Ultrashort echo-time MRI versus CT for skull aberration correction in MR-guided transcranial focused ultrasound: *In vitro* comparison on human calvaria

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**Purpose:** Transcranial magnetic resonance-guided focused ultrasound (TcMRgFUS) brain treatment systems compensate for skull-induced beam aberrations by adjusting the phase and amplitude of individual ultrasound transducer elements. These corrections are currently calculated based on a preacquired computed tomography (CT) scan of the patient’s head. The purpose of the work presented here is to demonstrate the feasibility of using ultrashort echo-time magnetic resonance imaging (UTE MRI) instead of CT to calculate and apply aberration corrections on a clinical TcMRgFUS system.

**Methods:** Phantom experiments were performed in three *ex-vivo* human skulls filled with tissue-mimicking hydrogel. Each skull phantom was imaged with both CT and UTE MRI. The MR images were then segmented into “skull” and “not-skull” pixels using a computationally efficient, threshold-based algorithm, and the resulting 3D binary skull map was converted into a series of 2D virtual CT images. Each skull was mounted in the head transducer of a clinical TcMRgFUS system (ExAblate Neuro, Insightec, Israel), and transcranial sonications were performed using a power setting of approximately 750 acoustic watts at several different target locations within the electronic steering range of the transducer. Each target location was sonicated three times: once using aberration corrections calculated from the actual CT scan, once using corrections calculated from the MRI-derived virtual CT scan, and once without applying any aberration correction. MR thermometry was performed in conjunction with each 10-s sonication, and the highest single-pixel temperature rise and surrounding-pixel mean were recorded for each sonication.

**Results:** The measured temperature rises were ~45% larger for aberration-corrected sonications than for noncorrected sonications. This improvement was highly significant ($p < 10^{-4}$). The difference between the single-pixel peak temperature rise and the surrounding-pixel mean, which reflects the sharpness of the thermal focus, was also significantly larger for aberration-corrected sonications. There was no significant difference between the sonication results achieved using CT-based and MR-based aberration correction.

**Conclusions:** The authors have demonstrated that transcranial focal heating can be significantly improved *in vitro* by using UTE MRI to compute skull-induced ultrasound aberration corrections. Their results suggest that UTE MRI could be used instead of CT to implement such corrections on current 0.7 MHz clinical TcMRgFUS devices. The MR image acquisition and segmentation procedure demonstrated here would add less than 15 min to a clinical MRgFUS treatment session. © 2015 American Association of Physicists in Medicine. [http://dx.doi.org/10.1118/1.4916656]

Key words: transcranial MR-guided focused ultrasound, ultrashort echo time (UTE) MRI, bone segmentation, skull aberration correction

1. INTRODUCTION

Magnetic resonance-guided high-intensity focused ultrasound (MRgFUS) is an emerging surgical technique that provides a much less invasive alternative to traditional surgery for treating a variety of disorders.1–3 Some of the most attractive potential applications are in the brain, since MRgFUS offers the ability to thermally ablate deep-brain lesions and other focal targets.
without performing a craniotomy or otherwise disturbing the surrounding healthy tissue.\textsuperscript{4–6}

One of the main technical challenges associated with transcranial focused ultrasound of the brain is the presence of the cranium itself, which distorts and attenuates the ultrasound beam, inhibiting the ability to transfer enough acoustic energy to the target location to reach ablative temperatures. This challenge has been addressed by developing large-aperture transducer arrays consisting of hundreds of individually powered ultrasound transducer elements.\textsuperscript{7–10} Such arrays are designed to surround the upper part of the cranium and maximize the sonicated surface area, which minimizes intensity at the skull for a given total acoustic energy. Beam aberrations caused by cranial bone in the path of the ultrasound beam can then be compensated for, by adjusting the phase and amplitude of the radiofrequency (RF) power driving each transducer element, in order to maintain a tight beam focus at the target location.\textsuperscript{11,12}

In current clinical MRgFUS systems, these aberration corrections are calculated based on a preacquired x-ray computed tomography (CT) scan of the patient’s head. The CT scan is imported into the treatment planning software and aligned with MR images obtained \textit{in situ}, to match the current position of the skull with respect to the transducer array. The planning software then performs numerical simulations of acoustic wave propagation to determine the appropriate phase and amplitude settings for each transducer element based on a three layer model (water/bone/brain)\textsuperscript{13,14} or a heterogeneous model of the skull’s internal structure.\textsuperscript{15–17}

CT is used to generate the required skull map because it provides high-resolution images with excellent bone contrast, which makes it easy to identify bone pixels using a robust quantitative threshold. However, overall workflow for MRgFUS surgical procedures would be improved if the necessary bone map could instead be derived from a magnetic resonance imaging (MRI) scan obtained \textit{in situ}. Using MRI would avoid the inconvenience of obtaining a separate CT scan, streamlining treatment planning by eliminating the need to import the images and align them with MR images obtained \textit{in situ}. The CT scan is imported into the treatment planning software and aligned with MR images obtained \textit{in situ}, to match the current position of the skull with respect to the transducer array. The planning software then performs numerical simulations of acoustic wave propagation to determine the appropriate phase and amplitude settings for each transducer element based on a three layer model (water/bone/brain) or a heterogeneous model of the skull’s internal structure.

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MRI is not commonly used to image the skull, due to low MR signal density and extremely short $T_2^*$ decay time in cortical bone. Thus, one strategy for constructing a skull map from conventional MR images is to infer the presence of bone at pixel locations lacking measurable signal. However, this strategy can lead to erroneous classification of bone pixels since there is no way to definitively distinguish between air and bone using this approach. Although the misidentification of bone pixels can be minimized by incorporating sophisticated morphological analysis into the segmentation algorithm,\textsuperscript{24} such analysis tends to be computationally intensive and thus could be prohibitively time consuming for real-time application \textit{in situ}.

Ultrashort echo-time (UTE) MRI is an emerging pulse-sequence technique that enables the weak, short-lived signal from cortical bone to be captured and imaged.\textsuperscript{25} Thus, UTE MRI can image the skull directly, yielding bone contrast that is weaker than CT but that still offers the ability to positively identify bone pixels on MR images. The purpose of the present work is to demonstrate the feasibility of using MR-derived skull maps to improve transcranial focal heating in a clinical MRgFUS brain system. To achieve this goal, we developed a dual-echo UTE pulse sequence and computationally efficient image segmentation procedure and used these tools to generate binary bone maps of human skull phantoms. Transcranial focused ultrasound was then performed in conjunction with MR thermometry in each of the phantoms—using aberration corrections calculated from the binary bone maps, using aberration corrections calculated from CT scans, and without applying any corrections—and the measured temperature elevations were compared.

2. METHODS

Experiments were performed in three skull phantoms, each consisting of an \textit{ex-vivo} human skull filled with tissue-mimicking hydrogel (ATS Laboratories, Bridgeport, CT). One skull was purchased from Skulls Unlimited (Oklahoma City, OK), later referred as skull #1. The other two skulls were extracted from human heads obtained from the Virginia Department of Health’s State Anatomical Program as part of a previous project.\textsuperscript{26} Both specimens provided by this mechanism were full organ donors at the time of death. Heads were defleshed and cleaned. To allow easy access to the interior of the cranium, the skull cap was sliced off using a surgical bone saw. All three skulls were stored in air at room temperature for some time before performing the experiments described here.

The tissue-mimicking hydrogel was liquefied at 55°C in a microwave oven dedicated to research. The liquid hydrogel was poured into the skull base and inverted skull cap, each of which was lined with kitchen plastic wrap. Both pieces were then cooled in a refrigerator to approximately 5°C for 8 h. After allowing the hydrogel to cool and set, both hydrogel “half-brains” were removed and stored in a refrigerator to inhibit bacterial growth. (Even though all skulls had been carefully cleaned, we have observed that a biofilm can appear at the surface of the skull if the hydrogel stays in direct contact with the skull for too long.) The two pieces of the skull were then reattached, using plastic cable ties inserted through several pairs of holes drilled on either side of the seam.

Prior to each experiment, the skull was degassed overnight inside a homebuilt vacuum chamber partially filled with water. The skull was completely immersed in the water, and the air above the water was evacuated using a vacuum pump. This procedure accelerated the infusion of water into any void spaces in the bone matrix, eliminating air bubbles that would impede sonication while also restoring moisture lost during the phantom preparation, to better approximate \textit{in-vivo} conditions. For imaging, the degassed skull was transferred to a water-tight
plastic container, and strips of gelatin were placed between the outside of the skull and the walls of the container to fix the skull in place. The container was then completely filled with water, both to preserve moisturization and to mimic the conditions present during sonication, and the top of the container was sealed in place to prevent leaks during imaging.

Each skull was imaged with both CT and MRI. CT was performed using a clinical scanner (Discovery CT750 HD, GE Healthcare, Waukesha, WI). CT imaging parameters included reconstruction diameter = 250 mm, matrix = 512 × 512, and slice thickness = 0.625 mm, resulting in a voxel size of 0.488 × 0.488 × 0.625 mm. MRI was performed using a clinical 3 T scanner (Trio, Siemens Medical Solutions, Malvern, PA) and standard multichannel head coil, using the dual-echo UTE pulse sequence described below. Three-dimensional MR images were acquired on a 192 × 192 × 192 matrix with 240 mm field of view, yielding isotropic 1.25 mm native resolution. The original image matrix was then interpolated onto a finer grid, resulting in a final voxel size of 0.625 × 0.625 × 0.625 mm.

A 3D map of the skull was created from the MR images by applying the algorithm explained in detail below. Virtual CT data were constructed from this map by assigning 1000 Hounsfield units to bone pixels and replacing the header entries corresponding to matrix size, slice location, slice thickness, patient position, and pixel size with appropriate values.

Following imaging, the skull was removed from the water-tight container and the top of the cranium was removed by clipping the plastic cable ties. The hydrogel “brain” was placed in the cranial cavity and the top of the skull was reattached using new cable ties. The skull phantom was then returned to the vacuum chamber for final degassing, in preparation for sonication.

For the sonication experiment, the skull phantom was mounted in the 0.7 MHz head transducer of a clinical MRgFUS system (ExAblate Neuro, Insightec, Israel) using a custom mounting plate and water-retention membrane [Fig. 4(a)]. The space between the transducer and the skull was flooded with temperature-regulated degassed water. Multiplane scout MR images were acquired, and the transducer position was mechanically adjusted to select a central target location inside the phantom brain. The transducer and phantom were then locked in place, and a final set of scout MR images was acquired.

One of the CT image sets (either real or virtual) was then loaded into the MRgFUS system and manually aligned with the scout MR images. Continuous-wave ultrasound sonications, each of 10 s duration, were performed at several different target locations within the electronic steering range of the transducer, with and without aberration corrections applied. Finally, the other CT data set was imported and aligned, and identical sonications were performed at the same target locations using aberration corrections calculated from this CT data set.

The power settings and target locations for each sonication are given in Table I for all three phantom experiments. Both low power (400 AW) and high-power (700 AW) sonications were performed in the first skull phantom. Only high-power (750 AW) sonications were performed in the second and third skull phantoms. Proton resonance frequency (PRF) based thermometry was performed during sonication, using the standard tools incorporated into the MRgFUS system, and the highest single-pixel temperature rise and surrounding-

| Target location | Power (acoustic watts) | No aberration corrections | CT-based corrections | UTE-based corrections |
|-----------------|------------------------|---------------------------|----------------------|----------------------|
|                 | Peak/mean (°C)         | Δx/Δy (mm)                | Peak/mean (°C)       | Δx/Δy (mm)           | Peak/mean (°C)       | Δx/Δy (mm) |
| Skull #1        |                        |                           |                      |                      |                      |            |
| Center          | 400                    | 6/4                       | 1.4/2.8              | 8/7                  | 0.8/3.2              | 9/7        | 0.7/3.2 |
| Right           | 400                    | 7/6                       | 1.1/2.7              | 8/7                  | 0.6/3.1              | 8/7        | 0.5/2.9 |
| Left            | 400                    | 3/2                       | 1.5/2.9              | 4/3                  | 0.5/2.7              | 5/4        | 0.3/2.9 |
| Center          | 700                    | 10/8                      | 1.2/2.4              | 12/10                | 0.6/2.8              | 13/11      | 0.7/3.0 |
| Right           | 700                    | 10/9                      | 0.6/2.6              | 12/10                | 0.6/3.0              | 13/10      | 0.7/2.9 |
| Left            | 700                    | 5/4                       | 2.0/2.9              | —                    | —                    | 7/6        | 0.6/2.9 |
| Skull #2        |                        |                           |                      |                      |                      |            |
| Center          | 750                    | —                         | —                    | 18/14                | 0.5/0.8              | 18/15      | 0.5/1.2 |
| Superior        | 750                    | 12/10                     | 1.6/1.3              | 17/14                | 0.6/0.9              | 18/14      | 0.5/1.3 |
| Right           | 750                    | 9/8                       | 1.6/1.5              | 14/11                | 0.6/1.0              | 14/11      | 0.5/1.5 |
| Left            | 750                    | 7/7                       | 1.6/1.6              | 13/10                | 0.4/1.6              | 12/10      | 0.1/1.5 |
| Skull #3        |                        |                           |                      |                      |                      |            |
| Center          | 750                    | 14/12                     | 0.1/0.7              | 19/16                | 0.1/0.4              | 20/16      | 0.4/0.5 |
| Right           | 750                    | 12/10                     | 0.0/0.5              | 17/13                | 0.4/0.5              | 17/13      | 0.2/0.5 |
| Inferior        | 750                    | 9/7                       | 0.3/0.3              | 14/11                | 0.0/0.5              | 15/12      | 0.4/0.5 |
| Anterior        | 750                    | 11/10                     | 0.1/0.5              | 16/13                | 0.1/0.5              | 15/12      | 0.0/0.5 |

Table I. Detailed summary of sonication results. Sonications performed without electronic beam steering are labeled Center in the column Target location. All other sonications were performed at target locations steered 1 cm away from the natural center in the specified anatomical directions (right, left, superior, inferior, or anterior). Peak refers to the highest single-pixel temperature rise measured during the 10-s sonication, and mean refers to the mean temperature rise measured in the eight pixels surrounding the single-pixel peak. The distance measurements Δx and Δy refer to the displacement between the selected target location and the location of the hottest pixel along the lateral and anteroposterior directions, respectively.
pixel mean were recorded for each sonication. The location of the hottest measured temperature along the right–left (R–L) and anterior–posterior (A–P) directions in the 2D thermometric imaging plane was also recorded. The size and location of the measured temperature rises were compared for the three different sets of aberration corrections. Statistical significance was assessed by applying the paired student’s t-test to measurements performed at the same target location using different aberration corrections.

2.A. MRI pulse sequence

MR images were acquired using the dual-echo, RF-spoiled pulse sequence shown in Fig. 1. This UTE pulse sequence acquires k-space data on a fully sampled 3D spoke-radial trajectory. There are many different ways to determine the angular distribution of radial spokes for such a trajectory; the particular method used here has been fully described elsewhere. The same k-space ray is sampled twice following the nonselective excitation RF pulse, first at an ultrashort echo time of 80 μs and again at a conventional echo time of 2.54 ms, to acquire two inherently coregistered images I₁ and I₂ with different contrast weightings. Other pulse-sequence parameters included TR = 5.14 ms, flip angle = 20°, RF pulse duration = 100 μs, peak readout bandwidth = 1302 Hz/pixel (on the gradient flat-top), equivalent Cartesian matrix = 192 × 192 × 192, pixel resolution = 1.25 mm isotropic, total number of k-space spokes = 116,130, and total imaging time = 9 min 58 s.

Radial image reconstruction was performed directly on the scanner, using a custom analysis routine written in C++. This analysis routine makes use of standard gridding procedures for reconstructing non-Cartesian k-space data and compensates for gradient timing delays by allowing for an adjustable delay between the start of the data acquisition window and the start of the gradient ramp along each physical axis. The appropriate delay settings were estimated empirically, by visually optimizing the edge definition of a water phantom imaged with the same pulse sequence. The multichannel RF coil data were combined by first reconstructing separate images for each channel and then adding in quadrature to yield a single magnitude image at each echo time.

2.B. MR image segmentation

Our goal was to develop a completely automatic, computationally efficient algorithm for identifying bone pixels on our MR images. To achieve this goal, we developed an image segmentation procedure that separates tissue types based primarily on intensity thresholds applied to simple arithmetic combinations of the inherently coregistered images I₁ and I₂. The threshold values are determined from the statistical properties of the intensity distributions according to the rationale described below.

Figure 2 shows several contrast combinations that can be formed from our dual-echo MR image set. The images in the top row depict a single sagittal slice through the middle of the skull, extracted from the 3D MR images of the third skull phantom. The raw image magnitudes I₁ and I₂ are shown in (a) and (b), and the arithmetic combinations Iₐdiff = I₁ − I₂ and Iₐsum = I₁ + I₂ are shown in (c) and (d), respectively. The bottom row of Fig. 2 shows histograms of all pixel values from I₁, I₂, Iₐdiff, and Iₐsum, compiled over the entire 3D image matrix. Our segmentation procedure was guided by the following observations.

(A) There are four types of “tissue” in the imaged field of view: air, water, gelatin, and bone. These tissue types can be grouped into three basic classes: (1) air, which is characterized by low pixel intensity on both I₁ and I₂, (2) water/gelatin, which is characterized by high pixel intensity on both I₁ and I₂, and (3) bone, which is characterized by high pixel intensity on I₁ but low pixel intensity on I₂. Furthermore, there are many more class 1 pixels than class 2 pixels over the entire 3D image matrix, and there are vastly more class 2 pixels than class 3 pixels.

(B) The contrast between air pixels (class 1) and nonair pixels (class 2 + 3) is most distinct on Iₐsum [Fig. 2(d)].

Figure 1. Dual-echo UTE pulse sequence. The direction of the readout axis is varied for each repetition, to evenly sample a spherical region of k space. The UTE acquisition begins 20 μs after the end of the 100-μs RF pulse, which is the soonest allowed by our scanner, and k-space data are sampled on the initial ramp and flat-top of the readout gradient. The second echo is acquired using the same k-space trajectory, to minimize misalignment of the resulting images. The pulse sequence is RF-spoiled, and crusher gradients are applied along the physical z axis. The specifications of the readout gradient are ramp time = 150 μs, flat-top time = 310 μs, and amplitude = 24.5 mT/m.
and the histogram of $I_{\text{sum}}$ values [Fig. 2(h)] shows that there is essentially no overlap between the air and nonair distributions. Furthermore, the distribution of air pixel values [the tall, narrow peak in Fig. 2(h)] is approximately symmetric and all values are positive, which implies that nearly all values in the air distribution are less than twice the central value.

(C) The contrast between bone pixels (class 3) and nonbone pixels (classes 1 and 2) is most distinct on $I_{\text{diff}}$ [Fig. 2(c)], but there is some overlap between the bone and nonbone distributions [see inset of Fig. 2(g)]. Furthermore, the distributions of class 1 and class 2 pixel values are indistinguishable on $I_{\text{diff}}$.

Informed by these observations, we developed a segmentation algorithm that assigns each pixel location to one of the three classes defined in (A). The general outline of the algorithm is as follows: first, we perform a preliminary segmentation into three classes, based on intensity thresholds derived from and applied to the $I_{\text{diff}}$ and $I_{\text{sum}}$ pixel distributions, with the goal that the vast majority of the pixels assigned to a given class actually belong in that class. Then, we refine the threshold for separating class 2 and class 3 pixels to better account for partial-volume pixels. Finally, we apply a spatial connectivity requirement to the pixels in the bone class, to eliminate isolated pixels or groups of pixels that are clearly not part of the skull. The specific steps of our algorithm, along with the rationale behind each step, are as follows.

1. Segment air pixels based on the distribution of $I_{\text{sum}}$, by assigning all pixel locations with $I_{\text{sum}} < 2 \times \text{median}(I_{\text{sum}})$ to class 1.

Rationale: Based on observation (B), the vast majority of air pixels have $I_{\text{sum}}$ values less than twice the central value of the air pixel distribution. And because there are many more air pixels than nonair pixels, the median of all pixel values is a decent approximation to the central value of the air pixel distribution. Therefore, twice the median of the entire $I_{\text{sum}}$ distribution is an easily calculable yet reasonable threshold to use for assigning pixel locations to class 1.

2. Segment the remaining (nonair) pixels into class 2 or class 3 based on their $I_{\text{diff}}$ values. To accomplish this, we aim to find a threshold below which the vast majority of remaining pixels belong to class 2 and above which vast majority belong to class 3. To arrive at this threshold value, we first find the median $M$ of the nonair $I_{\text{diff}}$ pixel values. Then, we compute the root-mean-squared difference $\sigma_L$ between $M$ and all nonair pixel values less than $M$. Finally, we assign all nonair pixels with $I_{\text{diff}} \leq M + 5\sigma_L$ to class 2 and assign all nonair pixels with $I_{\text{diff}} > M + 5\sigma_L$ to class 3.

Rationale: Based on observation (A), the vast majority of nonair pixel locations belong to class 2, so once again the median of the combined class 2 + 3 distribution is a good estimate of the central value of the class 2 distribution. The class 2 + 3 distribution is asymmetric, however, since virtually all bone pixels lie in the right tail. Thus, the left-width of the class 2 + 3 distribution provides a good estimate of the half-width of the class 2 distribution. Finally, in the approximation that the class 2 pixel values are normally distributed, nearly all values will lie within 5 standard deviations of the central value.
3. Refine the threshold derived in the previous step as follows: compute the median value $M_2$ of $I_{\text{diff}}$ for all pixels previously assigned to class 2, and compute the median value $M_3$ of $I_{\text{diff}}$ for all pixels previously assigned to class 3, and take the average of these medians as the refined threshold. That is, reassign all pixel locations with $I_{\text{diff}} > (M_1 + M_2)/2$ to class 3.

**Rationale:** The threshold used in step 2 for separating class 2 from class 3 was derived purely from the class 2 distribution. To better estimate a proper threshold, and to appropriately handle partial-volume pixels containing both class 2 (water/gelatin) and class 3 (bone) tissues, we should consider values in class 3 as well. Since we believe that the vast majority of pixels initially assigned to class 2 or class 3 actually belong in those classes, the medians of the initial class 2 and class 3 distributions are good approximations to the medians of the actual distributions. Thus, the midpoint between these median values is a reasonable threshold to use for separating class 2 and class 3.

4. Finally, clean up spatial outliers in the bone pixel map by enforcing a spatial connectivity requirement as follows: find all distinct, six-connected objects among class 3 pixel locations in the 3D image matrix and take the largest such object to be the skull.

**Rationale:** There is some overlap between the class 2 and class 3 distributions on $I_{\text{diff}}$, which will lead to some incorrect class assignments using a purely threshold-based segmentation. If the spatial density of erroneously assigned pixels is low, the vast majority can be eliminated by enforcing the simple connectivity requirement used here.

The image segmentation procedure described here was programmed in MATLAB (MathWorks, Natick, MA) on an ordinary laptop computer. Three-dimensional bone maps were constructed for each skull phantom, by applying this segmentation procedure to the dual-echo MR images obtained from each skull.

### 3. RESULTS

Figure 3 shows near-final segmentation results from the third skull phantom, before enforcing the spatial continuity requirement in step 4. The images in the top row of Fig. 3 depict the same sagittal view of $I_1$ shown in Fig. 2(a), but segmented into (a) class 1 pixels, (b) class 2 pixels, and (c) class 3 pixels. A spatial outlier is visible on the right side of the upper edge of the bone image in (c). The bottom row of Fig. 3 shows histograms of $I_1$ values for all members of (d) class 1, (e) class 2, and (f) class 3, compiled over the entire 3D image matrix. The vertical scale of the histogram axes decreases by two orders of magnitude from left to right across the figure. A surface rendering of the final MR-derived bone map of this

![Image](image-url)
skull is shown in Fig. 4(b), viewed from the same angle as the photograph in Fig. 4(a).

Figure 5 shows the transducer phase corrections computed by the treatment planning software for the sonications performed in the third skull phantom. Each panel shows a map of all 1024 transducer elements and the RF phase setting used for each. The MR-based phase corrections in (a) and CT-based phase corrections in (b) appear similar, but both differ greatly from the uncorrected settings shown in (c).

Thermometry results for individual sonications in each skull phantom are given in Table I. At every tested target location, the measured temperature rise was greater for both of the sonications performed using aberration correction than for the sonication performed without applying aberration correction.
correction. Temperature results from the high-power sonications are displayed graphically in Fig. 6. Each bar represents the average temperature rise for all high-power sonications performed using the indicated aberration correction method. The total length of the bar is proportional to the single-pixel peak temperature rise, and the lighter portion of each bar represents the difference between the single-pixel peak and the surrounding-pixel mean. The thin error bars represent the standard error in the mean of the individual peak temperature measurements.

The measured peak temperatures were significantly larger for the aberration-corrected sonications than for the corresponding noncorrected sonications ($p < 10^{-4}$ for CT-based correction and $p < 10^{-5}$ for MR-based correction), but there was no significant difference between the peak temperatures achieved using CT-based and MRI-based aberration correction ($p = 0.3$). Calculated as a percentage of the peak temperature rise achieved without applying aberration correction, the average improvement using CT-based aberration correction was 45% and the average improvement using MR-based aberration correction was 46%.

Furthermore, the average difference between the single-pixel peak temperature and the surrounding-pixel mean was significantly larger for aberration-corrected sonications than for noncorrected sonications. The single-pixel peak temperature was 24% greater than the surrounding-pixel mean with CT-based aberration correction, 25% greater with MR-based correction, and only 14% greater without applying aberration correction, indicating that in addition to a higher peak temperature, a tighter ultrasound focus was achieved by correcting for skull-induced ultrasound beam aberrations. This focal improvement was statistically significant in both cases ($p = 0.047$ for CT-based correction versus no correction and $p = 0.044$ for MR-based correction versus no correction).

Position results are displayed graphically in Fig. 7. Each marker represents the average displacement ($\Delta x, \Delta y$) between the hottest pixel and the chosen target, for all sonications performed in a given skull using a given aberration correction method. The thin error bars represent the standard deviations along each principal axis. For skulls #1 and #2, the right–left displacement was significantly smaller ($p < 0.03$) for the aberration-corrected sonications than for the noncorrected sonications, while the mean anterior–posterior displacement was similar for all methods. There was no significant difference between the measured displacements for CT-based and UTE-based aberration corrections.

Finally, we note that the geometric center of the transducer was aligned furthest from the geometric center of the cranial dome, and thus furthest from a typical thalamic target for this transcranial MRgFUS (TcMRgFUS) system, in the first skull experiment. This non-ideal configuration likely contributed to the relatively large position error (~3 mm) and substantially lower focal heating observed in skull #1. The smaller position errors observed in skulls #2 and #3 are more consistent with the typical lesion placement error (~1 mm) previously reported.
during thalamotomy of essential tremor patients using the same TcMRgFUS system.  

4. DISCUSSION

The long-term goal of the work described here is to compute and apply UTE MR-based aberration corrections in living human subjects. A significant consideration for in-vivo application of the bone-mapping procedures used here is the presence of additional tissue types in a real human head. On the pulse-sequence side, the water/fat chemical shift must be accounted for in the UTE pulse-sequence design. In the dual-echo pulse sequence used here, we specifically chose TE$_2$ − TE$_1$ = 2.46 ms, which corresponds to a 2π phase difference between water and fat signals at the exact field strength of our MR scanner (2.89 T). This ensures that water and fat will have the same phase relationship at both echo times, yielding optimum subtraction of pixels containing both fat and water tissues. Therefore, the exact pulse sequence described here would be a suitable starting point for in-vivo application.

On the image segmentation side, the identification of bone pixels based purely on intensity thresholds might be more complicated in vivo. Although bone is the brightest tissue on $I_1$ in our skull phantoms, this will not be the case in a real human head. The fast pulse sequence described here is inherently $T_1$ weighted, and the flip angle is chosen to maximize the MR signal from bone, which has relatively short $T_1$. At this flip angle, the MR signal from long-$T_1$ species such as water is heavily suppressed, so they appear less intense than bone on $I_1$ despite their much higher proton density. In a living brain, cerebrospinal fluid will be similarly hypointense. However, brain tissue and fat have intermediate $T_1$ values and high proton density and thus will have intensities that compete with bone on both $I_1$ and $I_{diff}$. Therefore, any threshold-based segmentation algorithm will likely need to rely heavily on the arithmetic combination $I_{diff}/I_{sum} = (I_1 - I_2)/(I_1 + I_2)$, rather than $I_{diff}$, since dividing by $I_{sum}$ further suppresses tissues that are bright on both $I_1$ and $I_2$.

The use of UTE MRI instead of CT for brain procedure planning has been explored in other contexts, most notably for calculating PET attenuation corrections in hybrid PET/MR scanners. The motivation for that application is essentially identical to ours, namely, to eliminate the complications associated with a separately acquired planning CT. However, attempts to use purely threshold-based tissue segmentation for computing the required attenuation maps have yielded mixed results. In some studies, it was found that bone tissue could not be adequately segmented within the fine structures of the inner ear and paranasal sinuses based on MR signal intensity alone. Such deficiencies are not relevant to transcranial focused ultrasound, however, because the head transducer only covers the upper part of the cranium. Furthermore, sonication through air cavities (sinuses) is systematically avoided during treatment because air interfaces reflect ultrasound. It is evident from Figs. 3(b) and 3(c) that some of the facial bone pixels in this skull phantom were misclassified as class 2 and therefore did not appear in the bone map, but this did not compromise our sonication results. In general, we expect that threshold-based segmentation will be much more robust for the relatively thick bony structures of the upper cranium.

In the present study, we found that thermal rises obtained with both MR-based and CT-based transducer corrections were significantly larger and more tightly focused than those obtained without applying any corrections. Both sets of corrections were calculated automatically using the algorithm currently implemented in the ExAblate 4000 device, which is based on a ray-tracing computation (proprietary of Insightec) derived from Ref. 13, and all sonications were performed at 710 kHz. We emphasize that our findings are strictly applicable only at this frequency. Fry and Barger showed that higher ultrasound frequencies were more affected by the presence of the human skull than lower frequencies. Thus, more sophisticated aberration correction algorithms may be required for higher frequency operation.

Ray tracing takes into account the thickness and shape of the skull but not the internal structure (mainly, trabecular versus cortical bone). It has been shown that taking into account the internal structures of the skull improves the focusing quality at 1.5 MHz. Recent in vitro $^{16,36,37}$ ex vivo $^{17,38}$ and in vivo $^{19,39}$ works performed at 1 MHz used a full 3D finite difference simulation to calculate the phase shifts induced by the skull bone in order to take into account the fine details of skull structure revealed by CT. Although our results suggest that a binary bone map constructed from UTE MRI may be entirely sufficient for aberration correction at frequencies substantially less than 1 MHz, a more sophisticated acquisition and segmentation scheme capable of resolving and segmenting the fine internal structure of the cranial bones may be necessary for MRI to successfully compete with CT at higher frequencies.

In addition to beam aberration correction, a secondary purpose of the planning CT scan for transcranial focused ultrasound procedures is to identify calcified brain lesions that should be avoided during treatment, because such lesions will absorb acoustic energy more strongly than normal brain tissue and can lead to undesired heating away from the target. Current TcMRgFUS treatment planning includes manual calcification detection guided by CT images; transducer elements pointing at these calcifications are then automatically switched off. Thus, to completely replace the need for a planning CT, UTE MRI must be able to adequately depict these calcifications in the brain. It was recently shown that calcified arterial plaque appears very similar to cortical bone on UTE images, which suggests that calcified brain lesions might be identifiable using the same techniques appropriate for cranial bone segmentation. In the present study, we could not acquire UTE MR images while the skull phantom was positioned in the MRgFUS system because our UTE pulse sequence was developed on a different MR scanner platform. Besides availability of the required pulse sequence, another potential obstacle to in-situ application of UTE MR imaging for brain treatment planning is availability of an appropriate RF coil. The MRgFUS system used for the present study relies on the scanner’s built-in body coil for imaging the head. Although the body coil is adequate
for low-resolution anatomic imaging and thermometry, it may not provide sufficient SNR for high-resolution imaging and robust segmentation of cortical bone. A close fitting head coil such as the one used in the present study offers several-fold higher SNR than the body coil. The clean separation between noise and non-noise pixel distributions on \( I_{\text{sum}} \) [Fig. 2(h)] and the relatively small overlap between bone and not-bone pixel distributions on \( I_{\text{det}} \) [Fig. 2(g)] are key to the success of the segmentation algorithm used here. If the noise was several-fold larger, however, it is clear from the histograms shown in Fig. 2 that the ability to segment images based on simple thresholds would be severely compromised. Therefore, the feasibility of in-situ application of the UTE techniques demonstrated here would be greatly enhanced by software and hardware and improvements to existing transcranial MRgFUS systems.

5. CONCLUSIONS

We have demonstrated the feasibility of obtaining high-resolution (1.25 mm isotropic) maps of cranial bone in ex-vivo human skulls, by applying a computationally simple segmentation algorithm to dual-echo UTE MR images, and have shown that these MR-derived bone maps can be used to improve transcranial focal heating in a clinical brain FUS system. On average, the peak temperature rise measured during MR-based aberration-corrected sonications was 46% higher than the peak temperature rise measured without applying aberration corrections, and the difference between the single-pixel peak temperature and surrounding-pixel mean, which reflects the sharpness of the thermal focus, was 25% for MR-based aberration-corrected sonications versus 14% using uncorrected settings. Both of these improvements were statistically significant and were consistent with results obtained using CT-based aberration correction. The location of the peak temperature rise along the right–left and anterior–posterior directions was also measured for each sonication, but spatial differences between CT-based and MR-based correction methods were small and not statistically significant.

The dual-echo UTE pulse sequence used for this ex-vivo study should be equally applicable in vivo, but the bone segmentation algorithm might have to be modified to accommodate additional tissue types (especially fat) that were not present in our skull phantoms. Our goal here was not to develop a generally applicable method for segmenting UTE MR images, but rather to develop an effective and robust algorithm for identifying bone pixels on the particular images acquired for this phantom study. However, it is encouraging that we were able to accomplish this goal using a relatively simple analysis procedure, and our success in this regard offers promise that it may be possible to develop a similarly simple yet robust procedure for use in vivo. In the present study, the total MR scan time was 10 min for each skull phantom, and image reconstruction and segmentation took an additional 4 min. Thus, if similar time efficiency could be achieved in situ, the entire process demonstrated here would add less than 15 min to a clinical brain procedure. If UTE MR can also detect calcifications in the brain, the need for pretreatment CT imaging might be completely eliminated.

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