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NEUROMODULATION (D DOUGHERTY, SECTION EDITOR)

A Review of Low-Intensity Transcranial Focused Ultrasound for Clinical Applications

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Abstract The field of therapeutic focused ultrasound neuromodulation has made great advances in the last few years. While no clinical trials of focused ultrasound neuromodulation are yet underway, several human experiments have recently been conducted. There are many potential uses of this new technology, including treatment of numerous psychiatric and neurologic disorders, as well as a brainmapping tool for discoveries in basic science. In this review, we examine recent research data on the use of focused ultrasound in neuronal tissue, animal models, and humans. We also investigate ideal parameters for neuromodulation as well as potential mechanisms.

Keywords Focused ultrasound · Neuromodulation · BRAIN · Imaging · Treatment

Introduction

Therapeutic focused ultrasound uses low energy sound waves that pass through the skin and skull without surgery, and can be focused with precision essentially anywhere in the brain to modulate neural activity. This type of highly targeted, yet non-invasive, neuromodulation offers the possibility of new therapies for numerous neurologic and psychiatric conditions including epilepsy, depression, anxiety disorders, and traumatic brain injury. While no clinical trials of therapeutic focused ultrasound neuromodulation have yet been conducted, in the past few years, it has moved even closer to becoming a reality.

A few years ago, we wrote a review summarizing the state of focused ultrasound neuromodulation, arguing that the field was ready for first-in-human studies. Experiments in multiple animal models demonstrate that focused ultrasound (FUS) is highly focused, safe, and effective at neuromodulation. Subsequently, several studies have been published on focused ultrasound neuromodulation in humans.

The need for a technology like FUS is large and other non-invasive neuromodulation techniques—such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (TDCS)—are beginning to be utilized more broadly for treatment of neurologic or psychiatric disorders. Other forms of non-invasive neuromodulation—such as electroconvulsive therapy (ECT)—have been used for decades. However, these all suffer from limitations in terms of either spatial specificity, or are not useful as a general tool for neuromodulation. A general tool for neuromodulation may not only lead to new therapies but also new ways of diagnosing as well as opening new pathways for scientific discovery.

rTMS cannot be focused in three dimensions, and thus is limited to superficial targets. Similarly, TDCS also cannot be focused, nor can ECT. And while rTMS and TDCS appear to have many general applications, ECT, while very effective at treating depression, does not appear to generalize to other applications.

In contrast to other technologies, ultrasound (US) can be focused in three dimensions in a highly targeted manner. It also appears to not be disease specific and thus generalizable to many different conditions. FUS's ability to precisely modulate region-specific brain activity may translate into safe and long-lasting therapeutic applications.

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Repeated use of suppressive FUS may have a long-term effect, just as repeated use of TMS can have a long-term neuromodulating effect in depression. We envision that after using an MRI for initial targeting, subsequent treatment can be done in a doctor's office.

There are many potential uses of this exciting new technology. Aside from treating disorders, it is possible that FUS could be used in pre-surgical mapping as well as diagnosis of various disorders, and as a brainmapping tool for discoveries in basic science. The last several years have seen great advances in expanding applications, understanding of mechanisms, and even the first human testing (Table 1).

FUS Neuromodulation in Humans

In our previous review [14], we discussed the early evolution of focused ultrasound neuromodulation, beginning with the first attempts to study ultrasound's effect on neuronal tissue in the 1920s [15] and progressing through until today. Even nearly 60 years ago, Fry predicted that focused ultrasound (US) would have a major impact on neurology, including surgical treatments [16], as well as for investigating structure and function of brain circuitry [17]. While early studies of focused ultrasound primarily centered on high-intensity ultrasound for tissue ablations, in the last decade, there has been a surge in research on low-intensity focused ultrasound, not for surgery but for neuromodulation.

The neuromodulatory effects of FUS have been demonstrated numerous times in recent studies in multiple animal models. Based on pulse parameters, studies have shown that FUS can stimulate or suppress neural activity. FUS stimulation previously discussed includes stimulation of hippocampal slices [18], as well as motor cortex [19]. FUS has also been shown to suppress visual-evoked potentials [19], and even epileptic activity [20]. These varied effects and applications illustrate the potential of low-intensity focused ultrasound pulsation (LIFUP) to be a general neuromodulation tool.

Furthermore, and perhaps most importantly, FUS can be effective at neuromodulation without causing tissue damage [12, 18, 19, 21]. No studies have shown that FUS induced tissue damage in the absence of heating, unless they utilized contrast agents to enhance cavitation effects [14]. Therefore, FUS appears safe, even at intensities several times higher than the FDA limit for diagnostic ultrasound (720 mW/cm, [15]).

Based on the safety profile of FUS, in our previous review, we recommended that human experiments should be conducted. Subsequently, three ultrasound neuromodulation experiments in humans have been reported within the last 2 years.

One human study at the University of Arizona looked at the therapeutic use of transcranial ultrasound on mood and affect. This study utilized a standard clinical ultrasound device. While they did not specifically use focused ultrasound, the results may still be applicable [1•]. Participants were volunteer patients suffering from chronic pain. The ultrasound probe was applied by a physician to the scalp over the posterior frontal cortex, contralateral to maximal pain. The ultrasound machine itself was operated by a separate investigator, which allowed this study to be conducted in a double-blind fashion. Transcranial ultrasound was administered in standard B-mode for 15 s. Before and after treatment, subjects completed subjective reports on pain and mood. All subjects received both US and placebo in a randomized order. The results showed that brief US exposure led to improvement in mood and global affect that persisted for at least 40 min.

A second set of studies on humans examined the effect of transcranial focused ultrasound on evoked potentials, and the ability to enhance sensory discrimination. In these studies, FUS was administered to the scalp over somatosensory cortex during concurrent stimulation of the median nerve. The results showed that FUS significantly decreased amplitude of several stimulus-evoked potentials [2•]. In addition, FUS altered EEG dynamics of intrinsic EEG activity as well as in evoked potentials in a frequency-band dependent manner [22]. These results illustrate that FUS stimulation can modulate brain electrical activity.

This study also demonstrated that FUS neuromodulation of somatosensory cortex had an effect on perception. When subjects were asked to discriminate between touch stimuli on their hands, FUS improved both spatial and temporal discrimination.

Importantly, this study did not report any adverse events despite using a spatial-peak, temporal-average intensity (I_{spta}) of 8.6 W/cm [15], which is an order of magnitude greater than the FDA limit for I_{spta} for diagnostic US imaging of 720 mW/cm [15]. Although, the spatial-peak pulse-average intensity (I_{sppa}) of 23.87 W/cm [15] is well below the FDA limit for diagnostic US imaging of 190 W/cm [15]. The study cautiously utilized short duration sonications (0.5 s) in order to prevent thermal damage. However, these FDA limits are for diagnostic US imaging only. No such limits exist for FUS neuromodulation. Because the FDA does not have predefined limits for FUS neuromodulation, these data are useful in helping determine what FUS doses can be considered safe.

Recently, Yoo [23] presented a third human study that targeted somatosensory cortex. All subjects participating in the study reported sensations of movement. The results further demonstrate the ability of FUS neuromodulation to affect human perceptions.

While all of the above studies aimed to target specific locations in the human brain, none of them utilized functional imaging as a confirmation that the target region was affected. The lack of functional imaging makes it difficult to document where the focus of stimulation was located, and further show that activity in this region was in fact modulated. While the study from Legon et al., which utilized EEG, provided some

Table 1 Summary of ultrasound parameters and results from selected papers

Author	Year	Ultrasound parameters[a]	Description	Result
Hameroff et al.[1•]	2013	Organism: humans Frequency: 8 MHz Duration: 15 s Parameters: Other pulse parameters not stated Energy: I_{spta}=152 mW/cm^2 Note: this was not focused ultrasound	In human subjects with chronic pain, a physician applied a standard clinical US transducer to the scalp over the posterior frontal cortex.	Brief sonification led to improvements in mood that persisted for at least 40 min.
Legon et al.[2•]	2014	Organism: humans Frequency: 500 kHz Duration=0.5 s exposure Energy: I_{spta}=8.6 W/cm^2 PRF=1 kHz Pulse duration=0.36 ms Stimulus duration=0.5 s	FUS was applied to the scalp of human subjects over the somatosensory cortex. For a sensory input, the median nerve was stimulated using electrodes attached to the wrist. EEG was recorded to measure the neuromodulatory effect. In a separate part of the study, subjects also underwent a two-point and temporal discrimination tasks during FUS.	During median nerve stimulation (MNS), FUS over somatosensory cortex modulated the amplitude of both short-latency and late-onset stimulus-evoked potentials. FUS also briefly modulated the spectral composition of the EEG both before and after MNS.
Yoo et al. [3]	2011	Organism: rats Frequency: 650 kHz Duration: 20 min Energy: I_{spta}=300 mW/cm^2 TBD=0.5 ms PRF=100 Hz	Transcranial FUS was applied to the thalamus of anesthetized rats. Time from recovery of anesthesia—as indicated through physiological/behavioral changes—was measured for both sonicated and unsonicated rats.	LIFUP decreased recovery time from anesthesia.
Deffieux et al. [4]	2013	Organism: monkeys Frequency: 320 kHz Duration: Pulse duration=100 ms Single pulse. Energy: I_{spta}≈23.3 mW/cm^2	FUS was administered to the scalp over the left frontal eye fields on two awake macaque rhesus monkeys that had been trained to perform an antisaccade (AS) task. Saccade latencies were measured and compared between ipsilateral, contralateral, and no sonication.	LIFUP administered to left frontal eye fields during antisaccade (AS) task significantly modulated AS latencies, in particular delaying ipsilateral AS.
Kim et al. [5]	2014	Organism: rats Frequency: 350 and 650 kHz Duration: stimulus duration=300 ms Energy: I_{spta}=2.5–2.8 W/cm^2 TBD=1–5 ms PRF=variable	Transcranial FUS was administered to the somatomotor area of the rat brain. Different pulsing parameters (tone burst duration, pulse-repetition frequency, duty cycle, and sonication duration) and intensities were utilized.	Identified parameters that were most effective at eliciting tail movement.
Kim et al. [6, 7]	2013/2014	Organism: rats Frequency: 350 kHz Duration: 40 min Energy: 3 W/cm^2 I_{spta} TBD=0.5 ms PRF=1 kHz Stimulus duration=300 ms 2 s of interstimulus intervals	Transcranial FUS was applied to the thalamus of rats during 2-deoxy-2-[18F] fluoro-D-glucose (FDG) PET. The area of altered metabolism was measured.	Based on FDG PET, FUS sonication of the unilateral thalamic area brain area showed elevated glucose uptake. Area of increased metabolism was much smaller than traditionally defined size of the acoustic focus.
Scarcelli et al. [8]	2014	Organism: mice Frequency: 1.68 MHz Duration: 120 s Energy:	Transcranial FUS was applied the hippocampi of mice along with a microbubble contrast agent. The number of proliferating cells and new neurons was measured.	FUS significantly increased the number of proliferating cells as well as the number of new neurons in the dentate gyrus of the dorsal hippocampus.

Table 1 (continued)

Author	Year	Ultrasound parameters[a]	Description	Result
		TBD=10 ms PRF=1 Hz frequency average peak pressures=0.96 MPa. Note: also used microbubbles		
Choi et al. [9]	2013	Organism: rat hippocampal cells Frequency: 500 kHz Parameter: PRF=10–100 Hz TBD=20 μs Duration: 55-s stimulations over 5 min Energy: average I_{spta}=16.1–92.8 mW/cm^2	Hippocampal neurons from rat embryos were extracted and placed on a multi-electrode array. Changes in neural network activity were recorded during FUS sonication.	Increased spiking and bursting in hippocampal neurons. Effects persisted beyond the stimulation period.
King et al. [10]	2014	Organism: mice Frequency: 500 kHz Duration: 80 ms Energy: 3 W/cm^2 (continuous wave ultrasound)	Transcranial FUS was applied to the rostral and caudal regions of the mouse motor cortex. Motor responses were measured by electromyography.	Highly localized stimulation of different parts of the mouse motor cortex.
Younan et al. [11]	2013	Organism: rats Frequency: 320 kHz Duration: 80 ms Energy: TBD=230 μs PRF=2 KHz duty cycle=50 % and the total burst duration was 250 ms. Pressure=0.4–1 MPa	Transcranial FUS was administered to the scalp over motor cortex of anesthetized rats. Acoustic pressure and depth of anesthesia were varied, and the threshold for motor activation was measured through video observation.	TUS could reliably cause motor activation and was dependent on pressure and depth of anesthesia.
Min et al. [12]; Yang et al. [13]	2011; 2012	Organism: rats Frequency: 650 kHz Duration: 20 min Energy: I_{spta}=175 mW/cm^2 TBD=0.5 ms PRF=100 Hz Based on (Yoo 2011)	Using microdialysis in the frontal lobes of live rats, extracellular levels of several neurotransmitters were measured during transcranial FUS focused on the thalamus.	FUS focused at the thalamus significantly increased extracellular concentrations of dopamine (DA) and serotonin (5-HT) and decreased GABA.

[a] The spatial peak–pulse-average intensity I_{sppa} is the maximum intensity in the beam averaged over the pulse duration. The spatial peak–temporal average intensity is the maximum intensity in the beam averaged over the pulse repetition period. ISPTA is the best measure of the amount of heat delivered to a tissue by ultrasound

amount of this information, EEG does not have a good 3D spatial resolution. Further studies would benefit from utilizing MR guidance with fMRI feedback to clarify targeting and document the effect of neuromodulation.

Refining Parameters and Expanding Applications

While human experiments have shown the feasibility of transcranial focused ultrasound neuromodulation in humans, animal experiments continue to clarify ranges of usefulness of FUS parameters in different animal models using a variety of methodologies.

Research has even extended to non-human primates. In macaques, FUS administered to the left frontal eye fields during an antisaccade (AS) task significantly modulated AS latencies, in particular delaying ipsilateral AS [4].

Animal work has also demonstrated even wider-ranging applications for focused ultrasound. In anesthetized rats, FUS applied to thalamus decreased the time to emergence of voluntary movement as well as reflexive response to pinch [3]. This suggests that FUS may be useful in treating disorders of consciousness such as vegetative state.

FUS can also help grow new neurons. In one study, focused ultrasound with microbubbles increased hippocampal neurogenesis in adult mice [8]. This has implications for any neurodegenerative disorder, and particularly Alzheimer's. Other studies have also shown that FUS can even impact neural cell growth and morphology [24].

More realistic models have led to better approximation of focal pressure and size [25], and animal work has demonstrated that FUS can have excellent targeting. For example, focused ultrasound in rats caused increase in glucose metabolism with high spatial specificity [6]. In addition, while the size of the acoustic focus is generally described as the full-width at half maximum (FWHM), this same group found that the neuromodulatory area of FUS is much more localized, and is better approximated to be full-width at 90 % maximum. The neuromodulatory area was 3.7 mm in cross-sectional diameter and 5.6 mm long, compared to the FWHM, which was 6.5 mm in diameter and 24 mm in length. Thus, the neuromodulatory area was almost half the diameter and one-fourth the length of the conventional size of the acoustic focus [7]. Even within the tiny mouse motor cortex, it is possible to stimulate rostral and caudal regions separately [10].

Due to physical principals, the lower the frequency of US, the larger the focal area. And yet, higher frequency US signal experience severe attenuation by the skull. One group found a clever possible workaround. Using two transducers of approximately 2 MHz (2.25 and 1.75 MHz), they were able to create "modulated focused ultrasound," which had an effective frequency of 500 kHz, but a very small focus [26]. They were able to modulate the mouse brain with very high spatial specificity. However, while this is an interesting technique, it may not be as effective in human applications, as frequencies above approximately 700 kHz get extremely attenuated by the human skull.

While high spatial specificity is clearly evident, there is still a wide disagreement about the minimum intensity necessary for neuromodulation. One group stimulated the somatomotor areas of the rat brain to observe tail movement. Despite systematically altering several parameters, including tone burst duration, center frequency of the ultrasound transducer, duty cycle, and stimulus duration, the lowest effective I_{spta} was 2.5 W/cm [15], which is still 3.5 times higher than the FDA limit [5]. It is becoming more and more clear that FUS neuromodulation has a mechanical mechanism, and is thus pressure dependent [11]; yet it is unclear what the ideal pressures and intensities are. While several groups find that neuromodulation requires stimulation above the FDA diagnostic intensity limit [10], several other groups have achieved effective stimulation below the limit of 720 mW/cm [1•, 3, 12, 13, 15], and some have found that much lower intensities still work, even well below 720 mW/cm [15, 4, 9]. While depth of anesthesia likely plays a role [11], it cannot fully explain the wide disparity in values. Nor can it be explained by transcranial attenuation.

There is also a disagreement about the relative effectiveness of pulsed vs continuous stimulation. While most groups used pulsed sonication, one group found that continuous sonication was slightly more effective [27]. Although for continuous US their sonication durations were quite short, ranging from 20 to 480 ms. However, regardless of the ideal parameters for FUS, all these studies agree that effective neuromodulation can be achieved without tissue damage.

Mechanism of Neuromodulation

Several studies have been conducted to clarify mechanisms of action of focused ultrasound neuromodulation. The neuromodulatory effect appears to be mediated through mechanical interaction with the tissue [28]. In one study, focused ultrasound was used to modulate conduction of action potentials along an axon. This study showed that action potential amplitude and velocity were reduced proportional to the cumulative radiation force, thus pointing to a mechanical mechanism.

In particular, the neuromodulatory effect likely comes through cavitation within the lipid bilayer of the neuron cell membrane [29, 30]. Studies suggest that the physical pressure changes of the ultrasound beam actually move the lipid bilayer, and altering the space within bilayers, causing changes in membrane capacitance. Additionally, other fluid-mechanical properties may also play a role [31].

Some evidence suggests that FUS causes direct activation of neurons and synaptic vesicle release [21], while other evidence suggests that it does not directly activate neurons but rather increases neuronal excitability [9]. Further work is necessary to determine the exact effect of TUS on neuronal activity.

Neurochemical changes are also important to consider. While changes in neurochemistry may not be the primary mode of action of FUS, its effects on membranes alter the release of neurotransmitters. Evidence shows that FUS can modulate levels of various neurotransmitters. Using microdialysis, combined with FUS focused on the thalamus of rats, two studies from the same group demonstrated that FUS increased the concentrations of extracellular dopamine (DA) and serotonin (5-HT) [12] while decreasing extracellular GABA [13].

Conclusion

We need to continue with animal experiments that can clarify parameters, mechanisms of actions, and possible but yet unknown hazards of FUS use. However, we need to proceed with carefully designed safety and efficacy studies that could be conducted in populations where possible future benefits outweigh the risks. Some of those studies that stay under the FDA limits for diagnostic US could be conducted under IRBs supervision as in Hameroff, Yoo, and Legon studies. A human clinical trial is currently under way at UCLA testing the safety of a single-element transducer. Although, new generations of brain-stimulating FUS devices, possibly utilizing multi-array designs, may offer better targeting.

Initial targeting may need to use structural and functional MRI to document the focus position and response within the brain. It is possible to do targeted focused ultrasound outside an MRI environment using MRI data and optical tracking [32]. While these methods were developed with rodents, they could easily be translated to humans. This type of image guidance offers the possibility of multiple FUS treatments in an office setting, not requiring an MRI, improving the feasibility of repetitive FUS similar to rTMS.

Despite the exciting possibilities of clinical trials, so far, no focused ultrasonic neuromodulation devices have yet been approved by the FDA. The approval process will most likely be tedious depending on the ultrasound intensity necessary for effective neuromodulation or brainmapping. So far, human experiments have utilized intensities under the FDA guideline for diagnostic ultrasound and were subthermal. If the intensities can stay under the FDA limits for diagnostic ultrasound, the process will likely be shorter.

It would be helpful to clearly differentiate the different types of therapeutic focused ultrasound. Low-intensity focused ultrasound pulsation (LIFUP) is administered intermittently and subthermally for the purpose of neuromodulation. By contrast, high-intensity focused ultrasound (HIFU) is administered continuously and produces heating of the brain tissue utilized in surgical ablation. The current studies suggest that LIFUP could be used in humans therapeutically. However, if intensities need to be above the FDA guidelines for diagnostic US or will become thermally noxious (e.g., increase regional brain temperature by 2–3° C), the safety of human experiments will need to be thoroughly evaluated and possibly the FDA and the scientific community would need to develop new safety guidelines for therapeutic neuromodulatory focused ultrasound.

Compliance with Ethics Guidelines

Conflict of Interest Alexander Bystritsky reports other from Brainsonix, during the conduct of the study, outside the submitted work. In addition, Dr. Bystritsky has several patents with royalties paid and a major stock holder of Brainsonix corporation. He also has several patents or pending patents. Alexander Korb reports grants from The Gerald J and Dorothy R Friedman NY Foundation for Medical Research, and personal fees from the Pacific Institute of Medical Research, during the conduct of the study.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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