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Editorial: Magnetic Resonance-Guided Focused Ultrasound: Physical Principles and Biomedical Applications

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Editorial on the Research Topic

Magnetic Resonance-Guided Focused Ultrasound: Physical Principles and Biomedical Applications

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Magnetic resonance-guided focused ultrasound (MRgFUS) is a non-invasive technique used in more than ninety clinical trials as an alternative to standard treatments for neurological, oncological and musculoskeletal diseases. Indeed, magnetic resonance (MR)-guidance allows targeted treatments through a wide range of focused ultrasound (FUS) intensities inducing mechanical, thermal, and neuroelectric effects on the tissue while preserving surrounding organs-at-risk. This Research Topic gathered contributions from experts in MRgFUS and summarized recent and impactful results supporting clinical and preclinical research obtained with high and low acoustic intensities regimes.

The application of MR-guidance in thermal ablations through high-intensity focused ultrasound (HIFU) is currently the subject of a number of studies and clinical trials aiming at treating medically refractory essential tremor, Parkinson's disease, neuropathic pain [1] as well as breast, liver, prostate, and brain cancers [2]. Gagliardo et al. present a retrospective analysis of patient- and sonication-related parameters in a group of patients undergoing unilateral ventral intermediate nucleus (Vim) thalamotomy through HIFU using a system integrated into a 1.5-T magnetic resonance imaging (MRI) unit. Their results confirm that the skull density ratio (SDR) is critical in determining thermal effects induced during sonication. Also, the authors suggest that energy deposition and SDR dependence need careful consideration and should be prescribed in a personalized manner.

At the other end of the acoustic spectrum, low-intensity focused ultrasound (LIFU) is frequently used under MR-guidance for locally and reversibly eliciting excitatory and inhibitory neuromodulation [3, 4] or to facilitate drug and gene delivery through the permeabilization of the blood-brain barrier (BBB) [5–9]. The emergent idea of using FUS to modulate brain activity and neurovascular coupling demonstrates great potential to help understand brain functioning and treat brain diseases. Kamimura et al. describe the main potential mechanisms of ultrasound-based neuromodulation and how combining MRI with multimodal stimulation approaches can help advance the field. There are multiple hypotheses about the potential mechanisms through which ultrasound induces neuromodulation, mainly based on depolarization through mechanical

deformation of the cell membrane and heat deposition. Other forms of ultrasound interactions with tissue can also be obtained with non-linear frequency mixing [10] generated by specifically designed transducers [11]. In this context, multimodal stimulation, coupled with neuroelectric or MRI, may provide an opportunity to understand the multiple factors that play a role in neuron functioning and how FUS interferes with it. In turn, this may elucidate the spatial and temporal scales of the mechanisms of action involved, the differential effect of FUS neuromodulation on different types of brain cells, and therefore the role of specific white matter pathways to neuronal network dynamics and animal behavior. In addition, a multimodal approach involving the combination of genetic, magnetic, ultrasonic, and other stimulation techniques to excite, inhibit, or regulate neuronal activity could be beneficial for both main symptoms and comorbidities. In turn, this may lead to patient-specific customization of neuromodulation interventions according to overall anamnestic picture. Furthermore, the use of MRI can provide insights into brain structure and activity and hence support FUS-based neuromodulation through targeting, safety evaluation, and the evaluation of brain function and mechanisms.

The intersection of engineering and health science enables the investigation of FUS's ability to interfere with brain activity in a safe, customized, and non-invasive manner. FUS can probe spatially specific brain regions non-invasively [4, 12], and in the case of peripheral nerves, the pulsing regime dictates excitatory or inhibitory effects [13–16]. Pouget et al. demonstrate that transcranial ultrasound stimulation using a repetitive pulse sequence can modulate the visuo-motor behavior of non-human primates, demonstrating for the first time that repetitive transcranial ultrasound (rTUS) assisted by neuronavigation [17] can have a sustained effect on monkey behavior with a quantified return-time to baseline (18–31 min).

Since its discovery in 2001, MR-guided LIFU-induced drug delivery has received widespread attention. LIFU, in conjunction with intravenously injected gas-encasing microbubbles (MBs), can reversibly disrupt the blood-brain barrier (BBB), hence allowing the targeted delivery of drugs or other active biological molecules in the brain. Conti et al. revise the state of the art in current MRI hardware and methods used in BBB opening protocols both in preclinical and clinical settings. The authors show that FUS systems developed for preclinical experiments are mostly constituted by single-element transducers, compatible with MRI field strength between 7T and 9.4T [8, 18, 19]. On the other hand, most clinical trials use a commercial 1024-element US phased array (INSIGHTEC, Haifa, Israel), which can be integrated into MRI scanners operating both at 1.5T and 3T [20]. These systems allow the delivery of nanometer-scale particles to the brain tissue [21, 22] to treat amyotrophic lateral sclerosis [23], Alzheimer's and Parkinson's disease [20, 24], as well as glioblastoma [25].

Cancer therapy can also be enhanced by applying MR-guided LIFU to deliver nanovectors capable of encapsulating drugs and releasing them following acoustic stimuli. Patrucco and Terreno

present an overview of preclinical studies illustrating the *in vivo* potential of MRI-guided drug release protocols triggered by thermal and mechanical ultrasound-induced effects, where MRI is used to monitor release processes but also to evaluate therapeutic outcomes.

Microbubble specifications play a major role in LIFU-induced BBB disruption [26]. Originally designed as imaging contrast agents, microbubbles can be engineered specifically for therapeutic applications with increased stability and penetration into the blood or loaded with MRI contrast agents to image their biodistribution [27]. Also, microbubble characteristics such as size, concentration, gas and shell composition, dissolution, and clearance rate can influence BBB permeability and inflammatory response [28]. Pouliopoulos et al. describe an original study on the temporal stability of lipid-shelled microbubbles during therapeutic LIFU exposure. Storage time decreases *in vitro* microbubble stability, reducing stable cavitation response and promoting microbubble collapse. Considering the natural concentration decay of their microbubbles, the authors demonstrate that efficient BBB opening could be performed over a period of 3 weeks after homemade microbubble activation. These findings suggest that repeated treatments using stored microbubbles are possible for both pre-clinical and clinical applications over several weeks.

Although most parts of MR-compatible US systems are developed to exploit MR images for US targeting, planning and confirmation, MR-compatible acoustic instrumentation can also be used for developing multimodal imaging improving both spatial and temporal resolution of MR and ultrasound imaging [29]. Hasegawa et al. present a flexible-shape ultrasonic array probe suitable for ultrasonic imaging of the brain and compatible with high-field MR environments. This probe can be easily adapted to fit head shape while its curved-surface and, in turn, the coordinates of the elements can be employed to correct B-mode images.

In conclusion, this Research Topic illustrates different uses of MR-guidance for FUS-based therapeutic strategies. MR is mostly used to create treatment planning and confirm targeting. In contrast, US can be used in manifold ways, e.g., by exploiting high intensities for non-invasive surgery or by inducing through low intensity, transient modulation of vasculature permeability and neural activity.

The ever-increasing use of various MRgFUS techniques for surgery and drug delivery suggests that we will witness their swift introduction into novel experimental clinical paradigms, as recently demonstrated by novel HIFU application such as e.g., in treatment of brain tumors, stroke, epilepsy, pain, and functional disorders as well as by LIFU applications for immunotherapy, gene, and cell therapy [30, 31].

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AC, HK, NT, and AN made contributions about the papers they edited. All authors drafted and revised the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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