Experimental Assessment of Skull Aberration and Transmission Loss at 270 kHz for Focused Ultrasound Stimulation of the Primary Visual Cortex

Lucia Albelda Gimeno, Eleanor Martin, Olivia Wright, Bradley E. Treeby*
Department of Medical Physics and Biomedical Engineering, University College London, London, UK
*Email: b.treeby@ucl.ac.uk

***Abstract*—Transcranial focused ultrasound is a rapidly emerging method for non-invasive neuromodulation and stimulation. However, the skull causes a significant acoustic barrier and can reduce the focal intensity and alter the position and shape of the focus compared to free-field. In this study, the insertion loss and focal distortion due to the skull bone were quantified using three *ex vivo* human skulls and a focused ultrasound transducer operating at 270 kHz targeted on the approximate positions of the left and right primary visual cortex. Compared to free-field, the average insertion loss was -9.8 dB (± 2.2 dB), while the average focal shift was 1.7 mm (± 0.56 mm) in the lateral direction and 2.8 mm (± 4.2 mm) in the axial direction. Overall, the acoustic aberrations were small compared to the size of the focal volume, meaning effective stimulation at this frequency can likely be achieved without patient-specific targeting. However, the insertion loss was significant and should be considered when selecting the target focal intensity for human studies.**

***Index Terms*—focused ultrasound, neuromodulation, skull bone, insertion loss, aberration, visual cortex**

I. Introduction

Transcranial focused ultrasound is a rapidly emerging method for non-invasive neuromodulation and stimulation [1]. A number of recent studies using single-element ultrasound transducers have shown that ultrasound can safely and effectively modulate cortical brain activity with high-spatial specificity [2]. However, the skull causes a significant acoustic barrier and can reduce the focal intensity and alter the position and shape of the focus compared to free-field [3]. For this reason, many human neuromodulation studies have utilised low frequency transducers (below 500 kHz) to reduce the attenuation and refraction caused by the skull [4]. However, even at low frequencies, the skull attenuation can be considerable. For example, Fry and Barger reported an insertion loss of -6 dB for adult parietal bone for frequencies below 500 kHz [5], and Brinker *et al.,* reported an insertion loss of -10 dB after propagating through the rear of a sectioned skull specimen at 272 kHz [6]. In a simulation study, Lee *et al.,* reported significant variability in the predicted insertion loss across 19 subjects when targeting the primary visual cortex, with values ranging from -1.5 to -10 dB [1].

In this study, the distortion effects of the skull were quantified experimentally using three *ex vivo* human skulls and a focused ultrasound transducer operating at 270 kHz targeted on the approximate location of the left and right primary visual cortex. The aim was to quantify both the insertion loss and focal distortion that occurs when using low frequency focused ultrasound transducers for neuromodulation.

This work was funded in part by the Engineering and Physical Sciences Research Council (EPSRC), UK, under grant numbers EP/L020262/1, EP/P008860/1, EP/P008712/1, and EP/S026371/1.

II. Methods

A two-element spherically-focused bowl transducer was used for the study (H-115, Sonic Concepts, Bothell, WA, USA). The transducer had two annular rings of equal area with an outer aperture diameter of 64 mm and a geometric focus of 63.2 mm. The transducer was driven at 270 kHz with a 17 cycle burst at a pulse repetition frequency of 100 Hz using a pair of signal generators (33500B, Keysight, Wokingham, UK) and amplifiers (A075 and A300, E&I, Rochester, NY, USA). The phase delay between the two elements was set to 55° giving a focal length of 43.5 mm and a -3 dB focal size of 5 mm (lateral) by 30 mm (axial) in water. The two elements were driven with equal voltages adjusted to give a focal pressure of 260 kPa. (Note, as the wave propagation was linear and the signal-to-noise ratio was sufficient, this value had no direct bearing on the calculated values.)

Ultrasound transmission through three *ex vivo* human skulls was measured. The skulls were obtained under a material transfer agreement in accordance with the UK Human Tissue Act. In all skulls, the superior section of the parietal and frontal bones had previously been surgically removed. Prior to the experiments, the skulls were placed in a plastic container filled with deionised water and degassed for 48 hours at -400 mbar. After degassing, the skulls were positioned in a automated scanning tank containing deionised water (Precision Acoustics, Dorchester, UK) using a laser cut Perspex mount. The acoustic focus of the transducer was targeted at the approximate location of the left or right primary visual cortex using skull landmarks (see Fig. 1), giving six measurement locations across the three skulls. The distance between the exit plane of the transducer and the skull surface was fixed at 10 mm using a 3D printed stand-off.

For each measurement location, a calibrated 0.2 mm needle hydrophone with a right-angle connector (Precision Acoustics, Dorchester, UK) was used to measure a planar scan perpendicular to the beam axis with a step size of 1.5 mm. The beam maximum was located and the largest planar scan possible was

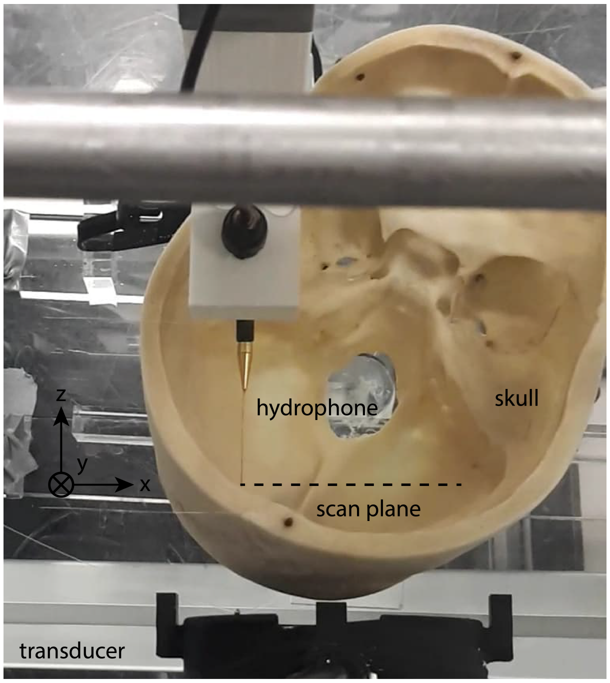

Fig. 1. Photograph of experimental setup showing a skull with the skull-cap removed, transducer with 3D printed stand-off, needle hydrophone with right angle connector, and position of the scan plane. The acoustic focus of the transducer is targeted at the approximate location of the primary visual cortex on the right side of the brain.

acquired. The size of the scan plane and the distance from the transducer varied between skulls and cortices depending on the skull geometry and the size of the sphenoid bones. For each measurement location, the skull was then removed, and a reference measurement was acquired in water to allow direct comparison of the fields with the alignment of the transducer preserved. The approximate thickness of the skull for each measurement location was also measured using a micrometer.

The drive voltages and the acquired hydrophone voltage signals were digitised using an oscilloscope (DSOX3024A, Agilent Technologies, Santa Clara, CA, USA). The signals were obtained using a time-window where the field had approximately reached steady state (i.e., including several round trips through the skull, but before reflections from the measurement equipment had arrived). The hydrophone calibration was then applied, and the amplitude and phase at 270 kHz were extracted. The axial position of the scan plane for each measurement location was calculated using the time-of-flight from the reference measurement in water.

For each measurement, the complex pressure was zero padded asymmetrically in order to create a 73 $\times$ 73 point grid (with a point spacing of 1.5 mm) preserving the $(0, 0)$ coordinate in the measurement plane. The recorded pressure planes were then projected using the angular spectrum method to obtain the full 3D field (using `angularSpectrumCW` in k-Wave [7], [8]). The projected field was then upsampled by a factor of 8 using Fourier interpolation to increase the fidelity of the data processing. The position and magnitude of the spatial peak pressure and the size of the -3 dB focal volume were extracted. The width and length of the focus were computed from lateral and axial profiles through the position of maximum pressure. For each measurement location, the change in these values was calculated by comparing the skull and water-only measurements.

III. Results

The measured and projected fields for the six skull measurement locations along with a reference measurement in water are shown in Fig. 2. The results for the focal size, change in focal volume, focal shift, and insertion loss are shown in Table I.

When the skull is present, on average the acoustic focus (position of maximum pressure) was shifted closer to the transducer, with a small decrease in the focal volume, and a small reduction in the length of the focus. However, there was some variability in these values, with the axial focal position and the focal volume both increasing and decreasing depending on the specific skull geometry and transducer alignment. The lateral shifts were very small, with a maximum shift of 2.4 mm, and an average of 1.7 mm. The shape of the focal volume was relatively constant (see Fig. 2), remaining approximately elliptical. Overall, the changes were small relative to the size of the acoustic focus, particularly the shifts in focal position.

For all measurement locations, the insertion loss was significant, ranging from -6.6 to -13.5 dB with an average insertion loss of -9.8 dB. On a linear scale, this corresponds to a 90% reduction in intensity. Thus for an intensity of 16.6 W/cm^2 in water (as used in [1]), on average the intensity in the brain would be 1.7 W/cm^2. The insertion loss was broadly correlated with skull thickness, although skull density and composition are also important factors [9].

IV. Discussion

Overall, these results show that the measured acoustic aberrations (i.e., changes in the focal position and the focal volume) due to the skull bone at 270 kHz are small relative to the size of the acoustic focus. This means effective neuromodulation using focused bowl transducers at this frequency can likely be achieved without patient-specific targeting. This agrees with previous results, for example, Hynynen and Jolesz demonstrated qualitatively similar ultrasound pressure amplitude distributions at 248 kHz after propagation through the top part of a formaldehyde-fixed skull [3], while a simulation study by Deffieux and Konofagou showed similar acoustic aberrations to those reported here for a 300 kHz transducer and a hippocampus target [10].

While the aberrations are small, the measured insertion loss due to the skull is significant. This must be considered when selecting the target focal intensity for human studies. In particular, the variability between skulls (also demonstrated in [1]) means that care should be taken when defining acoustic output parameters such that the lowest insertion loss values are used when calculating safety metrics and exposure conditions.

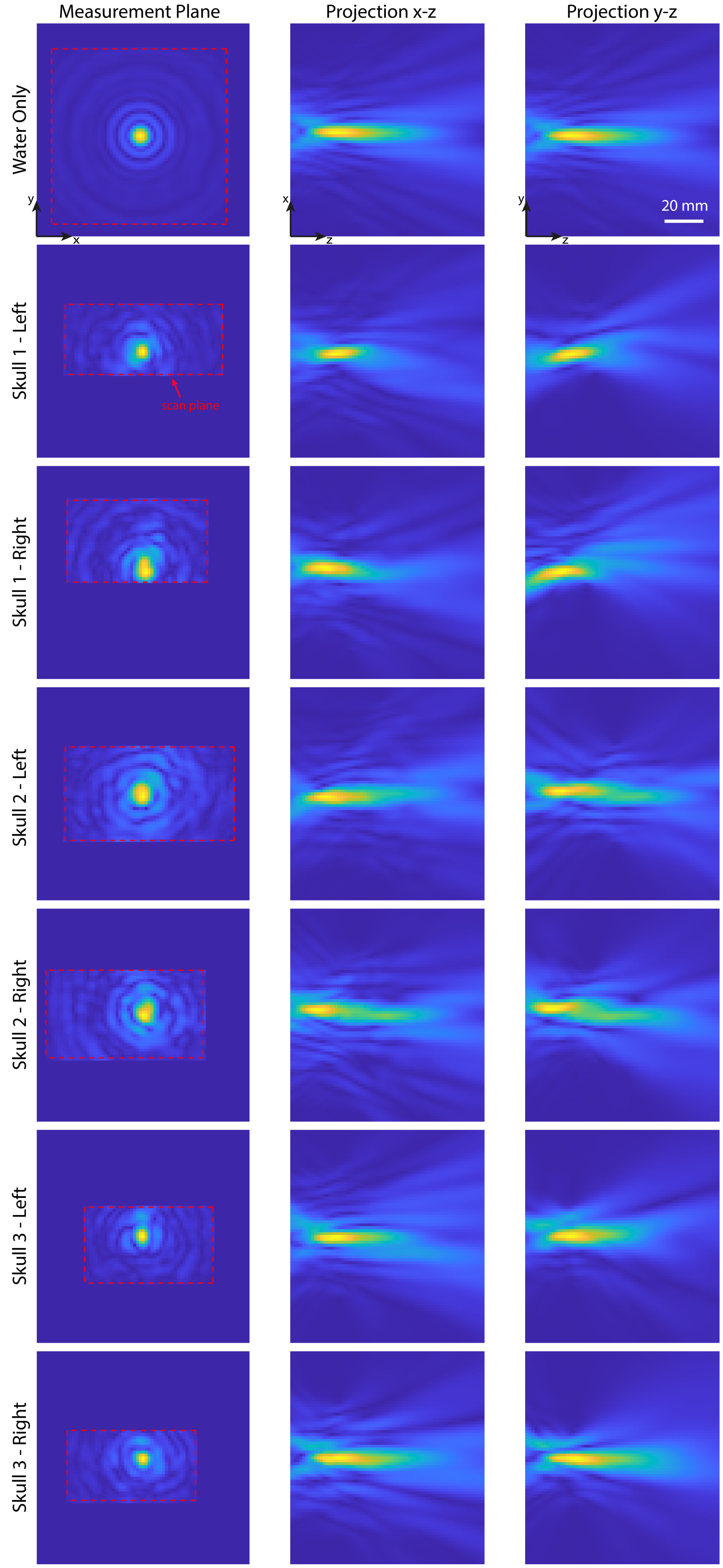

Fig. 2. (Left Column) Measured acoustic pressure in the measurement plane after zero padding. The scan plane is shown with the red dashed line. (Middle and Right Columns) Slices through the projected pressure field. The slices intersect the position of the maximum acoustic pressure, and the horizontal axis shows the field from 20 to 120 mm. The coordinate axes are shown in Fig. 1. Note, the colour scale for all plots is individually normalised.

TABLE I

MEASURED VALUES FOR THE FOCAL DISTORTION AND INSERTION LOSS DUE TO THE SKULL WHEN USING A FOCUSED ULTRASOUND TRANSDUCER AT 270 KHZ. THE WIDTH AND LENGTH OF THE FOCAL REGION IN WATER WAS 5 MM AND 30 MM, RESPECTIVELY. ALL VALUES ARE GIVEN TO TWO SIGNIFICANT FIGURES. THE LATERAL AND TOTAL FOCAL SHIFTS ARE GIVEN AS ABSOLUTE VALUES.

Skull	Cortex	Thickness [mm]	Focal Size [mm]		Change in Focal Volume [%]	Focal Shift [mm]			Transmission Loss [dB]
			width	length		lateral (abs)	axial	total (abs)	
1	left	7.3	4.9	18	-30	1.3	0.38	1.4	-8.3
1	right	7.2	5.4	21	-6.7	2.4	-3.8	4.5	-6.6
2	left	7.5	5.0	29	-6.8	2.1	-6.2	6.5	-9.7
2	right	7.5	5.0	20	35	2	-9.9	10.1	-9.3
3	left	7.9	5.1	24	-15	1.5	0.38	1.5	-13.5
3	right	8.4	5.3	31	14	0.78	2.1	2.2	-11.7
mean ($\pm$std)			5.1 ($\pm$0.18)	24 ($\pm$4.7)	-1.4 ($\pm$21)	1.7 ($\pm$0.56)	-2.8 ($\pm$4.2)	4.4 ($\pm$3.2)	- 9.8 ($\pm$2.2)

Regarding the specific setup used in the study, there are several things to note. First, although the *ex vivo* skulls were immersed in water (rehydrated) and degassed, the properties of the bone may differ from skull bone *in vivo* [11]. Second, the measurements were conducted using relatively short tone-bursts, and thus do not capture the effects of standing waves, which may be important for some targets [10]. Third, in some cases, it was not possible to capture a large field-of-view in the planar scans (see red-dashed lines in Fig. 2). While the scan planes were aligned as close as possible to the acoustic focus, this may introduce some errors in the projections using the angular spectrum method.

ACKNOWLEDGMENT

The authors thank Precision Acoustics for provision of the right-angle hydrophone connector, and Charlotte Stagg and Adam Thomas for helpful discussions regarding brain and skull landmarks.

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