Abstract—High-resolution transcranial ultrasound imaging in humans has been a persistent challenge for ultrasound due to the imaging degradation effects from aberration and reverberation. These mechanisms depend strongly on skull morphology and have high variability across individuals. Here, we demonstrate the feasibility of human transcranial super-resolution imaging using a geometrical focusing approach to efficiently concentrate energy at the region of interest, and a phase correction focusing approach that takes the skull morphology into account. It is shown that using the proposed focused super-resolution method, we can image a 208-µm microtube behind a human skull phantom in both an out-of-plane and an in-plane configuration. Individual phase correction profiles for the temporal region of the human skull were calculated and subsequently applied to transmit—receive a custom focused super-resolution imaging sequence through a human skull phantom, targeting the 208-µm diameter microtube at 68.5 mm in depth and at 2.5 MHz. Microbubble contrast agents were diluted to a concentration of 1.6×10⁶ bubbles/mL and perfused through the microtube. It is shown that by correcting for the skull aberration, the RF signal amplitude from the tube improved by a factor of 1.6 in the out-of-plane focused emission case. The lateral registration error of the tube’s position, which in the uncorrected case was 990 µm, was reduced to as low as 50 µm in the corrected case as measured in the B-mode images. Sensitivity in microbubble detection for the phase-corrected case increased by a factor of 1.48 in the out-of-plane imaging case, while, in the in-plane target case, it improved by a factor of 1.31 while achieving an axial registration correction from an initial 1.885-µm error for the uncorrected emission, to a 284-µm error for the corrected counterpart. These findings suggest that super-resolution imaging may be used far more generally as a clinical imaging modality in the brain.

Index Terms—Brain mapping, brain vasculature, contrast-enhanced ultrasound, microbubbles, phase aberration correction, super resolution, transcranial, transcranial focusing.

I. INTRODUCTION

T}HE ability to detect and to image small vessels in the human brain is crucial, especially in the context of neurodegenerative disorders such as Alzheimer’s disease [1] and vascular dementia [2], as well as in the assessment of stroke-related pathologies [3]. To appropriately identify the presence of cortical or subcortical infarcts or other stroke lesions using imaging methods, high spatial resolution is required [4]. Three-dimensional computed tomography angiography (CTA), one of the gold-standard imaging methods of brain vessels, can reliably resolve structures down to 0.4 mm [5]. Magnetic resonance angiography (MRA) offers comparable resolution with an effective voxel size of 0.39 mm [6], while 2-D digital subtraction angiography (DSA) offers reconstruction down to a pixel size of 0.34 mm [7]. With venous vessel sizes in the brain measuring as small as a few micrometers [8], the importance of increasing the resolution of standard imaging methods is evident.

Super-resolution ultrasound imaging has shown great promise in the field of vascular imaging. Also, referred to as ultrasound localization microscopy (ULM) [9], [10] among other terms, this imaging technique has gained tremendous popularity during recent years, has been used to generate microscopic maps that surpass the ultrasound diffraction limit, and can potentially produce images resolving vascular structures with diameters in the range of 8–19 µm laterally, thus providing a λ/10 resolution limit [9], [11].

Inspired by the use of fluorescent “blinking targets” in optical super-resolution methods, ULM in ultrasound uses gas-filled encapsulated microbubbles with a mean diameter on the order of a few microns as contrast agents that are injected in the blood flow. These microbubbles stochastically appear and disappear in the field of view [12], [13]. At sufficiently low concentrations, the appearing microbubbles can be spatiotemporally separated, allowing for their localization at a subwavelength level [10].

One of the challenges of ULM is the isolation of the microbubbles from the surrounding tissue in the background. To achieve microbubble separation, various filtering methods have been employed, such as high-pass spatiotemporal filters that can distinguish fast-moving components from slow ones [9], temporal median filters for calculating the background [14], or threshold-based averaging filters [11] for removing background signals. Singular value decomposition (SVD) filters [10], [15] can also be used for the separation by exploiting the variation in the coherence length between...
the microbubbles and tissue, which is especially useful when the bubbles and tissue are moving at the same velocity, i.e., in the case of a frequency overlap. Following the filtering process, microbubbles can be localized using centroid detection techniques [16], which are robust and computationally efficient. Alternatively, in recent work, cross-correlation algorithms have been used to localize microbubble appearances [17]. Other localization methods explored in the literature include localizing either the onset of the microbubble backscatter signal or the first point at which the signal intensity has reached 50% of its maximum [18].

Early work in super-resolution imaging by Viessmann et al. [16] showed that microtubes of a diameter of 216 μm can be resolved in vitro with a 2-MHz transmit frequency. Errico et al. [9] proposed the injection of microbubble contrast agents at a concentration of 2 × 10^8 bubbles/mL and the use of a plane-wave compounded ultrafast imaging sequence, allowing for the generation of a super-resolved image within a clinically reasonable duration (150 s). Using this method, they produced super-resolved images of a rat brain that showcased structures as small as 8 μm. Other studies have also verified the method’s in vivo feasibility. For example, Ackermann et al. [14] imaged tumor angiogenesis in a tumor-bearing mouse and estimated microbubble flow speeds within the vessels, and Lin et al. [10], [19] produced super-resolved images of tumor angiogenesis with vessel sizes ranging from 5 to 150 μm. Even more recently, the method’s potential for tumor diagnosis has been shown in a clinical setting [20].

Although its capabilities far surpass the resolution limits of conventional ultrasound, super-resolution imaging is not devoid of challenges, especially from a clinical perspective. Depth penetration is a challenge in the in vivo environment, mainly as a result of the drop-off in bubble detectability with imaging depth, which can be attributed to several mechanisms, including attenuation, reverberation, multiple scattering effects, and off-axis clutter that significantly degrade the images. Compared to conventional imaging, these effects are compounded by the low amplitude of the emissions, which is used to avoid microbubble destruction. Even though this is not an issue in shallow regions of interest, e.g., when imaging around 2 cm of depth [10], [11], imaging at greater depths has also been demonstrated. In recent studies, 150-μm-sized microtubes have been successfully resolved at a depth of 6 cm through the abdominal body wall, in an ex vivo experiment using a multi-focus approach [17].

Another challenge lies in the fact that to satisfy the separability condition, which is a prerequisite for bubble isolation and localization, a low concentration of microbubbles is used. When combined with the low flow rate in vessels (especially capillary vessels that have a flow rate in the order of 2 μL/min [21]), this results in the need for the acquisition of a considerable number of frames (on the order of thousands) to fully populate a vessel [19], [22]. This, subsequently, results in prolonged acquisition times which poses a challenge not only for patient time management, but also for motion correction, which attempts to reduce artifacts caused by breathing or heart cycles [23]. Recent studies have, however, used higher contrast agent concentrations to increase the size of the region of interest imaged while maintaining a short acquisition time [24].

In the context of using ultrasound in the human brain, in imaging and in therapy, the biggest challenge is ultrasonic propagation through the skull. The heterogeneous nature of the human skull bone at a microscopic level causes considerable distortion of the ultrasonic beam, in the form of resolution compromising reverberations, refraction [25], multiple scattering, reflection between bone and tissue interfaces, and mode conversion, with the latter three being the main sources of attenuation [26], while absorption plays a secondary role at the higher frequencies used in imaging [27]. More specifically, the skull thickness, density, and sound velocity tend to vary across the length of the transducer causing phase aberration of the wavefront. The combination of these factors results in a decrease in amplitude, as well as a 3-D shift in the position of the target in the resulting image.

To overcome this persistent challenge, several phase aberration correction techniques, based on time reversal [28], [29], speckle brightness [30], and pitch-catch methods [31], have been developed. A large number of phase correction techniques have been developed for transcranial focused ultrasound therapy. Focused ultrasound can thermally or mechanically destroy malignant brain tissue. This topic has been investigated for the last six decades and has seen a resurgence in the last two decades, due to its noninvasive nature and its potential for localized ablation and efficient penetration [32]. Correction techniques have been successfully applied to correct the focal position accuracy and intensity on emission in transcranial ultrasound therapy, with registration error corrections with respect to the treatment location ranging from 0.5 to 2.3 mm [33], [34]. Such techniques have also been shown to substantially improve the image quality and target resolution through the skull both in real-time and in conventional imaging [35].

It should be noted that in therapy, a one-way correction is necessary for the improvement of target focusing, whereas in imaging, the correction must be calculated and applied twice, on both the emission and the reception. This makes the process more sensitive to the quality of the correction. Moreover, when compared to ultrasound imaging, ultrasound therapy is performed at lower frequencies, in which the skull behaves in a less challenging way when compared to higher frequencies. This is due to several mechanisms, including the fact that the trabecular structure size distribution is comparable to the wavelengths employed in higher frequency imaging (100–150 μm) [36], that lower frequencies are less attenuated, and that lower frequencies are less sensitive to aberration from the skull morphology.

The difficulties present in transcranial imaging have stalled its growth compared to therapy, and other imaging methods are usually preferred to depict the brain vasculature at high resolution. Most significant work in transcranial brain imaging has been performed using transcranial Doppler ultrasound (TCD), a robust method in vascular imaging and flow measurements in the brain that has been used for more than 50 years [37]. Due to its ability to record cerebral hemodynamic changes in real-time, TCD is often paired with cognitive studies [38]. Color
Doppler imaging (CDI) can demonstrate the relative direction and velocity of blood flow in brain vessels, superimposed on a conventional B-mode ultrasound image of the stationary tissue. Doppler imaging is subject to the same limitations as conventional ultrasound as far as image quality is concerned, namely, significant registration errors and insufficient spatial resolution for the detection of subwavelength targets. To address these limitations, groups have employed 3-D helmet-like array structures with 3-D Doppler capabilities in conjunction with phase corrections [39], which can generate images of millimeter-sized vascular structures, but they are still not capable of imaging smaller vessel anomalies and capillary structures, which require subwavelength resolution.

One of the pioneering studies in the field of super-resolution transcranial imaging showed that a 255-μm radially sized microtube can be successfully super-resolved transcranially using a sparse hemispherical receiver array at 612 kHz [22]. This type of array is typically used in therapeutic applications, which use frequencies lower than the clinical imaging frequencies, lowering the resolution. Furthermore, grating lobes from the sparse transducer spacing reduce the contrast, and the helmet-like form factor requires a water path, which limits the clinical imaging translatable of such a design. Even with a total accumulation of 3000 frames, it was challenging to fully populate the tube with detected bubbles, leaving some uncertainty in the exact shape and size of the tube. Compared to the imaging proposed here, it is expected that the higher frequency of 2.5 MHz, which will increase the aberrating effects of the skull, could, nevertheless, improve the resolution by a factor of 4. The versatility of the multipletarget focused emission in the present work also allows for more effective energy deposition, especially in a scattering environment if it were to be applied in vivo. The transmit–receive aberration correction proposed, here, should improve the image accuracy and quality. Finally, the conventional clinical transducer array, on which these imaging sequences rely, has been used extensively in clinical imaging and does not suffer from any translatability restraint.

Here, we demonstrate the feasibility of super-resolution imaging of 208-μm targets through an ex vivo human skull, by performing experiments using focused ultrasound and high frame-rate focused sequences on a clinical phased ultrasound transducer array. Two experimental configurations are presented, imaging a microtube placed in the out-of-plane direction and in the in-plane direction with respect to the transducer, both with a diameter of 208 μm and at a depth of 68.5 mm. Phase corrections that take into account the individual skull morphology are applied to improve the sensitivity in bubble detection and the accuracy of target registration in both lateral and axial dimensions. Microcomputed tomography-derived maps of a human skull are converted into acoustical properties and then used as input to a custom simulation tool (called fullwave) that we have developed to model acoustic propagation through the skull [40]–[42]. Simulations of acoustic propagation through the skull are used to determine the expected maximum theoretical improvements for phase-corrected imaging of subresolution targets.

**II. METHODS**

A cleaned human skull specimen was cut in half across the sagittal suture. The temporal region of the skull was used for imaging since it is relatively thin and therefore provides a good acoustical window. To remove air trapped in the porous structure of the skull, it was degassed for 12 h in water using a vacuum pump. A sketch of the experimental setup can be seen in Fig. 1. A custom-designed skull and transducer holder was 3-D printed and used to rigidly secure the skull in place with respect to the transducer. Since the phase correction is sensitive to movement, this holder ensured that the skull remained immobile throughout the duration of the whole experiment and also allowed for the attachment and detachment of the skull for different acquisitions, hence ensuring the stability and repeatability of the experiment. In addition, an adjustable microtube holder was built to secure a thin-walled polycarbonate microtube, with an inner diameter of 208 μm and an outer diameter of 250 μm (Paradigm Optics, Inc., WA, USA), in place. The holder can rotate by 90° around the axial dimension, which allowed the microtube to move from an out-of-plane configuration to an in-plane one. These parts were placed in a 56-L tank filled with degassed water.

Lipid-encapsulated microbubble contrast agents containing decafluorobutane were formulated as described in the previous work [43] and were diluted to a concentration of 1.6 × 10⁶ bubbles/mL. These microbubbles were measured with an Accusizer (Accusizer 780, PALS-Particle Sizing Systems, FL, USA) and typically have a mean diameter of less than 1 μm. A pump-driven syringe was attached to one end of the tube to induce constant flow of the microbubble contrast agent solution. The syringe was refilled through a continuously mixed reservoir of microbubble solution at a refill rate of 75 μL/min. This configuration allowed for the establishment of uninterrupted, continuous flow, as well as the capability of replacing the reservoir when needed. Since bubbles can burst and aggregate in the bottom of the container, to ensure that the concentration remains constant throughout the experiment, the bubble reservoir was mixed as well as replaced, and flow was reestablished, after every 6 min.
The root-mean-square value for the difference in time between the two profiles, after the offset between the two profiles has been subtracted, was measured as 90.3 ns.

Imaging was performed with a Verasonics Vantage research scanner (Verasonics, Inc., Redmond, WA, USA) and a P4-1 phased array transducer transmitting 1-cycle pulses at 2.5 MHz and at a frame rate of 700 Hz. A focused wave with a focal depth set at the position of the microtube was emitted. A more detailed description of the imaging sequence is given in Section II-B.

The two experiments, with the microtube in two different orientations with respect to the transducer, as well as the extraction of the correction are described in detail in Sections II-A–II-C.

A. Phase Profile Extraction for Focal Correction

Prior to mounting the skull, a microtube filled with air, oriented in the out-of-plane direction with respect to the imaging field, was aligned at the center of the transducer, laterally, and at 6.85 cm of depth. A single full-aperture focused emission, with the parameters mentioned above and with an amplitude of 168 kPa, targeted the microtube position. The whole aperture was also used to receive the RF data.

This data served as a reference while computing the skull-distorted version of the tube profile and the relative lag between the two. As expected, the backscattered reflection from the microtube appears as a hyperbolic phase profile. The phase associated with the microtube was isolated and flattened by subtracting the equivalent delay of the focused emission, which was also a hyperbola. In principle, the emitted focused profile should be identical to the backscattered phase profile. However, this was not exactly true, due to minor alignment errors in the positioning of the microtube. These alignment errors can be attributed to the manual alignment of the microtube. A cross-correlation algorithm, which correlates data from each channel of the transducer to a reference channel of the same data set, was applied to extract the microtube profile.

Subsequently, without perturbing the position of the tube and the transducer, the skull was mounted on the special holder and stabilized so that it remained in a fixed registered position throughout the experiment. A second acquisition, using the same single focus sequence, was performed at the same target, but at 2.21 MPa to account for the attenuation from the skull and to deliver approximately the same pressure amplitudes at the microtube location. The raw data acquired through the skull shown in Fig. 2(a) correspond to the backscattered signal from the microtube, after it has crossed the skull twice, on emission and reception. The interaction of the pulse with the skull causes variations in amplitude arising from interference in parts of the phase profile, as well as a distortion of the shape, which is no longer hyperbolic. The same process, of flattening the image and correlating to a reference channel, was repeated as described above and yielded the skull-distorted phase profile. The extracted skull-distorted profile is plotted on top of the raw data as a black solid line.

The tube profile and the skull-distorted tube profile can be seen in Fig. 2(b). An average offset of 6.32λ was measured between the two profiles. This offset is caused by the significant difference in the speed of sound between the skull and the medium. These profiles are also notably different in shape, which is a direct result of the aberration caused by the skull. The root-mean-square value for the difference in time between these two profiles, after the offset between the two profiles has been compensated for, can also serve as a quantitative measure of skull-induced aberration. In this particular acoustic window, an aberration in time was estimated to be 90.3 ns (0.07λ). The skull-distorted profile served as input to the phase-corrected version of the sequence that was implemented on the Vantage system to apply the correction on emission, and later, the relative difference between the two profiles was used to correct on reception. The final B-mode images were thus corrected both ways.

B. Out-of-Plane Experiment

Once the profiles were extracted, microbubble flow was established in the microtube. Three acquisitions were performed. First, the microtube-only, second, a skull-microtube experiment using an uncorrected conventional emission, and finally, a skull-microtube experiment with the focusing correction on emission and reception. To apply the correction on emission, the previously extracted skull-distorted profile was inverted in time and was used as a delay input in the single-focus sequence described in Section II-A.

For each of the three acquisitions, 1000 frames were recorded. In the absence of the skull, a 168-kPa emission was used, whereas when the skull is mounted, a 1.35-MPa emission was used. Although the skull is absent, lower pressures must be applied to ensure that the bubbles will not burst, whereas with the attenuating skull present, higher pressures can be applied, still within a mechanical index lower than 1.5. Note that the amplitude is lower while the microbubble flow is being imaged, as compared to the 2.21 MPa used in Section II-A for the air-filled microtube imaging, to further ensure the integrity of the microbubbles, but at the same time provide sufficient energy.

To correct on reception, each channel of the raw data from the corrected emission acquired was delayed accordingly to the relative lag between the tube profile and the skull-distorted profile. This yields data that are corrected both ways. Following this step, all three data sets were beamformed using a λ/12 spaced grid and a conventional delay-and-sum algorithm.
As a first microbubble detection step, an SVD filter was applied to the beamformed ultrasound images to isolate bubble appearances from the static background [15], by removing the highest two singular values. A range of values from 1 to 5 was explored for each emission case, in both the out-of-plane and in-plane configurations, and the final values were selected with the metric of success being noise minimization and bubble appearance frequency and brightness. Values greater than five were found to produce only background noise in all cases. A centroid localization algorithm was used to localize the microbubbles in the filtered images on a 40-μm grid. A bubble size filter was used to only detect bright spots that have a size larger than one wavelength, which is the minimum size of a point spread function (PSF). An upper limit was not set for the bubble filter, since in a confined environment of a single microtube, and at a low concentration, we do not expect clusters of bubbles with a significantly large size that would alter our resulting images. The accumulation of the position of all the detected bubbles among the 1000 acquired frames leads to the final super-resolution image.

### C. In-Plane Imaging

The microtube was subsequently placed in-plane with respect to the imaging plane. Three different cases were studied: no skull (the microtube alone), an uncorrected conventional emission through the skull, and a corrected emission through the skull on emission and reception. To scan the entire length of the tube, the full aperture was steered along different angles. The imaging field was divided into 96 different locations spanning a distance of 30 mm, spaced at a constant interval of λ/2. The steering angle was calculated based on the grid spacing and ranged from −0.2 to 0.2 rad. The focal depth was kept constant at 6.85 cm for all focusing locations. The whole aperture was also used to receive 1000 frames at each focal position. This resulted in a full field scan comprising 96 separate full-field super-resolution images. This is due to the fact that although the foci are localized, microbubbles are detected up to 1 mm away from the target position. The 96 individually generated super-resolution images were combined, by arithmetic summation, to produce the final super-resolved image depicting the whole microtube.

### D. Simulations

The fullwave simulation tool is a numerical solver based on finite differences in the time domain (FDTD) [40], which can be used to model ultrasound propagation with a high dynamic range. This tool has been extensively used for various acoustic applications. A few examples include simulating the thermal effects of focused ultrasound in transcranial brain therapy [44], modeling of acoustic cavitation risk in the brain [45], and transcranial focused ultrasound parameter optimization [46].

Here, this numerical tool was used to produce 2-D simulations in which the experimental conditions were closely mimicked. The sources of image degradation in ultrasound imaging depend not only on the aberration of phase profile clutter, which are corrected, but also on multiple scattering or reverberation artifacts, which are not corrected [42], [47]. Simulations also provide a more controlled acoustical environment, where the properties of interest can be investigated without the interference of the experimental setup. The aim of the simulations is to determine the imaging improvements under a best-case phase aberration correction scenario and allow us to investigate the one-way distortion of the ultrasonic beam, which can, in turn, provide us with a more effective means to phase correct.

A CT scan of the same skull specimen used in the experiment was converted to the speed of sound, attenuation, and density maps that were used in the simulations. A 2-D field of view from the temporal region of the skull was selected. The maps of the simulation were calibrated with amplitude measurements at the focus to match the experimental pressure conditions. The density and speed of sound maps were calculated as linearly scaled versions of the CT image in Hounsfield units with the maximum values of 1850 kg/m³ and 2900 m/s, respectively [48], [49]. This map conversion process has been previously used and validated for focused ultrasound surgery and has been used for transcranial simulations with the fullwave tool [42], [49]. The size of the simulation field was
80 mm in depth and 32 mm in width. Transmitted pulses had the same parameters as described in the experimental setup. The grid size was set to 38.5 μm, which is equivalent to 16 points per wavelength, and a Courant–Friedrichs–Lewy [50] condition of 0.3 was used. A target, with a single-pixel size, was placed at 6.85 cm in depth. The transducer was located at the top of the medium and the maximum pressure of 2.21 MPa at the emission was matched to hydrophone measurements for the P4-1 transducer. Simulations were performed on a Linux Fedora 25 (v.4.10.13-200.fc25.x86_64) system running Intel Xeon E5-2630 v4 Processors at 2.20 GHz. The simulation code was written in C and was on only one thread. Postprocessing was performed on MATLAB. Each simulation for each individual emission case has a duration of 7 min. Although we are currently using only one thread to run each simulation, the system’s parallel capabilities can be exploited to reduce the total time for multiple simulations.

The simulated acquisition process was the same as the experimental process described previously in Section II-A. Three acquisitions were performed: one of the microtube without the skull, an uncorrected emission through the skull, and finally, a corrected emission through the skull. To derive the correction profile, the target was used as a point source, i.e., the experimentally described pulse was emitted directly from the target, propagating the wave through the skull, which was then received by the transducer above the skull (one-way travel). In this manner, the wave crosses the skull only once, hence undergoes half the distortion. The received raw data were processed as described in Section II-A. By means of correlation, a skull-distorted profile was directly detected. A second emission was performed by adding this profile to the focused delay emitted from the transducer, which constituted the corrected emission. The received data were first corrected on reception, following the same process of imposing a relative lag to each channel, and then beamformed as previously described in Section II.

III. RESULTS

A. Out-of-Plane Imaging and Simulations

The B-mode images from the out-of-plane target experiment, shown in Fig. 3, can be used to characterize the conventional delay-and-sum PSF of the imaging system. The reference PSF of the microtube without the skull is shown in (a) and the B-mode image generated by the conventional uncorrected focused emission is shown in (b). The skull causes the point target to shift both laterally, as a result of aberration, and to move shallower, possibly as a result of aberration and definitely due to the increase in the average speed of sound. The shape of the PSF in (b) also appears to be degraded when compared to the microtube-only B-mode image in (a). In the B-mode image generated by the corrected emission [Fig. 3(c)], the maximum signal amplitude compared to the uncorrected B-mode increases by a factor of 1.6 (3.9 dB), defined as the ratio of amplitudes $I_c/I_u$ where $c$ stands for the corrected and $u$ for the uncorrected emission. In this image, the position appears to have been corrected and the shape also qualitatively improved. In both uncorrected and corrected B-modes [Fig. 3(b) and (c)], the skull is visible in the first 10 mm of depth, followed by a reverberation zone spanning approximately 20 mm.

To quantify the improvement produced by the phase correction, beamplots are plotted for each emission case in Fig. 4. The beamplots were calculated by averaging across all the frames and extracting the profile as a function of lateral position at the depth where the target exhibited its maximum amplitude, since there is an offset in depth between the B-modes for each acquisition and a global depth cannot be determined. Fig. 4(a) shows the experimental beamplots derived from the three B-modes, corrected and uncorrected through the skull and the microtube-only, on a normalized decibel scale. The difference in the position of the maximum of the main lobe between the corrected, uncorrected cases, and the microtube (ground truth) yields the lateral registration error $\Delta L$. The registration error, laterally, was measured as 50 μm for the corrected case and 990 μm for the uncorrected
case yielding an improvement of 940 μm. Registration errors were also estimated axially, referred to as ΔD, to be 300 and 1790 μm, respectively, exhibiting a 1490-μm improvement. The sidelobes for the tube profile in Fig. 4(a) are not symmetrical and deviate slightly from a classical point target shape due to minor alignment issues, and due to the fact that the microtube was manually aligned using live imaging; therefore, there was a human error component present. Furthermore, since a solution of microbubbles was being imaged, the exact position of the microbubble can deviate from the actual center of the transducer and center of the microtube. The uncorrected profile is substantially degraded in shape, with asymmetrical sidelobes that are hard to discern. The sidelobe amplitude is 10.5 dB for the left sidelobe (LSL) and 3.7 dB for the right sidelobe (RSL). After applying the correction, the shape, especially of the main lobe, appears to be partially restored; however, the sidelobes remain high. Specifically, the LSL has an amplitude of 9 dB, whereas the right has an amplitude of 7 dB. At −6 dB, the main lobe width (MLW) of the corrected profile is estimated at 2533 μm (522 μm larger than the width of the microtube only profile), whereas the width of the uncorrected profile is estimated at 4454 μm (2443 μm larger), due to its degradation in shape.

The improvements from experimental phase aberration correction were compared with the best-case scenario from the simulations. These simulated plots [Fig. 4(b)] show the B-mode beamplots from the same three scenarios, namely, for the corrected, uncorrected, and microtube-only emissions. The registration error is laterally 62.5 μm for the corrected case and 625 μm for the uncorrected case, an improvement of 562.5 μm.

Axially, the registration error is 210 μm for the corrected B-mode image, and 620 μm for the uncorrected B-mode, an improvement of 410 μm. In addition, the amplitude increased by a factor of 2.76 for the corrected B-mode when compared to the uncorrected counterpart. Fig. 4(b) shows that the shape of the tube without the skull is as expected for a point target that is perfectly centered. The uncorrected emission through the skull degrades the shape of the sidelobes and causes a noticeable lateral error due to aberration effects from the skull. After applying the correction derived from the one-way distorted profile, one could expect an almost full restoration of the shape and position of the beamplot. However, that is not the case even in this gold-standard setting. At −6 dB, the MLW for the corrected emission is estimated at 2060 μm, which is larger by 430 μm compared to the microtube, and the size and symmetry of the sidelobes still deviate considerably, with the LSL at 21.7 dB lower than the main lobe and the right one at 12.3 dB lower. Although the aberration was completely removed in the simulation, multiple reverberations within the skull and between the skull and transducer, which cannot be corrected with a phase delay, still have a degrading effect on the image quality.

The super-resolved images produced from the out-of-plane experiment are shown in Fig. 5 for the conventional uncorrected emission in (a), and the corrected emission in (b), both through the skull. By qualitatively assessing the images, an evident degradation in the shape of the microtube is observed in (a), especially in the lateral direction. The shape after the application of the correction appears substantially improved and rounded in (b). Sensitivity in bubble detection for the corrected and uncorrected emissions through the skull was calculated as the sum of bubble counts among all the accumulated frames (1000 used in this case). Specifically, in the uncorrected case, 700 bubble events were detected compared to 1040 bubble events in the corrected case, which amounts to an improvement in sensitivity of a factor of 1.48, defined as the ratio of counts, for the corrected case. If we were to assume no bubble destruction due to handling or acoustic pressure, for a single out-of-plane acquisition that lasts 3 s, for the given flow rate and microbubble concentration of \(1.6 \times 10^9\) bubbles/mL, we can place an upper bound of 6000 bubbles that could possibly be detected. Since the corrected acquisition detects 1040 bubbles, this implies that at least 17.3% of the total bubbles are being detected.

To quantify the detection accuracy of the microtube in both directions, the sum of the bubble counts as a function of (a) lateral and (b) axial positions is shown in Fig. 6. The corresponding microtube-only profiles are included for reference. In Fig. 6(a), the lateral profiles have a registration error of 80 μm for the corrected super-resolved image, while for the uncorrected images, the error is 480 μm, as estimated by the center of mass of the bubble positions. The size estimations of the detected microtube are also made by

![Fig. 5. Super-resolved images for the (a) uncorrected and (b) corrected emissions through the skull. Scale in both cases is normalized number of bubble counts.](Image)

![Fig. 6. Sum of bubble counts as a function of (a) lateral position and (b) depth, for the uncorrected and corrected super-resolved images. The tube profiles are also provided for reference and registration error estimation ground truth. Sensitivity improves by a factor of 1.48 for the corrected case.](Image)
TABLE I
SUMMARY COMPARISON FOR THE OUT-OF-PLANE EXPERIMENT

|                  | Experimental B-mode images | Simulation B-mode images | Super-Resolution images |
|------------------|-----------------------------|--------------------------|-------------------------|
|                  | \(\Delta L\) (\(\mu m\)) | \(\Delta D\) (\(\mu m\)) | \(I_c/I_u\) | RSL (dB) | LSL (dB) | MLW (\(\mu m\)) | \(\Delta L\) (\(\mu m\)) | \(\Delta D\) (\(\mu m\)) | RSL (dB) | LSL (dB) | MLW (\(\mu m\)) | \(I_c/I_u\) | Counts | Counts |
| Corrected        | 30                          | 500                      | 1.6  | 3.7  | 10.4 | 2243        | 62.3 | 210          | 2.76 | 12.3 | 21.7 | 2200        | 80            | 2000   | 1040   | 148          |
| Uncorrected      | 900                         | 1700                     | -      | 3.7  | 10.4 | 2243        | 62.3 | 620          | -    | 13.3 | 12.2 | 2200        | 480           | 2000   | 700    | -            |
| Tube             | -                           | -                        | -      | 16.1 | 14   | 2011        | -    | -            | 12.2 | 12.2 | 1630 | -            | -              | 1001   | -      | -            |

Fig. 7. Super-resolved images for (a) corrected emission through the skull, (b) uncorrected emission through the skull, and (c) microtube without the skull. Scales are in a number of bubble counts. (d) Laterally averaged counts as a function of depth for the corrected and uncorrected images with the skull and the microtube-only as a reference. Solid boxes show the location from where plot (d) was generated.

measuring the full-width at half-maximum (FWHM) for the curves. The corrected emission curve laterally estimates the size of the microtube at 200 \(\mu m\), while in the uncorrected case, the size is estimated at 1 mm. Note that the actual size of the microtube is 208 \(\mu m\). A histogram analysis was performed with bubble events binned on a 40 \(\mu m \times 40 \mu m\) grid to calculate the bubble appearance frequency as a function of radial distance from the center. Considering the detected center of the tube during the corrected emission, 72% of the total counts were found inside a 200-\(\mu m\) diameter, whereas the equivalent percentage for the uncorrected emission, for the corresponding detected center, is 41%. This is comparable to previous reports [22].

In Fig. 6(b), the registration error in depth is 200 \(\mu m\) for the corrected super-resolved image and 2000 \(\mu m\) for the uncorrected counterpart, an improvement of 1800 \(\mu m\). The corrected emission curve as a function of depth estimates the FWHM axial size of the microtube at 240 \(\mu m\), while in the uncorrected case, the equivalent size is estimated at 160 \(\mu m\). The deviation from the actual size in the axial direction is in the \(\lambda/20\) range for the corrected emission profile.

These registration error estimations, for both the B-mode and super-resolved images, in both directions, as well as the beamplot characteristics are summarized in Table I, where \(\Delta L\) denotes the lateral registration error, \(\Delta D\) for the registration error in depth, \(I_c/I_u\) is the amplitude improvement ratio, RSL is the RSL amplitude, LSL is the LSL amplitude, and MLW stands for the main lobe width. MLW estimations were performed at 6 dB of intensity. The estimates made from the B-mode images and the super-resolved images are consistent, with a maximum deviation of \(\lambda/20\) between them.

B. In-Plane Transcranial Imaging

The super-resolved images of the in-plane corrected and uncorrected emissions through the skull as well as the microtube without the skull are shown in Fig. 7(a)–(c), respectively. For the uncorrected super-resolved image in (b), when compared to the microtube-only super-resolved image in (c), a deviation from the true shape of the tube as well as an offset in depth can be qualitatively observed. However, even without applying a correction, the whole length of the microtube can still be resolved and observed, albeit with a large error in position. Both the shape and the offset in depth are improved after the application of the correction, as shown in Fig. 7(a). For the corrected emission, 79,965 bubble appearance events are detected, which, compared to 61,198 events in the uncorrected emission, reveals an improvement of 31% in sensitivity in bubble detection. By comparing the number of detected bubbles to the total expected number of bubbles flowing through the tube for an acquisition of a duration of 4 min, and while still assuming zero bubble destruction, a volume of 300 \(\mu L\) would pass through the tube.

Based on our concentration, a total of 480,000 bubbles would be expected and 79,965 were detected, i.e., 16.7% of the total expected bubbles. This sensitivity can also be calculated using a static estimate. For a tube of this given diameter, at the given
concentration and with a length of 20 mm, assuming steady-state conditions in the flow, and that bubbles are not detected more than once, we would expect 1100 bubbles to be present in the field of view at any given instant. We are detecting approximately 80 bubbles per single frame in time, therefore that would give us an estimate of 7% for the sensitivity. The lower limit of sensitivity is thus, depending on the approach and the assumptions made, between 7% and 16.7%. As a reference, the total bubble counts for the tube without the skull, which were at a lower pulse pressure, are 53427.

Fig. 7(d) shows the bubble sum profiles as a function of depth for a given central lateral position, which is highlighted in Fig. 7(a)–(c) with boxes. The profile of the microtube without the skull is provided as an actual position reference. Axial size estimates of the detected microtube for all three aforementioned cases are given by the FWHM of each curve. In both uncorrected and corrected emissions through the skull, the axial size of the microtube is estimated at 200 μm. The registration error between the true position of the microtube, the detected position for the uncorrected image, and the corrected image in depth was estimated and then averaged for each lateral position spanning across the central 8-mm region of the tube. This yielded an estimate of 284 ±58 μm for the corrected emission and 1885 ±196 μm for the uncorrected emission.

IV. Discussion

We have shown that super-resolution imaging through a human skull specimen of out-of-plane and in-plane microtubes with a size of 208 μm (λ/3) is feasible at 2.5 MHz, even without phase correction depending on the application and the desired accuracy. In the uncorrected out-of-plane emission case, the shape of the microtube was degraded laterally and the accuracy of the size of the microtube was estimated at 1 mm, while its central position was approximated at 480-μm off-center. Nevertheless, there were a sufficient number of microbubble appearances to indicate the presence and approximate position of the microtube. Furthermore, phase correcting reduced the lateral registration error to 80 μm as measured in the super-resolved images. In the case of imaging the in-plane target through the skull, an adequate amount of microbubbles was detected to fully populate the vessel-like structure even without phase correcting. This, however, may not always be the case in an in vivo setting where attenuating tissue is present. Scattering from the tissue is expected to further decrease the detectability of the microbubbles and may increase the need for correction. Furthermore, another improvement that would benefit detectability would be the use of microbubbles of mean diameter larger than 1 μm, considering the low frequency at which the experiments are performed.

Here, using a 2.5-MHz probe, the predicted diffraction-limited resolution is restricted to a minimum of 308 μm. However, according to Desai et al. [51], the theoretical resolution limit based on the Cramer–Rao lower bound is a few microns (2.1 μm) for a frequency of 3 MHz in liver (λ/244). In practice, however, for injected microbubbles, Desai et al. [52] reported an upper bound of λ/11 in resolution using a 1.75-MHz probe. In a more recent work, Christensen-Jeffries et al. [11] have resolved vascular structures as small as 20 μm (λ/10). Although an explicit resolution analysis has not been performed here, one would expect the resolution limit to be at best comparable to these results. It is more likely, however, that the added reverberation and aberration that the human skull introduces would lower this resolution estimate.

In addition to the lateral registration error, the shape of the tube prior to the correction is also notably degraded in shape laterally, even in the super-resolved images, as shown in Fig. 5(a). This stems from the fact that the PSF, which is used by the centroid localization algorithm, is distorted, as shown in Fig. 3(b). This degrades the estimate of its geometric center. This could possibly be corrected by using a distorted PSF as a reference in a correlation-based localization. After correcting for aberration, the shape of the PSF is not fully restored, even in the best-case scenario provided by our simulations, which completely removes aberration. This shows that reverberation, which is not removed, has additional degrading effects on the image. It is also worth mentioning that even in the corrected case, some distortion of the PSF persists. This could be attributed to reverberations from the skull, which cannot be corrected in this manner. Moreover, the lateral degradation of the tube shape as seen in the out-of-plane case is not evident in the in-plane configuration due to the direction of the tube with respect to the imaging plane. Even when targeting a single focal position laterally, multiple neighboring microbubble events are still detected along the lateral axis.

The axial registration errors are largely a product of the speed of sound mismatch between the values for the skull and the water, and assuming that the skull’s density distribution is homogeneous, it should be a constant global offset. That is, however, not exactly the case, since the shape of the skull is not perfectly flat. If we were to estimate the actual speed of sound values, based only on the information from the phase profiles, that would be 1520 m/s through the skull, as opposed to 1482 m/s for the tube in water. This would provide us with a registration error of approximately 1.9 mm, which is very close to the final uncorrected images. The fact that this improves to the range of 200 μm means that the correction on reception, which compensates the effect of the speed of sound mismatch is effective, but what is more important and leads us to accept this correction as satisfactory is the fact that it appears to be global, as shown in the shape of the corrected in-plane tube in Fig. 7(a), i.e., in an in vivo setting, as long as the axial correction is spatially homogeneous, it should not pose a limitation.

A single-phase aberration correction profile was determined for the center of the field, and it was then applied to the entire field of view. This was performed under the assumption that a local correction is still effective across a lateral field of 30 mm, while also assuming that the distance of propagation between the skull and the transducer is sufficiently small. A more sophisticated version of the correction process would determine a specific correction for each imaging position, laterally and in depth. To obtain correction profiles that are
specific not only to the imaging location, but also correspond to the steering angle being used, we would use simulation tools to precalculate the corrections. This could be similar to previous full-wave simulations that were performed for human transcranial focused ultrasound therapy [41], [42]. Nevertheless, in the current work, the imaging results did not show a noticeable decrease in bubble detection events, resolution, or accuracy as a function of lateral position, suggesting that the small distance assumption was valid.

Full-wave simulations of transcranial propagation, which provided a theoretical best-case scenario, showed improvements in both registration error and amplitude. The lateral registration error was 62.5 μm for the corrected image, and there was an improvement of almost λ from the uncorrected image, as well as a significant amplitude correction of a factor of 2.74. These simulation results, therefore, suggest that there may be room for improvement in the experimental phase aberration correction implementation. However, the simulations also show that the width and shape of the main lobe and sidelobes are not fully restored with phase aberration correction. This phenomenon was also observed experimentally and it is consistent with the interpretation that amplitude aberration and multiple reverberations also play a significant role in image quality. Except for phase distortion, the skull also reduces the amplitude of the initial pulse, which may be partially compensated with amplitude correction techniques.

A limitation of the method as it was implemented is that it is challenging to extract a correction from an aligned point target in vivo, since it is impossible to find such a target occurring naturally. This limitation has been previously addressed in focused ultrasound therapy, where precalculated simulation-derived corrections for a specific registered location of the skull can be used [33]. These corrections can be produced as described in Section II-D and provided the CT scan used is accurately registered to the actual skull, they can be employed to phase correct a given region of interest, as previously performed in therapy transcranial ultrasound [34], [41], [42].

Currently, ultrasound is limited to the larger vascular structures in the brain (Circle of Willis, larger arteries); however, the ability to image 200-μm targets suggests that smaller vascular structures in regions ranging from the mesencephalon to the cerebellum can be detected using the temporal window of the skull. Furthermore, since this method relies on the localization of individual bubbles, it can also be applied to track the microbubbles in the blood flow and provide velocity estimations at a higher resolution than traditional Doppler imaging.

V. Conclusion

In summary and conclusion, transcranial super-resolution imaging through a human skull is feasible at a frequency of 2.5 MHz, even without applying a phase correction, and with an existing clinical transducer. With the placement of the transducer in the temporal skull window when combined with phase correction, images of vessel-mimicking microtubes of a diameter of 208 μm with a lateral registration error as low as 80 μm were produced. The correction in the out-of-plane configuration thus reduced the error to the λ/8 range and increased sensitivity by a factor of 1.48 in the super-resolution images, as compared to the uncorrected emission.

In the in-plane configuration, the microtube was detectable with and without correction; however, the correction increased sensitivity by a factor of 1.31 as compared to the uncorrected counterpart. This method has the potential to significantly improve the resolution and accuracy necessary for brain vascular mapping scenarios.

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