Hypothesis

The Neuroscientist
XX(X) 1–12

DOI: 10.1177/1073858409348066
http://nro.sagepub.com
SAGE

Noninvasive Neuromodulation with Ultrasound? A Continuum Mechanics Hypothesis

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Abstract

Deep brain stimulation and vagal nerve stimulation are therapeutically effective in treating some neurological diseases and psychiatric disorders. Optogenetic-based neurostimulation approaches are capable of activating individual synapses and yield the highest spatial control over brain circuit activity. Both electrical and light-based neurostimulation methods require intrusive procedures such as surgical implantation of electrodes or photon-emitting devices. Transcranial magnetic stimulation has also shown therapeutic effectiveness and represents a recent paradigm shift towards implementing less invasive brain stimulation methods. Magnetic-based stimulation, however, has a limited focusing capacity and lacks brain penetration power. Because ultrasound can be noninvasively transmitted through the skull to targeted deep brain circuits, it may offer alternative approaches to currently employed neuromodulation techniques. Encouraging this idea, literature spanning more than half a century indicates that ultrasound can modulate neuronal activity. In order to provide a comprehensive overview of potential mechanisms underlying the actions of ultrasound on neuronal excitability, here, I propose the continuum mechanics hypothesis of ultrasonic neuromodulation in which ultrasound produces effects on viscoelastic neurons and their surrounding fluid environments to alter membrane conductance. While further studies are required to test this hypothesis, experimental data indicate ultrasound represents a promising platform for developing future therapeutic neuromodulation approaches.

Keywords

ultrasound, neuromodulation, deep-brain stimulation, fluid dynamics

Some of the most commonly employed neuromodulation approaches used today require invasive procedures. For example, deep brain stimulation (DBS) and vagus nerve stimulation (VNS) require the surgical implantation of chronic stimulating electrodes (Fig. 1A). These neurostimulation techniques, however, do show promise for use in managing a bewildering array of psychiatric disorders and neurological diseases (Wagner and others 2007). Recent expansion of the neurostimulation field has been fueled by observations that individual synapses and neurons can be excited and/or inhibited with millisecond resolution using optogenetic approaches (Zhang and others 2007). This photonic control of neural activity can be used to induce sleep-wake cycles in mice (Adamantidis and others 2007), map intact brain circuits (Ayling and others 2009; Petreanu and others 2007), and control motor behavior (Gradinaru and others 2007) (Fig. 1B-D). Despite the unrivaled spatiotemporal specificity and promising future of optical control, it will continue to require the expression of exogenous proteins as well as an implanted light source (Aravanis and others 2007). Thus, a current challenge for neuroscience is to identify new stimulation strategies, which balance efficacy with the degree of necessary invasiveness. Considering its ability to act upon biological tissues (ter Haar 2007) and its noninvasive transmission through skull bone in a focused manner (Clement 2004; Clement and Hynynen 2002; Hynynen and Jolesz 1998), ultrasound (US) represents a centerpiece around which novel noninvasive neuromodulation approaches can be developed.

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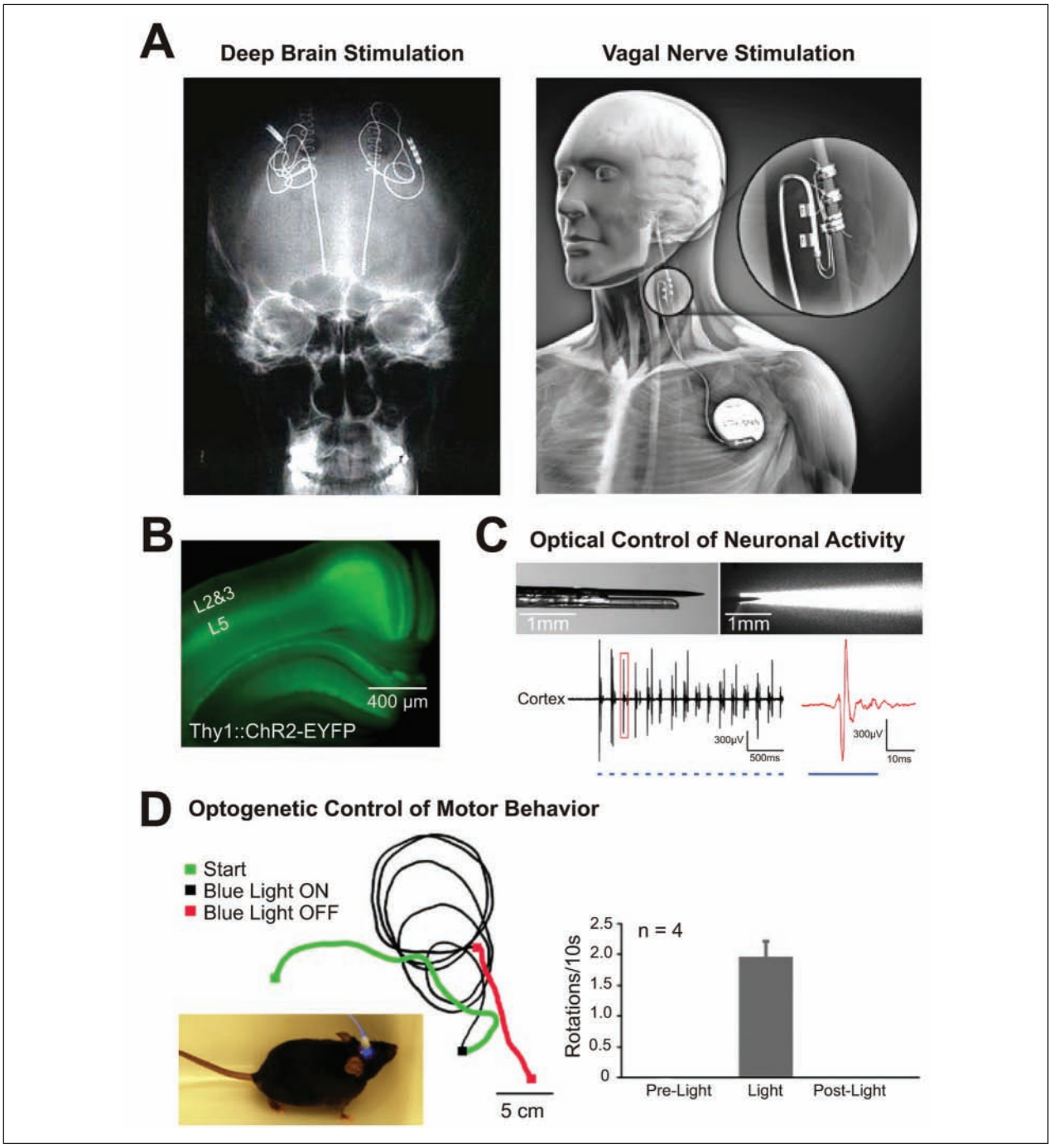

Figure 1. Illustrations depicting some currently employed invasive neuromodulation strategies. (A) An x-ray (left) illustrating a pair of deep brain stimulating electrodes implanted in a human patient (image compliments of Dr. Helen S. Mayberg). A medical illustration (right) depicting a vagal nerve–stimulating electrode implanted in a human patient (image compliments of Cyberonics Inc.). (B) Image of the cortex from a Thy-1:ChR2-EYFP mouse illustrating ChR2 expression. (C) The top images illustrate the type of implantable optrode used to transmit 473-nm photons for activation of ChR2 while simultaneously recording neuronal activity in vivo. The bottom images illustrate ChR2-activated cortical potentials obtained in an intact mouse using an optrode described above. (D) Illustration depicting the ChR2-mediated control of motor behavior by activating pyramidal neurons of Thy-1:ChR2-EYFP transgenic mice by optogenetically stimulating the right motor cortex. Panels B to D modified with permission from the *Journal of Neuroscience* (Gradinaru and others 2007).

Brief Overview of US

In general terms, US is a sound wave (acoustic pressure) in a frequency range above human hearing detection levels (>20 KHz). Due to its physical properties, specifically its ability to be transmitted long distances with little energy loss in certain materials, US is used in a wide range of medical and industrial applications. The influence of US on biological tissues has been studied since the late 1920s (Harvey and others 1928). In nervous tissues, US has been studied across a range of uses from thermal ablation to modulation of neuronal activity (Fry 1968; Gavrilov and others 1996; Hynynen and Clement 2007; Hynynen and Jolesz 1998; Tyler and others 2008). Ultrasound has a proven safety record gained through its extensive diagnostic medical imaging uses and in an array of physiotherapies (Dalecki 2004). Routine medical imaging relying on pulse-echo signals is typically conducted in a frequency range from 1 to 15 MHz, while therapeutic applications typically employ a US frequency of about 1 MHz (O'Brien 2007). With respect to brain imaging applications, US can be used in photoacoustic tomography (PAT) to provide images of brain lesions due to the differential absorption/scattering coefficients of photons transmitted from specific dye lasers (Wang and others 2003). To monitor functional brain activity, PAT can similarly detect the oxygenation of hemoglobin as well as other hemodynamic signals (Wang and others 2003; Yang and Wang 2008). In the future, applications currently employed in other tissues may find use in the brain. Some examples are US imaging apoptotic activity during antitumor therapies (Banihashemi and others 2008) and imaging of muscle deterioration in animal models of muscular dystrophy (Ahmad and others 2009).

Ultrasound can be transmitted into tissues through several different modes in either pulsed or continuous waveforms and can influence physiological activity by acting through thermal and/or nonthermal (mechanical) mechanisms (Dalecki 2004; Dinno and others 1989; O'Brien 2007; ter Haar 2007). Ultrasound can be broadly defined as low intensity or high intensity (ter Haar 2007). High-intensity focused ultrasound (HIFU) used for thermal ablation (coagulative necrosis) typically requires power levels exceeding 1000 W/cm^2, while noninvasive mechanical bioeffects of US have been described at power levels ranging from 30 to 500 mW/cm^2 (Dalecki 2004; Dinno and others 1989; O'Brien 2007; ter Haar 2007). In order to acquire a better understanding of US and its biophysical actions, the reader is referred to recent reviews (Dalecki 2004; O'Brien 2007; ter Haar 2007).

Ultrasonic Modulation of Neuronal Activity

Ultrasound as a means of exciting (Gavrilov and others 1976) and reversibly suppressing (Fry and others 1958) neuronal activity was shown to be effective on a gross level several decades ago. In the 1950s, William Fry and colleagues provided the first evidence showing that US could induce lesions in brain tissues, which might provide therapeutic benefit. In these studies, the investigators used high-intensity US to treat patients suffering from movement disorders associated with Parkinson disease (Fry 1954; Fry 1956; Fry 1958; Meyers and others 1959). Despite its preliminary success, US as a neurotherapeutic tool was mostly discounted by the medical community because, at the time, it was difficult to focus US through the human skull and their procedures required craniotomy (Foley and others 2007).

Prior to the work of Fry and colleagues, evidence that US could stimulate excitable tissues had already emerged. In 1929, Edmund Newton Harvey published a set of ground breaking observations first describing that US could stimulate nerve and muscle fibers (Harvey 1929) (Fig. 2A). It was later described that sensory-evoked potentials in the cat primary visual cortex could be reversibly suppressed by transmitting US through the lateral geniculate nucleus (Fry and others 1958) (Fig. 2B). Intriguingly, it has also been documented that US can stimulate neuronal activity in the cat brain (Foster and Wiederhold 1978).

In cat saphenous nerve preparations, US differentially affects the activity of Aδ and C fibers depending on the fiber diameter, US intensity, and US exposure time (Young and Henneman 1961). Focused US has been shown to activate deep nerve structures in the human hand by producing tactile, thermal, and pain sensations (Gavrilov and others 1976). Other excitatory and/or inhibitory actions of US have been observed in peripheral nerve preparations (Lele 1963; Mihran and others 1990; Tsui and others 2005), cat spinal cord (Shealy and Henneman 1962), rodent hippocampal slices (Bachtold and others 1998; Rinaldi and others 1991; Tyler and others 2008), cat and rabbit cortex (Velling and Shklyaruk 1988), and human cranial nerves (Magee and Davies 1993). Collectively, these observations raise several issues calling for further studies. A particularly perplexing one concerns the mechanisms underlying US-mediated modulation of neuronal activity: what are they?

Potential Mechanisms underlying US-mediated Modulation of Neuronal Activity

The above studies provide evidence that the electrical activity of both peripheral and central neural circuits can be modulated using US; however, they do not specifically address the mechanisms underlying these effects. With respect to the observations that high-intensity US can suppress neuronal activity, one mechanism proposed is the disruption of synaptic contacts by US (Borrelli and others 1981). This particular hypothesis stems from observations that high-intensity US (300 W/cm^2) disrupts the ultrastructure of central synapses by depleting synaptic vesicle clusters, widening synaptic clefts, and decreasing the sizes of the presynaptic and postsynaptic densities (Borrelli and others 1981). Different hypotheses have been put forth to explain the stimulatory actions of US on neurons. It has been suggested that mechanical changes in membrane tension produced by US may increase the electrical activity of cells by altering ionic flux (Dinno and others 1989; Velling and Shklyaruk 1988). Investigations aimed at studying the influence of US on membrane conductance lend support to this hypothesis.

Ultrasound can induce reversible increases in the internal Ca^{2+} concentrations of fibroblasts (Mortimer and Dyson 1988), and in rat thymocytes, US can modulate K^+ influx and efflux (Chapman and others 1980). Many of the voltage-gated ion channels (sodium, calcium, and potassium channels) expressed in neurons, as well as neurotransmitter receptors, possess mechanosensitive properties that render their gating kinetics sensitive to transient changes in lipid bilayer tension (Morris and Juranka 2007; Sukharev and Corey 2004). Given that many voltage-gated ion channels possess some mechansosensitivity, acoustic radiation forces conferred by the actions of US on lipid bilayers may lead to the opening of classic voltage-gated channels. In neurons, whether the activity of ion channels is sensitive to US has remained unknown until recently. Using modern optical imaging approaches to monitor ionic conductance in hippocampal neurons, it was shown that US is capable of stimulating voltage-gated Na^+ and Ca^{2+} channel activity sufficient to evoke action potentials and trigger synaptic transmission (Tyler and others 2008) (Fig. 2C). While these results are intriguing, they merely hint at potential mechanisms of action and do not fully unravel how US achieves such effects. One potential hypothesis stemming from those observations is that US produces local membrane depolarization, which in turn activates voltage-gated Na^+ channels. An additional hypothesis is that US is capable of inducing conformational changes in protein structure, which may modulate ion channel activity (Johns 2002). Other issues have yet to be resolved. For instance, it is not known if the actions of US on neuronal excitability are mediated by thermal and/or nonthermal (mechanical) mechanisms. Thus, it is apparent that several fundamental issues need to be addressed before we can grasp an understanding of the mechanisms underlying US modulation of neuronal activity.

Continuum Mechanics Hypothesis of Ultrasonic Neuromodulation

The brain is composed of discrete cellular boundaries where fluids (including lipid bilayers) interface with one another. The mechanical wave properties of acoustic pressure generated by US will have consequences on these brain fluids. With respect to the local actions of US, one might consider the extracellular space to be a continuous medium. Further support of this notion comes from an examination of the Knudsen number ($Kn = \lambda / L$, where λ is the molecular mean free path length, and L is the characteristic length scale for the physical boundaries of interest). Thus, for the problem of how US affects the dynamics of cerebrospinal fluid (CSF) in the extracellular space of the brain, the λ of water ($\approx 3 \times 10^{-10}$ m) provides a reasonable estimate for that of CSF (especially considering that large molecular proteins found in CSF and intracranial pressure would further reduce λ values). Then taking the extracellular space between cells in the brain (L) to be $\approx 10^{-8}$ m, a Kn value of 0.03 is calculated. When $Kn < 0.1$, continuum mechanics (opposed to quantum mechanics when $Kn \gg 1$) formulations are valid and can be applied (Chung 2007).

Combining a continuous extracellular space with the presence of both Newtonian (CSF) (Bloomfield and others 1998) and non-Newtonian (viscoelastic cell membranes) fluids in the brain prompted formation of the continuum mechanics hypothesis of ultrasonic neuromodulation. The hypothesis states that US can noninvasively modulate neuronal activity through a combination of pressure/fluid/membrane actions involving stable cavitation and acoustic streaming (microjet formation, eddying, and turbulence) in addition to acoustic radiation force, shear stress, Bernoulli effects, and other fluid-mechanical consequences, which stem from small acoustic impedance mismatches (boundary conditions) between lipid bilayers, surrounding intracellular/extracellular fluids, and interleaved cerebrovasculature (Table 1 and Fig. 3D-E).

To begin further evaluating this hypothesis, I conducted several experimental studies and include data from some of these experiments to illustrate the following: 1) the viscoelastic responses of neurons produced by

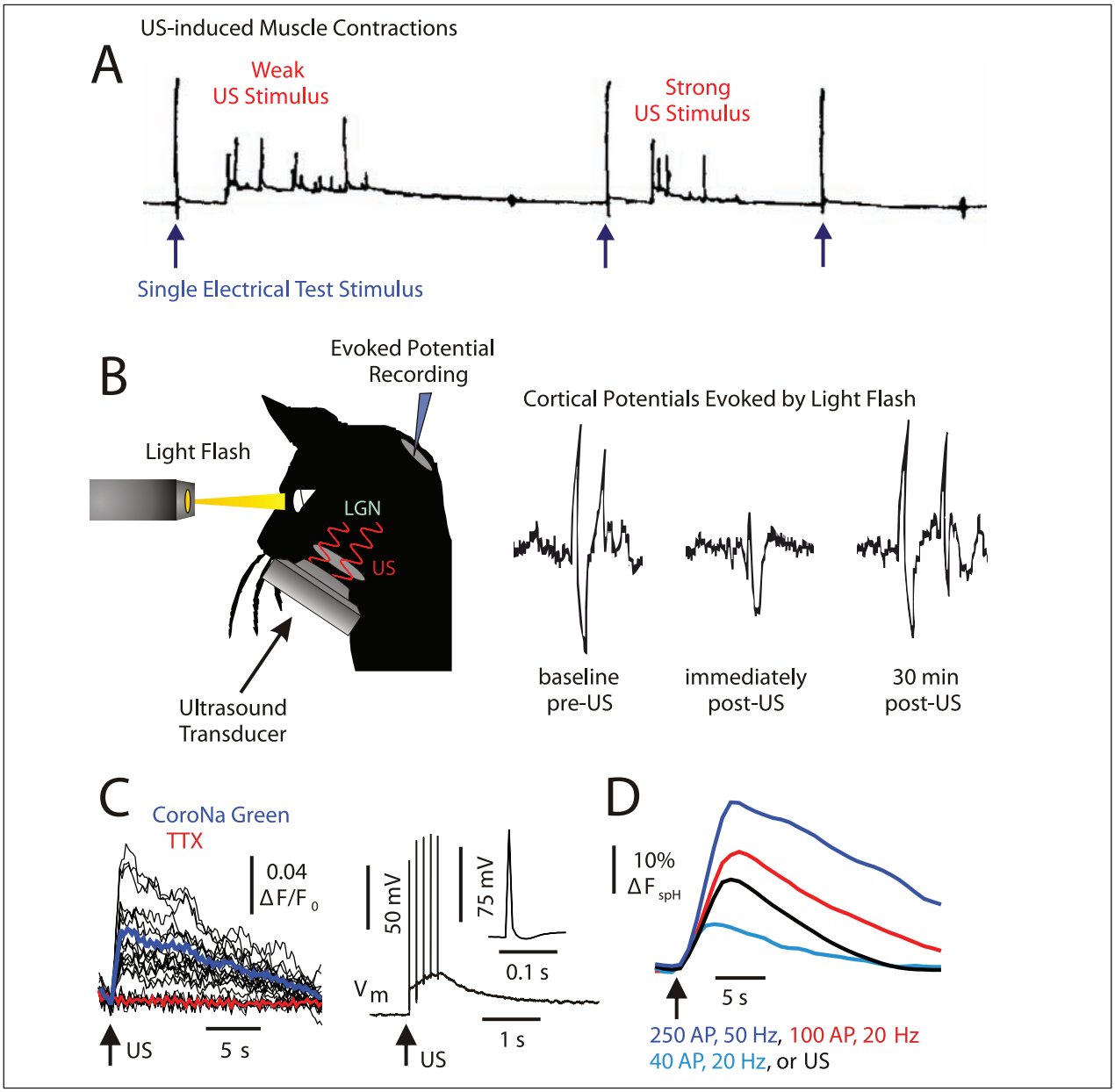

Figure 2. Ultrasound (US) and its influence on neuronal activity. (A) Illustration of data obtained by Edmund Newton Harvey (1929) first showing that US can trigger muscle contractions in part by acting on nerves. Muscle contractions in response to weak (left) and strong (right) US stimulation are shown in between contractions induced by electrical test stimuli (blue arrows) for comparison. (B) Graphical illustration of experiments conducted by William Fry and colleagues (1958) first demonstrating that US can induce reversible suppression of sensory-evoked activity. Images illustrate the experimental set-up (left) and traces obtained (right) from experiments in which light-evoked cortical potentials were recorded from V1 before, immediately after, and 30 minutes following transmission of US transmitted to the lateral geniculate nucleus (LGN) of intact cats. (C) Sodium imaging traces (left) obtained from hippocampal CA1 neurons showing that US triggers sodium transients by activating TTX-sensitive channels. Membrane voltage traces (right) recorded in a CA1 pyramidal neuron in which 5 brief pulses of US triggered 5 action potentials. (D) Average synaptopHluorin responses obtained from hippocampal Schaffer collateral pathways in response to electrical field stimulation or stimulation with US alone illustrate neurotransmitter release is evoked by US stimulation. Panels C and D were modified from Tyler and others 2008.

Table 1. Acoustic Properties of Brain Tissues and Mechanical Bioeffects of Ultrasound

Speed of Sound, Media Density, and Acoustic Impedance

The speed of sound (c) varies in different media (biological fluids including tissues in this case) depending on the bulk modulus and density (ρ) of a given medium. The physical properties of the medium determine its characteristic acoustic impedance (Z), defined as $Z = \rho c$. An acoustic impedance mismatch is defined as the difference in Z across 2 media ($Z_2 - Z_1$) and establishes a boundary condition. Acoustic impedance mismatches at cellular interfaces underlie many bioeffects of ultrasound (US) and serve as the basic principle enabling diagnostic imaging by causing US to be differentially reflected and transmitted (O'Brien 2007). Although beyond the scope of this article, the transmission, absorption, reflection, refraction, scattering, and attenuation coefficients of US for given media must also be taken into account when considering how US fields influence brain activity. The boundary conditions established by cellular interfaces can contribute to fluid behaviors, which likely influence neuronal activity. The table below highlights examples of acoustic impedance mismatching, which exists in the brain and its surrounding tissues.

Acoustic Streaming and Cavitation

When US propagates through biological tissues, the periodic pressure variation produced by US triggers streaming by momentum transfer from a resonant particle or compressible boundary object to its surrounding fluid environment (Nyborg 1998). Streaming can lead to the formation of eddy currents, liquid microjets, and other turbulent actions in fluids (Fig. 3B), which can modulate cellular membrane permeability (Sundaram and others 2003). Streaming can also be caused by acoustic cavitation. Cavitation occurs when US pressure variation leads to the creation and oscillation of small gas/vapor-filled cavities (or microbubbles) resident in fluids (Leighton 2007; Nyborg 1998). There are 2 primary types of cavitation. Inertial cavitation refers to the nonlinear expansion and collapse of bubbles followed by implosion or explosion (Fig. 3C). Depending on the size of the gas cavities present, the intensity and duration of US exposure, and the frequency of US transmitted, inertial cavitation can destroy tissues. Stable cavitation, on the other hand, does not readily produce tissue damage because it does not involve violent bubble explosion or collapse (Fig. 3C) and can safely mediate US-induced changes in cellular membrane conductance (Dinno and others 1989).

Summary

With respect to US, the brain is composed of a seemingly infinite number of boundary conditions. In normal physiological settings, the membrane potential permitting neuronal excitability is ultimately governed by structured events occurring across intracellular and extracellular fluid interfaces of neurons, as well as the viscoelastic membrane properties of their lipid bilayers and membrane-embedded protein ion channels. Thus, one might posit the actions of US on brain fluid dynamics to trigger changes in neuronal excitability. How does this hypothesis fit with previous observations conducted in neurons? Recent observations indicate US can lead to the activation of voltage-gated sodium and calcium channels, thereby eliciting action potentials and synaptic transmission (Tyler and others 2008). Changes in ionic conductance produced by acoustic streaming and stable cavitation occurring near neuronal membranes might, in theory, be able to produce slight membrane depolarization. In turn, these actions could be sufficient to activate voltage-gated channels, thereby mediating neurostimulation by US.

Tissue/Media	c (m/s)	ρ (kg/m^3)	Z (kg/s/m^2) $\times 10^6$
Air	333	0.0012	0.0004
Water	1480	1000	1.48
CSF	1515	1006	1.52
Skull	4080	1912	7.80
Brain	1505–1612	1030	1.55–1.66
Fat	1446	920	1.33
Artery	1532	1103	1.69
Blood	1566	1060	1.66
Muscle	1542–1626	1070	1.65–1.74

Goss and others 1978; Ludwig 1950.
CSF = cerebrospinal fluid.

US, 2) the presence of acoustic streaming and turbulent flow produced by compressible bubbles approximating the size of neurons, and 3) the presence of stable cavitation in response to US pulses previously shown capable of increasing neuronal activity (Fig. 3A-C). In further support of the hypothesis, the Euler equation and Naiver-Stokes equations can be used to predict some actions of US on fluid behaviors (Myers and others 2008; Nyborg 1998); US alters the membrane turbidity, fluidity, and conductance of cells (Dinno and others 1989; Sundaram and others 2003); and US can modulate neuronal excitability as discussed in the above sections. While continuum mechanics are useful for describing some aspects of brain tissue behavior in response to US, statistical mechanics also describe fundamental behaviors. Future biophysical studies are required for the above ideas and to further elucidate mechanisms underlying US-mediated neuromodulation.

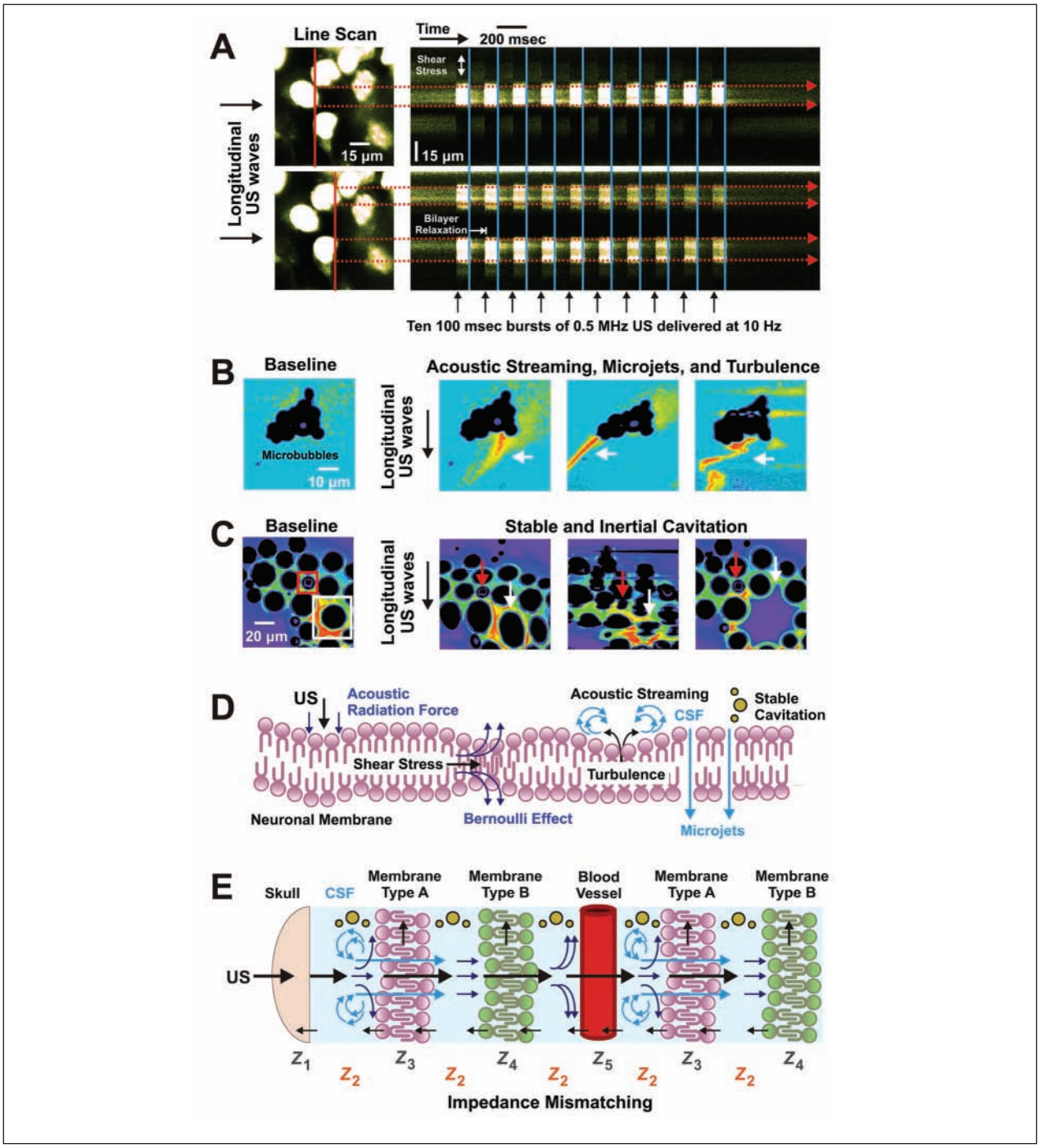

Figure 3. Mechanisms proposed to underlie ultrasonic neuromodulation. (A) Confocal line scans (solid red line; 2-ms acquisition rate) illustrating the influence of radiation force produced by longitudinal ultrasound (US) on CA1 pyramidal neurons in an acute hippocampal slice stained with a fluorescent membrane dye (DiO). Membrane compression in response to US pulses (black arrows) is indicated by an increase in fluorescence intensity within the indicated regions of interest (dotted red lines), while the effects of shear stress can be observed by elevated pixel intensities extending vertically beyond the highlighted regions of interest. A horizontal smearing of elevated pixel intensities following the termination of US pulses (blue vertical lines) illustrates millisecond membrane relaxation times and neuronal viscoelasticity. (B) Time-lapsed confocal images of microbubbles in a fluorescent dye-containing solution serve to illustrate acoustic streaming, microjet formation, and fluid turbulence in response to US (white arrows). (C) Similar to B except a small microbubble can be seen undergoing stable cavitation (red box/arrows), while a larger microbubble undergoes inertial cavitation before exploding (white box/arrows). (D) Illustration depicting some of the proposed fluid mechanical actions by which US can modulate neuronal activity. (E) Similar to D but illustrated in a composite model of brain tissue, where different cellular interfaces establish boundary sites having different properties due to acoustic impedance mismatches.

Transcranial Focusing of US

The skull represents a major obstacle when considering the transmission of US into the intact brain. The skull reflects, refracts, absorbs, and diffracts US fields. The acoustic impedance mismatches between the skin-skull and skull-brain interfaces present additional challenges for transmitting and focusing US through the skull into the intact brain. Based on modeling data of transmission and attenuation coefficients, as well as experimental data, the optimal gain for the transcranial US transmission and brain absorption occurs at frequencies <0.70 MHz (Hayner and Hynynen 2001; White and others 2006a; White and others 2006b). Because the feasibility of using US as a tool for noninvasive neuromodulation is being questioned, the ability to focus acoustic pressure through the intact skull is crucial for success.

Ultrasound can indeed be focused through human skulls using phased transducer arrays through methods known as magnetic resonance guided focused ultrasound (MRgFUS) (Clement and Hynynen 2002; Hynynen and others 2004; Hynynen and Jolesz 1998; Hynynen and others 2006; Jolesz and others 2005) (Fig. 4). Although the spatial resolution for focusing US is currently limited by the acoustic wavelength employed, recent advances in focusing US with adaptive optics (Zhang and others 2009) should permit US to gain spatial resolutions below the diffraction limits as has been recently achieved in optical microscopy (Abbott 2009). Based on observations reported in studies investigating US focusing through human skulls (Clement and Hynynen 2002; Hynynen and others 2004; Hynynen and Jolesz 1998), it appears that US may confer spatial resolutions similar to those achieved by DBS electrodes. With regards to spatial specificity, optogenetic-based neurostimulation approaches will likely remain superior to other neuromodulation techniques including US because they can be used to stimulate genetically targeted subpopulations of neurons in intact brain circuits (Zhang and others 2007). Before the feasibility of using MRgFUS for targeted neuromodulation in human patients can be properly determined, however, functional studies designed to examine how focused US influences intact brain circuits must be conducted by independent research groups for cross-validation across different animal models.

Potential Biohazards of US in Brain Tissue

Ultrasound can destroy biological tissues, so the potential for biohazardous effects must be taken into consideration. Many of the biohazards associated with US stem from its ability to induce large thermal fluctuations and/or inertial cavitation damage in soft tissues. Inertial cavitation differs from the stable cavitation previously mentioned in that inertial cavitation results in the explosion/implosion of microbubbles/gas bodies (Fig. 3C and Table 1). Due to the lack of large gas bodies in most soft tissues including the brain (Dalecki 2004), using low-intensity US for neuromodulation is unlikely to produce damage arising from inertial cavitation.

In soft tissues, inertial cavitation rarely induces damage at pressures <40 MPa (except for in lung, intestinal, and cardiac tissues in which damage from inertial cavitation can occur at pressures ~2 MPa due to the presence of large gas bodies) (Dalecki 2004). Ultrasound having peak rarefactional pressures <1 MPa has been found effective for stimulating neurons in the absence of cavitational damage (Tyler and others 2008). With respect to US intensities, evidence exists that acoustic intensities of about 50 mW/cm^2 are capable of modulating neuronal activity (Tyler and others 2008), whereas other studies have used intensities exceeding 600 W/cm^2 to ablate brain tissues (Hynynen and others 2004). Suggesting safe use, the lower US intensities shown effective in triggering neuronal activity are below the output limits established by the United States Food and Drug Administration for diagnostic imaging purposes.

The potential for damage arising from repeated, long-term US exposure also needs to be considered. It was recently reported that chronic stimulation of hippocampal slices with US intensities sufficient to trigger neuronal activity does not produce membrane or tissue damage (Tyler and others 2008). Demonstrating the need for caution, however, US exposure, albeit at intensities higher than those used for routine fetal imaging, is capable of producing some disruption of neuronal migration in the cortex of developing mouse embryos (Ang and others 2006). Thus, carefully designed safety studies are required before the possibility of using US for noninvasive neuromodulation can be further ascertained.

Future Considerations and Conclusions

Clearly, the studies reviewed above illustrate that US may provide a promising tool for modulating neuronal function. Several critical issues arising from these studies need to be addressed in order to properly evaluate the possibility of implementing US for neuromodulation. Due to the near chaotic nature of the continuum mechanics likely to underlie some of its effects, it is not likely the mysteries of how US can achieve neuromodulation will be untwined in the near future. Although we may not be close to understanding the underlying mechanisms, progress for developing US as a neuromodulation tool can still be driven forward with proper attention and strategic

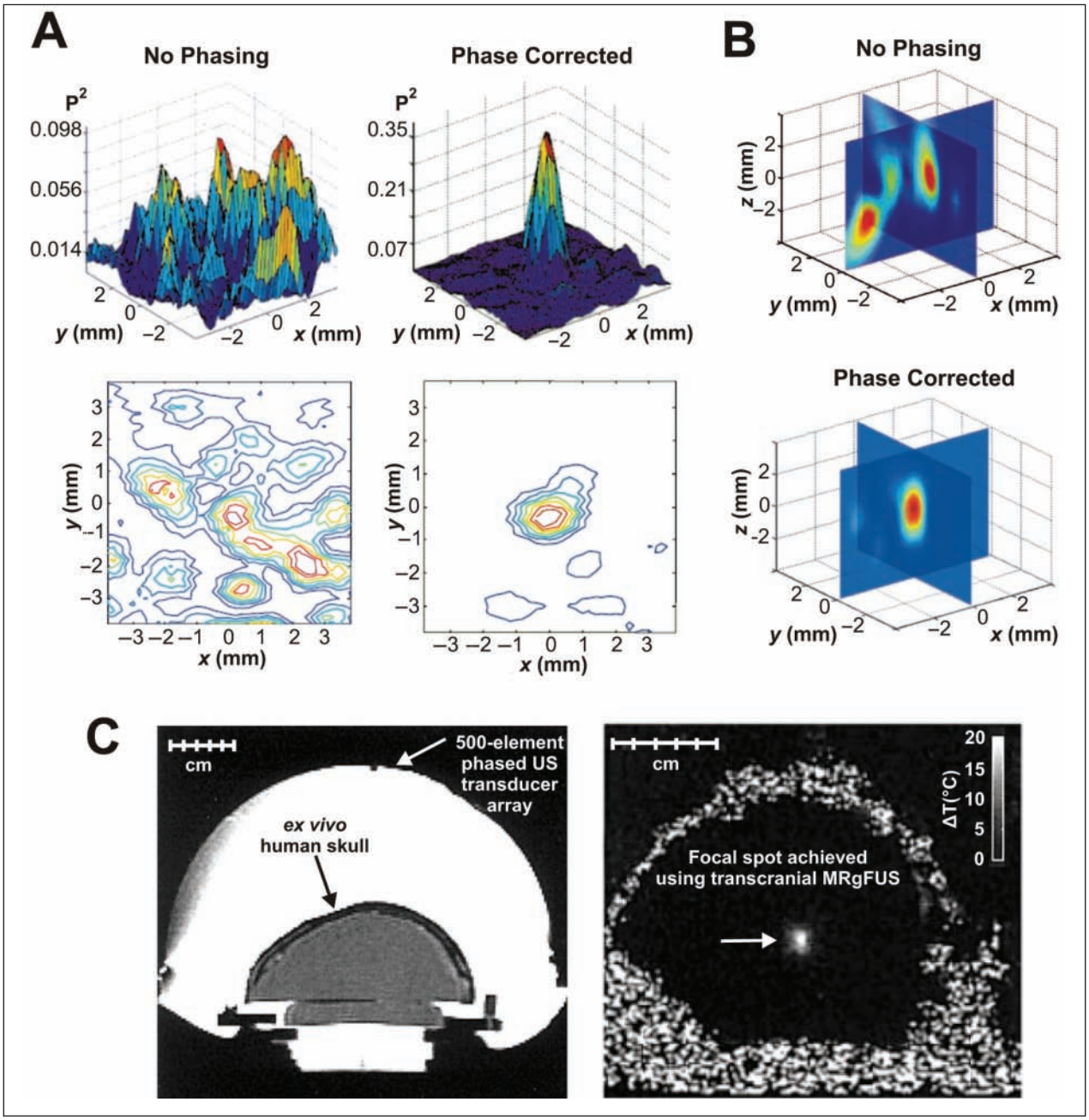

Figure 4. Ultrasound (US) can be noninvasively focused through human skull bone. (A) Relative pressure fields obtained by transmitting US through ex vivo human skulls without phase correction (left) and by applying phase correction algorithms to a 320-element phased US transducer array (right). (B) Similar to A but illustrating relative pressures plotted over a 3-dimensional volume for uncorrected (top) and phase-corrected (bottom) transcranial US. Panels A and B were modified with permission from *Physics in Medicine and Biology* (Clement and Hynynen 2002). (C) The magnetic resonance imaging (MRI) picture illustrates a phantom-filled ex vivo human skull mounted inside a 500-element phased US transducer array in a hemispheric arrangement (left). The MRI thermometry image on the right illustrates a focal increase in temperature produced by transmitting high-intensity focused ultrasound (HIFU) from the phased US transducer array. Panel C was modified with permission from *Magnetic Resonance in Medicine* (Hynynen and others 2004).

focus. For example, translational-based studies can be designed to identify general trends. This is especially true because even the most basic questions have yet to be resolved. For example, it is not known if high-intensity US consistently produces reversible suppression of neural activity while low-intensity US acts to produce neuronal excitation.

Illustrating even broader neuromodulation potential, there are several reports that US may be useful for sonoporation in gene therapy (Fischer and others 2006; Newman and Bettinger 2007), HIFU ablation of diseased brain tissue (Hynynen and others 2004; Hynynen and others 2006; Jolesz and others 2005), promoting nerve regeneration (Lazar and others 2001; Raso and others 2005), conducting sonothrombolysis following stroke (Alexandrov and others 2004; Tsivgoulis and Alexandrov 2007), and for mediating reversible BBB disruption to achieve targeted drug delivery in the brain (McDannold and others 2008; Raymond and others 2008). Hence, US seems to represent a near ideal approach for noninvasively modulating neuronal function despite our presently limited knowledge of its underlying mechanisms. If US is shown to be useful for neuromodulation through continued and carefully choreographed investigations, it may someday obviate the need for surgical implantation of stimulating electrodes currently used for DBS, thereby spawning a fresh generation of brain stimulation techniques.

Declaration of Conflicting Interests

The author declared a potential conflict of interest (e.g., a financial relationship with the commercial organizations or products discussed in this article) as follows: William J. Tyler, Ph.D., has filed 2 patents on using ultrasound for stimulating neuronal activity and is the cofounder of a medical device company.

Funding

The author disclosed receipt of the following financial support for the research and/or authorship of this article: Funding provided by US Army Research Development Engineering Command Grant 00W911NF-09-1-0431

References

Abbott A. 2009. Microscopic marvels: the glorious resolution. Nature 459:638–9.

Adamantidis AR, Zhang F, Aravanis AM, Deisseroth K, de Lecea L. 2007. Neural substrates of awakening probed with optogenetic control of hypocretin neurons. Nature 450(7168):420–4.

Ahmad N, Bygrave M, Chhem R, Hoffman L, Welch I, Grange R, and others. 2009. High-frequency ultrasound to grade disease progression in murine models of Duchenne muscular dystrophy. J Ultrasound Med 28(6):707–16.

Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, and others. 2004. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. N Engl J Med 351(21):2170–8.

Ang ES Jr., Gluncic V, Duque A, Schafer ME, Rakic P. 2006. Prenatal exposure to ultrasound waves impacts neuronal migration in mice. Proc Natl Acad Sci U S A 103(34):12903–10.

Aravanis AM, Wang LP, Zhang F, Meltzer LA, Mogri MZ, Schneider MB, and others. 2007. An optical neural interface: in vivo control of rodent motor cortex with integrated fiberoptic and optogenetic technology. J Neural Eng 4(3):S143–56.

Ayling OG, Harrison TC, Boyd JD, Goroshkov A, Murphy TH. 2009. Automated light-based mapping of motor cortex by photoactivation of channelrhodopsin-2 transgenic mice. Nat Methods 6(3):219–24.

Bachtold MR, Rinaldi PC, Jones JP, Reines F, Price LR. 1998. Focused ultrasound modifications of neural circuit activity in a mammalian brain. Ultrasound Med Biol 24(4):557–65.

Banihashemi B, Vlad R, Debeljevic B, Giles A, Kolios MC, Czarnota GJ. 2008. Ultrasound imaging of apoptosis in tumor response: novel preclinical monitoring of photodynamic therapy effects. Cancer Res 68(20):8590–6.

Bloomfield IG, Johnston IH, Bilston LE. 1998. Effects of proteins, blood cells and glucose on the viscosity of cerebrospinal fluid. Pediatr Neurosurg 28(5):246–51.

Borrelli MJ, Bailey KI, Dunn F. 1981. Early ultrasonic effects upon mammalian CNS structures (chemical synapses). J Acoust Soc Am 69(5):1514–6.

Chapman IV, MacNally NA, Tucker S. 1980. Ultrasound-induced changes in rates of influx and efflux of potassium ions in rat thymocytes in vitro. Ultrasound Med Biol 6(1):47–58.

Chung TJ. 2007. General continuum mechanics. New York: Cambridge University Press.

Clement GT. 2004. Perspectives in clinical uses of high-intensity focused ultrasound. Ultrasonics 42(10):1087–93.

Clement GT, Hynynen K. 2002. A non-invasive method for focusing ultrasound through the human skull. Phys Med Biol 47(8):1219–36.

Dalecki D. 2004. Mechanical bioeffects of ultrasound. Annu Rev Biomed Eng 6:229–48.

Dinno MA, Dyson M, Young SR, Mortimer AJ, Hart J, Crum LA. 1989. The significance of membrane changes in the safe and effective use of therapeutic and diagnostic ultrasound. Phys Med Biol 34(11):1543–52.

Fischer AJ, Stanke JJ, Omar G, Askwith CC, Burry RW. 2006. Ultrasound-mediated gene transfer into neuronal cells. J Biotechnol 122(4):393–411.

Foley JL, Vaezy S, Crum LA. 2007. Applications of high-intensity focused ultrasound in medicine: spotlight on neurological applications. Applied Acoustics 68:245–59.

Foster KR, Wiederhold ML. 1978. Auditory responses in cats produced by pulsed ultrasound. J Acoust Soc Am 63(4):1199–205.

Fry FJ, Ades HW, Fry WJ. 1958. Production of reversible changes in the central nervous system by ultrasound. Science 127(3289):83–4.

Fry WJ. 1968. Electrical stimulation of brain localized without probes: theoretical analysis of a proposed method. J Acoust Soc Am 44(4):919–31.

Fry WJ. 1954. Intense ultrasound: a new tool for neurological research. J Ment Sci 100(418):85–96.

Fry WJ. 1956. Ultrasound in neurology. Neurology 6(10): 693–704.

Fry WJ. 1958. Use of intense ultrasound in neurological research. Am J Phys Med 37(3):143–7.

Gavrilov LR, Gersuni GV, Ilyinsky OB, Sirotyuk MG, Tsirulnikov EM, Shchekanov EE. 1976. The effect of focused ultrasound on the skin and deep nerve structures of man and animal. Prog Brain Res 43:279–92.

Gavrilov LR, Tsirulnikov EM, Davies IA. 1996. Application of focused ultrasound for the stimulation of neural structures. Ultrasound Med Biol 22(2):179–92.

Goss SA, Johnston RL, Dunn F. 1978. Comprehensive compilation of empirical ultrasonic properties of mammalian tissues. J Acoust Soc Am 62(2):423–55.

Gradinaru V, Thompson KR, Zhang F, Mogri M, Kay K, Schneider MB, and others. 2007. Targeting and readout strategies for fast optical neural control in vitro and in vivo. J Neurosci 27(52):14231–8.

Harvey EN. 1929. The effect of high frequency sound waves on heart muscle and other irritable tissues. Am J Physiol 91(1):284–90.

Harvey EN, Harvey EB, Loomis AL. 1928. Further observations on the effect of high frequency sound waves on living matter. Biol Bull 55(6):459–69.

Hayner M, Hynynen K. 2001. Numerical analysis of ultrasonic transmission and absorption of oblique plane waves through the human skull. J Acoust Soc Am 110(6):3319–30.

Hynynen K, Clement G. 2007. Clinical applications of focused ultrasound-the brain. Int J Hyperthermia 23(2):193–202.

Hynynen K, Clement GT, McDannold N, Vykhodtseva N, King R, White PJ, and others. 2004. 500-element ultrasound phased array system for noninvasive focal surgery of the brain: a preliminary rabbit study with ex vivo human skulls. Magn Reson Med 52(1):100–7.

Hynynen K, Jolesz FA. 1998. Demonstration of potential noninvasive ultrasound brain therapy through an intact skull. Ultrasound Med Biol 24(2):275–83.

Hynynen K, McDannold N, Clement G, Jolesz FA, Zadicario E, Killiany R, and others. 2006. Pre-clinical testing of a phased array ultrasound system for MRI-guided noninvasive surgery of the brain: a primate study. Eur J Radiol 59(2):149–56.

Johns LD. 2002. Nonthermal effects of therapeutic ultrasound: the frequency resonance hypothesis. J Athl Train 37(3): 293–9.

Jolesz FA, Hynynen K, McDannold N, Tempany C. 2005. MR imaging-controlled focused ultrasound ablation: a noninvasive image-guided surgery. Magn Reson Imaging Clin N Am 13(3):545–60.

Lazar DA, Curra FP, Mohr B, McNutt LD, Kliot M, Mourad PD. 2001. Acceleration of recovery after injury to the peripheral nervous system using ultrasound and other therapeutic modalities. Neurosurg Clin N Am 12(2): 353–7.

Leighton TG. 2007. What is ultrasound? Prog Biophys Mol Biol 93(1–3):3–83.

Lele PP. 1963. Effects of focused ultrasonic radiation on peripheral nerve, with observations on local heating. Exp Neurol 8:47–83.

Ludwig GD. 1950. The velocity of sound through tissues and the acoustic impedance of tissues. J Acoust Soc Am 22(6):862–6.

Magee TR, Davies AH. 1993. Auditory phenomena during transcranial Doppler insonation of the basilar artery. J Ultrasound Med 12(12):747–50.

McDannold N, Vykhodtseva N, Hynynen K. 2008. Blood-brain barrier disruption induced by focused ultrasound and circulating preformed microbubbles appears to be characterized by the mechanical index. Ultrasound Med Biol 34(5):834–40.

Meyers R, Fry WJ, Fry FJ, Dreyer LL, Schultz DF, Noyes RF. 1959. Early experiences with ultrasonic irradiation of the pallidofugal and nigral complexes in hyperkinetic and hypertonic disorders. J Neurosurg 16(1):32–54.

Mihran RT, Barnes FS, Wachtel H. 1990. Temporally-specific modification of myelinated axon excitability in vitro following a single ultrasound pulse. Ultrasound Med Biol 16(3):297–309.

Morris CE, Juranka PF. 2007. Lipid stress at play: mechanosensitivity of voltage-gated channels. In: Hamill O, Simon S, Benos D, editors. Mechanosensitive ion channels. Current Topics in Membranes, Vol. 59. San Diego: Academic Press. p 297–338.

Mortimer AJ, Dyson M. 1988. The effect of therapeutic ultrasound on calcium uptake in fibroblasts. Ultrasound Med Biol 14(6):499–506.

Myers MR, Hariharan P, Banerjee RK. 2008. Direct methods for characterizing high-intensity focused ultrasound transducers using acoustic streaming. J Acoust Soc Am 124(3):1790–802.

Newman CM, Bettinger T. 2007. Gene therapy progress and prospects: ultrasound for gene transfer. Gene Ther 14(6):465–75.

Nyborg WL. 1998. Acoustic streaming. In: Hamilton M, Blackstock D, editors. Nonlinear acoustics. San Diego: Academic Press. p 207–31.

O'Brien WD Jr. 2007. Ultrasound-biophysics mechanisms. Prog Biophys Mol Biol 93(1–3):212–55.

Petreanu L, Huber D, Sobczyk A, Svoboda K. 2007. Channelrhodopsin-2-assisted circuit mapping of long-range callosal projections. Nat Neurosci 10(5):663–8.

Raso VV, Barbieri CH, Mazzer N, Fasan VS. 2005. Can therapeutic ultrasound influence the regeneration of peripheral nerves? J Neurosci Methods 142(2):185–92.

Raymond SB, Treat LH, Dewey JD, McDannold NJ, Hynynen K, Bacskai BJ. 2008. Ultrasound enhanced delivery of molecular imaging and therapeutic agents in Alzheimer's disease mouse models. PLoS ONE 3(5):e2175.

Rinaldi PC, Jones JP, Reines F, Price LR. 1991. Modification by focused ultrasound pulses of electrically evoked responses from an in vitro hippocampal preparation. Brain Res 558(1):36–42.

Shealy CN, Henneman E. 1962. Reversible effects of ultrasound on spinal reflexes. Arch Neurol 6:374–86.

Sukharev S, Corey DP. 2004. Mechanosensitive channels: multiplicity of families and gating paradigms. Sci STKE 2004(219):re4.

Sundaram J, Mellein BR, Mitragotri S. 2003. An experimental and theoretical analysis of ultrasound-induced permeabilization of cell membranes. Biophys J 84(5):3087–101.

ter Haar G. 2007. Therapeutic applications of ultrasound. Prog Biophys Mol Biol 93(1–3):111–29.

Tsivgoulis G, Alexandrov AV. 2007. Ultrasound-enhanced thrombolysis in acute ischemic stroke: potential, failures, and safety. Neurotherapeutics 4(3):420–7.

Tsui PH, Wang SH, Huang CC. 2005. In vitro effects of ultrasound with different energies on the conduction properties of neural tissue. Ultrasonics 43(7):560–5.

Tyler WJ, Tufail Y, Finsterwald M, Tauchmann ML, Olson EJ, Majestic C. 2008. Remote excitation of neuronal circuits using low-intensity, low-frequency ultrasound. PLoS ONE 3(10):e3511.

Velling VA, Shklyaruk SP. 1988. Modulation of the functional state of the brain with the aid of focused ultrasonic action. Neurosci Behav Physiol 18(5):369–75.

Wagner T, Valero-Cabre A, Pascual-Leone A. 2007. Noninvasive human brain stimulation. Annu Rev Biomed Eng 9:527–65.

Wang X, Pang Y, Ku G, Xie X, Stoica G, Wang LV. 2003. Noninvasive laser-induced photoacoustic tomography for structural and functional in vivo imaging of the brain. Nat Biotechnol 21(7):803–6.

White PJ, Clement GT, Hynynen K. 2006a. Local frequency dependence in transcranial ultrasound transmission. Phys Med Biol 51(9):2293–305.

White PJ, Clement GT, Hynynen K. 2006b. Longitudinal and shear mode ultrasound propagation in human skull bone. Ultrasound Med Biol 32(7):1085–96.

Yang X, Wang LV. 2008. Monkey brain cortex imaging by photoacoustic tomography. J Biomed Opt 13(4):044009.

Young RR, Henneman E. 1961. Functional effects of focused ultrasound on mammalian nerves. Science 134:1521–2.

Zhang F, Wang LP, Brauner M, Liewald JF, Kay K, Watzke N, and others. 2007. Multimodal fast optical interrogation of neural circuitry. Nature 446(7136):633–9.

Zhang S, Yin L, Fang N. 2009. Focusing ultrasound with an acoustic metamaterial network. Phys Rev Lett 102(19): 194301–4.