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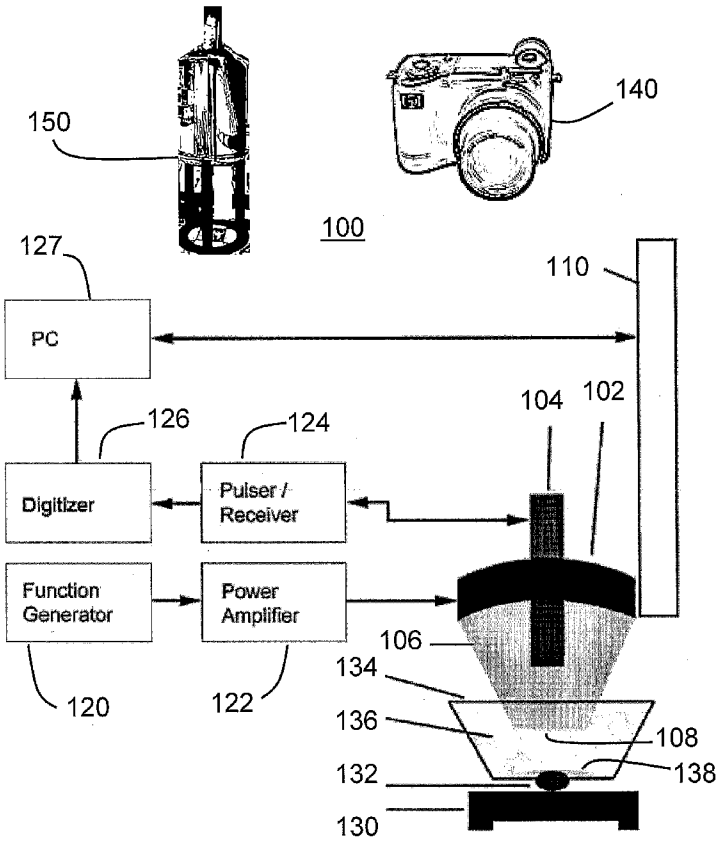

(57) Abstract: A system and method for opening the blood-brain barrier in the brain of a subject is disclosed. In some embodiments, a region of the brain of a subject is targeted for opening; and a focused ultrasound beam is applied through the skull of the subject to the targeted region to open the blood-brain barrier in the brain of the subject.

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SYSTEMS AND METHODS FOR OPENING OF THE BLOOD-BRAIN BARRIER OF A SUBJECT USING ULTRASOUND

SPECIFICATION

Cross Reference to Related Applications

This application claims the benefit of U.S. Provisional Patent Application serial No. 60/718,582, filed on September 19, 2005, entitled "Methods and Apparatus for Localized Drug-Delivery in the Brain of a Subject Using Focused Ultrasound," which is hereby incorporated by reference in its entirety herein.

BACKGROUND OF THE INVENTION

Field of the Invention

The disclosed subject matter relates to a system and methods for treatment of the brain of a subject, and more particularly to opening the blood-brain barrier of a subject.

Background

Many neurologic disorders remain intractable to treatment by therapeutic agents because of the brain's natural defense, the blood-brain barrier (BBB). The BBB is a specialized vascular system consisting of endothelial cells with highly selective membranes connected together by tight junctions. This system impedes entry of virtually all large molecules from blood to brain tissue, rendering otherwise potent neurologically active substances and drugs ineffective simply because they cannot be delivered to where they are most needed. As a result, traversing the BBB is often a rate-limiting factor in brain drug delivery development

Many of the techniques currently being investigated to deliver drugs through the BBB have disadvantages. For example, the process of "lipidization" incorporates lipid groups to the polar ends of molecules to increase the permeability of the agent. While this technique increases the permeability of the drug in the targeted brain region, it does not have a localized effect and also increases permeability throughout the entire body. Consequently, drug dosage must be limited because of the risk of side effects. Another technique under study is neurosurgically-based drug delivery methods, where drugs are introduced into a region by a needle. The drug introduced by the needle spreads through diffusion and is typically localized

to the targeted region. However, the diffusion mechanism does not allow for molecules to travel far from their point of release. In addition, the needle procedure invasively traverses untargeted brain tissue, potentially causing unnecessary damage. Other techniques utilize solvents mixed with drugs or adjuvants (pharmacologic agents) attached to drugs to disrupt the BBB through dilation and contraction of the blood vessels. However, this disruption is typically not localized within the brain, and the solvents and adjuvants used are potentially toxic. According to another technique, by studying the structure and function of transporters endogenous to the cell membrane of the endothelial cells, intense chemical modifications of drugs may allow their passage through these transporters. While this approach may provide a delivery technique specific to the brain, it requires special attention to each type of drug molecule and a specific transport system, resulting in a time consuming and costly process. Moreover, the drug transport may nevertheless not be completely localized to the targeted region.

Other techniques to open the BBB include use of focused ultrasound (FUS). However, several studies have shown that currently known FUS techniques, while locally disrupting the BBB, often also causes undesired tissue damage.

The introduction of microbubbles in conjunction with FUS has been found to open the BBB transiently. However, the approach is highly invasive and unacceptable for use with human subjects since it requires performing a craniotomy on the subject, replacing the skin, and allowing the wound to heal prior to sonication. In addition, the FUS fields were generated by a complicated array including a 16-sector transducer, in which each sector was driven with separate identical radio-frequency signals generated by a multichannel driving system. The multi-element transducers for multi-phasing are costly and difficult to manufacture.

All of these above-described techniques have inherent disadvantages. Accordingly, there is a need in the art for a system which can open the BBB barrier in a transient, localized and non-invasive manner, and which overcomes the limitations of the prior art.

SUMMARY

Systems and methods for opening the blood-brain barrier in the brain of a subject are disclosed. In some embodiments, the systems and methods include targeting a region of the brain of a subject for opening; and applying an ultrasound

beam through the skull of the subject to the targeted region to open the blood-brain barrier in the brain of the subject.

In some embodiments, applying an ultrasound beam through the skull of the subject may include generating an ultrasound beam by a single-element focused transducer. In some embodiments, applying an ultrasound beam through the skull of the subject may include generating an ultrasound beam by a plurality of single-element focused transducers. Applying a focused ultrasound beam through the skull of the subject may comprise generating a focused ultrasound beam having a frequency of about 1.525 MHz. Applying a focused ultrasound beam through the skull of the subject may comprise generating a focused ultrasound beam having an acoustic pressure at the focus of about 0.5 to 2.7 MPa.

In some embodiments, applying a focused ultrasound beam through the skull of the subject may include generating a focused ultrasound beam having a burst rate of about 10 Hz. Applying a focused ultrasound beam through the skull of the subject may comprise generating a focused ultrasound beam having a burst duration of about 20 ms. The ultrasound beam may include a plurality of shots having a duration and a delay between successive shots. The duration of the shots may be about 30 seconds. The delay between successive shots may be about 30 seconds.

In some embodiments, the method may further include administering a molecule to the subject for passage across the BBB. The molecule may include a drug, a contrast agent, or microbubbles into the bloodstream of the subject. Microbubbles may be filled with a drug or a contrast agent or a combination of the above. The focused ultrasound beam comprises a focus and applying a focused ultrasound beam through the skull of the subject may include generating a focused ultrasound beam having an acoustic pressure at the focus of about 0.8 MPa.

In some embodiments, targeting a region of the brain comprises targeting selected brain tissue. In some embodiment, targeting a region of the brain comprises targeting the vasculature surrounding selected brain tissue. Targeting may include locating at least one anatomical landmark of the subject. The method may further include positioning the focus of the ultrasound beam a predetermined distance from the anatomical landmark. Targeting a region of the brain may further comprise generating an image of the subject and the member. In some embodiments, targeting a region of the brain may comprise positioning the focus by reference to the image.

A technique for targeting a region of the brain may further comprise positioning a member on adjacent said anatomical landmark, generating an image of the subject and the member, and positioning the focus by reference to the image.

Further features of the disclosed subject matter will be apparent from the accompanying drawings and the following detailed description of illustrative embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1(a) is a diagram illustrating the system in accordance with an embodiment of the present invention.

FIG. 1(b) is a diagram illustrating the system in accordance with another embodiment of the present invention.

FIG. 2 illustrates a beam profile of an ultrasound beam in water in accordance with an embodiment of the present invention.

FIG. 3 illustrates a beam profile of an ultrasound beam through an *ex vivo* skull in accordance with an embodiment of the present invention.

FIG. 4 illustrates a top view of a subject's skill indicating anatomical landmarks.

FIGS. 5-6 illustrate a technique for targeting a portion of the brain of a subject by reference to the anatomical landmarks of the skull in accordance with an embodiment of the present invention.

FIG. 7 illustrates a histology cross section through the brain of a subject indicating the portion of the brain to be targeted in accordance with an embodiment of the present invention.

FIG. 8 illustrates a lateral 2-D raster scan of an apparatus for targeting a portion of the brain of a subject in accordance with an embodiment of the present invention.

FIG. 9(a) illustrates a T1 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.0 MPa and 10 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 9(b) illustrates a T1 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.0 MPa and 35 minutes

after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 9(c) illustrates a T1 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.0 MPa and 95 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 10(a) illustrates a T1 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.5 MPa and 10 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 10(b) illustrates a T1 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.5 MPa and 35 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 10(c) illustrates a T1 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.5 MPa and 95 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 11(a) illustrates a T2 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.5 MPa and 20 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 11(b) illustrates a T2 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.5 MPa and 50 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 12(a) illustrates a T1 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.7 MPa and 10 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 12(b) illustrates a T1 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.7 MPa and 35 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 12(c) illustrates a T1 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.7 MPa and 95 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 13(a) illustrates a T2 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.7 MPa and 20 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 13(b) illustrates a T2 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 2.7 MPa and 50 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 15 minutes before sonication.

FIG. 14 illustrates a T1 MRI scan of a horizontal slice of a subject brain obtained after sonication with a pressure amplitude of 0.8 MPa and 95 minutes after gadolinium injection in accordance with an embodiment of the present invention. Optison was injected 1 minute before sonication.

FIGS. 15(a)-(b) illustrate histologic sections using a crystal violet stain of the hippocampus, taken after sonication at 2.7 MPa without Optison injection.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

A system and technique for providing an opening in the BBB of a subject using focused ultrasound is described herein. Although the biochemical processes that result in the opening of the BBB is not completely understood, the term "opening the BBB" shall be generally used herein to refer to an increased susceptibility of the BBB to passage of molecules therethrough.

Figure 1(a) illustrates an exemplary system for providing ultrasound waves, designated system 100. Ultrasound waves were generated by a FUS transducer, such as single-element circular-aperture FUS transducer 102. In the exemplary embodiment, FUS transducer 102 has a center frequency of 1.525 MHz, focal depth of 90 mm, an outer radius of 30 mm and an inner radius of 11.2 mm. FUS transducer 102 (Riverside Research Institute, NY) may be provided with a hole in its center for receipt of an imaging transducer, such as a single-element diagnostic transducer 104 (Riverside Research Instiute, NY). In an exemplary embodiment,

diagnostic transducer 104 has a center frequency of 7.5 MHz with a focal length of 60 mm. FUS transducer 102 and diagnostic transducer 104 may be positioned so that the foci of the two transducers are properly aligned. In the exemplary embodiment, a cone 106 filled with degassed and distilled water may be mounted on the transducer system 100. The cone may be manufactured from a clear plastic, such as polyurethane. The water may be contained in the cone 106 by capping it with a material considered substantially "transparent" to the ultrasound beam, such as a ultrathin polyurethane membrane 108 (Trojan; Church & Dwight Co., Inc., Princeton, NJ, USA).

The transducer assembly, which may include the FUS transducer 102 and the diagnostic transducer 104, may be mounted to a computer-controlled 3-D positioning system 110 (Velmex Inc., Lachine, QC. Canada), including motors VXM-1 and VXM-2 used in the exemplary embodiment. It is understood that other positioning systems may be incorporated for positioning the transducer assembly with respect to the targeted tissue.

In an exemplary embodiment, the FUS transducer 102 may be driven by a function generator 120, e.g., function generator HP33150A, manufactured by Agilent Technologies, Palo Alto, CA, USA, through an amplifier 122, such as 50-dB power amplifier 3100L (ENI Inc., Rochester, NY, USA). The diagnostic transducer 104 may be driven by a pulser-receiver system 124, such as pulser-receiver 5052PR (Panametrics, Waltham, MA, USA) connected to a digitizer 126, such as digitizer CS14200 (Gage Applied Technologies, Inc., Lachine, QC, Canada). It is understood that the above-described components may be modified or replaced with other components, as is known in the art, for producing the ultrasound beams described herein. PC 128 typically may include a processor, such a CPU (not shown), and may be any appropriate personal computer, or distributed computer system including a server and a client. For example, a computer useful for this system is Dell Precision 380 personal computer. It is understood that any personal computer, laptop, or other processor that can load software and communicate with the various components discussed herein may be used. A memory unit, such as a disk drive, flash memory, volatile memory, etc., may be used to store software for positioning and operating the transducer assembly, image data, a user interface software, and any other software which may be loaded onto the CPU.

In another embodiment, system 100' may include a transducer assembly having an array of a plurality of single-element FUS transducers 104 and 105 which may be targeted to different regions of the brain of the subject. (Figure 1(b)). Each FUS transducer 104, 105 in the array may be fired individually, thereby permitting opening of the BBB in several locations without repositioning the transducer assembly.

Prior to sonication and in order to verify undistorted propagation through the skull, a scan, such as a 3-D raster-scan (lateral step size: 0.2 mm; axial step size: 1.0 mm), of the beam of the FUS transducer 102, may optionally be performed in a large water tank containing degassed water with a needle hydrophone having a needle diameter on the order of about 0.2 mm (Precision Acoustics Ltd., Dorchester, Dorset, UK.) The dimensions of the beam provided by the FUS transmitter 102 may have a lateral and axial full-width at half-maximum (FWHM) intensity of approximately 1.32 and 13.0 mm, respectively, that in some embodiments may be approximately equal to the dimensions of the beam after propagation through the skull (see, e.g., Figure 2).

System 100 also includes a platform for the subject. In the exemplary embodiment, the platform for the subject may be a polyurethane bed 130 for a smaller subject 132, such as a mouse. In this configuration, the membrane 138 may be placed over the subject 132. In other embodiments, the platform may be a hospital bed or surgical table, in which a larger subject (such as a human subject) may be laid prone or supine and the transducer assembly positioned on top of the region of the skull targeted.

Additional component(s) of the system 100 may include a targeting system for locating the focus of the FUS transducer 102 in the brain of the subject 132. In an exemplary embodiment, the targeting system may include a plurality of members, such as thin metal bars, e.g., 0.3 mm thin metal bars, fabricated from an acoustically reflective material, such as, e.g., paper clips. As will be described in greater detail below, the metal bars are placed on several landmarks of the skull of the subject to create a layout, or grid. Brain structures to be targeted, such as the hippocampus, are known to be located a particular distance from these landmarks. An image, such as a lateral 2-D raster scan, of the grid configuration is made using the diagnostic transducer 104. The location of the desired brain structure is identified relative to this grid. The focus of the FUS transducer may then be positioned to

precisely target the desired brain structure. In another exemplary embodiment, the targeting system may include other imaging devices, such as a digital camera 140. For example, a digital camera may be used to photograph the head of the subject. The relevant landmarks may be identified in the photograph, and the focus of the FUS transducer targeted to a location relative to the landmarks. In addition, other MRI targeting equipment, as is known in the art, may be used for targeting the desired brain structure.

An exemplary method for delivering the molecule through the BBB is described herein. The subject is positioned on a platform. Subjects may be positioned in a prone position, and may be anesthetized for the sonication procedure. The degassed and distilled water bath 134 may be suspended over the subject's head. Ultrasound gel may be used to reduce any remaining impedance mismatches between the thin plastic layer 138 and the subject's skin. The transducer assembly may be placed in the water bath with its beam axis perpendicular to the surface of the skull.

The focus of the transducer is positioned inside the subject's brain. The focus may be targeted to a region of the brain, such as the desired brain tissue, e.g., the hippocamus, or to the vasculature of the brain, e.g., arteries, ventricles, arterioles, and capillaries of the brain (see, e.g., Figure 12(a) which targets the posterior cerebral artery). As discussed above, a targeting technique, such as the grid positioning method, may be used in an exemplary embodiment. In this method, the anatomic landmarks are used for targeting purposes. The location of the brain structure or vascular region were assumed relative to the landmarks based on known brain and skull anatomy. A grid consisting of thin metal bars may be placed in the water bath on top of the skull and in alignment with these landmarks. Using this grid positioning system, the brain structure may be reproducibly targeted when assumed to be at a location relative to the metal bars. An image, such as a lateral 2-D raster-scan, of the grid using the diagnostic transducer may be made and the location of the brain structure identified relative to this grid. The focus of the FUS transducer may then be placed in position by measuring distance with the diagnostic transducer. Targeting may also be performed by taking an image of the subject by photographic equipment, such as a digital camera.

The FUS transducer supplies the focused ultrasonic waves to the targeted area. For example, pulsed-wave FUS may be applied in a series of bursts having delays between bursts. In an exemplary embodiment, the burst rate is about 5

to 15 Hz, the burst duration is 20 ms, and the duty cycle is 20%. Exemplary acoustic pressures at the focus may be 0.5 to 3.0 MPa. According to this embodiment, the FUS was applied in a series of five shots lasting, e.g., 10-40 seconds each, with a delay between each shot of about 10-40 seconds. The FUS sonication procedure may be performed once or more on the subject's brain. The acoustic pressure values may be determined experimentally, for example, obtained from the values found in degassed water and corrected using the attenuation values of a skull similar to the subject's skull.

Following sonication, as described hereinabove, the BBB opens, thereby facilitating the passage of a molecule through the BBB. Such molecule may be a drug, medication or pharmaceutical compound, protein, antibody or biological material, chemical substance, contrast agent, or any other material to pass through the BBB. Such molecule may be administered to the subject by any known method. For example, the molecule may be injected into a vein of the subject. The molecule may administered intraperitoneally by a catheter. In some embodiments, the molecule may be administered orally. The administration of the molecule to the subject may occur prior to sonication, during sonication, or following sonication.

For example, an ultrasound contrast agent may be administered to the subject. Ultrasound scans of the subject may be used to determine whether the BBB has opened. A bolus of ultrasound contrast agent, e.g., Optison containing microbubbles, may be injected into a vein of the subject prior to sonication. In an exemplary embodiment, a 10 μL bolus (approximately 0.4 mL/kg) of Optison containing microbubbles having a mean diameter: 3.0 to 4.5 μm and a concentration of 5.0 to 8.0 X 108 bubbles per mL may be injected into the right femoral vein of the subject fifteen minutes prior to sonication. High-resolution echocardiogram equipment may be used following sonication to determine the presence of the ultrasound contrast agent. Microbubbles containing material such as a contrast agent or a drug may be administered to the subject for traversal of the BBB.

An MRI contrast agent may also be administered to the patient for passage through the BBB. MRI scans may be used to monitor opening of the BBB. In order to facilitate MRI scans during the procedure, an MRI system 150 maybe incorporated into the equipment described hereinabove. TI- and T2-weighted MRI scans may be obtained using a 1.5 T, 3.0 T, 9.4 T, or other, system (Bruker Medical; Boston, MA. USA). For example, 0.5 mL of MRI contrast agent gadolinium

(Omniscan; Amersham Health, AS Oslo, Norway) may be administered intraperitoneally via a catheter to depict BBB opening (Barzó et al. 1996). Intraperitoneal injection allows for the slow uptake of the MRI contrast agent into the bloodstream (Moreno et at 2006). After injection of the MRI contrast agent, a series of scans may be performed on the subject. For example, six alternating Tl-weighted and T2-weighted fast spin-echo image scans, using the following specifications: a repetition time/echo time (TR/TE) of 4000 ms/9.2 ms; rapid acquisition with relaxation enhancement: 16; field of view (FOV) of 1.92 x 1.92 cm; matrix size of 256 X 256; number of slices: 10; slice thickness: 0.6 mm; slice gap: 0.1 mm; number of excitations (NEX): 10, 15 and 45.

Contrast-enhanced behavior may be followed for a period of time after injection of the contrast agent, to assess the time course of BBB opening. Detection of BBB opening may be detected by comparing an area of a nonsonicated homogeneous brain region with sonicated regions. Increased pixel intensity values of the sonicated regions which are increased above the values of the nonsonicated regions by a predetermined value, e.g., 2.5 standard deviations, are determined to be a contrast-enhanced region, revealing BBB opening. Higher resolution analysis may be used over an extended time period to determine the path of deposition of the molecule through the BBB.

EXAMPLE: *Ex Vivo FUS Administration in Mouse*

The effect of the mouse skull on the ultrasound beam propagation using a single-element transducer was investigated with skulls of Brown CB57-b16 type mice (Charles River Laboratories, Wilmington, MA, USA; mass: 23 to 28 g). The skull was excised and degassed in saline. Each skull was separately placed and held stationary in a tank filled with degassed water, such as the water bath discussed herein. The transducer assembly was submerged in the water tank and held stationary above the excised skull, with its focus placed 3 mm beneath the top of the skull. A needle hydrophone suspended from a computer-controlled 3-D positioning system was then placed at the beam focus. Two-dimensional lateral beam profiles at the focus without and with the skull were then measured. These measurements were made through several regions of the skull. Attenuation values were obtained by taking the difference between the pressure amplitude measured through the skull and the pressure amplitude measured in water and then dividing by the pressure amplitude

in water. The mean attenuation value was finally obtained by averaging over the six attenuation values measured in six different skulls.

Ultrasound through the parietal bones on the left and right halves of the sagittal suture were found to provide the least amount of attenuation (~18.1% of the pressure amplitude) when compared with other regions of the skull. The beam profile of the ultrasound beam at its focus in water only is illustrated in Figure 2, and through an *ex vivo* skull in Figure 3. The intensity values are in dB below the peak value. The full width at half maximum (FWHM) intensity was 1.33 mm through the skull and 1.32 mm when no skull was present. The change in the location of the focus as a result of skull aberration was lower than the resolution allowed by the needle hydrophone (needle diameter: 0.2 mm). The pressure field measurements revealed no significant distortion of the ultrasound beam shape or focus location.

EXAMPLE: *In Vivo FUS Administration in Mouse*

Brown CB57-b16 type mice (Charles River Laboratories, Wilmington, MA, USA; mass: 23 to 28 g) were used in sonication procedures. The mice were anesthetized with a mixture of ketamine (Fort Dodge Animal Health, Fort Dodge, IA, USA; concentration: 75 mg per kg of body mass) and xylazine (Ben Venue Laboratories, Bedford, OH, USA; concentration: 3.75 mg per kg of body mass). Before sonication, the hair on the top of the mouse heads was removed using an electric trimmer and a depilatory cream. After sonication, but before MRI scanning, the mice were switched to administration of isoflurane to simplify the long anesthesia procedure necessary for MRI scanning. During all imaging procedures. the vital signs of the mice were continuously monitored.

The mouse subject 132 was anesthetized and placed prone on the platform 130 (Fig. 1). A water bath 134, the bottom of which consisted of an ultrathin acoustically and optically transparent plastic layer 138, was filled with degassed and distilled water 136 and suspended over the anesthetized mouse's head 132. Ultrasound gel was used further to reduce any remaining impedance mismatches between the thin plastic layer 138 and the mouse skin. Finally, the FUS transducer 102 was placed in the water bath 134 with its beam axis perpendicular to the surface of the skull of the mouse subject 132.

The focus of the transducer 102 was positioned inside the mouse brain using a grid positioning method, as discussed above. In this method, the sutures of

the mouse skull seen through the skin were used as anatomic landmarks for targeting purposes. The location of the hippocampi were assumed relative to the sutures based on the mouse brain and known skull anatomy, as illustrated in Figure 4. The landmarks of the mouse skull 400 include the sagittal suture 402, the frontal bone 404, the interparietal bone 406, the left parietal bone 408, and the right parietal bone 410. As illustrated in Figure 5, a grid consisting of three equally spaced 0.3-mm thin F2 metal bars was placed in the water bath 134 on top of the skull 404 and in alignment with these sutures. The first bar 420 was aligned parallel and along the sagittal suture 402, and the second bar 424 was attached perpendicularly to the first bar and in alignment with the suture between the parietal and interparietal bone. In CB57-b16 type mice, these were the sutures that could be clearly seen through the skin. The third bar 422 was placed 4 mm away from and parallel to the second bar. Using this grid positioning system, Figure 6 illustrates that the location of one of the hippocampi (indicated by circle 440) was reproducibly targeted when assumed to be at mid-distance (arrow 442) between the parallel bars and 2 mm away from the center bar (arrow 444). The actual location of the hippocampus 446 is indicated in the histology slice shown in Figure 7. A lateral 2-D raster-scan 800 of the grid using the diagnostic transducer 104 was made and the location of the hippocampus was identified relative to this grid (Fig. 8). The focus of the FUS transducer 102 was placed 3 mm beneath the top of the skull by measuring distance with the diagnostic transducer 104. Using the grid positioning method and depth calculations, precise, accurate and reproducible targeting of the hippocampus of the mouse brain was performed.

To determine the accuracy of this positioning system, a separate set of preliminary experiments was performed. It was determined that the intended target was within 0.5 mm of the actual focus. Considering the 1.32-mm lateral FWHM beam used in these experiments, the grid positioning method was sufficiently precise to have the FUS beam consistently overlap the hippocampus of the murine brain. It is understood that more precise adjustments may be made as required by the subject and the particular organ or structure receiving sonication.

Ultrasound contrast medium was administered for transport across the BBB. A bolus of 10 μL (approximately 0.4 mL/kg) of ultrasound contrast agent (Optison) that contained microbubbles (mean diameter: 3.0 to 4.5 μm: concentration: 5.0 to 8.0 X 108 bubbles per mL) was injected into the right femoral vein of the

mouse approximately 15 minutes before sonication (Table 1). Pulsed-wave FUS (burst rate: 10 Hz; burst duration: 20 ms; duty cycle: 20%; acoustic pressures at the focus: 2.0, 2.5 and 2.7 MPa) was then applied in a series of five shots lasting 30 seconds each with a 30 second delay between each shot. The FUS sonication procedure was performed once in each mouse brain. The acoustic pressure values were obtained from the values found in degassed water and corrected using the attenuation values of the skull, as discussed above. The sonications were focused at the left hippocampus of the mouse brain, and the right hippocampus was not targeted and acted as the control. The pressure values 2.0, 2.5 and 2.7 MPa were selected after a preliminary study that determined the threshold of BBB opening to be around 2.5 MPa, given the aforementioned set-up parameters.

Time (min.)	Procedure
0	Administration of anesthesia
15	Injection of Optison
30	Sonication
45	Start of T1 MRI scan acquisition (15 averages)
60	Injection of gadolinium
60	Start of T1 MRI scan acquisition (10 averages)
70	Start of T2 MRI scan acquisition (10 averages)
80	Start of T1 MRI scan acquisition (15 averages)
95	Start of T2 MRI scan acquisition (15 averages)
110	Start of T1 MRI scan acquisition (45 averages)
155	Start of T2 MRI scan acquisition (45 averages)

TABLE 1

To investigate the effect of the 15-minute delay between Optison injection and sonication, the presence of Optison in the bloodstream after such a time delay was verified. A separate study was performed, in which two mice were injected with Optison intravenously (IV) and their left ventricles were imaged with a high-resolution ultrasound system (Visual Sonics; Toronto, Ontario, Canada: frequency: 35 MHz). The echocardiograms indicated that Optison was still present at least 30 minutes after IV injection, and its concentration in the bloodstream was steadily decreasing over time. Although Optison was still present beyond 30 minutes, no further monitoring was performed. Finally, to further investigate the importance of the concentration of Optison (and, thus, timing of sonication post injection) on the BBB opening and the pressure amplitude used, the previously described sonication procedures were performed at 1-minute post injection of 25μL of Optison at the lower pressure amplitude of 0.8 MPa.

The administration of an MRI contrast agent through the BBB was observed by use of TI- and T2-weighted MRI scans using a 9.4 T system (Bruker Medical; Boston, MA. USA) (Table 1). The mice were placed in a plastic tube with a 3.8-cm diameter birdcage coil attached and were inserted vertically into the magnet. Approximately 15 minutes after sonication, but before MRI contrast agent injection, a TI-weighted spin-echo MRI scan was obtained (TR/TE: 246.1 ms/10 ms; BW: 50,505.1 Hz; matrix size: 256 X 256; FOV: 1.92 X 1.92 cm; slice thickness: 0.6 mm: NEX: 10, 15 and 45). These images were useful to determine whether FUS had caused tissue damage. Once the first scan was completed, 0.5 mL of MRI contrast agent gadolinium (Omniscan; Amersham Health, AS Oslo, Norway) was administered intraperitoneally via a catheter to depict BBB opening. Intraperitoneal injection allowed for the slow uptake of the MRI contrast agent into the bloodstream. After injection of the MRI contrast agent, a series of six alternating Tl-weighted and T2-weighted fast spin-echo image scans (TR/TE: 4000 ms/9.2 ms; rapid acquisition with relaxation enhancement: 16; FOV: 1.92 X 1.92 cm; matrix size: 256 X 256; number of slices: 10; slice thickness: 0.6 mm; slice gap: 0.1 mm; NEX: 10, 15 and 45) were performed after each mouse (Table 1).

Contrast-enhanced behavior was followed for a period of 140 minutes after injection of gadolinium, to assess the time course of BBB opening. For each MRI scan, a 15 X 15 pixel area of a nonsonicated homogeneous brain region was averaged. The entire MRI scan was then divided by this averaged value. The left (FUS-targeted) and right (control) hippocampi were compared in each mouse and any pixel intensity value above 2.5 standard deviations was determined to be a contrast-enhanced region, revealing BBB opening. Thresholding by 2.5 standard deviations was used because it provided a significantly clear differentiation between unaffected and BBB-opened regions in all mouse experiments. The approximate area of the BBB opening region was then calculated by counting the pixels above the threshold.

In most cases, no visible damage was detected on the T1 MRI scans obtained after sonication and before MRI contrast agent injection. Gadolinium was then injected to determine whether the BBB was opened. After sonication at a peak pressure amplitude of 2.0 MPa and injection with MRI contrast agent, no contrast enhancement was observed, as illustrated in Figures 9(a)-(c), which depict T1 MRI scans of horizontal slices of a single mouse brain approximately 3mm beneath the top of the mouse skull. Figure 9(a) was taken 10 minutes after gadolinium injection,

Figure 9(b) was taken 35 minutes after gadolinium injection, and Figure 9(c) was taken 95 minutes after gadolinium injection. No contrast enhancement was discernible.

At 2.5 and 2.7 MPa, MRI contrast agent injection depicted BBB opening (Figs. 10-13). A temporal analysis of this opening was made over a 140 minute period, revealing leakage of the MRI contrast agent from the posterior cerebral artery (PCA) or its adjacent arterioles and capillaries to the surrounding brain tissue. Sonication at a peak pressure amplitude of 2.5 MPa allowed for a highly localized opening of the BBB near the PCA, as illustrated in Figures 10(a)-(c) Figures 12(a)-(c) shows how, after sonication at a peak pressure amplitude of 2.7 MPa (as in the 2.5 MPa), the gadolinium first appears in the PCA only (10 min post injection, Figure 12(a)), then slowly permeates throughout the surrounding regions (35 min post injection, Figure 12(b)), eventually encompassing the entire left hippocampus (95 min post injection, Figure 12(c)). On T2 MRI scans, BBB opening resulted in a decrease in pixel intensity and the area affected was in good agreement with what was seen on the TI MRI scans (see, Figures 11(a)-(b) and Figures 13(a)-(c)). Over the time studied, the area of contrast enhancement increased (Table 2).

Pressure amplitude (MPa)	Area of contrast enhancement (mm^2)		
	At time = 10 minutes	At time = 10 minutes	At time = 10 minutes
2.0	0	0	0
2.5	0	8.40	33.1
2.7	33.5	116	152

TABLE 2

Thus, at high resolution a detailed temporal and spatial analysis of the region enhanced by the MRI could be obtained, including accurate measurement of the region being affected by the BBB opening. For example, the vessel density and size appear to play a significant role in the way that the MRI contrast agent permeates the BBB. Figures 12(a)-(c) show how the MRI contrast agent first appears in the PCA or the region around the PCA (see, Fig. 12(a)) and then slowly permeates throughout the region (see, Figures 12(b) and 13(a)), eventually reaching the entire left hippocampus (see, Figures 12(c) and 13(b)). The method may thus be capable of determining the path of deposition of the molecule administered, e.g., contrast agent in this case, or of

the drug release. In the exemplary study, the ultrasound focus encompassed an area greater than the PCA, but the initial dominant contrast enhancement appeared to occur in this region. At lower intensities (see, Figures 10 and 11), the opening of the BBB seems initially to be localized in the same blood vessel but only in the vessel branch that is parallel to the beam axis. The characteristic of drug delivery in the brain using this method will vary according to the vessel characteristics of the region where the focus of the ultrasound beam is positioned.

The extent of the region where BBB opening occurred also varied with ultrasound pressure amplitudes (see, Figures 10-13). At the pressure amplitude of 2.0 MPa, there was no opening of the BBB, and the area of BBB opening increased with the pressure amplitude above 2.5 MPa.

Finally, when the timing of Optison injection was changed from 15 minutes to 1 minute before FUS sonication and the injection was increased to 25 μL, opening of the BBB occurred at a far lower threshold of 0.8 MPa. Figure 14 illustrates a T1 MRI scan obtained after sonication with a pressure amplitude of 0.8 MPa and 95 minutes after gadolinium injection. Option was injected 1 minute prior to sonication. Earlier injection and, thus, higher Optison concentration allowed for a reduced pressure amplitude necessary for BBB opening.

The procedure for opening the BBB in a subject described herein may be used in connection with cultured cells or on subjects, such as humans. For use in human subjects, the noninvasive FUS technique on the intact skull is a requirement. Targeting techniques may include locating anatomical landmarks as discussed above or using known stereotactic procedures. The increased thickness of the human skull when compared with the mouse skull may require the use of a lower frequency transducer, the frequency of 1.525MHZ may be lowered to about 10-200 kHz. The bolus of microbubbles or contrast agents to be used would be adjusted to account for the larger mass in the case of human subjects.

It will be understood that the foregoing is only illustrative of the principles of the invention, and that various modifications can be made by those skilled in the art without departing from the scope and spirit of the invention. Moreover, features of embodiments described herein may be combined and/or rearranged to create new embodiments.

CLAIMS

What is claimed is

1. A method for opening the blood-brain barrier in the brain of a subject comprising:

targeting a region of the brain of a subject for opening; and

applying an ultrasound beam by a single-element transducer through the skull of the subject to the targeted region to open the blood-brain barrier in the brain of the subject.

2. A method according to claim 1, wherein applying an ultrasound beam by a single-element transducer through the skull of the subject comprises applying an ultrasound beam by a plurality of single-element transducers through the skull of the subject.

3. A method according to claim 1, wherein applying an ultrasound beam comprises applying a focused ultrasound beam.

4. A method according to claim 1, wherein applying an ultrasound beam through the skull of the subject comprises generating an ultrasound beam having a frequency of about 1.525 MHz.

5. A method according to claim 1, wherein the ultrasound beam comprises a focus and wherein applying an ultrasound beam through the skull of the subject comprises generating an ultrasound beam having an acoustic pressure at the focus of about 0.5 to 2.7 MPa.

6. A method according to claim 1, wherein applying an ultrasound beam through the skull of the subject comprises generating an ultrasound beam having a burst rate of about 10 Hz.

7. A method according to claim 1, wherein applying an ultrasound beam through the skull of the subject comprises generating an ultrasound beam having a burst duration of about 20 ms.

8. A method according to claim 1, wherein applying an ultrasound beam through the skull of the subject comprises applying a plurality of shots having a duration and a delay between successive shots.

9. A method according to claim 8, wherein the duration of the shots is about 30 seconds.

10. A method according to claim 8, wherein the delay between successive shots is about 30 seconds.

11. A method according to claim 1, further comprising administering a molecule to the subject for passage across the blood-brain barrier.

12. A method according to claim 11, wherein administering a molecule comprises a drug.

13. A method according to claim 11, wherein administering a molecule comprises a contrast agent.

14. A method according to claim 11, wherein administering a molecule comprises microbubbles.

15. A method according to claim 14, wherein administering a molecule comprises filled with a material selected from the group consisting of a drug and a contrast agent.

16. A method according to claim 11, wherein administering a molecule occurs prior to applying an ultrasound beam.

17. A method according to claim 11, wherein administering a molecule occurs after applying an ultrasound beam.

18. A method according to claim 1, wherein targeting a region of the brain comprises targeting selected brain tissue.

19. A method according to claim 1, wherein targeting a region of the brain comprises targeting a region of vasculature surrounding selected brain tissue.

20. A method according to claim 1, wherein targeting a region of the brain comprises locating at least one anatomical landmark of the subject.

21. A method according to claim 20, wherein the ultrasound beam comprises a focus and wherein targeting a region of the brain comprises positioning the focus of the ultrasound beam at a predetermined distance from the anatomical landmark.

22. A method according to claim 20, wherein targeting a region of the brain further comprises generating an image of the subject.

23. A method according to claim 22, wherein the ultrasound beam comprises a focus and wherein targeting a region of the brain comprises positioning the focus by reference to the image.

24. A method according to claim 20, wherein targeting a region of the brain further comprises positioning a member on adjacent said anatomical landmark and generating an image of the subject and the member.

25. A method according to claim 24, wherein the ultrasound beam comprises a focus and wherein targeting a region of the brain comprises positioning the focus by reference to the image.

26. A method for opening the blood-brain barrier in the brain of a subject comprising:

targeting vasculature adjacent selected brain tissue of a subject for opening; and

applying an ultrasound beam through the skull of the subject to the targeted vasculature to open the blood-brain barrier in the brain of the subject.

27. A method according to claim 26, wherein targeting vasculature adjacent selected brain tissue comprises targeting structures selected from the group consisting of arteries, ventricles, arterioles, and capillaries of the brain.

28. A method according to claim 26, wherein applying an ultrasound beam comprises applying a focused ultrasound beam.

29. A method according to claim 26, further comprising administering a molecule to the subject for passage across the blood-brain barrier.

30. A method according to claim 26, wherein targeting vasculature adjacent selected brain tissue of a subject comprises locating at least one anatomical landmark of the subject.

31. A method according to claim 29, wherein the ultrasound beam comprises a focus and wherein targeting vasculature adjacent selected brain tissue of a subject comprises positioning the focus of the ultrasound beam a predetermined distance from the anatomical landmark.

32. A method according to claim 29, wherein targeting a region of the brain further comprises generating an image of the subject.

33. A method according to claim 32, wherein the focused ultrasound beam comprises a focus and wherein targeting a region of the brain comprises positioning the focus by reference to the image.

34. A method according to claim 30, wherein targeting a region of the brain further comprises positioning a member on adjacent said anatomical landmark and generating an image of the subject and the member.

35. A method according to claim 34, wherein the focused ultrasound beam comprises a focus and wherein targeting a region of the brain comprises positioning the focus by reference to the image.

36. A system for opening the blood-brain barrier in the brain of a subject comprising:

a targeting assembly for targeting a region of the brain of a subject for opening; and

a transducer for applying an ultrasound beam through the skull of the subject to the targeted region to open the blood-brain barrier in the brain of the subject.

37. A system according to claim 36, wherein the transducer comprises a single-element focused transducer.

38. A system according to claim 36, wherein the transducer is adapted to generate a focused ultrasound beam having a frequency of about 1.525 MHz.

39. A system according to claim 36, wherein the ultrasound beam comprises a focus and wherein the transducer is adapted to generate a focused ultrasound beam having an acoustic pressure at the focus of about 0.5 to 2.7 MPa.

40. A system according to claim 36, wherein the ultrasound beam comprises a focus and wherein the transducer is adapted to generate a focused ultrasound beam having a burst rate of about 20 Hz.

41. A system according to claim 36, further comprising an introducer for introducing a molecule into the bloodstream of the subject for passage through the blood-brain barrier.

42. A system according to claim 41, wherein the introducer comprises a needle.

43. A system according to claim 41, wherein the introducer comprises a catheter.

44. A system according to claim 41, wherein the molecule comprises a drug.

45. A system according to claim 41, wherein the molecule comprises a contrast agent.

46. A system according to claim 36, wherein the targeting assembly comprises an imaging device.

47. A system according to claim 46, wherein the imaging device comprises a diagnostic ultrasound transducer.

48. A system according to claim 46, wherein the imaging device comprises photographic equipment.

49. A system according to claim 36, wherein the targeting assembly further comprises one or more members for placement on an anatomical landmark of the subject.

50. A system according to claim 36, wherein the targeting assembly is adapted to target a region of the brain by positioning the focus of the ultrasound beam a predetermined distance from an anatomical landmark of the subject.

51. A system according to claim 36, wherein the targeting assembly further comprises a positioning apparatus for moving the transducer to the targeted location.

52. A system for opening the blood-brain barrier in the brain of a subject comprising:

means for targeting a region of the brain of a subject for opening; and

means for applying an ultrasound beam through the skull of the subject to the targeted region to open the blood-brain barrier in the brain of the subject.

53. A system according to claim 52, wherein the means for applying an ultrasound beam comprises a single-element focused transducer.

54. A system according to claim 52, wherein the means for applying an ultrasound beam is adapted to generate a focused ultrasound beam having a frequency of about 1.525 MHz.

55. A system according to claim 52, wherein the focused ultrasound beam comprises a focus and wherein the means for applying a focused ultrasound beam is adapted to generate a focused ultrasound beam having an acoustic pressure at the focus of about 0.5 to 2.7 MPa.

56. A system according to claim 52, wherein the focused ultrasound beam comprises a focus and wherein the means for applying a focused ultrasound beam is adapted to generate a focused ultrasound beam having a burst rate of about 20 Hz.

57. A system according to claim 52, further comprising means for introducing a molecule into the bloodstream of the subject for passage through the blood-brain barrier.

58. A system according to claim 57, wherein the means for introducing a molecule comprises a needle.

59. A system according to claim 57, wherein the means for introducing a molecule comprises a catheter.

60. A system according to claim 57, wherein the molecule comprises a drug.

61. A system according to claim 57, wherein the molecule comprises a contrast agent.

62. A system according to claim 52, wherein the means for targeting comprises an imaging device

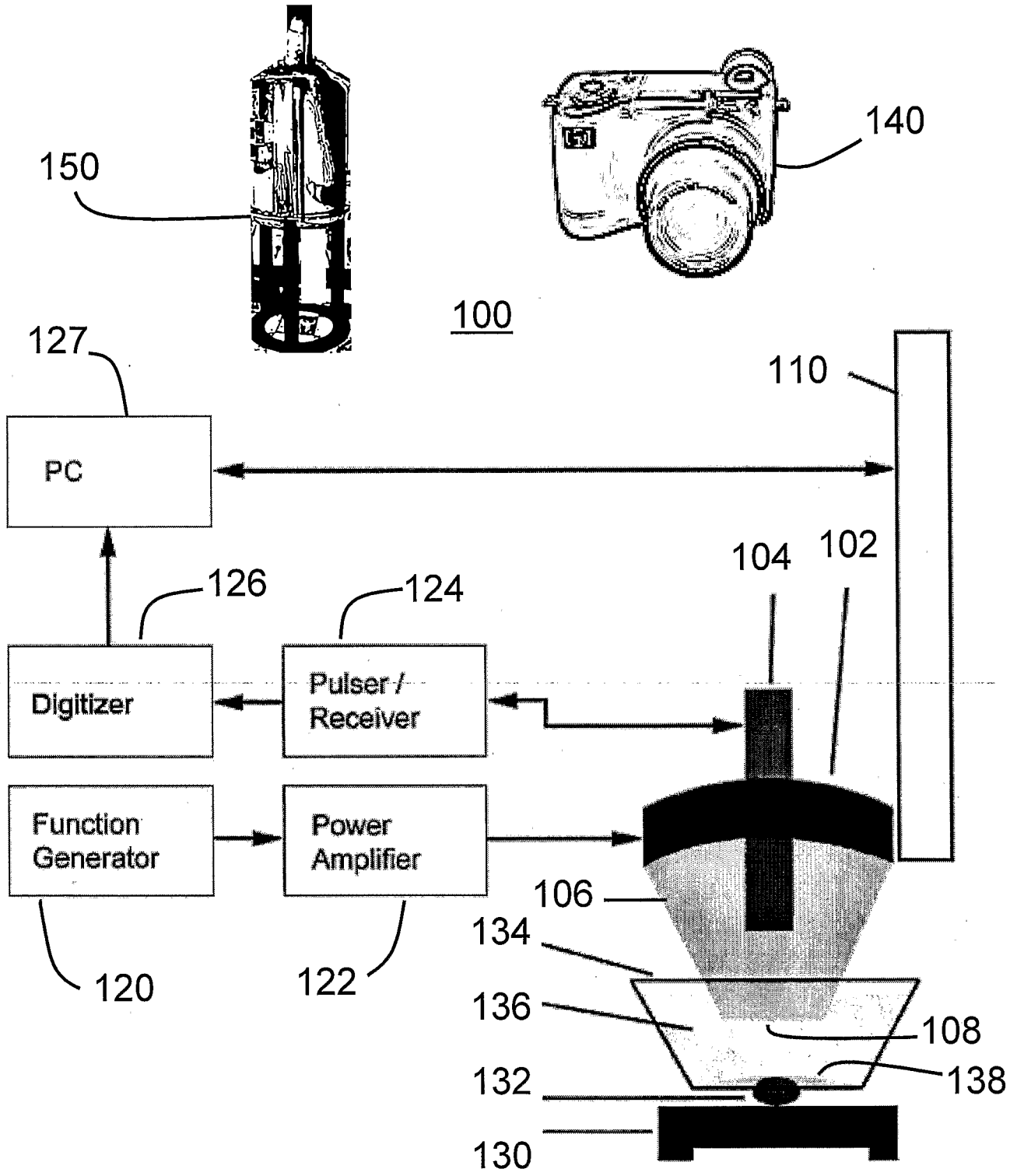
63. A system according to claim 62, wherein the imaging device comprises a diagnostic ultrasound transducer.

64. A system according to claim 62, wherein the imaging device comprises photographic equipment.

65. A system according to claim 52, wherein the means for targeting further comprises one or more members for placement on an anatomical landmark of the subject.

66. A system according to claim 52, wherein the means for targeting is adapted to target a region of the brain by positioning the focus of the ultrasound beam a predetermined distance from an anatomical landmark of the subject.

67. A system according to claim 52, wherein the means for targeting further comprises a positioning apparatus for moving the transducer to the targeted location.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Pulser / Receiver
Function Generator
Power Amplifier
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122

FIGURE 1(a)

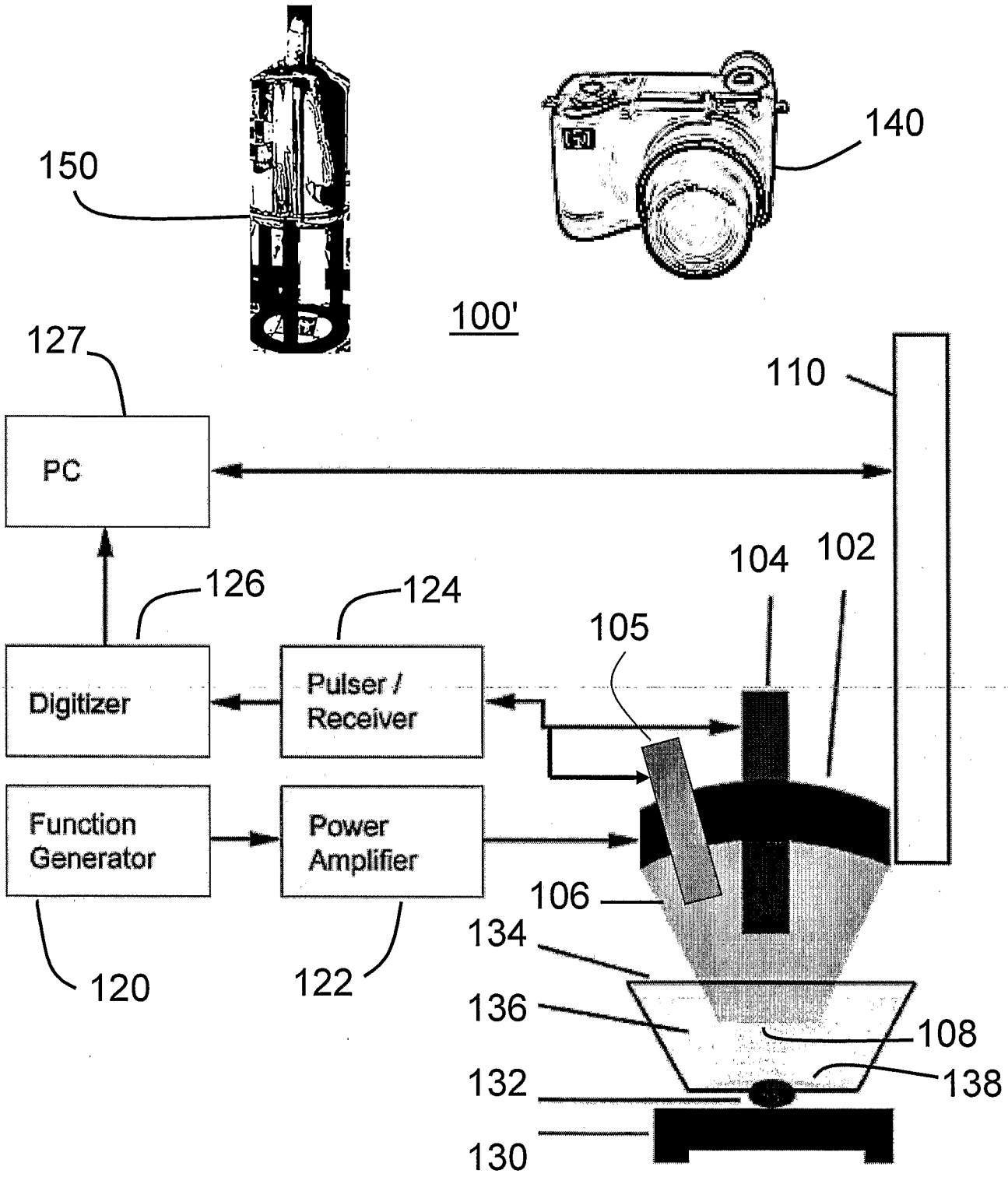
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FIGURE 1(b)

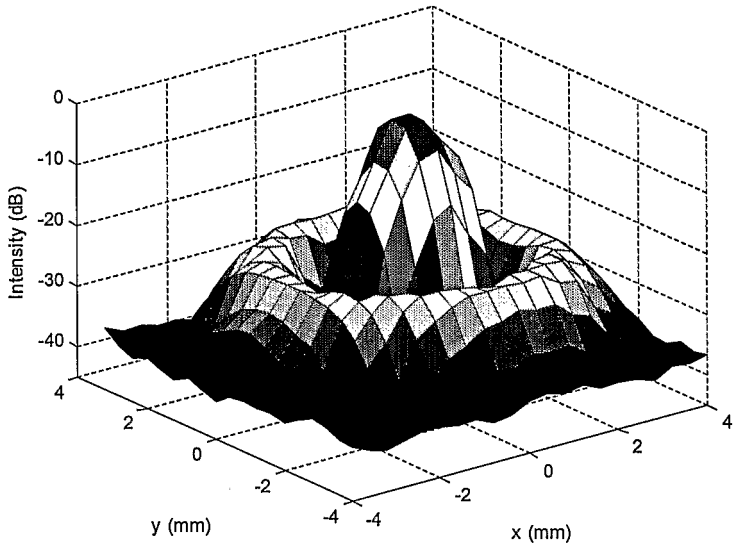

FIGURE 2

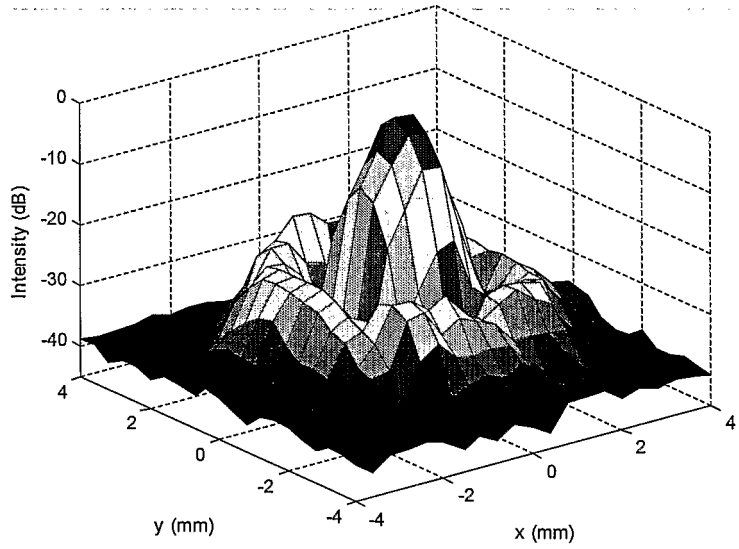

FIGURE 3

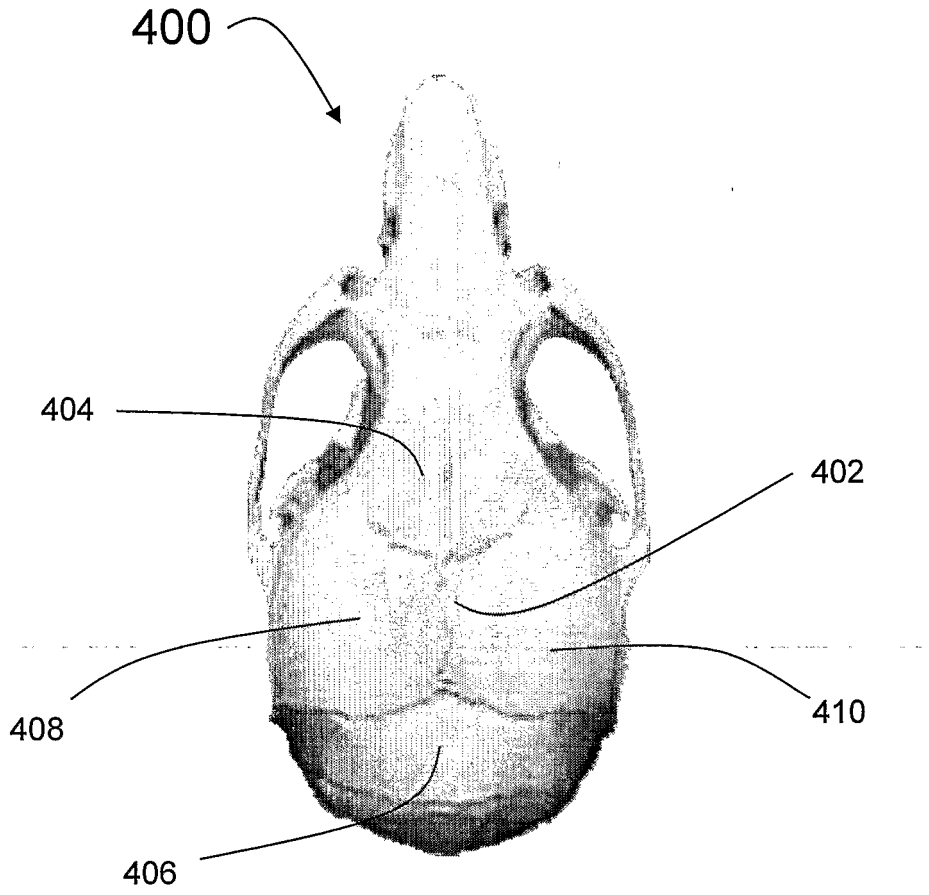

FIGURE 4

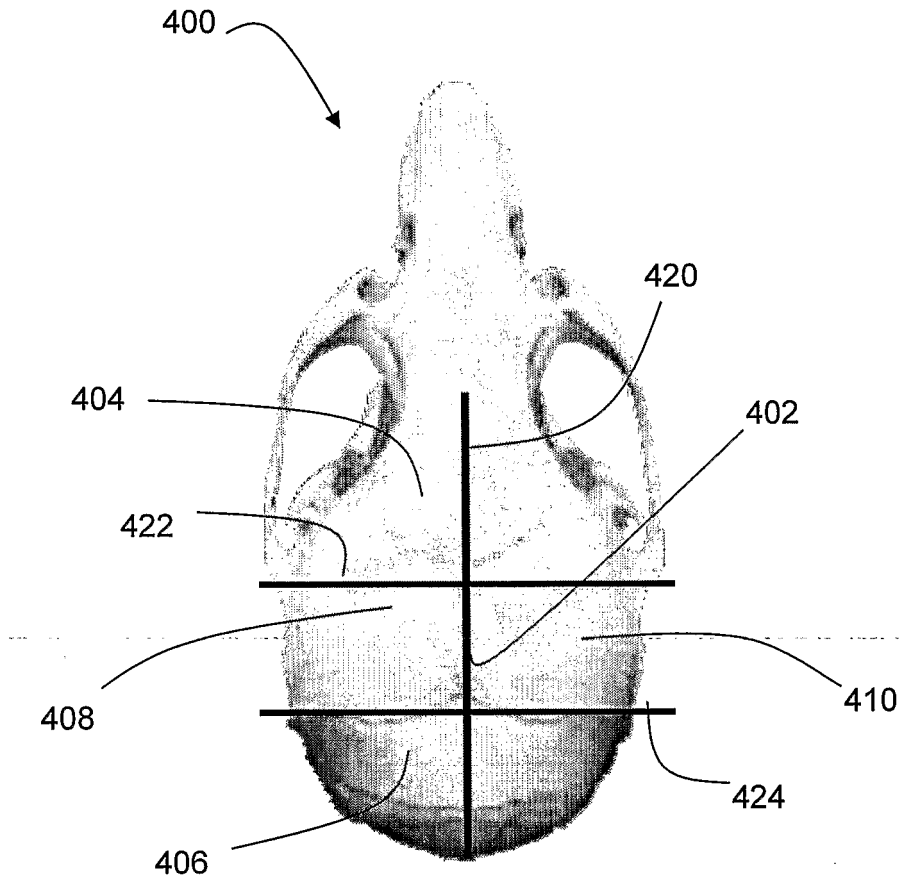

FIGURE 5

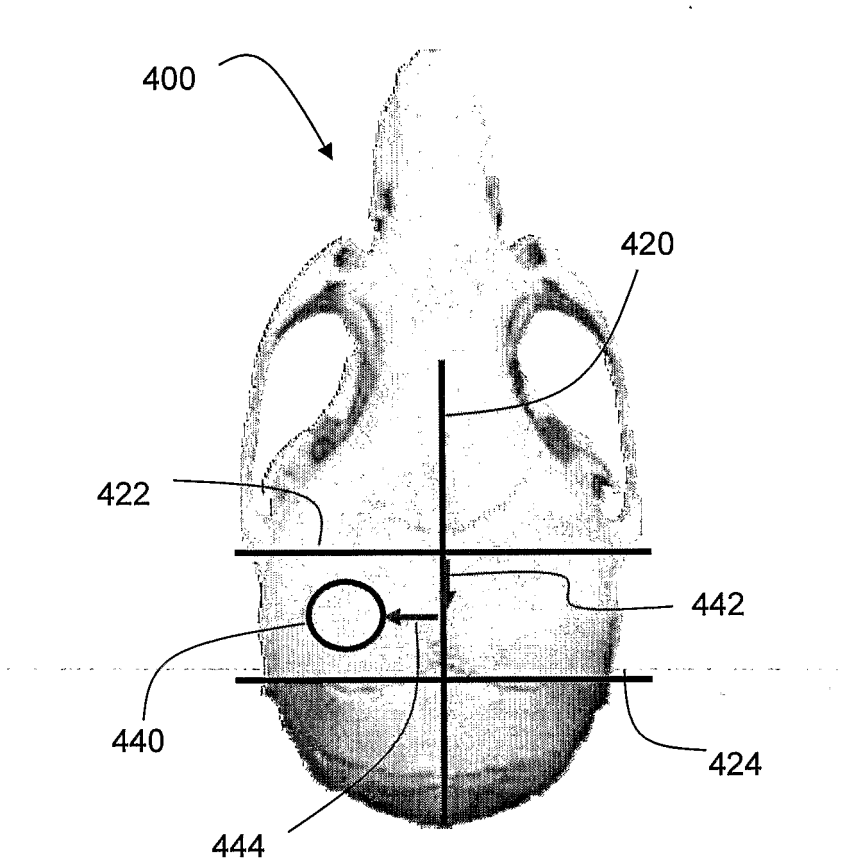

FIGURE 6

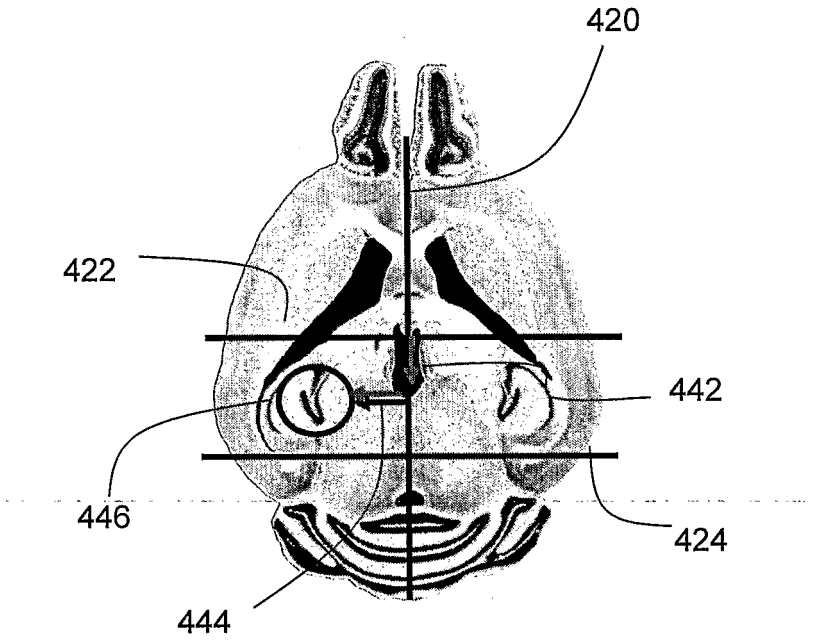

FIGURE 7

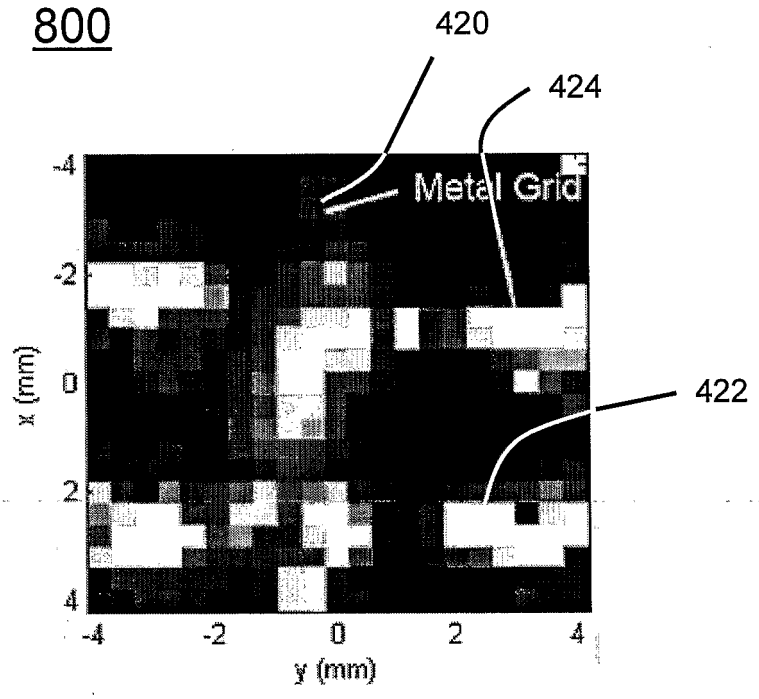

FIGURE 8

FIGURE 9 (a) FIGURE 9 (b) FIGURE 9 (c)

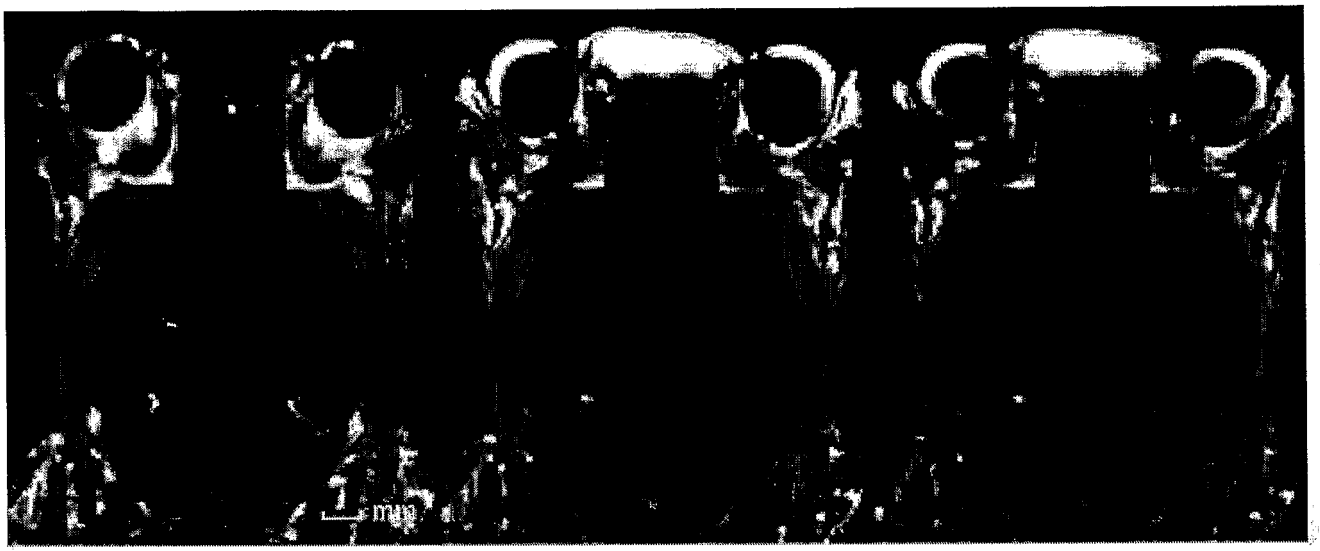

FIGURE 10 (a) FIGURE 10 (b) FIGURE 10 (c)

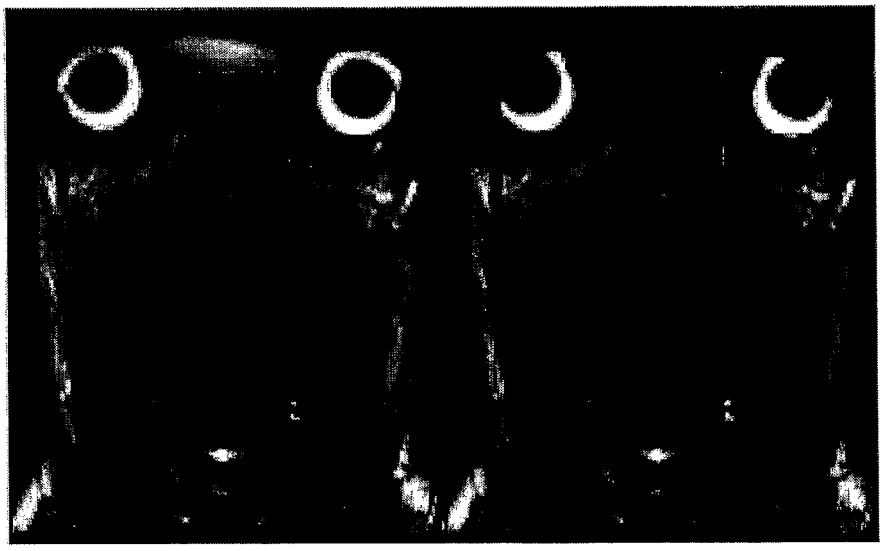

FIGURE 11(a) FIGURE 11(b)

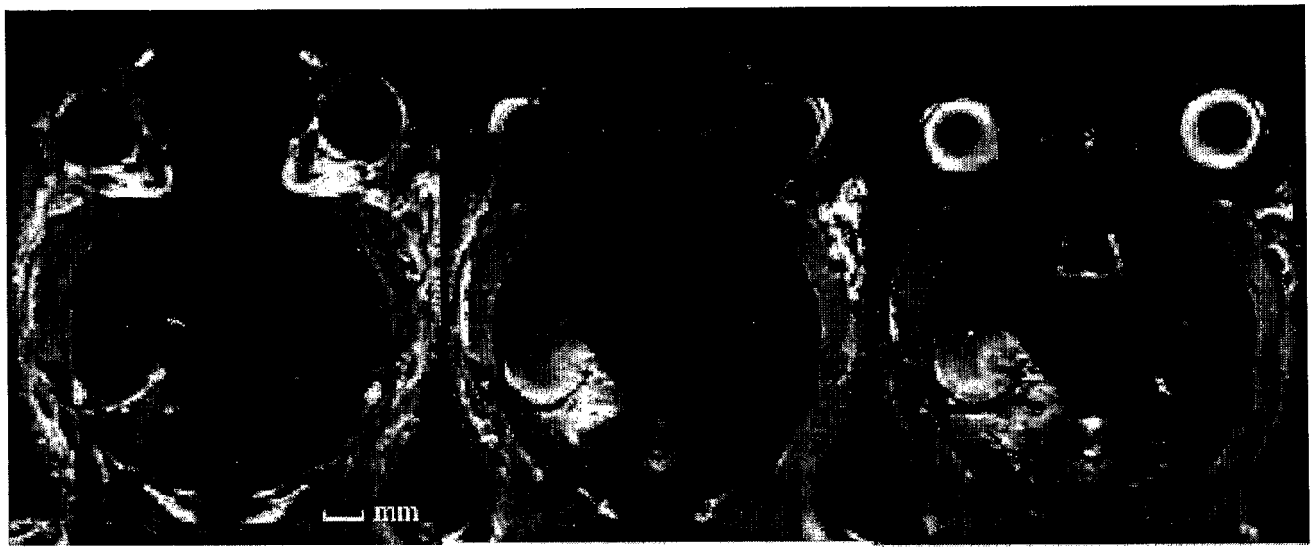

FIGURE 12 (a) FIGURE 12 (b) FIGURE 12 (c)

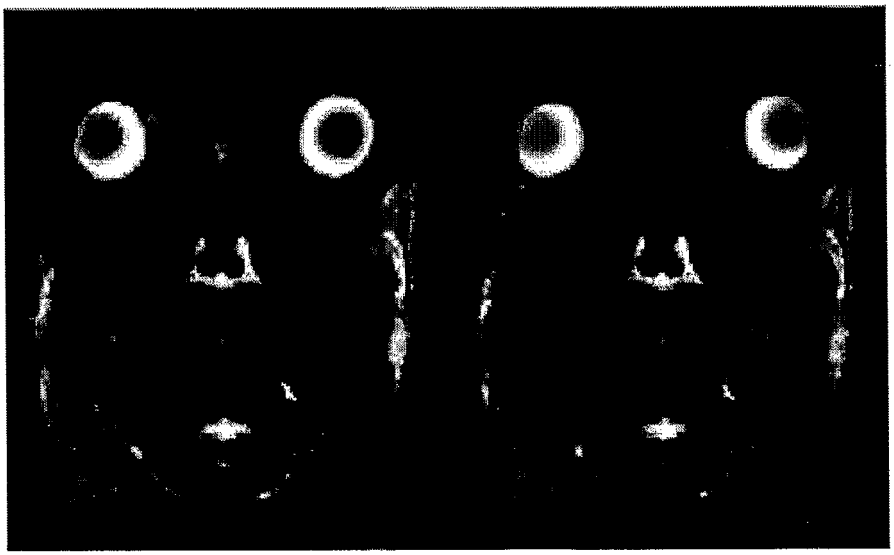

FIGURE 13(a) FIGURE 13(b)

FIGURE 14

FIGURE 15(a)

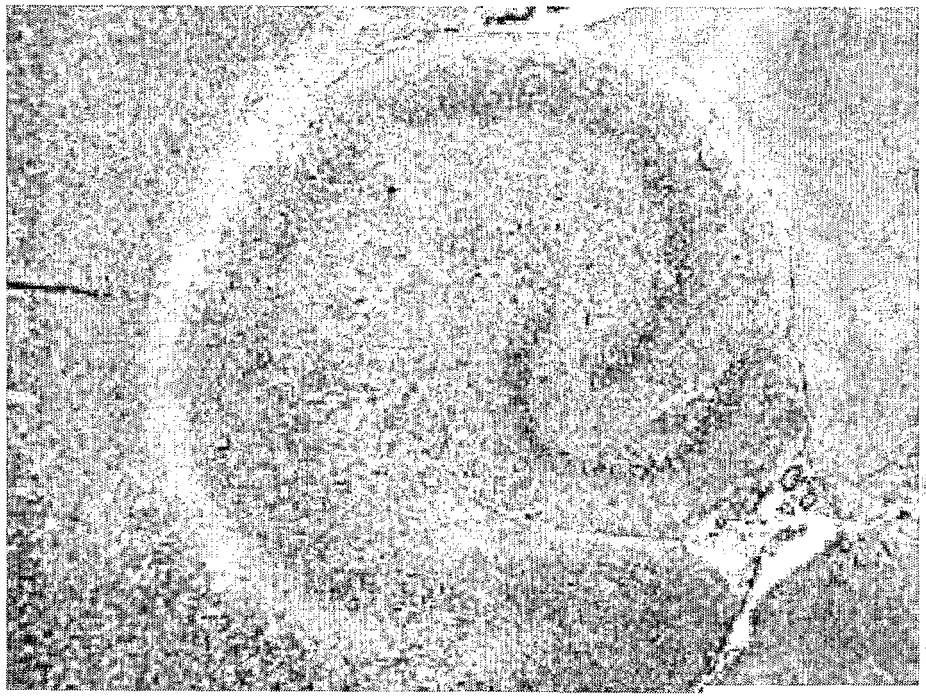

FIGURE 15(b)

专利名称(译)	使用超声波打开受试者的血脑屏障的系统和方法		
公开(公告)号	EP1937151A2	公开(公告)日	2008-07-02
申请号	EP2006803849	申请日	2006-09-19
[标]申请(专利权)人(译)	纽约市哥伦比亚大学理事会		
申请(专利权)人(译)	哥伦比亚大学纽约市受托人		
当前申请(专利权)人(译)	哥伦比亚大学纽约市受托人		
[标]发明人	KONOFAGOU ELISA E CHOI JAMES J PERNOT MATHIEU SMALL SCOTT A		
发明人	KONOFAGOU, ELISA, E. CHOI, JAMES, J. PERNOT, MATHIEU SMALL, SCOTT, A.		
IPC分类号	A61B8/00		
CPC分类号	A61M37/0092 A61B8/0816		
代理机构(译)	阿特金森JENNIFER		
优先权	60/718582 2005-09-19 US		
其他公开文献	EP1937151A4		
外部链接	Espacenet		

摘要(译)

公开了一种用于打开受试者大脑中的血脑屏障的系统和方法。在一些实施方案中，受试者的大脑区域被打开;聚焦超声波束通过受试者的头骨施加到目标区域，以打开受试者大脑中的血脑屏障。