PERSPECTIVE

Neuromodulation and ablation with focused ultrasound – toward the future of noninvasive brain therapy

With an aging patient population and an increased burden of neurological disease, the demand for noninvasive alternatives to open neurosurgical procedures is imperative. Noninvasive or minimally invasive approaches to targeting brain regions include transcranial magnetic stimulation (TMS), transcranial direct current stimulation, temporally interfering electric fields, and focused ultrasound (FUS). Among these modalities, FUS offers a unique combination of target specificity, deep brain penetration, and compatibility with real-time structural and thermal monitoring using magnetic resonance imaging (MRI) and MR thermometry. Depending on the intensity and frequency used, ultrasound can have either modulating or ablative effects on brain tissue. High-intensity MR-guided FUS (MRgFUS) is a noninvasive and effective alternative to conventional deep-brain stimulation and radiofrequency lesioning for essential tremor (ET), and is being investigated for other movement disorders, particularly Parkinson's disease. Wider clinical implementation of high-intensity ultrasound is challenged by limitations in target selection precision, technical barriers (such as variable penetration and heat deposition) and the possibility of lesion-related adverse effects (Schwartz et al., 2018). Emerging studies, including those from our group (Boutet et al., 2018) are striving to refine targeting of MRgFUS to improve safety and patient clinical outcomes. At the same time, low-intensity FUS (LIFUS) has been found to safely modulate brain activity in rodents, primates, and healthy human subjects (Fomenko et al., 2018). Clinical translation of LIFUS has been hampered however, by a poor understanding of the mechanisms of action, uncertainty over effective sonication parameters and intensities, and conflicting study results due to heterogeneous experimental protocols. In this perspective, the current state of both MRgFUS ablation and LIFUS neuromodulation will be presented. Ongoing technical challenges to delivering ultrasound to the brain, recent innovations in target and parameter selection, and future directions for this emerging nonsurgical alternative are also discussed.

High-intensity ultrasound: Currently approved by the Food and Drug Administration for clinical treatment of ET, high-intensity MRgFUS is also being investigated for other neurological indications such as Parkinson's disease. In a typical thalamotomy treatment protocol for ET, the awake patient is outfitted with a water-cooled headcap, stereotactic frame, and a dome-shaped array of 1024 US transducers (**Figure 1A**). Under MRI guidance and stereotactic navigation, beams of 600–700 kHz ultrasound are delivered to gradually heat and ablate the ventral intermediate (VIM) thalamic nucleus, culminating in a target temperature of 55–60°C. The best level of scientific evidence for this treatment is a prospective single-blinded randomized control trial (Oxford Centre of Evidence level 1b) enrolling 76 patients, of which 56 received unilateral MRgFUS VIM thalamotomy and 20 received sham. A 2-year follow-up analysis showed durable improvement by 56% of mean hand tremor scores, as well as lasting improvement in quality-of-life measures (Chang et al., 2018). In a recent systematic review of 151 ultrasound-treated patients, the most common adverse effects were: face or limb paresthesias (27%) due to heating of adjacent somatosensory thalamic nuclei, and gait instability (23%) (Dallapiazza et al., 2018). Other experimental indications for ultrasound ablation have included tremor-dominant Parkinson's disease, yielding a safety and efficacy profile similar to that of other surgical treatments such as deep brain stimulation and radiofrequency ablation (Zaaroor et al., 2018).

Low-intensity ultrasound neuromodulation: In the early 20th century, acoustic waves delivered at low-frequency and low-intensity were shown to modulate the activity of electrically-excitable tissues in the central and peripheral nervous system. Since then, many brain regions in animals and humans have been targeted with LIFUS to explore how acoustic energy can suppress or excite neural activity. Key parameters used to define a LIFUS sonication regime are: fundamental frequency (0.2–1.0 MHz), pulse repetition frequency, duty cycle, sonication duration, and intensity. Unlike MRgFUS, intensities are kept within the Food and Drug Administration guidelines to prevent thermal damage – typically < 190 W/cm^2 (Fomenko et al., 2018). Human cortical and subcortical sites that have been modulated by LIFUS have included the primary and secondary somatosensory cortices, visual cortex, primary motor cortex, thalamus, and the caudate nucleus (Fomenko et al., 2018). For instance, sonication of the visual cortex in healthy participants elicited subjective flashes of light, stimulation-related electroencephalogram changes, and activation of visual cortex as seen by functional MRI (Lee et al., 2016). Apart from temporary tinnitus, and brief paresthesias, no adverse effects have been reported from LIFUS.

Another burgeoning area of research in this field is unraveling the mechanisms responsible for neuromodulatory effects of ultrasound, which are poorly understood. Various theories such as mechanosensitive ion channels embedded within the neural membrane, oscillation of dissolved gas bubbles within the neural lipid bilayer, and radiation forces have been proposed through *in vitro* and *in vivo* preclinical experiments (Krasovitski et al., 2011). Additionally, neurophysiologic studies using combined LIFUS and TMS have begun to explore short-term plasticity measures to help explain ultrasound's effects on the motor circuit (Legon et al., 2018). In animal experiments, varying ultrasound delivery parameters such as sonication duration have been shown to either potentiate or suppress neural activity in the motor pathway, with short and long sonication times, respectively (Fomenko et al., 2018).

Challenges and future directions

***High-intensity ultrasound*:** Since MRgFUS uses software and phase-arrays to precisely define the sonication target (**Figure 1B**), a central goal in the field is to define a precise location within the VIM nucleus which leads to optimal patient outcomes. Recently, topological reconstruction in patients receiving MRgFUS for ET revealed a lesion area of maximal clinical effectiveness to be located in the inferio-posterior aspect of the VIM nucleus, near the adjacent ventro-caudalis nucleus (Boutet et al., 2018). Further investigations and long-term follow-up are needed to determine the sustainability of effects and to learn about the long-term structural and

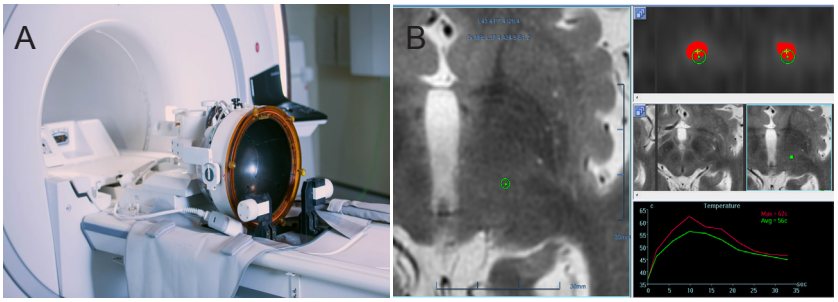

Figure 1 Focused ultrasound thalamotomy for treatment of essential tremor.
(A) Magnetic resonance-guided focused ultrasound device consisting of a head-mounted dome containing 1024 ultrasound transducers, integrated with an magnetic resonance imaging machine and patient table (with permission of InSightec Inc.); (B) magnetic resonance-guided focused ultrasound software interface for three-dimensional lesion planning and real-time thermometry measurement for ventral intermediate thalamotomy to treat essential tremor (with permission of InSightec Inc.).

functional evolution of thermal lesions and interconnected circuits.

Another central challenge to safe and effective ultrasound delivery to the brain resides in the complex response of biological tissue to acoustic waves. In MRgFUS, a water-cooled headcap is worn by patients during treatment to cool the skin to 15–20°C, to aid in diffusing thermal hotspots deposited within the scalp between sonications. Despite this precaution, a recent retrospective series showed that 7/30 patients treated with ablative ultrasound for movement disorders developed characteristic skull lesions between 1–3 months post-therapy. The lesions resembled bony infarcts, were oval-shaped with hypointense rims, and bilaterally distributed within the skull (Schwartz et al., 2018). Although the authors determined that higher overall treatment energies were more likely to produce these asymptomatic lesions, pre-treatment skull density or morphology did not seem to correlate with the location of these lesions. Conversely, some skull geometries are prohibitive of effective MRgFUS treatment because of insufficient heating at the focus. This can usually, but not always, be mitigated by calculation of the skull density ratio, where a skull density ratio < 0.4 is an exclusion criterion for ultrasound ablation. Future studies should record real-time thermal data from intervening tissues such as scalp, bone, and surrounding parenchyma during MRgFUS treatment in order to prevent unwanted thermal lesions and improve the targeting algorithm at the focus.

***Low-intensity ultrasound*:** When applying LIFUS for the purpose of neuromodulation, the effects of heating are negligible since a single low-powered transducer is used. Interestingly, no human study has collected structural neuroimaging data from a subject after receiving LIFUS. Such data would be of importantance to support the hypothesis that sonication parameters are safe and cause no occult thermal or inflammatory injury. However, a central problem in achieving precise neuromodulation is the poorly-understood effects of skull topology and density on the shape of the ultrasound focus. Computer simulations of single-element ultrasound propagation in the human skull have shown that skull thickness variation as small as 1 mm can produce complex effects such as distant standing waves, significant shifting of the acoustic beam and a 20% change in intensity at the focus (Robertson et al., 2017). Skull aberrations, variability in transducer placement, and methodological heterogeneity between experiments might explain some of the discrepancies in results found in recent human LIFUS literature. For instance, when sonicating the motor cortex, (Legon et al., 2018) found suppression of TMS-elicited motor-evoked potentials, as well as attenuation of intracortical facilitation compared to sham. In contrast, Gibson et al. (2018) found that targeting the motor cortex resulted in increased cortical excitability and heightened TMS-induced motor-evoked potentials. Importantly, the studies used different sonication parameters and timing of ultrasound delivery. Future trials should systematically examine the individual contribution of frequency, pulse timing, intensity, and total sonication time to neuromodulatory effects.

Conclusions: Ultrasound technology is emerging as a valuable addition to the armamentarium of neurosurgeons and neuroscientists. As a noninvasive option for treating movement disorders, MRgFUS has efficacy and durability comparable to surgery, with none of the hardware-related complications. Other experimental indications for MRgFUS lesioning include tumor ablation, obstructive hydrocephalus, and thrombolysis (Lee et al., 2019). Meanwhile, LIFUS is being explored for its ability to precisely modulate brain circuits noninvasively. More preclinical studies are needed to ascertain the complex effects of the skull on the ultrasound beam, as well as the long-term behaviour of neural tissue when exposed to acoustic waves.

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Anton Fomenko, Andres M. Lozano*
Krembil Research Institute, University Health Network, Toronto, Canada (Fomenko A, Lozano AM)
Division of Neurosurgery, Toronto Western Hospital, Toronto, Canada (Lozano AM)

***Correspondence to:** Andres M. Lozano, MD, PhD, Andres.Lozano@uhnresearch.ca.*
***orcid:** 0000-0001-8257-3694 (Andres M. Lozano)*
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