Low Intensity Focused Ultrasound for Epilepsy—
A New Approach to Neuromodulation

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Abstract
Patients with drug-resistant epilepsy (DRE) who are not surgical candidates have unacceptably few treatment options. Benefits of implanted electrostimulatory devices are still largely palliative, and many patients are not eligible to receive them. A new form of neuromodulation, low intensity focused ultrasound (LIFUS), is rapidly emerging, and has many potential intracranial applications. LIFUS can noninvasively target tissue with a spatial distribution of highly focused acoustic energy that ensures a therapeutic effect only at the geometric focus of the transducer. A growing literature over the past several decades supports the safety of LIFUS and its ability to noninvasively modulate neural tissue in animals and humans by positioning the beam over various brain regions to target motor, sensory, and visual cortices as well as frontal, eye fields, and even hippocampus. Several preclinical studies have demonstrated the ability of LIFUS to suppress seizures in epilepsy animal models without damaging tissue. Resection after sonication to the antero-mesial lobe showed no pathologic changes in epilepsy patients, and this is currently being trialed in serial treatments to the hippocampus in DRE. Low intensity focused ultrasound is a promising, novel, incisionless, and radiation-free alternative form of neuromodulation being investigated for epilepsy. If proven safe and effective, it could be used to target lateral cortex as well as deep structures without causing damage, and is being studied extensively to treat a wide variety of neurologic and psychiatric disorders including epilepsy.

Keywords
focused, ultrasound, low intensity focused ultrasound, neuromodulation, novel treatments, drug-resistant epilepsy

Introduction
Patients with drug-resistant epilepsy (DRE) who are not surgical candidates have unacceptably few treatment options. A few neurostimulatory devices are available including Responsive Neurostimulation (RNS), Deep Brain Stimulation (DBS), and Vagus Nerve Stimulation (VNS) which deliver electrical stimulation to the brain directly or via the vagus nerve, but these require permanent implantation which is undesirable to many patients. Benefits of these devices are still largely palliative, and many patients are not eligible to receive them. Other forms of neuromodulation, shown to be highly effective in neuropsychiatric disorders such as Transcranial Magnetic Stimulation (TMS) for tremor and Electroconvulsive Therapy (ECT) for depression, could potentially offer an alternative treatment for DRE. However, the effects of these and other noninvasive approaches have been limited mainly to the neocortex. For example, TMS—though noninvasive and highly effective for some psychiatric disorders—has produced disappointing outcomes in epilepsy, largely due to its inability to reach deeper structures in the brain commonly responsible for seizure onset, such as the hippocampus.

A new form of neuromodulation, focused ultrasound (FUS), is rapidly emerging, and has many potential intracranial applications. FUS can noninvasively target tissue with a spatial distribution of highly focused (to the millimeter) acoustic energy that ensures a therapeutic effect only at the geometric focus.
of the transducer. The physics of FUS are similar to clinical ultrasound imaging except that instead of spreading energy over an imaging region and recording as the waves echo back, the transducer in FUS is designed to only transmit the acoustic energy directly to a specific location (beam focus). Transcranial FUS has been studied for over 60 years.\textsuperscript{4} Its safety and utility have since been extensively analyzed for many medical uses. FUS is generally classified into two separate categories of high and low intensity.

High intensity FUS (HIFUS) is used for tissue ablation. The current clinical system for intracranial application utilizes >1000 tiny ultrasonic emitters in a hemispheric helmet around the head that converge intracranially, resulting in heating (ablation) of tissue at the beam focus. It is FDA approved for noninvasive thalamotomy, and has been truly transformative in treating essential tremor, as it can ablate deep targets (thalamus) without requiring a craniotomy.\textsuperscript{5} Incisionless ablation with HIFUS is currently being trialed in some focal epilepsies (NCT02804230), but it is limited to mainly midline lesions and effects are permanent, making it undesirable or unacceptable for many types of epilepsy that co-localize to tissue with critical neurologic function. It is being studied as an option for hypothalamic hamartomas, periventricular heterotopias, and other midline lesions. HIFUS is also being studied as a method to disrupt progression to bilateral tonic clonic seizures by ablating the anterior nucleus of the thalamus near the mammillothalamic tract (NCT03417297).

By contrast, low intensity focused ultrasound (LIFUS) is used for neuromodulation. It has been demonstrated to safely modulate neural tissue in animals and human subjects, is noninvasive, and painless.\textsuperscript{6-14} Most clinical studies using LIFUS to date have employed a single, geometrically-focused transducer to transmit an acoustic wave of mechanical energy (as opposed to electrical stimulation) through the skull to a focal target. LIFUS uses substantially lower intensity levels than HIFUS (HIFUS ∼1000 W/cm\textsuperscript{2} vs LIFUS ∼3 W/cm\textsuperscript{2}), so there is no ablative effect, tissue damage, or permanent anatomical changes.\textsuperscript{3,4} It also heats the skull less than HIFUS, which can allow for targeting a wider range of foci in the brain than are currently possible with thermal ablation.

**Preclinical Studies**

A growing literature over the past several decades supports the safety of LIFUS and its ability to noninvasively modulate neural tissue in animals by positioning the beam over various brain regions to target motor, sensory, and visual cortices as well as frontal eye fields and even hippocampus.\textsuperscript{15-21} LIFUS can produce both excitatory and inhibitory effects locally in the brain. Excitatory effects have been seen with sonication of the motor cortex of rodents and rabbits by evoking muscle movements contralateral to the site of sonication.\textsuperscript{15,20,21} By contrast, inhibitory effects including suppression of visually evoked potentials has also been observed.\textsuperscript{18,22} Similar findings have been demonstrated in larger animals with a rounded cranial convexity and skull thickness more similar to humans including sheep and non-human primates.\textsuperscript{23-25} LIFUS produced stimulus-locked effects on saccade latency when applied to frontal eye fields in macaques, and was also able to modulate discharges in the supplementary eye field, a reciprocally-connected brain region.\textsuperscript{17} Yang et al demonstrated fMRI blood oxygen level dependent (BOLD) activation to the primary somatosensory cortex of macaques by FUS, and Downs et al observed effects when sonicing the putamen.\textsuperscript{25,26} These are a few of many studies that illustrate how the desired neurophysiologic effect, excitatory or inhibitory, is influenced by several parameters including the intensity, pulse repetition frequency, duty cycle, and sonication duration.

Several preclinical studies have demonstrated the ability of LIFUS to suppress seizures in animal models without damaging tissue.\textsuperscript{27-30} Electrographic seizures were suppressed with sonication and recurrent seizures were reduced in a kainic-acid mesial temporal lobe epilepsy (mTLE) mouse model.\textsuperscript{28} A different study using the same model in rats demonstrated seizure termination with MR-guided LIFUS to the hippocampus, and another showed sonication delivered to the thalamus reduced the duration of pentylentetrazol-induced seizures.\textsuperscript{29}

**Clinical Trials in Humans**

Several pilot studies using LIFUS in healthy human subjects have elicited modulatory effects of auditory, visual, sensory, and motor functions.\textsuperscript{11-13} These studies demonstrate the safety of this novel technology in humans in addition to its ability to modulate neural tissue. Notably, Mueller et al\textsuperscript{16} showed that LIFUS treatments could alter EEG oscillations compared to sham. Legon et al\textsuperscript{31} delivered LIFUS to deep neural targets (sensory thalamus) by sonicating through the temporal bone in 40 human subjects and demonstrated resultant attenuation of P14 thalamic somatosensory evoked potentials and modulation of cortical oscillations. LIFUS is also being studied in disorders of consciousness. A report using LIFUS to treat a patient with severe brain injury and coma showed sonication to the thalamus was associated with increased level of arousal.\textsuperscript{32} There is also evidence of LIFUS-induced plasticity in the brain, with increased cortical excitability lasting beyond 30 minutes.\textsuperscript{33} An overview of human applications of this emerging technology notes that there have been no complications or adverse outcomes observed in any human studies thus far.\textsuperscript{34}

Several ongoing trials in humans are investigating LIFUS in a range of neurologic and psychiatric disorders including tremor, memory disorders, pain syndromes, disorders of consciousness, schizophrenia symptoms, opioid use disorder, obsessive compulsive disorder, and depression.\textsuperscript{34,35} More recently, LIFUS has been used in pilot studies in epilepsy as well. Stern et al\textsuperscript{36} delivered LIFUS to a unilateral antero-temporal region in a single session prior to a scheduled antero-mesial temporal lobe resection as treatment for DRE. The subsequent resection included the sonicated region for pathological examination of any potential tissue injury, and the temporal pole beyond the sonicated region as a control for comparison. Histologic examination of the resected tissue did
not identify any related apoptosis, necrosis, extravasation, acidophilic/ischemic neurons, or vascular damage. This was a small study with limited parameters, but the findings demonstrating safety of LIFUS to the human brain are pivotal. Early TMS and other neurostimulation trials provided very little such evidence of safety via histopathology prior to widespread use in humans.\textsuperscript{37} Safety determinations were essentially limited to post-treatment clinical evaluations and neuroimaging. Our group is trialing serial LIFUS treatments to adults with refractory mesial temporal lobe epilepsy, targeting the ultrasound beam focus directly to the affected hippocampus via the temporal acoustic window. Each subject undergoes 6 sonication sessions over several weeks. Thus far we have demonstrated safety in this population, there have been no adverse events or side effects.\textsuperscript{38} Though this is only a safety pilot trial, we have seen a positive signal regarding seizure reduction in some patients. These are very preliminary data on a small number of subjects and many questions remain, but results are encouraging and warrant further study.

**Mechanism of Action**

As with other forms of neuromodulation, the exact mechanism of how LIFUS alters human brain activity is largely unknown. A recent comprehensive review by Darmani et al\textsuperscript{39} breaks down proposed mechanisms into three categories: (1) cavitation, or eruption of ultrasound-induced gas bubbles that form inside the neural membrane changing its capacitance and/or structure, (2) increased membrane potassium channel conductance leading to reduced resting membrane potential and resultant increased firing, and (3) mechanosensitive membrane displacement by LIFUS’ radiation force resulting in excitation. Most of these proposed mechanisms are based on studies done in neocortex. The use of different LIFUS parameters allow for it to deliver either excitatory or inhibitory effects depending on the desired response. This is somewhat different than what we typically think of as “excitatory” or “inhibitory” in seizure neurophysiology. For example, one can imagine there are some epileptogenic foci we would want to inhibit, and others we may want to excite, such as those with predominantly inhibitory functions. When the target tissue is an epileptogenic focus, the effects of LIFUS seem to render it unable (or less able) to mount seizure activity for a period of time, while preserving the integrity of the cells.

**Current Challenges and Future Directions**

Low intensity focused ultrasound is a promising, novel, incisionless, and radiation-free alternative form of neuromodulation for epilepsy. It is still in its infancy, however, in terms of studies in human neuropsychiatric disorders. Considerable more data are needed before this new neurotechnology can come to efficacy trials. Safety of the device in epilepsy patients as a long-term or serial treatment option must be further established. The skull absorbs acoustic energy, so low transmission frequencies must be used to avoid skull heating during transcranial applications. Though many studies have demonstrated safety in animals and humans at low frequencies, the exact or maximum amount of energy that can be delivered to brain tissue safely without skull heating or thermogenic tissue damage remains unknown. At the same time, the intensities required for suppression of seizures in epileptogenic foci are also unknown. More comprehensive parameter testing in animals and further studies in epilepsy patients will be required to answer these questions. We know from RNS and DBS in epilepsy that neuromodulation is a process that takes time, often years, for patients to fully benefit from its effects. Though some neuromodulatory effects of LIFUS are immediate and transient, as noted above, further work is needed to determine the epilepsy-specific optimal parameters to employ, duration of effect, and number of treatments required over time.

The skull presents further complications in LIFUS because it can distort and displace the acoustic waves, making it more challenging to reach the intended target. There is a great deal of variation in human skull thickness, making the degree of beam distortion difficult to predict. In our pilot trial, we sonicate through the temporal acoustic window, which in most humans is the thinnest part of the skull, lacks trabeculae and is optimally oriented to the target, making it fairly straightforward to target the hippocampus. Expanding this treatment option to extra-temporal regions will require simulation mapping each individual’s skull dimensions. Computational skull modeling, derived from each subject’s head CT or brain MRI, is a complex process which is currently being developed and validated with ongoing studies.\textsuperscript{40-42} Further study in this area will also allow for use of LIFUS in a (paradoxically) less focused manner, to perhaps treat a broader area of cortex known to be epileptogenic, such as in some frontal lobe and other epilepsies.

Another challenge in using LIFUS for epilepsy lies in confirming target engagement (demonstrating the beam focus is where it was intended to be) and assessing neural efficacy (evaluating whether and how the tissue is being altered or modified). This is intrinsic with invasive devices such as DBS and RNS which are implanted with image guidance intraoperatively. HIFUS, though noninvasive, has intraoperative thermometry feedback for ablation in addition to MR-guidance during the procedure. TMS uses motor thresholds as confirmation of target engagement and dose. Target engagement and demonstration of neural efficacy is more challenging in LIFUS. Lee et al\textsuperscript{43} used the EEG recordings from implanted depth electrodes in adults undergoing invasive monitoring prior to epilepsy surgery to verify target engagement and neural efficacy of LIFUS. A robust and reliable process for this verification is still needed for patients without implanted electrodes. Our group is evaluating whether changes in resting state fMRI can be used to verify LIFUS’ neuromodulatory effects to the hippocampus. TMS was recently used to verify target engagement and modulation of lateral cortex with LIFUS, and another study used DBS recordings in an ex-vivo model for confirmation.\textsuperscript{33,44} More safety data are needed before recordings from implanted devices such as RNS or DBS in human subjects can be used to
verify LIFUS’ effects. One can envision how this method may also be used for noninvasive mapping of the human brain given its ability to transcranially elicit neurophysiologic and/or clinical responses from innumerable brain regions.

Lastly, in addition to neuromodulation, LIFUS has the ability to noninvasively open the blood–brain barrier (BBB) in a focal and reversible manner. This was first demonstrated in a trial of brain tumor patients where LIFUS was used to transiently open the BBB with intravenous microbubbles to enhance delivery of chemotherapeutic agents to the CNS. A similar method is being investigated in Alzheimer’s dementia. This exciting, novel form of targeted, noninvasive CNS drug delivery via LIFUS-facilitated BBB opening was also accomplished in a mouse model of status epilepticus resulting in seizure reduction, paving the way for first-in-human trials using this method for DRE.

In summary, LIFUS is an emerging, innovative neurotechnology that noninvasively delivers acoustic energy transcranially to modulate focal neural tissue with exquisite precision. If proven safe and effective, it could be used to target lateral cortex as well as deep structures without causing damage, and is being studied extensively to treat a wide variety of neurologic and psychiatric disorders including epilepsy. Substantial work is still needed to determine optimal sonication parameters and treatment paradigms for varying neural targets and disorders, but its future is promising.

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