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Non-invasive transcranial ultrasound therapy based on a 3D CT scan: protocol validation and in vitro results

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Abstract

A non-invasive protocol for transcranial brain tissue ablation with ultrasound is studied and validated in vitro. The skull induces strong aberrations both in phase and in amplitude, resulting in a severe degradation of the beam shape. Adaptive corrections of the distortions induced by the skull bone are performed using a previous 3D computational tomography scan acquisition (CT) of the skull bone structure. These CT scan data are used as entry parameters in a FDTD (finite differences time domain) simulation of the full wave propagation equation. A numerical computation is used to deduce the impulse response relating the targeted location and the ultrasound therapeutic array, thus providing a virtual time-reversal mirror. This impulse response is then time-reversed and transmitted experimentally by a therapeutic array positioned exactly in the same referential frame as the one used during CT scan acquisitions. In vitro experiments are conducted on monkey and human skull specimens using an array of 300 transmit elements working at a central frequency of 1 MHz. These experiments show a precise refocusing of the ultrasonic beam at the targeted location with a positioning error lower than 0.7 mm. The complete validation of this transcranial adaptive focusing procedure paves the way to in vivo animal and human transcranial HIFU investigations.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Focusing ultrasonic beams within organs enables controlled non-invasive destruction of tissue. This technique has been widely investigated since the second half of the 20th century (ter Haar and Coussios 2007, Hynynen and Clement 2007). Application of high intensity...
focused ultrasound (HIFU) to the head began in the early 1950s with the precursor works of Professor Fry (Fry et al 1954). In 1960 (Fry and Fry 1960), 50 patients affected by Parkinson’s disease were treated with total craniotomy. More than 50 years later, Lizzi and co-workers used HIFU beams in ophthalmology, for the treatment of glaucoma (Lizzi et al 1981) and intraocular tumour (Lizzi et al 1984). Since the early 1990s, research in many other application fields has been on the increase, and many HIFU medical systems are commercialized today or are under clinical trials for prostate (Gelet et al 1996), liver (Wang et al 2003), breast (Wang et al 2003) and uterine fibroid (Held et al 2006).

In the 1950s, Fry pointed out the potential of high-intensity focused ultrasound for deep located regions in the brain and the wide scope of therapeutic application (tissue ablation, Parkinson’s disease treatment). The feasibility of the practical clinical realization of brain surgery using HIFU to burn tumours has been demonstrated with a total craniotomy by the pioneer works of Fry (1958) and more recently by Hynynen and co-workers (Sun and Hynynen 1998, 1999). Some other applications of transcranial HIFU have also been developed. It has been demonstrated that focused ultrasound can increase the permeability of cell walls. It has also been shown by Hynynen and co-workers that burst ultrasound in the presence of an ultrasound contrast agent can disrupt the blood–brain barrier (Hynynen et al 2005). Extensive in vivo work is currently being carried out in this field mostly on small animals (Choi et al 2007) because of strong aberrations induced by the skull bone. Madio et al (1998) proposed the use of focused ultrasound at a lower energy level to activate at a distance gene expression using a thermosensitive promoter (hsp70). They managed to activate this promoter in vivo while keeping the temperature slightly below 43 °C so no irreversible lesion was caused.

Nonetheless, non-invasive brain HIFU still remains a challenge, as focusing inside the brain has been hindered by the presence of the skull along the beam travel path. A large discrepancy between the skull’s high acoustic speed of sound (about 3000 m s$^{-1}$) and the brain tissue’s low speed of sound (about 1540 m s$^{-1}$), combined with a severe attenuation of ultrasound in the bone, strongly degrades the beam shape. Owing to this severe attenuation and technical limitations, interest in HIFU brain therapy decreased in the 1970s. Recently, however, thanks to the introduction of piezoceramic and piezocomposite transducers capable of being driven at high voltages and the improvement of multichannel electronics, the ability to produce and control the shape and location of high intensity ultrasonic beams has been greatly improved (ter Haar and Coussios 2007). Recent studies showed that it was possible to correct the aberrations by using adaptive techniques. Phase aberration correction techniques are based on time-reversal processing (Thomas and Fink 1996, Tanter et al 1998) or phase conjugation focusing (Hynynen and Sun 1999) and have been shown to restore a good focusing quality down to 20 dB. For transcranial ultrasonic brain imaging, the focusing quality has been further improved down to 40 dB by correcting both phase and amplitude, thanks to spatio-temporal inverse filtering (Tanter et al 2000, 2001, Aubry et al 2001, Vignon et al 2006).

Fully non-invasive transcranial focusing techniques were proposed based on the use of previous acquisitions of the skull bone structure via magnetic resonance imaging (MRI, Hynynen and Sun 1999) or computed tomography (CT, Aubry et al 2003). The possibility of deducing acoustic properties of the skull from MRI or CT enables simulation of the transcranial propagation of ultrasonic waves and thus the proposal of adaptive corrections. Hynynen et al (1993) proposed using MR images to extract the skull profile, without information on the internal heterogeneity. Then, using a three-layer model (water–bone–brain), they numerically highlighted the necessity to perform phase correction to focus through the skull. However, such a simple model is not sufficient accurately to model the phase aberrations induced by the skull. Speed of sound and density maps can also be extracted from high-resolution CT images. Clement and Hynynen (2002) proposed an approach based on a layered wavevector-frequency
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Even though such a non-invasive approach does not take into account the internal structure of the skull bone, it enables restoring half of the maximum energy obtained with a ‘gold standard’ reference focusing at focus (hydrophone-based focusing). The study was performed at 740 kHz. According to their results, such an approach is an adequate solution for low-frequency sonications, with the advantage of offering a short computation time. At higher frequencies, the defocusing effect of the skull is more drastic as the wavelength tends to reach the size of local skull bone heterogeneities. The typical size of the trabecular structures of the diploe (inner structure of the skull) is 1 mm. Consequently for frequencies higher than 1 MHz, one would need to take into account the heterogeneities of the skull structure. Using a higher frequency provides several advantages for the brain therapy. First of all, the focal spot is smaller so the necrosis induced will be thinner. Second, the absorption in soft tissue is increased and so will be the energy deposited at focus. It also decreases the risk of unwanted reverberations of the HIFU beam in the closed cavity of the brain, as the beam is more attenuated during propagation than at low frequencies. Third, the antenna gain (the ratio between the transmit array aperture and the focal spot surface in the focal plane) is improved at higher frequencies. Finally, as the cavitation threshold is increased too, haemorrhages are less likely to occur during the treatment. This is the reason why a 3D finite differences code in the time domain (FDTD) has been proposed and experimentally validated using a linear 1D array (5 cm² active surface, Aubry et al (2003)). The technique consists of simulating the first step of a hydrophone-based time-reversal experiment in order to develop a complete non-invasive transcranial focusing protocol. Acoustic properties are deduced from CT images (Aubry et al 2003), and then the propagation through the skull is simulated with a 3D finite differences code. These preliminary results were devoted to proving the feasibility of using numerical simulations based on CT images instead of implantable hydrophones.

In this paper, this technique is extended to the use of a new 3D spherical array (285 cm² active surface) designed for trans-skull brain therapy. This protocol and this array could be used either for opening the blood–brain barrier or for HIFU treatment. The whole protocol based on propagation simulation is investigated in vitro for both human and primate skulls in order to study the applicability of such non-invasive transcranial brain therapy under practical clinical conditions.

2. Materials and methods

2.1. Protocol overview

The protocol used for non-invasive transcranial ultrasound therapy is based on protocols already existing in radiotherapy (Lightstone et al 2005). In radiotherapy, the patient first has an MR or CT exam using a stereotactic frame. In a second step, the treatment planning is performed (DICOM import and analysis, tumour volume and margins’ delineation, dose calculations, beam forming and positioning). Then, the patient is positioned in the treatment room. The exact positioning of the patient’s head with respect to the initial referential frame is ensured by the stereotactic frame.

For this in vitro ultrasound study, a human or monkey skull is mounted on a dedicated stereotactic frame. A positioning plate is attached to the frame. Positioning is achieved thanks to holes pierced in the plate (figure 1(a)). These holes are visible on CT scan images, so that the exact position of the skull is known in three dimensions. Density and speed of sound maps are obtained from these images (figure 1(b)), and then emission from a virtual source point inside the skull (figure 1(d)). The signals obtained on each channel are time-reversed, and then the emission signals are ready for the experiment (figure 1(e)). The stereotactic frame is mounted
2.2. Stereotactic positioning

This set-up plays an important role in three different steps of the process: CT scan, numerical computation and experimental scanning. The stereotactic frame is made of plexiglass (x-ray transparent) and the skull is stuck to the frame with epoxy glue. A plexiglass plate can be mounted onto this system in order to perform accurate positioning. Holes are pierced in the plate to determine tilts between the referential of the frame and that of the scanner. The positions of the holes are precisely known as reference, with a ±0.1 mm uncertainty.

For in vivo experiments such a frame would be replaced by a conventional stereotactic frame (Leksell 1983). Figure 2 shows a picture of the stereotactic frame mounted on the therapeutic probe.

2.3. Therapeutic probe

A new large spherically curved transducer array was constructed based on the previous array (Pernot et al 2007). This array consisted of 300 equally sized elements (8 mm diameter,
0.6 cm² active area, 1 MHz central frequency; Imasonic, Besançon, France). The 300 high power piezocomposite transducers are mounted in a sealed spherically curved holder with a 14 cm radius of curvature and placed in a semirandom way (randomness taking into account transducers’ geometry), in order to minimize secondary lobes. The transducers are connected to a 300-channel electronic driving system. Each electronic channel is individually programmable and relies on its own emission electronic board. This phased array was optimized for electronic beamsteering in HIFU applications and therefore the focus can be moved up to ±20 mm from the geometric focus by adjusting the delays of each channel (Pernot et al 2007).

In the following sections, the target location will thus be chosen to be less than 2 cm away from the geometrical focal point in order to have enough energy to induce a well-defined necrosis: on one hand, the pressure at the steered position must be higher than half of the maximal pressure at the geometrical centre (\( P > P_{\text{max}}/2 \)) and on the other hand, the pressure of the side lobes must be lower than one fifth of the pressure at the steered position (\( P_{\text{lobes}} < P/5 \)). For in vitro experiments, the therapeutic array is connected to a large water tank. The human skull mounted on the stereotactic frame is immersed in water and tightened to the probe (cf figure 2). This set-up is necessary for the skull to be positioned exactly as in simulation and for the focus to be located in the centre of the skull.

### 2.4. Skull preparation, CT scan and 3D matrix reconstruction

For this in vitro study, two dry skulls (human and macaque) were prepared. These skulls were mounted on two dedicated frames as shown in figure 3. They were immersed in deionized and purified water. These two sets were then put under a metal dome linked to a vacuum pump. The degassed, deionized and purified water fills up the bone heterogeneities and has the same acoustic properties as marrow and organic fluids.

Data acquired from the CT scanner are stored in the DICOM format (Bidgood et al 1997). A Matlab program was developed to be able to read these data in raw Hounsfield units (HU) for the 3D time domain finite differences simulation of ultrasonic wave propagation. All the CT images were read and the whole volume of the skull reconstructed, taking into
account the spatial resolution of the CT scanner. Relative positions of the target point to the ultrasonic transducers were calculated. Figure 4 shows a typical example of the skull matrix reconstruction.

2.5. Calculation of the acoustic properties of the skull

In a previous study Aubry et al. (2003) showed that the bone porosity, $\Phi$, can be derived from raw CT data in HU:

$$\Phi = 1 - \frac{HU}{1000}.$$ (1)

Acoustic properties (density, speed and acoustic absorption) of the skull are then deduced from the porosity map. Density is directly given by the porosity:

$$\rho = \rho_{\text{water}} \Phi + \rho_{\text{bone}} (1 - \Phi),$$ (2)

where $\rho_{\text{water}}$ is the density of water and $\rho_{\text{bone}}$ is the density of cortical bone.

The speed of sound map is harder to deduce from the skull porosity data. The diploe and the inner and outer tables have different mechanical properties. Acoustic waves propagating...
in the fluid and the solid media are coupled, which can be correctly described by the Biot theory (Haire and Langton 1999) if the wavelength is negligible compared to the size of the heterogeneities. Nevertheless at 1 MHz, the wavelength is of the order of magnitude of the heterogeneities, so that the Biot theory cannot be applied. Consequently, the simulation voxel has been considered as an effective medium (with mean acoustic properties). A linear relationship between the speed of sound and porosity has been used, according to Carter and Hayes (1977) who showed that the elastic modulus of bone is proportional to the effective density cubed:

\[ c = c_{\text{water}} \Phi + c_{\text{bone}} (1 - \Phi), \]

where \( c_{\text{water}} \) is the speed of sound of water and \( c_{\text{bone}} \) is the speed of sound of cortical bone. Thanks to in vitro measurements performed on pieces of monkey skull at the Laboratoire d’Imagerie Paramétrique (LIP, France), the following parameters were determined for the present study on monkeys (\( c_{\text{water}} = 1500 \text{ m s}^{-1} \), \( c_{\text{bone}} = 3100 \text{ m s}^{-1} \) in cortical bone and 2200 m s\(^{-1} \) on average in trabecular bone, \( \rho_{\text{water}} = 1000 \text{ kg m}^{-3} \), \( \rho_{\text{bone}} = 2200 \text{ kg m}^{-3} \)). Figure 5 shows an example of one slice in the 3D reconstructed matrix.

In order to estimate accurately the energy loss through the skull bone, the attenuation should also be derived from the CT scan through an empirical law. However, there are two different loss effects: on the one hand, ultrasonic absorption which induces skull heating and on the other hand, backscattering. This second effect is microscopic and high-resolution CT images are not good enough to quantify it exactly. Backscattering is locally averaged so it is impossible to have a constant experimental law on the whole skull volume. Ongoing work is addressing this modelling of absorption effects.

2.6. Propagation from the virtual source point to the therapy probe through the skull

Once the source location is chosen and the skull acoustic properties are calculated, the propagation of the wavefront from the virtual source to the prototype through the skull has to be simulated. Simulations were performed with a 3D finite differences (FDTD) program, called Acel, developed in our laboratory. It takes 2 h computational time to perform a 3D simulation through the skull bone structure. Basically, the program is based on a discretization of the linear acoustic wave equation in heterogeneous absorbing media:

\[ \left( 1 + \tau_0(r) \frac{\partial}{\partial t} \right) \left[ \frac{1}{\rho_0(r)} \nabla \cdot \left( \frac{1}{\rho_0(r)} \nabla p(r,t) \right) \right] - \frac{1}{c_0(r)^2} \frac{\partial^2 p(r,t)}{\partial t^2} = S_0(r,t), \]
where $\tau_0$ is the spatial distribution of the characteristic relaxation time of the absorption, $\rho_0$ is the spatial distribution of the density, $c_0$ is the spatial distribution of the speed of sound and $S_0$ is the spatial and temporal distribution of this acoustic source. This equation accurately models fluids with sound speed, density and absorption heterogeneities. Mode conversions and shear waves are not taken into account. Nevertheless, they can be neglected in first approximation as the wavefront incidence angle on the skull’s interface remains close to the normal incidence. The first in vitro experiments handled in the laboratory showed good agreement (Aubry et al 2003) and one study (Hayner and Hynynen 2001) demonstrated that the shear waves have no effect on the focusing for incidence angles up to $20^\circ$.

In order to reduce the computation time, the finite difference code was only performed from an arbitrary plane of transducers close to the skull bone. Propagation in brain tissues can be modelled by faster simulation approaches. Thus, the propagation in homogeneous volumes is realized by a ray-tracing code.

2.7. Time reversal and repositioning for in vitro experiment

The signal received on each individual transducer in the simulation is time-reversed and used as input for experimental validation. Time reversal is an adaptive technique to correct phase aberrations induced by the skull (Fink et al 2003). Basically, a pulse emitted by an acoustic source at the desired focus is recorded by the transducers’ matrix after propagation through the medium. Then, signals are time-reversed and re-emitted, so that the wavefront propagates back to the source as if the experiment was played backwards.

The skull has to be repositioned in the same configuration as in the computation. Therefore, the frame is mounted on the therapeutic probe with a submillimetric precision (0.1 mm error from the frame manufacturer, 0.4 mm error using the detection software: these errors induce a 0.7 mm error on the focus positioning). This error is acceptable in comparison to the focal spot size ($1.5 \times 1.5 \times 10.5$ mm$^3$).

3. In vitro results for the human skull

A first time reversal experiment in water was performed in order to correct for the small errors in the transducers’ positioning on the spherical mould surface. The delays recorded during this calibration step will be added for all following experiments to the transmit signals. Thus, it provides a therapeutic array with apparent individual elements perfectly aligned on a spherical shape. For all experiments, these delays will be added to the other delays to take into consideration these geometrical imperfections of the experimental array.

To test the validity of this 3D non-invasive protocol, three sets of emission signals were evaluated. The first set corresponds to emission signals without any correction and the second to corrected signals obtained using the time-reversal technique based on an implanted hydrophone. The last one corresponds to the emission signals obtained using the non-invasive time-reversal technique based on 3D CT treatment planning. The whole experiment was performed at seven different locations (each location was at least 1 cm away from the others) to test the reproducibility of this protocol (different acoustic properties’ spatial distributions).

Figure 6 shows typical beam plots (C-scans) of the transcranial ultrasonic beam recorded in the focal plane by the needle hydrophone. The spatial distribution of the acoustic intensity is represented in the focal plane. Owing to the large aberrations induced by a human skull, the focal spot obtained using a conventional cylindrical law (a) is extremely degraded. The acoustic energy deposition is $-10$ dB below the optimal focusing quality obtained by time reversal (b). Using the CT scan-based time-reversal technique (c), the local maximum of the
focal spot is only $-0.9$ dB below the acoustic energy obtained with the hydrophone-guided time-reversal technique (b). The focal spot positioning for CT scan-based time-reversal fits with the targeted position (positioning error in the focal plane: $0.32 \pm 0.08$ mm), and this technique provides sharp focusing ($-6$ dB width for the non-invasive time-reversal technique: $1.57 \pm 0.07$ mm for the minor axis and $2.12 \pm 0.04$ mm for the major axis; $-6$ dB width for the hydrophone-guided time-reversal technique: $1.64 \pm 0.03$ mm for the minor axis and $2.13 \pm 0.03$ mm for the major axis). The acoustic energy at the focal spot is about 80% ($80.02 \pm 0.87\%$) of the energy obtained with the hydrophone-based time-reversal technique.

Figure 7 shows projections of these focal spot along the $x$-axis and the $y$-axis in a linear scale. The pressure was measured at the focus for the hydrophone-based technique (which is our ‘gold standard’ in all our experiments). This pressure is equal to 25% of the pressure obtained in the absence of the skull bone.

The three different emission signals are also successively emitted channel-by-channel and the resulting signals are recorded at the focal location in order to estimate the quality of phase aberration corrections using the three sets of emission signals. The resulting B-mode images enable the remaining time-shift errors to be estimated quantitatively. The more appropriate the correction, the more signals emitted independently by each channel and received are in phase at focus. The hydrophone-guided time-reversal technique corresponds to the optimal
Figure 7. Energy profiles on the x-axis and y-axis. Dotted line: without any correction. Dashed line: using non-invasive time reversal. Solid line: hydrophone-based time reversal.

Figure 8. Normalized temporal signals received at focus for each individual element emission for three sets of emission signals: corrected by hydrophone-guided time reversal (a), non-invasive CT scan-based time reversal (b) and without any correction (c).
correction as shown in figure 8(a). The non-invasive aberration correction technique (b) strongly decreases the time gap between channels. The correction is not optimal but most signals are in phase ($\Delta t = 0.10 \pm 0.03 \mu s$ for the non-invasive time-reversal technique while $\Delta t = 0.83 \pm 0.10 \mu s$ without any correction; the sample frequency is 30 MHz so phase control precision is 0.033 $\mu s$). All signals are in phase at the focal point. In contrast, without any corrections (c), signals reach focus with a wide range of time delays. The delay variations reach up to 2 $\mu s$ (which corresponds to two periods for the 1 MHz excitations used in this study).

Figure 9 shows the acoustic energy distribution as a function of the phase error for both non-invasive time-reversal technique and for conventional focusing without any correction. According to Goodman (1985), the standard deviation on the phase signal received at focus for each individual element contribution should be less than one-eighth of a period ($T/8$) in order to have optimal constructive interferences. The dashed line in figure 9 corresponds to the Goodman criteria. Most of the energy satisfies this criterion (80.65% corresponding to 62.33% of the transducers) for the non-invasive time-reversal technique. Without any correction, only 15.32% (corresponding to 20% of the transducers) satisfies this criterion. Interestingly, these values correspond to the energy ratio obtained previously while comparing the acoustic intensity at focus for both techniques with the optimal acoustic intensity obtained by the hydrophone-guided time-reversal technique.

The signals recorded at focus were back-propagated numerically up to the skull bone surface. The phase error just before the inner plate of the skull bone (corresponding to brain tissues) is represented in figure 10 (2D projection viewed from the focus). Using conventional focusing, the wave field after transcranial propagation is strongly aberrated with distortions higher than a wavelength. These aberrations are heterogeneously distributed all over the skull bone surface. These strong phase aberrations are corrected by CT scan-based time reversal: the corrected beam is almost spherical after transcranial propagation, as depicted in figure 10(a).

4. *In vitro* results for the monkey skull

The same transcranial focusing protocol was applied to a monkey skull in order to prepare an *in vivo* preclinical study on macaques. A dedicated stereotactic frame was also built. As in the
previous section, the three sets of emission signals were compared. Aberrations caused by the monkey skull are smaller than the human one, so a conventional cylindrical law at a central frequency of 1 MHz (figure 11(a)) can provide a reasonable focusing, but focus positioning is approximate (±0.6 mm) and maximum intensity smaller than the ideal case corresponding to hydrophone-guided time-reversal (figure 10(b)): the energy deposited at the focal point is equal to 82.3% of the energy obtained using the invasive time-reversal technique for the non-invasive CT scan-based focusing technique while this ratio is equal to 74.6% without any correction. Positioning for CT scan-based time reversal is perfect, and focal intensity is higher without any correction, as depicted in figure 10(c). Figure 12 also shows projections of these beam plots (C-scans) along the x-axis and y-axis in the focal plane.

5. Discussion

The proof of the concept for CT treatment planning of transcranial ultrasonic beam was demonstrated in a previous paper (Aubry et al 2003): simulations were compared with experiments conducted using an ultrasonic linear array (conventional echographic array). By taking precisely into account the heterogeneities of the skull bone structure, the 3D FDTD simulation approach was able to predict accurately the phase and amplitude aberrations induced on the experimental wavefront even at high frequency (up to 1.5 MHz).

The present paper extends this technique into a complete 3D and non-invasive protocol for HIFU applications. The results demonstrate the potential of ultrasound brain therapy through an intact human skull bone. Aberrations are almost totally corrected by the 3D FDTD numerical prediction, as the pressure field reaches 90% of the pressure that would be obtained by using an implanted hydrophone. This confirms the possibility of reaching optimal focusing capabilities using a fully non-invasive 3D technique. These results are very promising considering that further improvements could be made: extensive work is currently being done on the anisotropy of the numerical simulation, on the extraction and the segmentation of the skull bone boundaries. Moreover, the receivers used in the numerical simulation are currently considered as point-like receivers and their geometry was not taken into consideration. Thanks
Figure 11. Beam plots in the focal plane showing the energy deposition in the focal plane, using any correction (a), real time-reversal focusing technique (b) and non-invasive time-reversal focusing technique (c).

to these updates the total energy deposition of the non-invasive time-reversal technique could be even higher and could increase the energy deposition in the focal spot.

Moreover, further analysis of the simulation process could help decreasing the temperature elevation on the skull by decreasing the total emitted power. In order to study the effect of switching off channels, a threshold has been applied to cancel the lowest signals (lower than the threshold). This threshold is determined on simulated signals’ amplitude and for comparison, the same channels, for both corrected and uncorrected data, are shut down for each value of the threshold. Figure 13 shows the effect of increasing the threshold on the focusing quality. Interestingly, the acoustic energy obtained at focus decreases very slowly as the threshold is increased and almost remains constant for thresholds lower than 30%. For the corrected signals, the percentage of channels which have a phase error below $T/8$ increases while the amplitude threshold increases. That is why the acoustic energy level (normalized on the hydrophone-guided time-reversal acoustic energy level) remains constant while the number
Figure 12. Energy profiles along the $x$-axis and $y$-axis. Energy levels are normalized on the hydrophone-based time reversal.

Figure 13. Amplitude threshold criteria applied on the non-invasive time-reversal technique (a) and focusing without any correction (b). Three plots are presented, respectively, corresponding to the percentage of transmit channels used, the percentage of acoustic intensity at focus and the percentage of channels for which the error on the estimation of phase aberrations remains below $T/8$.

of emission channels decreases. On the other hand, without any correction, the percentage of channels which have a phase error below $T/8$ remains lower than 25%.

This information could be useful with a view to clinical applications: for an amplitude threshold set to 30%, it can be seen that the pressure level remains the same whereas 20% of the channels have been turned off. This means that the emitted energy could be decreased by 20% while preserving the sharpness of the focusing and the pressure level at the focal spot. Reducing the emitted energy will reduce the heat dissipation in the skull bone, which can cause skin burns.

The full 3D FDTD simulation requires extensive computational resources. The speed of sound and density maps need to be sampled at $\lambda/10$, so that 16 GB of RAM is necessary to
store the whole set of maps. The whole 3D simulation requires 2 h of computation. This
duration is of the same order as the time needed for the dose calculation in a radiotherapy
protocol. Moreover, the simulation is able to provide 4D estimation (time and space) of the
pressure field during the treatment. Using this information, the skull bone heating and the
maximal peak pressure at focus can be predicted. For clinical applications, a measuring device
seems necessary during the treatment, such as MRI temperature monitoring as proposed by

The 3D HIFU prototype developed in our laboratory is able to deliver about 6.6 MPa
(linear extrapolation) behind the skull bone at the geometrical focus of the array. Considering
absorption effects in soft tissues (skin and brain), this maximal peak pressure is estimated to
5 MPa. According to the results presented in this paper, the transcranial therapeutic probe
is able to generate 4.5 MPa at focus using the fully non-invasive 3D protocol. According
to Dewey (1994), the theoretical thermal dose to apply in the brain to induce a necrosis is
25 eq min$^{-1}$. With 4.5 MPa, this dose would be reached in less than 1 s at the focal spot.

The full protocol has also been tested in a monkey skull bone model, in order to prepare an
in vivo preclinical study. The aberration correction also improves the focusing capability of the
array for monkey experiments. However, due to the smaller thickness of monkey skull bone,
enhancements of the non-invasive protocol are less impressive than for human applications.
Nevertheless, due to monkey skull aberrations, the focal spot can be tilted several millimetres
away from the desired location as shown in figure 11(a). Using the non-invasive correction
technique, the focal spot position is retrieved with a submillimetric precision. The pressure
peak amplitude at the desired location is increased by a factor of 2 using the correction
technique (figure 12). This leads to a four times higher energy deposit at the targeted position
for monkey transcranial experiments.

6. Conclusion

A non-invasive 3D protocol for transcranial brain tissue ablation was studied and validated
in vitro. In vitro experiments were conducted both on monkey and human skull specimens using
a 300 transmit elements array working at a central frequency of 1 MHz. These experiments
show a precise refocusing of the ultrasonic beam at the targeted location with a positioning error
lower than 0.7 mm. Using the fully non-invasive protocol based on 3D CT scan simulations,
the pressure peak amplitude at focus reaches 90% of the optimal focusing based on the use
of an implanted hydrophone. This complete in vitro validation of this transcranial adaptive
focusing procedure paved the way to in vivo animal experiments on monkeys performed in
the 2005–2008 period (Marquet et al 2007, Tanter et al 2007) and to forthcoming in vivo
human transcranial HIFU investigations. Moreover, this protocol can also be applied in
other transcranial focused ultrasound applications such as disrupting the blood–brain barrier
or activating gene expression. This work paves the way to non-invasive in vivo human
investigations.

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