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REVIEW ARTICLE

A review of low-intensity focused ultrasound for neuromodulation

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Abstracts The ability of ultrasound to be focused into a small region of interest through the intact skull within the brain has led researchers to investigate its potential therapeutic uses for functional neurosurgery and tumor ablation. Studies have used high-intensity focused ultrasound to ablate tissue in localised brain regions for movement disorders and chronic pain while sparing the overlying and surrounding tissue. More recently, low-intensity focused ultrasound (LIFU) that induces reversible biological effects has been emerged as an alternative neuromodulation modality due to its bi-modal (*i.e.* excitation and suppression) capability with exquisite spatial specificity and depth penetration. Many compelling evidences of LIFU-mediated neuromodulatory effects including behavioral responses, electrophysiological recordings and functional imaging data have been found in the last decades. LIFU, therefore, has the enormous potential to improve the clinical outcomes as well as to replace the currently available neuromodulation techniques such as deep brain stimulation (DBS), transcranial magnetic stimulation and transcranial current stimulation. In this paper, we aim to provide a summary of pioneering studies in the field of ultrasonic neuromodulation including its underlying mechanisms that were published in the last 60 years. In closing, some of potential clinical applications of ultrasonic brain stimulation will be discussed.

Keywords Focused ultrasound · Neuromodulation · Brain · Non-invasive

1 Introduction

In recent years, significant interests have been garnered in therapeutic applications of ultrasound (US) due to its ability to penetrate deep into tissue noninvasively. Development in ultrasound transducer technology has led to the ability to produce highly focused ultrasound (FUS) fields. These in conjunction with high spatial and temporal resolution imaging modality, such as magnetic resonance imaging (MRI), hold promise in treating several clinical disorders. FUS at high intensities, known as high-intensity focused ultrasound (HIFU), has been used to thermally ablate or mechanically fractionate soft tissues [1, 2]. In brain studies, for example, a number of clinical trials have been performed to study the feasibility of HIFU in the treatment of essential tremor and neuropathic pain [3, 4]. The basic principle behind the transcranial FUS involves focusing an ultrasound beam and delivering sufficient amount of acoustic energy into a small brain region of interest through the intact skull bone with a high degree of precision (of the order of several millimeters).

In contrast to HIFU that induces irreversible cell death, FUS at low intensities, known as low-intensity focused ultrasound (LIFU), has been shown to be capable of reversibly modulating region-specific brain function [5]. In general, "low intensity" is regarded as the magnitude of ultrasonic intensity similar to or below that typically used in diagnostic US examinations. A number of *in vivo* studies have demonstrated that LIFU can potentially be used to enhance or suppress neuronal activity without any concomitant brain damage [6–11]. Thus, there has been a

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rapidly growing interest in applying LIFU-mediated neuromodulation for treating neurological or psychiatric disorders [12–15]. LIFU-mediated neuromodulation has superior advantages over conventional neuromodulation techniques, such as deep brain stimulation (DBS), transcranial magnetic stimulation (TMS) and transcranial current stimulation (tCS). DBS technique, for example, requires a surgical procedure that causes risk of infection and immune responses [16]. Furthermore, both TMS and tCS are limited by the fact that the stimulation fields cannot be highly controlled due to the lacks of a spatial-specificity and a penetrability required for targeting a deep-seated brain region.

In this paper, we aim to provide a summary of pioneering studies in the field of ultrasonic neuromodulation including its underlying mechanisms, which were published in the last 60 years. Some of potential clinical applications of ultrasonic brain stimulation will also be discussed in detail.

2 Ultrasonic neuromodulation in animal studies

2.1 Central nervous system (CNS) stimulation

In 1958, Fry *et al*. [6] observed that transmitted FUS to lateral geniculate nucleus (LGN) of craniotomized cats led to partial suppression in electrophysiological responses recorded from the primary visual cortex, and Mazoue *et al*. [17] on the other hand found US-induced increased excitability of neuronal tissues. Later on, several studies demonstrated the effect of US on the neural fibers in hippocampal slice cultures and mammalian brains for temporally altering bioelectrical activities [11, 18, 19]. Network scale of neuromodulation in neural activity has been examined in cortical and subcortical regions of rats. Direct US stimulation to the cortex, thalamus, hippocampus and caudate nucleus of rats induced steady potential changes and induction of spreading depression in the cortex and deeper brain structures [20]. Sonication at low intensities (1–100 mW/cm^2) led to activation of the bioelectrical activity in the brain, whereas higher intensities (1–100 W/cm^2) caused a decrease in the electrocorticogram (ECoG) amplitude [21]. Non-cortical areas exposed to US radiation alleviated seizures and abnormal EEG activities in chemically induced epileptic cats [22].

In 2008, a ground-breaking work was published by Tyler group showing that US is capable of generating action potentials (APs) in central neurons, intracellular influx of Ca^{2+} and Na^{+} ions, and potentiated synaptic transmissions in CNS [23]. Many *in vivo* studies were subsequently carried out to investigate the excitatory and inhibitory effects of US on different brain regions of anesthetized animals using electromyography (EMG), electroencephalography (EEG), functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). Activation as well as selective suppression effects of LIFU on craniotomized rabbit brain function were confirmed by the results obtained from electrophysiology and fMRI studies [5]. A wide set of US parameter conditions have been tested and successfully employed to elicit motor responses in somatomotor cortices of lightly anesthetized mice [24–27] and rats [28–30]. The depth of anesthesia seems to play an important role in maximizing the neuromodulatory effect of LIFU. US parameters are needed to be refined in order to explore potential therapeutic applications since the evoked neuronal responses have only been observed in superficially anesthetized animals [25, 30]. In addition, LIFU applied to thalamus of anesthetized rats showed that US sonication significantly reduced the time to recover from ketamine/xylazine-induced anesthesia [31], which could be developed into potential US treatment in disorders of consciousness. Further evidence was discovered from large animal experiments showing that FUS sonication on primary sensorimotor (SM1) and visual (V1) region in sheep can elicit electromyographic responses from contralateral hind leg and electroencephalographic potentials, respectively [32].

2.2 Peripheral nervous system (PNS) stimulation

In 1928, the feasibility of using ultrasound to stimulate peripheral nervous system through experimenting with *ex vivo* frog and turtle neuromuscular preparations was firstly reported by Harvey [33]. In the 1990s, experiments were conducted on the response of electrical excitability of myelinated frog sciatic nerve *in vitro* [34, 35], which showed that US could increase or even decrease the compound action potential (CAP) amplitudes. Colucci *et al*. [36] attempted to use FUS to block the nerve conduction whereby the reduction of the action potential amplitude was observed. According to Foley *et al*. [37] FUS on rabbit sciatic nerves successfully led to the nerve conduction blockage followed by the axonal degeneration distal to the sonication site, which was confirmed by electrophysiological and histological analysis. It has also been observed that FUS applied to rat abducens nerve can elicit abductive eyeball movement ipsilateral to the hemispheric side of sonication [38]. Besides the FUS-induced excitation of abducens nerve function, another study later reported that FUS stimulation to vagus nerve could lead to inhibition in the rates of change of AP amplitudes decay and nerve conduction velocity with respect to time [39]. More recently, Wright *et al*. [40] reported that exposure of the isolated crab leg nerve bundle consisting of purely

unmyelinated axonal tissue to US can also produce action potentials.

3 Advances in human trials

It has been reported that tactile sensation, thermal (heat and cold), tickling, itching, and various types of pain from hand can be induced by FUS [41, 42]. The threshold values of different types of sensations measured by acoustic intensity were found to be dependent on US frequency and the location of sonicated region [43, 44]. It is also noteworthy that continuous US exposures did not induce any tactile sensations even with the same acoustic intensity used in pulsed mode to successfully elicit skin sensations. These studies reveal that pulsed US would be favorable for inducing the neuromodulatory sensation at the axon ending.

Hameroff *et al*. [45] reported improvement in subjective mood and pain reduction after transcranial US compared to placebo, when applying high-frequency US (8 MHz) for 15 s to the scalp over posterior frontal cortex. A more standardized human study was conducted to modulate the function of primary somatosensory cortex (S1) and found slight but significant changes in EEG responses [46] with the enhancement of the discrimination ability [47]. A similar study of the effects of US on S1 region has recently been performed to examine elicited gross activation of tactile sensations in hand areas contralateral to the sonicated hemisphere using image-guided transcranial FUS system [9]. In addition, they further investigated the various tactile sensations while simultaneously stimulating S1 and S2 in the later study [48]. Lee *et al*. [49] also reported that LIFU-mediated primary visual cortex (V1) stimulation could result in US-evoked potentials and elevated fMRI blood oxygen level-dependent (BOLD) signals in not only V1 but also associated network region functionally connected with the exposed area. Recently, a pilot study was also conducted to show the feasibility of using thalamic-LIFU to wake up a post-traumatic disorder of consciousness (DOC) patient [12], which was consistent with the animal study showing the effectiveness of thalamic-LIFU to promote recovery from ketamine/xylazine-induced anesthesia in rodents [31].

4 Biophysical mechanisms behind ultrasound neuromodulation

Despite the recent progress in the application of US neuromodulation, the exact mechanisms underpinning this phenomenon are poorly understood. A number of hypotheses have been proposed and tested both experimentally and numerically; however, the nature of the interaction of sound waves and neural tissue at cellular or molecular levels still remains unclear. In this section, we briefly review some of the possible mechanisms, which have been proposed to explain the role of US in neurostimulation.

Biological effects of US can result from heating, radiation force and acoustic cavitation [50]. Though heating due to absorption of acoustic energy may suppress neuronal activity by disrupting synaptic signalling pathways [51], only minimal increases in temperature (less than 0.1 °C) have been observed during the course of US neuromodulation [5, 24, 38, 40, 52]. Besides thermal effects, Tyler *et al*. [53] proposed that US stimulates neural activity by mechanically altering the state of mechanosensitive ion channels embedded within cellular membranes when propagating in neuronal tissue. Because mechanosensitive channels are types of transmembrane proteins in response to mechanical forces or stresses, US-induced tissue compression, tension or shear forces cause conformational changes (*i.e.* mechanical deformations), which could increase the probability of the channels opening. This then leads to ion flux, depolarisation and activation of voltage-gated ion channels followed by the generation of action potentials. Although this hypothesis has not been directly tested yet, Tyler *et al*. [23] and Kubanek *et al*. [54] experimentally observed the activation of voltage-gated sodium Na^{+}, calcium Ca^{++} and potassium K^{+} channels during FUS exposure.

Another possible mechanism underlying the ability of US to modulate the brain function is due to the presence of acoustic cavitation within the bilayer membrane [55, 56]. Cavitation has also been shown to temporarily open the blood–brain barrier (BBB), resulting in the enhancement of BBB permeability [57–59]. When an acoustic wave propagates through tissue with a strong tensile phase (negative pressure), submicron-sized vapour and/or gas pockets that originally dissolved in the medium can be drawn out to form small bubbles. These bubbles will then oscillate, expand and collapse when they are subjected to sufficiently large acoustic pressures. This is known as acoustic cavitation, and is a threshold effect, which depends acoustic pressure, temperature and insonation frequency [60, 61]. Krasovitski *et al*. [55] hypothesised that US-induced bubble cavitation in the intramembrane hydrophobic space between the two lipid leaflets of the cell membrane leads the bilayers to oscillate periodically, resulting in the activation of mechanosensitive proteins and/or the alteration of membrane permeability. To support their idea, the authors developed a mathematical model describing the interaction of US and biological tissue at cellular level, known as 'Bilayer Sonophore' (BLS) [55]. In follow-up study, Plaksin *et al*. [56] modified the BLS model and accounted

Table 1 Selected papers demonstrating ultrasonic excitation and suppression of neural activity

Experimental preparation	Pulse repetition frequency (kHz)	Sonication duration (s)	Duty cycle (%)	Fundamental frequency (MHz)	Acoustic intensity (W/cm^2)*	Outcome	Reference
In vitro: mice hippocampal slice culture	0–0.1	0.25–15	0–2.3, 74.6	0.44, 0.67	2.9 (I_{pa})	Stimulation of electrical activity and synaptic transmission	[19]
In vitro: rat hippocampal slice	200	Not specified	Not specified	0.5	40–110 (I_{spta})	Depressed fiver volley and cell population potentials, enhanced dendritic potential	[15]
In vitro: frog sciatic nerve	Not specified	0.0005	Not specified	2–7	100–800	Differential increase and decrease of evoked CAP amplitude	[30]
In vitro: frog sciatic nerve	–	300	100	3.5	1–3	Increase of evoked CAP amplitude at 1 W/cm^2 and decrease in CAP amplitude at 2–3 W/cm^2	[47]
In vitro: bullfrog sciatic nerves	–	30	100	0.661, 1.986	440	Decrease in action potential	[32]
Mouse: motor cortex	–	0.08	100	0.5	3	Motor responses were elicited, and measured by electromyography	[22]
Mouse: sensorimotor cortex, subcortical region	1	1	50	1.9	1.12–1.79 MPa	Hind limb movement with EMG responses, eyeball movement pupil dilation	[48]
Mouse: motor cortex	0.011–3	0.02–0.48	0.2–60, 100	0.25–0.6	0.01–79.02	Highly localized stimulation on motor cortex induced EMG responses	[21]
Mouse: brain	1.5	0.0587	30	0.5, 2	0.15–5.25 (I_{spta})	FUS induced spatially selective diverse movements	[23]
Mouse: cortex and hippocampus	1.2–3	0.027–0.333	19–86	0.25–0.5	0.021–0.163	Stimulation of neuronal activity and synchronous oscillations in the intact hippocampus	[20]
Rat: cerebral cortex	0.005, 0.01	10–40	50	4.6	5–100 V/cm^2	DC change, spreading depression	[16]
Rat: thalamus	0.1	20 min	5	0.65	6 (I_{sppa})	Decreased recovery time from anesthesia through indication with behavior and physiological changes	[27]
Rat: frontal lobe	0.1	20 min	5	0.65	3.5 (I_{sppa})	Significantly increased extracellular concentration of dopamine and serotonin and decreased in GABA	[49]
Rat: motor cortex	2	0.25	50	0.32	0.4–1 MPa	Motor activation was measured through video observation	[24]
Rat: motor cortex	1	0.03	50	0.35	3 (I_{spta})	Estimate the latency in tail movement elicited by transcranial FUS	[25]
Rat: motor cortex	0.1–2.8	0.2, 0.3, 0.4	30, 50, 70, 100	0.35, 0.65	2.5–2.8 (I_{spta})	Eliciting tail movement	[26]
Rabbit: sciatic nerve	Not specified	5	58	3.2	1930 (I_{spta})	Suppression of activity; nerve block	[33]
Rabbit: motor and visual cortex	0.01–1	0.5–2, 9	5, 50	0.69	3.3–12.6 (I_{sppa})	Bimodal modulatory effect of FUS-mediated fMRI BOLD signals	[5]
Monkeys: front eye field	–	0.1	100	0.32	2.9–5.1 (I_{sppa})	LIFU administered to Scalp over left frontal eye field significantly modulate latencies during AS task	[50]

Table 1 continued

Experimental preparation	Pulse repetition frequency (kHz)	Sonication duration (s)	Duty cycle (%)	Fundamental frequency (MHz)	Acoustic intensity (W/cm^2)*	Outcome	Reference
Crab: leg nerve	10	0.008	50	0.67	66, 118.1, 260 (I_{sptp})	US induced CAP response (self-inhibiting, localized)	[36]
Human: S1	1	0.5	36	0.5	23.87 (I_{sppa})	EEG responses, improved sensitivity of tactile discrimination	[43]
Human: S1	0.5	0.3	50	0.25	3 (I_{sppa})	Transient tactile sensations	[9]
Human: S1 and/or S2	0.5	0.5	50	0.21	35 (I_{sppa})	Tactile sensations from the hand contralateral to the stimulation (vibrotactile, pressure, warmth, and coolness)	[44]
Human: V1	0.5	0.3	50	0.27	16.6 (I_{sppa})	Phosphene perception, fMRI and EEG activation	[45]

*I_{pa} = pulse-average intensity, I_{spta} = spatial-peak temporal-average intensity, I_{sppa} = spatial-peak pulse-average intensity

for the dynamics of membrane change polarisation, capacitance and voltage-sensitive ion channels in a CNS neuron. Whilst their simulated neuronal responses under US excitation showed good agreement with *in vivo* brain stimulation results reported in King *et al*. [25, 62], to the best of our knowledge, no *in vivo* evidence validating the presence of intramembrane cavitation at low US intensities in an animal model has been published [10, 63].

5 LIFU safety considerations

A wide range of biological effects can be induced by ultrasound depending on the exposure parameters used (*e.g.* insonation frequency, acoustic pressure, intensity, pulse duration, pulse repetition frequency). At low intensities, for instance, reversible cellular effects can potentially be produced, whereas high-intensity ultrasound can lead to irreversible cell death through coagulative necrosis [1, 64]. US exposure conditions should therefore be chosen with caution, particularly in the case of ultrasonic neuromodulation where temporal modulation of neural activity in the absence of brain damage is essentially required.

The Food and Drug Administration (FDA) and other regulatory agencies such as the American Institute of Ultrasound in Medicine (AIUM) and the National Electrical Manufacturers Association (NEMA) have provided safety guidelines for diagnostic US examinations. These include regulations on US exposure conditions in terms of the thermal index (TI), mechanical index (MI), spatial-peak temporal-average intensity (I_{spta}) and spatial-peak pulse-average intensity (I_{sppa}) [65, 66].

For the sake of safety, the FDA currently stipulates the maximum allowed acoustic output level of diagnostic US system that [65, 67].

- the TI should be kept below a value of 6.0 (this value is not an upper limit for non-ophthalmic applications. A justification must be provided if TI $\geq$ 6.0);
- the MI must not exceed a value of 1.9;
- the maximum limit of the $I_{spta,\ derated}$ must be 720 mW/cm^2 or less;
- the maximum limit of the $I_{sppa,\ derated}$ must be 190 W/cm^2 or less.

Although the above regulations are set for diagnostic US examinations, these should also be treated as minimum requirements for ultrasonic neuromodulation treatment protocols. A number of studies reported that US at intensities below the FDA limits was able to modulate the neural activity with no signs of tissue damage in the brain [5, 30, 66] Acoustic intensities higher than the FDA limit but lower than the upper limit set by the International Electrotechnical Commission (IEC) for diagnostic medical

ultrasonic equipment (*i.e.* I_{spta} of 3 W/cm^2, [68]) have also been used to stimulate brain function. Lee *et al*. [49] found that the I_{spta} of 1.5 ± 0.9 W/cm^2 enabled the primary visual cortex in humans to be provoked without any adverse biological effects on the treatment sites. All these studies suggest that non-invasive ultrasonic brain stimulation is safe and could therefore be a powerful clinical therapy for treating neurologic patients. It should be noted, however, that a long-term follow-up study on the effects of US on the human brain has not been performed yet [69] and warrants further investigation (Table 1).

6 Conclusion

In this paper, we reviewed decades of pioneering studies on ultrasonic neuromodulation. Animal studies performed over the last 60 years have suggested that US stimulation could safely excite and inhibit neural activity. LIFU is also safe to be used in adult humans as acoustic energy can effectively penetrate through the human skull and can alter the brain function with intensities similar to or below that typically used in ultrasonography. LIFU, therefore, has the tremendous potential to improve the clinical outcomes of as well as to replace the currently available treatments for neurologic disorders such as DBS, TMS and tCS. Despite the lack of mechanistic understanding of the neural response to ultrasound, LIFU is already being pursued in many clinical applications. For example, simultaneous use of LIFU together with the real-time fMRI has been proposed to diagnose functional disorders, including obsessive convulsive disorder (OCD), depression, traumatic and hypoxic brain injury, stroke, Alzheimer's disease, psychiatric disorders and altered states of consciousness [5, 12–14, 70]. Recently, a portable transcranial ultrasound device (Neurosonx^{TM} SR, Cerevast Medical Inc., Redmond, WA), which transmits acoustic energy into motor cortex region to facilitate recovery and rehabilitation from acute stroke, has been developed and commercialized. Future studies should be focused on the optimization of US parameter for different therapeutic applications.

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