; two patients received two treatments. Obvious bone marrow lesions were detected at 3–15 months after TcMRgFUS in 40% (16/40) of these treatments. The damage was not evident at 24 h after treatment in any patient. The lesions appeared as an isointense or heterogeneous core surrounded by a hypointense rim, or for smaller lesions, simply a hypointense area. They were identified by comparing axial T2-weighted imaging acquired at 24 h and at 3–15 months after FUS. Representative images at both times from all patients can be found in the Supplemental Data.

Fig. 2 shows the examples of bone marrow damage in a patient that received two TcMRgFUS treatments. At three months after the first treatment, numerous damaged regions were observed. At four months after the second treatment, the lesions produced by the first treatment were still evident. New lesions were detected at this time on the temples and in an anterior location in addition to those produced by the first treatment.

Fig. 3 shows another example of the bone marrow lesions in a patient observed four months after TcMRgFUS, here along with heating predicted by the simulations. In the simulation, numerous spots were predicted with high temperatures. Comparison of isotherms with the lesion segmentations reveal that the location of the lesions was consistent with the predictions of the simulation. The simulation also predicted low-level heating just inside the skull bone in the subdural space; similar heating was observed in MRTI at the same location (Fig. 4).

Qualitatively, the locations and shapes of the bone marrow lesions were similar to the heated regions predicted by the simulations. Fig. 5 shows a 3D rendering of the outer skull surface

color-coded by the maximum temperature rise in the skull and the lesion locations superimposed. In almost every case, the lesions occurred in regions where the temperature was predicted to be elevated, and the shapes of the heated regions were similar to the lesions. However, there were also numerous locations where the simulations predicted high temperatures where lesions were not observed. These heated regions were often evident in dorsal portions of the skull and occurred when the 3–15 month MRI was obtained with thick slices, suggesting perhaps that lesions were present but not detected.

Fig. 6 shows the simulated heating for the 24 patients where lesions were not detected. Overall, the predicted heating was lower in most of those patients. However, four treatments had regions where the simulated heating was comparable to those where lesions were observed in other patients. Three of these cases had thick slices in the post-treatment MRI which may have failed to detect more subtle or smaller lesions.

Both the maximum and total energy used during each TcMRgFUS treatment were predictive of the onset for MRI-evident damage in the bone marrow (Fig. 7a–b). The threshold for damage was between 18.1–21.1 kJ (maximum energy applied) and 97–122 kJ (total energy applied). In contrast, the extent of the lesions at 3–15 months was not always well-predicted by the energy alone. The maps in Fig. 5 are sorted by the peak sonication energy used during each treatment. While overall the extent of the lesions increased as the energy increased, there were several cases that did not fit this trend. For example, treatment number 12 had extensive lesions after TcMRgFUS where the peak and total acoustic energy was 24.3 and 101 kJ, respectively. Treatment number 33, in contrast, had only small lesions after sonications at higher energies. The simulations predicted substantially higher skull temperatures in treatment 12 and lower temperatures in treatment 33.

The mean estimated temperature in the skull in the areas identified as lesions was $54.1 \pm 7.4^\circ\text{C}$. Areas not identified as lesions had a significantly ($P < 0.001$) lower mean temperature of $43.1 \pm 5.1^\circ\text{C}$. The temperature where the probability for observing a lesion was 50% was 59.2°C (Fig. 7c); a slightly lower threshold of 57.2°C was found when we only considered patients where the MRI at 3–15 months was obtained with a 2 mm slice thickness.

To further examine how well the size, location, and shape of the lesions was predicted by the simulations using different temperature thresholds, we calculated the Dice similarity coefficient (DSC) between the locations of isotherms and lesions segmentations across the skull surface. When all patients were considered, the temperature that resulted in the highest DSC was approximately 53°C (Fig. 8a). However, there was substantial variation among subjects (thin lines in Fig. 8a), and the overall similarity was low when the total lesion volume was small (Fig. 8b). We also calculated ROC curves for different threshold temperatures (Fig. 8c). At the temperature that had the highest DSC (53°C), the sensitivity was 94%, but the specificity was only 56%, a finding that reflects how the lesions were generally located where high temperatures were predicted, but that there were numerous areas where high temperatures were predicted but no lesions were found. The AUC of 0.87 suggests that the temperature was a good predictor of lesions.

Finally, we evaluated the volume of the lesions as a function of the acoustic energy (Fig. 8d) and the volume of the skull that was heated above 53°C (Fig. 8e), the value that produced the highest DSC in the analysis described above. The lesion volume increased linearly as a function of the acoustic energy for exposures greater than approximately 18 kJ (R^2 : 0.69). A good agreement was observed between lesion volume and the volume of the skull heated above 53°C (slope: 1.2 ± 0.1 ; y-intercept: $-1.5 \pm 2.0 \text{ cm}^3$; R^2 : 0.88).

IV. Discussion

Previous reports have studied skull heating during TcMRgFUS [17, 18]. Here we demonstrate that hotspots predicted by these simulations agree qualitatively with the locations of bone marrow lesions. While more work is needed to refine the simulations, these results providing initial clinical validation of these models.

Qualitatively, with few exceptions the bone marrow lesions appeared in regions where the simulations predicted elevated heating. However, there were multiple areas where the simulations predicted high temperatures, but lesions were not observed. This discrepancy could be due to several factors. First, the imaging was obtained 3–15 months after FUS, and some damage may have resolved by that time. Second, any damage in the cortical bone, which has no signal with standard MRI sequences, would not be detected. Finally, the cooling of the bone by the chilled water was not considered. Nevertheless, these results are promising to predict skull heating across the range of acoustic energies encountered in MRgFUS patients.

The wide range of acoustic energies needed to achieve a lesion at the focus arises due to varying skull properties. The energy used during treatment was predictive of whether or not bone marrow lesions were observed at 3–15 months after treatment, and the threshold for damage (18.1–21.1 kJ) is consistent with earlier work (15.5–25.8 kJ) [13]. However, the acoustic energy was not always predictive of the extent of the damage. In contrast, the acoustic and thermal simulations together appeared to predict both location and approximate shape of the resulting lesions. If the simulations could be performed before treatment, the absorption and subsequent heating could be taken into account, potentially allowing one to change how the energy is distributed over the head to better normalize the heating. With enough confidence in the simulations, one could potentially redistribute the energy delivered into the bone to better optimize the shape and size of the focus while maintaining a safe exposure level overall.

To use the simulations in this way, we need to validate the absolute temperature predictions. An important factor that was not investigated here is the effects of the active cooling on the baseline temperature of the scalp, bone, and brain surface. Methods developed to model hypothermia for the treatment of stroke [19] might be useful for such simulations.

We also need to validate our approach for acoustic absorption in the thermal model. We used a simple model that assumed that shear mode absorption dominated in the trabecular bone due to the complex internal structure. We used the shear absorption coefficient found by others in cadaver skulls [11] and a fixed density threshold to categorize cortical and

trabecular bone. We do not know if this methodology is correct or how it might vary between patients. For this reason, along with other limitations in the study and in the simulations described below, we did not anticipate that we would find perfect agreement between the simulated heating and the location and size of the thermal lesions or that the absolute temperature measurements would be accurate. Nevertheless, the patterns of heating qualitatively agreed with the location and size of the bone marrow lesions in many cases, the estimated threshold for thermal damage was reasonable, and quantitative comparisons of heating and lesion segmentation were promising. With more work understanding how we can estimate acoustic absorption based on CT-derived density and a better understanding of when and how we can detect thermal damage to the skull and bone marrow, we anticipate that acoustic and thermal simulations will be able to predict where excessive heating will occur.

This study had several limitations that influenced our ability to make accurate predictions. The MRI protocols at 3–15 months were set to image the lesion in the thalamus, not the skull. These protocols varied, and it appeared that some lesions may have been missed when thicker imaging slices were used. It is also possible that some bone marrow damage was resolved by the time that the imaging was obtained. Furthermore, since cortical bone does not have MRI signal in standard pulse sequences, any potential damage there was undetectable. It would be interesting to try ultra-short TE MRI to see if any changes are evident in cortical bone. Obtaining CT scans after TcMRgFUS or contrast-enhanced MRI could also be revealing.

The simulations also had several limitations. They were previously obtained with the heating at the focus in mind. Each element was individually simulated over a small volume and summed. While around the focus the total combined field could be fully reconstructed, the dimensions of the individual elemental simulations may have been insufficient to provide full coverage at the skull, leading to an underestimate of the total field. However, the main contribution from each element was included. The accumulated effects of multiple sonications were not taken into account. We also did not include shear mode conversion in the acoustic simulations. Since the TcMRgFUS system disabled elements with external angles greater than 25°, such effects may not be significant. Finally, as described above acoustic absorption may have been modeled incorrectly in the dipole in the thermal simulations. More work is needed to understand the role of these factors along with the active cooling so that the absolute temperature in the bone and the marrow can be accurately predicted. Despite these limitations, these results are promising for the prospect of predicting when and where excessive heating and bone marrow damage will occur with TcMRgFUS.

Finally, the bone marrow damage observed here and previously by Schwartz et al. [13] raise several questions. First, why was the bone marrow damage not evident at 24 h after FUS? In other contexts, inflammation that accompanies thermal necrosis is evident by 24 h, and edema associated with inflammation is generally seen in T2-weighted imaging at that time. Second, does thermally induced damage to the bone marrow affect transcranial focusing? It is known that focal heating often becomes progressively harder to achieve after several sonications are delivered [20]. Is this effect related to the bone marrow damage observed

here? Finally, while the bone marrow lesions are asymptomatic, does the extensive damage seen in some patients (such as patients 7 and 40) pose any risk? To answer these questions will require additional studies beyond the scope of the present work.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Methods, (a) CT scan data (sagittal reconstruction) of a patient with the transducer elements superimposed. For each element, a small volume was selected. The CT data was used to estimate the acoustic parameters (density, sound speed, attenuation) that were inputs to the acoustic simulation, (b) After all 993 elements were simulated, the resulting pressure fields were interpolated into a common reference frame and summed. The phase and magnitude of each element was set to the values used during treatment. This combined field was used with the bioheat equation to estimate the temperature rise

Fig. 2.

Example bone marrow lesions in an ET patient who was treated twice. (a) CT scan with the segmentations of the lesions superimposed. (b) T2-weighted MRI at 24 h reveal no evident lesions. (c-d): T2-weighted MRI obtained 3–4 months after the two treatments. All images were registered and interpolated to a common coordinate system. The lesions were identified by comparing axial T2-weighted obtained at 24 h and at 3–15 months after FUS. Representative axial images at both times are included for all patients in the Supplemental Data.

Fig. 3.

Simulated skull heating and bone marrow lesions from treatment 12. (a) Simulated heating in treatment 12. The outline of the skull from the CT scan is superimposed. Note how the heating extended into the scalp, (b) At 24 h after FUS, no skull lesions were observed. (c) T2-weighted MRI obtained four months after TcMRgFUS. (d) The same images with segmentations of the lesions and 57°C isotherms superimposed. All images and segmentations were registered and interpolated to the same reference frame. The lesion segmentations were made on axial MRI. Additional axial planes for this and all patients at both 24 h and 3–15 months after FUS can be found in the Supplemental Data.

Fig. 4.

Coronal MRTI and simulated heating obtained during a sonication in treatment 12. Heating just inside the skull bone (arrows) was observed in MRTI and predicted by simulation. The scalp was also heated. The temperature scale here was reduced to highlight this heating. Note that the bone does not appear to be heated in MRTI due to the lack of MRI signal. The images on the bottom have masked out the skull to highlight the low-level heating. The plot on the bottom shows the mean temperature distribution across the brain in the area indicated by the dotted lines in the lower right panel.

Fig. 5.

Skull heating and lesions. Maps of the outer skull surface are shown for 16 patients where bone marrow lesions were observed 3–15 months after TcMRgFUS. The maps are color-coded with the maximum temperature projections estimated by the simulations. The projections are rendered on the outer surface of the CT scan. The maps on the right show the locations of the lesions in magenta. In most cases, the locations of the lesions corresponded to regions where high temperatures were predicted by simulation. Except where noted, the post-FUS MRI was obtained at 3T with a 2 mm slice thickness. When thicker slices were used, high temperatures were often predicted in dorsal skull regions where lesions were not observed, suggesting perhaps lesions were present but not observed in MRI. The maps are sorted by the maximum acoustic energy used during the treatments. The treatment number and the maximum/total acoustic energy are shown; one patient received two treatments (*) 3 months apart. Treatment 9 was a pallidotomy for Parkinson's disease; others were thalamotomy for essential tremor. The "x" symbols indicate the location of the focal point.

Fig. 6.

Skull heating in 24 treatments where bone marrow lesions were not observed. The maps are color coded with the maximum temperature predicted by simulations of the sonication with the maximum energy for each treatment. The projections are rendered on the outer CT scan. Except where noted, the post-FUS MRI was obtained at 3T with a 2 mm slice thickness. The maps are sorted by the maximum acoustic energy used during each treatment; the treatment number along with the maximum and total acoustic energy used are noted. One patient received two treatments (*) 10 months apart. Treatment 10 was a pallidotomy for Parkinson's disease; others were thalamotomies for essential tremor. The "x" symbols indicate the location of the focal point.

Fig. 7.

Probability of bone marrow lesions, (a-b) Presence or lack of lesions plotted as a function of the maximum and total acoustic energy used during treatment. The probability for lesions is shown along with 95% CI. (c) Presence or lack of lesions as a function of the maximum temperature on the skull surface. Here, the analysis was done pointby-point. The individual temperatures points are shown by the small dots.

Fig. 8.

Agreement between lesion extent and simulated heating, (a) DSC comparing the areas of the lesions and isotherms on the skull surface at different threshold temperatures. Thin lines are from individual patients, (b) Best DSC as a function of lesion volume for each patient. (c) ROC analysis comparing specificity and sensitivity of predicting lesions across the skull surface (AUC: the area under the curve), (d-e) Lesion volume analysis. Lesion volume plotted as a function of the maximum energy used during treatment (e) and the volume of the skull that was estimated to have heated to at least 53°C (f), the best threshold found in (a).

TABLE I

Acoustic and thermal parameters used in the numerical model

Parameter	Water	Brain/scalp	Skull
Density (mg/kg ³)	1000	1030 ^a	from CT ^d
Sound speed (m/s)	1500	1560 ^a	from CT ^d
Attenuation at 660 kHz (Np/m)	0	4.36 ^b	from CT ^d
Absorption at 660 kHz (Np/m)	0		20.5 (cortical) ^c 41.0 (diploe) ^c
Thermal conductivity [W/(m·°K)]	-	0.51 ^a	0.43 ^a
Specific heat [J/(kg·°K)]	-	3640 ^a	1440 ^a
Perfusion coefficient (l/s)	-	8.33E-03 ^a	3.33E-04

^a
ref. [1]^b
ref. [9]^c
ref. [11]^d
ref [12]