Published in final edited form as:

Int J Imaging Syst Technol. 2012 September ; 22(3): 177–184. doi:10.1002/ima.22020.

Image-guided Navigation of Single-element Focused Ultrasound Transducer

Hyungmin Kim^{a,b}, Alan Chiu^a, Shinsuk Park^b, and Seung-Schik Yoo^{a,c}

^aDepartment of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

^bDepartment of Mechanical Engineering, Korea University, Seoul, Korea

^cSchool of Nano-Bioscience and Chemical Engineering, Ulsan National Institute of Science and Technology, Ulsan, Korea

Abstract

The spatial specificity and controllability of focused ultrasound (FUS), in addition to its ability to modify the excitability of neural tissue, allows for the selective and reversible neuromodulation of the brain function, with great potential in neurotherapeutics. Intra-operative magnetic resonance imaging (MRI) guidance (in short, MRg) has limitations due to its complicated examination logistics, such as fixation through skull screws to mount the stereotactic frame, simultaneous sonication in the MRI environment, and restrictions in choosing MR-compatible materials. In order to overcome these limitations, an image-guidance system based on optical tracking and pre-operative imaging data is developed, separating the imaging acquisition for guidance and sonication procedure for treatment. Techniques to define the local coordinates of the focal point of sonication are presented. First, mechanical calibration detects the concentric rotational motion of a rigid-body optical tracker, attached to a straight rod mimicking the sonication path, pivoted at the virtual FUS focus. The spatial error presented in the mechanical calibration was compensated further by MRI-based calibration, which estimates the spatial offset between the navigated focal point and the ground-truth location of the sonication focus obtained from a temperature-sensitive MR sequence. MRI-based calibration offered a significant decrease in spatial errors (1.9 ± 0.8 mm; 57% reduction) compared to the mechanical calibration method alone (4.4 ± 0.9 mm). Using the presented method, pulse-mode FUS was applied to the motor area of the rat brain, and successfully stimulated the motor cortex. The presented techniques can be readily adapted for the transcranial application of FUS to intact human brain.

Keywords

focused ultrasound; image-guidance; optical tracking; calibration; neuromodulation; brain; single-element transducer

Introduction

Departing from its traditional role in diagnostic imaging, therapeutic applications of ultrasound have been explored, with applications in such areas as hyperthermic tumor ablation, drug delivery, and adipose tissue reduction (Cheung and Neyzari, 1984; Frenkel, 2008; Adamo, Mazzocchi, Rossi and Scuderi, 1997). Since its conceptual demonstration in the reversible inhibition of visual processing in the 1950s (Fry, Ades and Fry, 1958), the use of ultrasound to modify the excitability of neural cells has been under investigation. Examples include the measurement of auditory nerve response to the ultrasound in cats (Foster and Wiederhold, 1978) and reported auditory sensation during the application of transcranial Doppler ultrasound in humans (Magee and Davies, 1993). Recently, the excitatory effects of ultrasound given in pulsed mode to the rodent's motor cortex have been demonstrated in excised brain tissue (Tyler et al., 2008) as well as in intact brain tissue (Tufail et al., 2010).

These previous studies, which were based on the unfocused application of acoustic beams to neural tissues, lacked spatial specificity of modulation, limiting its usage in targeted therapies. By concentrating the acoustic pressure on a specific region, delivery of focused acoustic energy to a tissue region as small as a grain of rice became possible (Lele, 1962). This technique, called focused ultrasound (FUS), has been utilized to induce thermal damages (thus ablate) to tumors in the soft tissue, such as the liver, breast, and uterus (ter Haar, 2007), or to break apart stones in the kidney, bladder or ureter, *i.e.*, lithotripsy, (Coleman et al., 1995) by applying acoustic waves with high intensity and high pressure.

The neurotherapeutic application of transcranial FUS presents challenges, since the skull acts as a sound absorber as well as a reflector with complex geometry in the acoustic beam path, leading to attenuation of the acoustic power and distortion of the beam profile. The use of low acoustic frequency, typically lower than 1 MHz (a much higher frequency is used in diagnostic ultrasound imagers), generally decreases acoustic attenuation and distortion. Only mild attenuation (22.5%) of the ultrasound beam was observed at 120 kHz through a human skull (Coussios, Holland and Shaw, 2002), while virtually most of the acoustic energy is attenuated at a frequency above 1 MHz. For these reasons, most commercially available transcranial FUS equipments utilize frequencies in the 200–700 kHz range.

In order to deliver highly-focused acoustic energy to a focal region of the brain through the skull, independent actuation of US elements in a phased array, arranged in a helmet-like fashion surrounding the skull, is employed (Clement et al., 2005). The desired location and intensities of acoustic focus is inversely projected back to each element to estimate its phase of the actuation based on the geometry of the beam path, accounting for phase aberration and attenuations from the brain tissue and the skull of the patient (obtained from the CT). This method has been utilized in tumor ablation (McDannold et al., 2010) as well as functional neurosurgery for pain treatment, such as medial thalamotomies (Martin et al., 2009), but requires sophisticated algorithms and intra-operative MR-guidance to plan and execute the sonication.

Capitalizing on the neuromodulatory capability of the ultrasound, it has been shown that FUS can selectively modulate (either elicit or suppress) the functions of specific brain areas (visual and motor areas) in rabbits (Yoo et al., 2011). The suppressive effect of FUS has also been observed on chemically-induced epileptic rats while sonicating the thalamic areas of the brain (Min et al., 2011). Thalamic application of FUS was also shown to modulate the level of cortical neurotransmitters (dopamine and serotonin) (Min et al., 2011) and to significantly shorten anesthesia time (Yoo et al., 2011).

In small animal studies involving rodents and rabbits, where the acoustic distortion is negligible due to thin skull thickness (less than 1mm), a single-element transducer can be effectively used to deliver the acoustic focus to the targeted tissue. A transducer with fixed geometrical shapes, typically a segmented sphere with a specific curvature, generates an acoustic pressure aimed at the specified focal point. Current techniques to localize the acoustic focus in *in vivo* brain tissue, achieved by moderately elevating tissue temperature (typically less than 40°C) and concurrent temperature-sensitive MR monitoring, inevitably confound the neural excitability. To avoid this confounding effect, tracking the focal point by the geometric relations of the transducer surface was suggested. For a single-element transducer setup, the use of a visual guidance system based on two laser beam pointers has been proposed for localizing the focal point over the scalp (Min et al., 2011). However, this system has sources of potential errors due to an assumption of a flat scalp surface, and coarse determination of the focal point. In order to overcome some of these limitations, an optical tracking system that characterizes and tracks the location of the ultrasound focus as well as the spatial orientation of the acoustic beam is presented.

Materials and Methods

Overview

The goal of the presented method is to detect the location of the virtual focal point of the ultrasound transducer, as well as the orientation of the sonication path using an optical tracking system (Vicra, Northern Digital Inc., ON, CA). The optical tracking camera used in the developed image-guided navigation system provides the spatial transformation (position and orientation) of a rigid-body tracker that consists of four infrared (IR) light-reflective spheres (NDI Passive Spheres, Northern Digital Inc., ON, CA). Based on the geometric relations among the spheres, the tracking camera automatically captures the location and orientation of the tracker from the background image in real-time. The FUS focus generated by the segmented-sphere piezoelectric ultrasound transducer is located along the center axis away from the inner surface of the transducer, as defined by the inner radius-of-curvature (ROC), according to the manufacturing specification (7 cm). The tracker is attached to the axis of the FUS transducer (along the injection path of the sonication) with a fixed spatial offset vector with respect to the sonication focus. We present two ‘calibration’ methods, *i.e.*, mechanical calibration and MRI-based calibration, to define this offset vector in the local coordinate system of the transducer.

Mechanical calibration was provided by detecting the concentric rotational motion of a rigid-body tracker, attached to a straight rod mimicking the sonication path. The rod was pivoted at the virtual FUS focus that is formed at center of the inner curvature of a specific

FUS transducer. Due to the presence of mechanical imperfections in the setup, such as manufacturing errors in transducer shape and the length of the rod, as well as an imperfect pivoting motion (done manually, which could result in deviation from the pivoting point), the further correctional calibration step was necessary to improve the accuracy of the calibration, as well as to account for the potential presence of the distortion of the sonication by the media. In this additional calibration, a rigid-body frame that contains both the sonication target and the FUS transducer (with a duplicated tracking marker attached) are imaged using MRI, and a temperature-sensitive MRI sequence is used to image the 'ground truth' location of the sonication focus by heating the gel phantom (silicon composite). After localizing this 'ground truth' coordinate, the difference in locations of the sonication focus identified from the mechanical calibration step is corrected to reflect a more realistic focal location in space. The calibrated FUS transducer was then used to navigate through the rat brain and to sonicate the motor area of the rat, to elicit its activation. The more detailed descriptions of the calibration steps are provided below.

FUS Transducer

The single element FUS transducer used in the present study was air-backed and of a segmented sphere shape (6cm in diameter, 7cm in radius of curvature), operating in 350 kHz in fundamental frequency. The acoustic pressure distribution near the focus, perpendicular to the sonication path, was mapped using hydrophone, (HNR500; Onda, Sunnyvale, CA) using the method described elsewhere (Yoo et al., 2011). The focus was roughly cigar-shaped (6.5mm in diameter, 11.5mm in length) at the full-width-at-half maximum (FWHM) of the acoustic pressure field at the focal plane. The centroid of the acoustic pressure above the FWHM was defined as the sonication focus.

Mechanical Calibration

A copper rod (5mm in diameter) with a pointed tip (angled 30 degrees from the axis of the rod) was attached to a rigid-body tracker as shown in Figure 1A. Based on the manufacturing specification (7 cm ROC), the tracker was positioned away from the tip of the rod with the same relative offset as the imaginary focal point. The initial estimation of the focal point was obtained by tracking the rod with the optical camera as it was manually pivoted around a small divot on an acrylic block (as shown in Figure 1B), and subsequently calculating the location of the pivot point using the software provided by the manufacturer of the tracking system (6D Architect, Northern Digital Inc., Waterloo, ON, Canada). Once the location of the focal point is estimated, the trajectory along the rod (*i.e.*, sonication beam path) was determined in the predefined direction (negative z-axis in Figure 1A) in the local tracker coordinate system.

MRI-based Calibration

The MRI-compatible calibration setup is illustrated in Figure 2A. All the parts were made with plastic materials (Delrin or Acryl) to enable housing the sonication setup and tracking accessories in a MRI environment. To spatially register the coordinates of the sonication setup and its corresponding representation in the MR images, seven donut-shaped, multi-modal (MR/CT) fiducial markers (PINPOINT, Beekley Corp., Bristol, CT) were affixed

onto the acrylic surface of the sonication setup, surrounding the gel phantom. We ensured all the fiducial markers were not placed on the same plane. The location of the middle hole of the markers, 1.27 mm in diameter, was used to register the corresponding locations between the virtual MR space and the physical space. The silicon composite MR gel phantom (Action Pilot Cushion, Action Products, Inc., Hagerstown, MD) was placed on the frame, and a rubber sheet (~ 5mm in thickness) was placed below the gel phantom to minimize the effect of reflected acoustic waves. The phantom was then sonicated at an acoustic intensity of $5.78 \text{ W/cm}^2 I_{\text{sppa}}$ (spatial-peak pulse-averaged intensity) in continuous mode for 30 sec without damaging the phantom by the generation of excessive heat.

Immediately after the sonication, the gel phantom was imaged by a MR scanner (3 Tesla, GE Medical Systems, Waukesha, WI) with a temperature-sensitive spin-echo MRI sequence (TE/TR=11.8/500 ms, echo-train-length=4, matrix=256×128, field-of-view=16×16cm², slice thickness=3mm) (Yoo et al., 2011). The MRI scan was performed in both coronal and sagittal directions, alternately two times, with each scan lasting about 12 seconds. While changing the direction of the scan plane, the gel was cooled down for 5 minutes without sonication. Then, the areas which showed a temperature rise was visualized by subtracting the baseline image (obtained prior to sonication) from the images after the sonication, (as shown in Figure 2B). The focal location was obtained from the centroid of the heating area in the subtracted MR image in the MRI coordinate system ($\mathbf{f}_M$). In addition to temperature-sensitive MR scans, T₁-weighted MR images were acquired with a 8-channel head phased-array coil (8HR Brain, GE Healthcare) to provide volumetric space for the navigation which includes fiducial markers in FOV, using a 3D fast spoiled gradient recalled (3D FSPGR) sequence (TR/TE = 8.0/3.2, flip angle = 20°, matrix = 256×256, field of view = 14cm, slice thickness=1mm, number of slices = 236).

While maintaining the relative spatial relationship between the transducer and gel, the whole phantom was moved outside of the MR scanner (on a wheeled bed), and the rigid-body optical tracker was attached to the frame and the transducer holder, denoting their local coordinate systems as {R} and {S} in Figure 2C, respectively. Then, the coordinates in the physical space was registered with the corresponding MRI coordinate system {M} by using the fiducial markers on the frame. The calibrated offset vector ($\mathbf{f}_S$) in the transducer's local coordinate system {S} was calculated using the following spatial relationship, represented in multiplication of 4×4 homogeneous transformation matrices and 4×1 positional vectors with homogeneous term: $\mathbf{f}_S = \mathbf{T}_{SMfM} = \mathbf{T}_{CS}^{-1} \mathbf{T}_{CR} \mathbf{T}_{MR}^{-1} \mathbf{f}_M$, where $\mathbf{T}_{CS}$ and $\mathbf{T}_{CR}$ were provided by the tracking information from optical tracking camera, while the $\mathbf{T}_{MR}$ was defined by the registration between the fiducial markers and its corresponding MR representation.

Comparison of the focal location from the suggested calibration methods with the ground-truth

Since the 'ground truth' coordinate of the FUS focus was obtained by locating the heat signature in alternating coronal (XZ plane) and sagittal (YZ plane) scans, the localization accuracy was achieved on the order of effective in-plane resolutions (*i.e.*, 0.625mm), which was in sub-millimeter scale. In terms of through-plane (*i.e.*, z-direction) resolution, the data was interpolated to sub-millimeter scale to accommodate three-dimensional spatial

rotational operation. The coordinates of navigated focal point was internally tracked in double digits floating point in the navigation software. Subsequently, the coordinates of the heating spot was rounded to the nearest floating value in 0.5mm step.

The coordinates of the navigated focal point based on the initial mechanical calibration displayed in the navigation software was compared with the coordinates of the heated spot from the MR images. Since both of them are represented in the same MRI coordinate system, simple measurement of 3D Euclidean distance was applied to represent the spatial error. Then, we calculated spatial errors along three axes, X(left/right), Y(posterior/anterior), and Z(superior/inferior), adopting a convention used in diagnostic radiology. The navigated focal point location was then updated by applying the offset calculated by the MRI-based calibration method described above, and re-compared with the ground-truth focal point location in the MRI-coordinate system by measuring 3D Euclidean distances, and spatial errors in each direction.

Application for FUS neuromodulation in rats

After updating the information obtained from the MRI-based calibrated step, the image-guided navigation system was applied to localize and track the FUS focus given to a rat brain to excite the motor cortex, eliciting tail movements. The animal experiments in this study were conducted under institutional review and approval by the Harvard Medical Area Standing Committee on Animals.

In order to provide detailed anatomical information of the rat for image-guidance system, an MRI scan was performed. Prior to MR imaging, a male Sprague–Dawley rat (331g) was anesthetized with an intraperitoneal injection of a ketamine/xylazine mixture of 80:10 mg/kg. Then, the rat was fixed on the MRI-compatible stereotactic frame (SRP-AR, Narishige, Japan), as shown in Figure 3B (shown without the transducer), where the seven fiducial markers were affixed onto the frame as described (*i.e.*, placed in locations that are not in a same plane). T₁-weighted anatomical MR images were acquired by a high-field (3T) MR scanner (GE Medical Systems, Waukesha, WI) with a QUADKNEE coil. Specifically, a spoiled gradient recalled (SPGR) sequence (TR/TE = 18.8/minimum, flip angle = 12°, matrix = 512×256, field of view = 14cm, slice thickness=1mm, number of slices = 116) was used to obtain 3D volume data of the head. The rat was returned to the animal facility after the scan, and the sonication experiment was conducted on a separate day.

To use the MR data of the rat obtained on a separate day for navigation, the dimensions of the head anatomy of the rat should not change significantly over time. In order to verify this assumption, the sizes of several cranial structures, the length between (1) left and right ear inlets, (2) right ear inlet and nasion, and (3) right ear inlet and the anterior tip of the snout, were measured (n=4; normal feeding and growth environment, weight range 271–368g) over a period of 35 days (10 measurements) using a digital caliper. The data showed a plateaued growth curve during this weight segment (in the results section), suggesting the MR data of the rat can be used for a short time interval (~30 days).

For the neuromodulatory experiment, the rat (n=3, 272–359g) was anesthetized with an intraperitoneal injection of a ketamine/xylazine mixture of 80:10 mg/kg. After anesthetizing

the rat, the head was shaved to enhance ultrasound transmission through the scalp. The rat was then positioned on the fixation frame at the same position previously achieved during the MRI, as shown in Figure 3B. To ensure the fixation location is faithfully duplicated, the ear bars were aligned with the interaural line, and maintained at the same locations, utilizing the stereotactic frame/rulers as a guide. Once the rat was securely restrained, the FUS transducer was coupled to the rat's head through a degassed water bag, while additional hydrogel was applied onto the interfacing scalp.

The specific functional spot on the rat brain cortex that elicits tail movement was targeted using the developed navigation technique. Tail movement is more distinctively observable than other body movements (*e.g.*, whisker or paw movement), facilitating the detection by a motion detector. The coordinates of the sonication spot (~2mm posterior to Bregma along the midline) was determined using a functional atlas generated by transdural electrical stimulation on the motor cortex of the rat (Fonoff et al., 2009) (as shown in Figure 3A and 3B), as referenced to the mid inter-aural line.

The rat in the physical space was then registered to the virtual MRI space by digitizing the corresponding fiducial markers in the MRI data. The registration accuracy, as characterized by the fiducial registration error (FRE), was determined by the root-mean-squares error (RMSE) of the paired-point registration, and then confirmed using a registration probe on the location of the fiducial markers on the frame and a few distinctive anatomical landmarks (ear canals, snout, eye center) on the rat. Then, the tracking priority was changed to the transducer from the registration probe, and the corresponding calibration offset was selected according to the focal geometry of the transducer.

Once the navigated focal point reached the planned target site, the sonication was initiated. The bursts of pulsed waves were generated by two successive function generators (33210A, Agilent, Santa Clara, CA) at the pulse-repetition frequency (PRF) of 1kHz, tone-burst duration (TBD) of 0.5ms, sonication duration of 300 msec, and sonication interval of 2 sec, and transmitted to the transducer through a linear power amplifier (240L, ENI Inc., Rochester, NY). Considering the ultrasound attenuation factor (~87%) through the rodent skull *in situ* (Kinoshita, McDannold, Jolesz and Hynynen, 2006), the resulting spatial-peak pulse-average intensity (I_{sppa}) was 9.1 W/cm², and the corresponding mechanical index (MI) was 0.9 (where peak negative pressure was 0.5 MPa). The equivalent spatial-peak temporal-average intensity (I_{spta}) was calculated as 4.5 W/cm² with 50% of duty factor. The elicited tail movement signal was acquired by the Piezo Electric Pulse Transducer (MLT1-1010/D, AD Instruments, CO), amplified (PowerLab 8/30, AD Instruments, CO) and recorded (LabChart 7, AD Instruments, CO) at a sampling rate of 1 kHz. In order to remove noise in recorded tail movements due to respiratory or heart motions, the signals were filtered with a low pass filter (3Hz).

Results

Overview

The results of mechanical calibration from five independent sessions were reproducible over 0.1 mm of standard deviation along all three axes, which provided the initial estimation of

the focal point in the image-guidance system. The distance between the heating spot from each of the three independent temperature-sensitive MRI sessions and the navigated focal point based on the mechanical calibration, was 4.4 ± 0.9 mm. After applying the offset vector in the navigation system based on the suggested MRI-based calibration method, the distance between the heating spot and the navigated focal point was cross-compared between independent MRI sessions, which resulted in a distance of 1.9 ± 0.8 mm (57% decrease compared with the data from mechanical calibration)

Comparison of mechanical and MRI-based calibration results

Mechanical calibration was conducted five times to estimate an initial location of the focal point for the navigation system. As a result of mechanical calibration, the focal point location was calculated as 18.1 ± 0.1 mm, 0.9 ± 0.1 mm, -130.0 ± 0.1 mm with respect to the local coordinate system of the tracker attached to the transducer. Three independent sessions of MRI-based calibration were conducted after the initial mechanical calibration. For each session, the relative location of the transducer and the gel was adjusted by reattaching the transducer to the phantom and rotating the gel phantom to vary the measurement conditions. The location of the heating spot was localized by successive MRI scans in the coronal and sagittal directions as shown in Figure 4A.

The coordinates of the focal point based on the initial mechanical calibration result was compared with the location of the acoustic focus identified from temperature-sensitive MRI. The FRE value obtained from registering the MRI-compatible FUS apparatus to the corresponding MR images was maintained at less than 1mm (in RMSE). The averaged spatial distance between the navigated spot given by the mechanical calibration and the heating spot identified by temperature-sensitive MRI was calculated as 4.4 ± 0.9 mm, as shown in the last column in Table 1.

After updating the offset vector from the MRI-based calibration, the coordinates of the navigated acoustic focal spot was cross-compared with the ground-truth focal point obtained from the other MRI session (Table 2). The results showed that the averaged spatial error, as presented in averaged spatial distance between the navigated and the ground-truth location of the acoustic focus, was reduced to 1.9 ± 0.9 mm (57% decrease compared with the mechanical calibration result). The difference between the navigated focal point and the ground truth obtained by the same MRI sessions was 0.1 ± 0.0 mm (not shown on the table).

Cranial growth measurement in rats and neuromodulation

Repeated Measures ANOVA (Davis, 2002) was conducted for the cranial growth data to examine if the skull dimensions changed during the MRI imaging and FUS experimentation. No statistically significant changes were found in conducted measurements in the weight range of 271–360g ($p=0.19$ for the length between left and right ear inlets, $p=0.07$ for the length between right ear inlet and nasion, $p=0.09$ for the length between right ear inlet and the anterior tip of the snout). The results indicate that instead of acquiring individual MR images, MRI data from a single rat can be used for navigation through different animals, at least in the specified weight range. The resulting tail movement was visually observed from

all the animals as the tail movements were synchronized with the sonication intervals (2 seconds). An example of detected tail movement is shown in Figure 5.

Discussion

In this study, calibration methods for an image-guided navigation system with a single-element FUS transducer were presented. Mechanical calibration alone did not offer sufficient spatial accuracy in estimating the acoustic focus (*i.e.*, on the order of 4–5 mm, for the FUS focal size of 6.5mm in diameter). There was significant improvement (57% decrease in spatial error with respect to the ground truth characterized by temperature-sensitive MR scans) in the navigated focal point accuracy with the addition of the MRI-based calibration method. The methods were applied to localize the specific functional area on the rat's brain that successfully elicited the tail movement. The successful stimulation with minimal variation around the planned target site confirmed the validity of the image-guided navigation system on a rat.

Imperfections in the manufacturing process of the transducer and its applicator/holder would affect the accuracy of the initial calibration result based on the mechanical calibration method alone. Furthermore, the pivoting-based calibration, which is based on least-squares fitting of the collected transformations by the optical tracking camera, could produce errors due to inconsistencies in the contact point between the metal rod and the divot on the acrylic block during pivoting. In order to increase reproducibility in the pivot motion, the use of robotic manipulation on the divot point, combined with the use of a divot with a tighter fit might be introduced. As an alternative to the pivot-based calibration, a single point calibration method on a special marker with a pre-defined geometry can be used (Gumprecht, Widenka and Lumenta, 1999). Based on the known divot location in the special tracker coordinate system, the tip offset with respect to the transducer's tracker coordinate system can be deduced by using spatial transformations provided by the optical tracking camera. Thus, errors in the manual collection of transformations (200–300 samples) and its numerical calculation for pivot-based calibration could be avoided.

Although the MR-based calibration method significantly improved the accuracy of the mechanical calibration, there are still potential sources of error. Since the registration matrix was used for correlating the physical and virtual MRI spaces in the MR-based calibration procedure, fiducial localization errors (FLE) in the physical and virtual space could affect the calibration accuracy. In order to reduce FLE, MRI-compatible markers with a smaller digitization point (compared to the 1.29 mm diameter one used in our implementation), similar to commercial bone-implantable markers or socket-type skin-adhesive markers, (Maurer et al., 1997; Watanabe et al., 2009) could be adopted. In addition to lowering FLE, optimal placement of the markers, with respect to the target areas, would also decrease the target registration error (TRE) at the focus, which is known to be associated with the spatial arrangement of the fiducial markers, as registration accuracy decreases away from the markers (Fitzpatrick, West and Maurer, 1998).

It is also notable that a degree of geometric distortion may exist during the use of the MRI-based calibration procedures due to the presence of magnetic field inhomogeneity. However,

the spin-echo sequence (for heat-sensitive MRI) as well as the 3D SPGR sequence (for anatomical MRI) are less susceptible to the field inhomogeneity, when compared to 2D gradient-echo sequences. In addition, potential spatial errors that are often associated with MRI of the large skull/air interfaces in human (Baldwin et al., 2007; Wang, Doddrell and Cowin, 2004), are not likely to play an important role in imaging a gel phantom. The spatial accuracy can be further improved by conducting MRI measurements using multiple combinations of spatial encoding directions, or by applying distortion correction schemes based on the ground-truth images, such as computed tomography (CT) scans (Sumanaweera et al., 1995). In addition, Non-isotropic voxel size of MRI data acquisition in the presented method required a spatial interpolation, which may results in associated error. Acquiring MRI images in isotropic voxel size, for example, at sub-millimeter slice thickness using 3D encoding schemes for higher signal-to-noise ratio (SNR), will improve the accuracy of the presented method.

MRI data from a single rat was used for navigation in different animals in similar weights (271–360g), as supported by the plateaued growth of the cranial structure. In order to extend the application of this study to a wider weight range of rats, morphing of template MRI data to individual rat anatomy based on the anatomical features (such as the location of the eye ball, snout, or inter-aural distances) could minimize the differences between template MR images and the subject animal. The addition of functional atlas information, registered to the template anatomical data, may offer automated localization of the specific functional brain area to be sonicated, without requiring a manual definition of anatomical references on individuals. It is important to note that the reproducibility in positioning rats in the same location on the fixation frame is one of the critical factors for accurate navigation.

Minimal distortion of the acoustic beam profile in the presented rodent FUS experiment was assumed, which is reasonable for a transcranial application of low ultrasound frequency (*i.e.*, 350 kHz) through a thin rodent skull (less than millimeters in thickness). For the transcranial FUS application in large animals and humans, more significant distortion of the focal point through the skull is anticipated due to the thick and complex skull geometries (such as shape and sinus in the skull bone). A correction of phase-aberration using multi-arrayed FUS transducers will help to alleviate the situation.

Multi-array transducers are advantageous over single-element transducers, due to its high degree of freedom to reach the small brain area located deep inside of the brain. However, single-element based FUS can also be reliably delivered to the area close to the skull-base by using lower fundamental frequency, *e.g.*, 250 kHz. By using low acoustic intensity with a single-element transducer, the possibility of unwanted skull heating (with lower thermal index) and standing wave formation could be minimized. In addition, the sonication trajectory could be targeted through the thin temporal bone area to minimize the focal point distortion and absorption. Correction of the focal point can also be achieved by simulating skull transmission based on image data (*e.g.*, skull model extracted from CT or MRI). Although increased wavelength (accompanied by adopting lower ultrasound frequency) lowers the possibility of sound beam distortion, caution is warranted in applications in human since it sacrifices the minimum size of acoustic focus (*i.e.*, losing spatial specificity) and increases risks of higher mechanical index.

Regardless of the method of FUS delivery, *in vivo* localization of the focal point via an imaging approach will be conducive to confirming the location and shape of the acoustic focus, for example, using the technique called MR-ARFI (Acoustic Radiation Force Impulse) imaging. ARFI visualizes the local tissue displacements generated by the radiation force of sonication without heating the tissue. However, current MR-ARFI methods still require relatively high acoustic intensity, on the order of $> 100\text{W}/\text{cm}^2$, (Kaye, Chen and Pauly, 2011), which may not be suitable for *in vivo* FUS application for neuromodulatory studies that utilize fractional power. A novel method with greater sensitivity toward the acoustic power is awaited.

Image-guided navigation with a single-element transducer may simplify the examination protocols for the intra MR-guided transcranial application of FUS by separating the MRI-acquisition and sonication sessions. The presented mechanical and MRI-based calibration methods were shown to be effective in estimating the focal spot in the image-guided navigation system, however, the utility of MRgFUS should not be devaluated due to this superior flexibility in controlling size and/or the location the sonication target. By use of lower fundamental frequency, the distortion of the focal spot *in vivo* is expected to be minimized. Further study is needed to investigate the efficacy of FUS-mediated functional neuromodulation and its spatial guidance, considering its safe application.

Acknowledgments

This work was supported by grants from the National Institute of Health (R21 NS074124 to Yoo) and Ulsan National Institute of Science and Technology (to Yoo), as well as the National Research Foundation of Korea (Korean Ministry of Education, Science and Technology, 2010-0027294 to Park).

References

- Adamo C, Mazzocchi M, Rossi A, Scuderi N. Ultrasonic liposculpturing: Extrapolations from the analysis of *in vivo* sonicated adipose tissue. *Plast Reconstr Surg*. 1997; 100:220–226. [PubMed: 9207679]
- Baldwin LN, Wachowicz K, Thomas SD, Rivest R, Fallone BG. Characterization, prediction, and correction of geometric distortion in 3 t mr images. *Med Phys*. 2007; 34:388–399. [PubMed: 17388155]
- Cheung AY, Neyzari A. Deep local hyperthermia for cancer therapy: External electromagnetic and ultrasound techniques. *Cancer Res*. 1984; 44:4736s–4744s. [PubMed: 6467228]
- Clement GT, White PJ, King RL, McDannold N, Hynynen K. A magnetic resonance imagingcompatible, large-scale array for trans-skull ultrasound surgery and therapy. *J Ultrasound Med*. 2005; 24:1117–1125. [PubMed: 16040827]
- Coleman AJ, Kodama T, Choi MJ, Adams T, Saunders JE. The cavitation threshold of human tissue exposed to 0.2-mhz pulsed ultrasound: Preliminary measurements based on a study of clinical lithotripsy. *Ultrasound Med Biol*. 1995; 21:405–417. [PubMed: 7645132]
- Coussios CC, Holland CK, Shaw GJ. Transmission of a large unfocused 120-khz and 1-mhz ultrasound beam through the human skull. *The Journal of the Acoustical Society of America*. 2002; 112:2433.
- Davis, CS. Statistical methods for the analysis of repeated measurements. New York: Springer; 2002.
- Fitzpatrick JM, West JB, Maurer CR. Predicting error in rigid-body point-based registration. *IEEE transactions on medical imaging*. 1998; 17:694–702. [PubMed: 9874293]
- Fonoff ET, Pereira JF Jr, Camargo LV, Dale CS, Pagano RL, Ballester G, Teixeira MJ. Functional mapping of the motor cortex of the rat using transdural electrical stimulation. *Behavioural Brain Research*. 2009; 202:138–141. [PubMed: 19447290]

- Foster KR, Wiederhold ML. Auditory responses in cats produced by pulsed ultrasound. *J Acoust Soc Am*. 1978; 63:1199–1205. [PubMed: 649878]
- Frenkel V. Ultrasound mediated delivery of drugs and genes to solid tumors. *Adv Drug Deliv Rev*. 2008; 60:1193–1208. [PubMed: 18474406]
- Fry FJ, Ades HW, Fry WJ. Production of reversible changes in the central nervous system by ultrasound. *Science*. 1958; 127:83–84. [PubMed: 13495483]
- Gumprecht HK, Widenka DC, Lumenta CB. Brainlab vectorvision neuronavigation system: Technology and clinical experiences in 131 cases. *Neurosurgery*. 1999; 44:97–104. discussion 104–105. [PubMed: 9894969]
- Kaye EA, Chen J, Pauly KB. Rapid mr-arfi method for focal spot localization during focused ultrasound therapy. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. 2011; 65:738–743.
- Kinoshita M, McDannold N, Jolesz FA, Hynynen K. Noninvasive localized delivery of herceptin to the mouse brain by mri-guided focused ultrasound-induced blood-brain barrier disruption. *Proc Natl Acad Sci U S A*. 2006; 103:11719–11723. [PubMed: 16868082]
- Lele PP. A simple method for production of trackless focal lesions with focused ultrasound: Physical factors. *J Physiol*. 1962; 160:494–512. [PubMed: 14463953]
- Magee TR, Davies AH. Auditory phenomena during transcranial doppler insonation of the basilar artery. *J Ultrasound Med*. 1993; 12:747–750. [PubMed: 8301715]
- Martin E, Jeanmonod D, Morel A, Zadicario E, Werner B. High-intensity focused ultrasound for noninvasive functional neurosurgery. *Annals of neurology*. 2009; 66:858–861. [PubMed: 20033983]
- Maurer CR, Fitzpatrick JM, Wang MY, Galloway RL, Maciunas RJ, Allen GS. Registration of head volume images using implantable fiducial markers. *IEEE transactions on medical imaging*. 1997; 16:447–462. [PubMed: 9263002]
- McDannold N, Clement GT, Black P, Jolesz F, Hynynen K. Transcranial magnetic resonance imaging-guided focused ultrasound surgery of brain tumors: Initial findings in 3 patients. *Neurosurgery*. 2010; 66:323–332. discussion 332. [PubMed: 20087132]
- Min B-K, Bystritsky A, Jung K-I, Fischer K, Zhang Y, Maeng L-S, Park SI, Chung Y-A, Jolesz FA, Yoo S-S. Focused ultrasound-mediated suppression of chemically-induced acute epileptic eeg activity. *BMC Neuroscience*. 2011; 12:23. [PubMed: 21375781]
- Min B-K, Yang PS, Bohlke M, Park S, Rvago D, Maher TJ, Yoo S-S. Focused ultrasound modulates the level of cortical neurotransmitters: Potential as a new functional brain mapping technique. *International Journal of Imaging Systems and Technology*. 2011; 21:232–240.
- Sumanaweera TS, Glover GH, Hemler PF, van den Elsen PA, Martin D, Adler JR, Napel S. Mr geometric distortion correction for improved frame-based stereotaxic target localization accuracy. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. 1995; 34:106–113.
- ter Haar G. Therapeutic applications of ultrasound. *Prog Biophys Mol Biol*. 2007; 93:111–129. [PubMed: 16930682]
- Tufail Y, Matyushov A, Baldwin N, Tauchmann ML, Georges J, Yoshihiro A, Tillery SIH, Tyler WJ. Transcranial pulsed ultrasound stimulates intact brain circuits. *Neuron*. 2010; 66:681–694. [PubMed: 20547127]
- Tyler WJ, Tufail Y, Finsterwald M, Tauchmann ML, Olson EJ, Majestic C. Remote excitation of neuronal circuits using low-intensity, low-frequency ultrasound. *PLoS ONE*. 2008; 3:e3511. [PubMed: 18958151]
- Wang D, Doddrell DM, Cowin G. A novel phantom and method for comprehensive 3-dimensional measurement and correction of geometric distortion in magnetic resonance imaging. *Magn Reson Imaging*. 2004; 22:529–542. [PubMed: 15120173]
- Watanabe Y, Fujii M, Hayashi Y, Kimura M, Murai Y, Hata M, Sugiura A, Tsuzaka M, Wakabayashi T. Evaluation of errors influencing accuracy in image-guided neurosurgery. *Radiological physics and technology*. 2009; 2:120–125. [PubMed: 20821109]

- Yoo SS, Bystritsky A, Lee JH, Zhang Y, Fischer K, Min BK, McDannold NJ, Pascual-Leone A, Jolesz FA. Focused ultrasound modulates region-specific brain activity. *Neuroimage*. 2011; 56:1267–1275. [PubMed: 21354315]
- Yoo SS, Kim H, Min BK, Franck E, Park S. Transcranial focused ultrasound to the thalamus alters anesthesia time in rats. *Neuroreport*. 2011; 22:783–787. [PubMed: 21876461]

Figure 1.

(A) Calibration of a single-element transducer with geometrically equivalent metal rod. (B) A photograph of experimental setup for mechanical calibration (C) Calibration of metal rod by pivoting around a stationary point in space.

Figure 2.

(A) Overall setup of MRI-based calibration using single element transducer. (B) Example of heating spot localization on successive MRI scans along coronal plane: image before sonication (left), image after sonication, (middle) subtracted image (right). The scale bar on the right bottom indicates 10 mm. (C) Spatial transformation relationship between coordinate systems used for MRI-based calibration: each bracket notation represents the coordinate system attached to {C} camera, {R} reference tracker, {S} sonication transducer tracker and {M} MR images. (D) Actual photograph of the experimental MRI-phantom setup.

Figure 3.

(A) A planned target sonication site for inducing tail movement on image-guided navigation software (~2mm posterior to Bregma along midline) (B) A 3D illustration of the sonication site; the green cone shape represents sonication path.

Figure 4.

(A) Localized heating spot from successive temperature-sensitive MRI scans in coronal and sagittal planes. (B) Navigated focal spot based on mechanical calibration.

Figure 5.

The signals recorded from tail movements on a single rat (3Hz low pass filter was applied to the raw acquisition data) showed that there were synced movements in the given sonication intervals (2 seconds).

Table 1

Comparison of navigated focal point coordinates obtained by mechanical calibration with ground-truth focal point coordinates obtained by temperature-sensitive MRI (all units in mm, X,Y,Z axis represents left/right, posterior/anterior, superior/inferior direction, respectively)

Navigated Focal Point Coordinates obtained by Mechanical Calibration				Ground-truth Focal Point Coordinates obtained by Temperature-sensitive MRI				Distance							
Session	X	Y	Z	Session	X	Y	Z	3D	X	Y	Z				
1	0.6	-80.4	1.0	1	-4.5	-81.5	2.0	5.3	5.1	1.1	1.1				
2	10.8	-83.2	8.4	2	7.5	-82.5	9.5	3.6	3.3	0.7	1.1				
3	11.2	-84.5	-0.3	3	7.0	-84.0	0.5	4.3	4.2	0.5	0.8				
Average												4.4	4.2	0.8	1.0
Standard deviation												0.9	0.9	0.3	0.2

Table 2

Comparison of navigated focal points coordinates obtained by MRI-based calibration with heating spot coordinates obtained by temperature-sensitive MRI (all units in mm, X,Y,Z axis represents left/right, posterior/anterior, superior/inferior direction, respectively)

Navigated Focal Point Coordinates obtained by MRI-based Calibration				Ground-truth Focal Point Coordinates obtained by Temperature-sensitive MRI				Distance			
Session	X	Y	Z	Session	X	Y	Z	3D	X	Y	Z
2	-2.7	-79.7	2.4	1	-4.5	-81.5	2.0	2.6	1.8	1.8	0.4
3	-3.6	-79.8	2.2	1	-4.5	-81.5	2.0	2.0	0.9	1.7	0.2
1	5.5	-84.3	8.8	2	7.5	-82.5	9.5	2.8	2.0	1.8	0.7
3	6.5	-82.6	9.1	2	7.5	-82.5	9.5	1.0	1.0	0.1	0.4
1	5.9	-85.7	0.2	3	7.0	-84.0	0.5	2.1	1.1	1.7	0.3
2	7.8	-83.9	0.8	3	7.0	-84.0	0.5	0.8	0.8	0.1	0.3
Average								1.9	1.3	1.2	0.4
Standard deviation								0.8	0.5	0.9	0.2