Transcranial magnetic resonance-guided focused ultrasound indications

- Transcranial magnetic resonance-guided focused ultrasound for neurological applications: industry challenges, innovations, and future directions
- Intraprocedural Three-Dimensional Imaging Registration Optimizes Magnetic Resonance Imaging-Guided Focused Ultrasound and Facilitates Novel Applications
- State of Practice on Transcranial MR-Guided Focused Ultrasound: A Report from the ASNR Standards and Guidelines Committee and ACR Commission on Neuroradiology Workgroup
- Clinical neurophysiology in the treatment of movement disorders: IFCN handbook chapter
- Cavitation Feedback Control of Focused Ultrasound Blood-Brain Barrier Opening for Drug Delivery in Patients with Parkinson's Disease
- Update in the clinical application of focused ultrasound
- Role of deep brain stimulation in management of psychiatric disorders
- DBS, tcMRgFUS, and gamma knife radiosurgery for the treatment of essential tremor: a systematic review on techniques, indications, and current applications

Since then advances in phased array transducers and magnetic resonance imaging technology have resurrected the ultrasound as a noninvasive therapeutic for a plethora of neurological conditions ranging from embolic stroke and intracranial hemorrhage to movement disorders and brain tumors. In the same way that stereotactic radiosurgery has fundamentally changed the scope and treatment paradigms of tumor and specifically skull base surgery, focused ultrasound has a similar potential to revolutionize the field of neurological surgery. In addition, focused ultrasound comes without the general complexity or the risks of ionizing radiation that accompany radiosurgery. As the quest for minimally invasive and noninvasive therapeutics continues to define the new neurosurgery, the focused ultrasound evolves to join the neurosurgical armamentarium [1].

In contrast to traditional ablative interventions, transcranial MRgFUS surgery is entirely imaging-guided and uses continuous temperature measurements at the target and surrounding tissue taken in real-time. Unlike Gamma Knife radiosurgery, MRgFUS surgery can make a lesion immediately and does not use ionizing radiation. Moreover, since no metallic device is implanted, MR imaging-based diagnosis is not restricted throughout life.

The objective of the research in the last decade was to be able to apply FUS also to the treatment of intracranial neoplastic diseases, using both the thermal effects (thermal ablation) and, above all, the ability to permeabilize Blood Brain Barrier (BBB) and modify the tumor microenvironment. This may allow the use of drugs that are currently poorly active on the CNS or active at high doses and selectively, minimizing the side effects and substantially modifying the prognosis of patients affected by these diseases. In the future, targeted drug delivery, immunotherapy and gene therapy will probably become main players in the treatment of brain neoplasms, finding a precious aid in MRgFUS. In this way, it will be possible to directly intervene on tumor cells while preserving healthy tissue at the same time [2].

Magnetic resonance imaging-guided focused ultrasound surgery (MRgFUS) is especially appealing for applications in the brain where target volumes have to be accessed with high precision without

inflicting collateral damage to surrounding healthy tissue. In 2013 a MRgFUS system was CE certified for the treatment of functional neurological disorders, such as chronic neuropathic pain and movement disorders. Currently, some 400 patients have been treated worldwide using this system, which is also undergoing clinical testing for the treatment of primary brain tumors and brain metastases [3)].

The MRgFUS procedure is clinically established in particular for the treatment of symptomatic uterine fibroids, followed by palliative ablation of painful bone metastases. Furthermore, promising results have been shown for the treatment of adenomyosis, malignant tumors of the prostate, breast and liver and for various intracranial applications, such as thermal ablation of brain tumors, functional neurosurgery and transient disruption of the blood-brain barrier [4)].

For transcranial brain therapy, the skull bone is a major limitation, however, new adaptive techniques of phase correction for focusing ultrasound through the skull have recently been implemented by research systems, paving the way for HIFU therapy to become an interesting alternative to brain surgery and radiotherapy [5)].

The thermal injury to nervous tissue within a specific threshold of 50°C to 60°C with the tissue near the sonication center yielding the greatest effect; adjacent tissue showed minimal changes. Additional studies utilizing this technology are required to further establish accurate threshold parameters for optic nerve thermo-ablation [6)].

Future clinical applications of magnetic resonance imaging-guided high-intensity focused ultrasound (MRgHIFU) are moving toward the management of different intracranial pathologies.

Transcranial focused ultrasound (FUS) can noninvasively transmit acoustic energy with a high degree of accuracy and safety to targets and regions within the brain.

Transcranial focused ultrasound (tcFUS) is an attractive noninvasive modality for neurosurgical interventions. The presence of the skull, however, compromises the efficiency of tcFUS therapy, as its heterogeneous nature and acoustic characteristics induce significant distortion of the acoustic energy deposition, focal shifts, and thermal gain decrease. Phased-array transducers allow for partial compensation of skull-induced aberrations by application of precalculated phase and amplitude corrections.

Technological advances, including phased-array transducers and real-time temperature monitoring with magnetic resonance thermometry, have created new opportunities for FUS research and clinical translation.

Simulation-based approaches to calculate aberration corrections may aid in the extension of the tcFUS treatment envelope as well as predict and avoid secondary effects (standing waves, skull heating). Due to their superior performance, simulationbased techniques may prove invaluable in the amelioration of skull-induced aberration effects in tcFUS therapy. The next steps are to investigate shear-wave-induced effects in order to reliably exclude secondary hot-spots, and to develop comprehensive uncertainty assessment and validation procedures [7)].

In a report, investigators sought to establish the ability of transcranial focused ultrasound (tFUS) to modulate brain activity in the human primary somatosensory cortex [8)].

see Magnetic resonance guided focused ultrasound

Legon et al employed a single-element tFUS transducer to transmit a 0.5 MHz pulsed wave for 500

ms. The acoustic power of the tFUS waveform used was well below the maximum recommended limit for diagnostic imaging applications. The authors first characterized the acoustic pressure field emitted from the tFUS transducer in an acoustic test-tank. Next, a magnetic resonance imaging-based 3-D simulation model of a human head was created to estimate acoustic field distribution in the brain during tFUS. Ultimately the authors assessed the neuromodulating influence and spatial resolution of tFUS targeted to Brodmann area 3b by examining effects on somatosensory evoked potentials (SEPs) and sensory detection thresholds via within-subjects, sham-controlled, blinded design study of 12 volunteers. Primary endpoints included amplitude of short-latency and late-onset evoked potentials by median nerve stimulation, as well as two-point and frequency discrimination tasks. The focal volume of the ellipsoid acoustic beam produced was 0.21cm3 at 50% maximum intensity line and demonstrated spatial resolution of 4.9mm laterally and 18mm axially when focused through the human skull. Electrophysiologic studies demonstrated that tFUS targeted to Brodmann area 3b significantly reduced the amplitude of short-latency and late-onset evoked cortical activity elicited by median-nerve SEPs. The effects of tFUS on SEP activity were abolished when targeted to brain regions 1 cm posterior or 1 cm anterior to the postcentral gyrus. Functional investigations revealed that tFUS targeted to somatosensory cortex significantly enhanced discrimination of pins at closer distances as well as frequency of air puffs, without affecting response bias or task attention. Additionally, the authors noted that volunteers did not report thermal or mechanical sensations due to tFUS transmission through the scalp. Similarly, there were no reports of perceptual differences between the sham and tFUS conditions. These data demonstrate that a pulsed acoustic beam created by a single-element 0.5-MHz tFUS transducer for 500 ms can be used to transiently and noninvasively modulate neuronal activity in the cortex of humans. tFUS may transiently shift the balance of neuronal activity in favor of local inhibition, perhaps through either dampening thalamocortical excitation or increasing interneuron inhibitory firing. One hypothesis for the paradoxical improvement in somatosensory discrimination provided by the authors is through filtering by local inhibition. In other words, the inhibition produced by tFUS may reduce spatial spread of cortical excitation resulting in restricted neuronal population activation and a more precise cortical representation of tactile stimuli. Although this study provided evidence that the influence of tFUS can be restricted to discrete modules of cortex, it did not elucidate which cellular structures tFUS most affects. Further studies are needed to characterize whether neurophysiologic effects vary according to anatomic location and/or cytoarchitectonic division. One of the most enticing applications of tFUS is the possibility of noninvasive, functional brain mapping of both cortical and sub-cortical structures and circuits. Subablative sonication targeting the ventral intermediate region of the thalamus has already been used to provide functional target confirmation prior to lesioning with MR guided high-intensity FUS. However, the current study highlights the nondestructive capabilities of tFUS and inspires exploration of potential applications in both the research and clinical settings. [9].

High Intensity focused ultrasound (HIFU) is a novel, totally non-invasive, image guided therapy that allow for achieving tissue destruction with the application of focused ultrasound at high intensity. This technique has been successfully applied for the treatment of a large variety of diseases, including oncological and non-oncological diseases. One of the most fascinating aspects of image-guided ablations, and particularly of HIFU, is the reported possibility of determining a sort of stimulation of the immune system, with an unexpected “systemic” response to treatments designed to be “local” [10].

Focused Ultrasound (FUS), in conjunction with microbubbles, is the only technique that can induce localized blood brain barrier opening noninvasively and regionally. FUS may thus have a huge impact in trans-BBB brain drug delivery. The primary objective is to elucidate the interactions between ultrasound, microbubbles and the local microenvironment during BBB opening with FUS, which are responsible for inducing the BBB disruption. The mechanism of the BBB opening in vivo is monitored

through the MRI and passive cavitation detection (PCD), and the safety of BBB disruption is assessed using H&E histology at distinct pressures, pulse lengths and microbubble diameters. It is hereby shown that the BBB can be disrupted safely and transiently under specific acoustic pressures (under 0.45 MPa) and microbubble (diameter under 8 µm) conditions [11)].

Ultrasound-induced opening of the BBB significantly enhances the intracerebral concentration of both temozolomide (TMZ) and irinotecan (CPT-11) CPT-11 in rabbits [12)].

The effects of focused ultrasound (FUS) on neuronal activity have been studied since the 1920s, and in animals have been shown to modulate activity of peripheral nerves, the retina, spinal reflexes, hippocampus, and motor cortex.

Unlike high intensity, continuous ultrasound (US), FUS can exert nondestructive mechanical pressure effects on cellular membranes and ion channels without producing cavitation and thermal injury. Animal studies have demonstrated the ability of FUS to reversibly suppress visual evoked potentials, modulate activity of the frontal eye fields, and disrupt seizure activity, all in the absence of cellular damage.

Advances in transcranial Magnetic resonance guided focused ultrasound have renewed interest in lesioning procedures in functional neurosurgery with a potential role in the treatment of neurological conditions such as chronic pain, brain tumours, movement disorders and psychiatric diseases. While the use of transcranial MRI-guided focused ultrasound represents a new innovation in neurosurgery, ultrasound has been used in neurosurgery very earlier [13)].

A transcranial MRgFUS system has been developed for treatment of brain lesions through an intact skull [14)].

The method is currently limited to central brain targets due to skull heating and other factors. An alternative ablative approach combines very low intensity ultrasound bursts and an intravenously administered microbubble agent to locally destroy the vasculature.

It is feasible to use a clinical TcMRgFUS system to ablate skull base targets in nonhuman primates at time-averaged acoustic power levels at least 2 orders of magnitude below what is needed for thermal ablation with this device. The results point to the risks associated with the method if the exposure levels are not carefully controlled to avoid inertial cavitation in the acoustic beam path. If methods can be developed to provide this control, this nonthermal approach could greatly expand the use of TcMRgFUS for precisely targeted ablation to locations across the entire brain [15)].

Despite its limits (temperature, vascularization), the human cadaver model is effective for studying the accuracy of MRgHIFU brain therapy. With the 1-MHz system investigated here, there is millimetric accuracy [16)].

Magnetic resonance guided focused ultrasound has been developed as a less-invasive surgical tool aimed to precisely generate focal thermal lesions in the brain.

Magnetic resonance guided Laser interstitial thermotherapy (MRgLITT) has become an increasingly relevant therapy for tumor ablation due to its minimally invasive approach and broad applicability

across many tissue types. The current state of the art applies laser irradiation via cooled optical fiber applicators in order to generate ablative heat and necrosis in tumor tissue. Magnetic resonance temperature imaging (MRTI) is used concurrently with this therapy to plan treatments and visualize tumor necrosis. Though application in neurosurgery remains in its infancy, MRgLITT has been found to be a promising therapy for many types of brain tumors [17].

see Stereotactic guided laser interstitial thermotherapy.

Transcranial magnetic resonance-guided focused ultrasound for Parkinson's disease

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Transcranial magnetic resonance-guided focused ultrasound for tremor

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Pain

This system is used to treat patients with central neuropathic pain [18] [19].

Neurooncology

see High Intensity focused ultrasound for tumor.

Epilepsy

MRgFUS thermal ablation of the mesial temporal lobe structures relevant in temporal lobe epilepsy is feasible in a laboratory model. Longer sonications were required to achieve temperatures that would create permanent lesions in brain tissue. Heating of the skull base occurred with longer sonications. Blocking algorithms would be required to restrict ultrasound beams causing skull base heating. In the future, MRgFUS may present a minimally invasive, non-ionizing treatment of MTLE [20].

Blood brain barrier disruption

Transcranial focused ultrasound exposure in the presence of microbubbles was used to open the blood-brain barrier (BBB) to enhance bevacizumab penetration into the CNS in healthy and glioma-

bearing mice. Bevacizumab concentration was quantitated with high-performance liquid chromatography, and Western blot testing was performed to confirm the specific biologic form in the CNS. Penetration of bevacizumab into brain tissue was estimated in vivo by means of contrast material-enhanced MR imaging and quantitative gallium 68 (68Ga)-bevacizumab micro-positron emission tomography, and glioma progression was longitudinally followed with T2-weighted MR imaging. Hematoxylin-eosin staining and cluster of differentiation 31 immunostaining were used to assess morphologic changes and vascular inhibition at histologic examination. The two-tailed Student t test and the Mantel-Cox log-rank test were used for statistical analyses, with a significance level of .05. Results Focused ultrasound significantly enhanced bevacizumab penetration into the CNS by 5.7- to 56.7-fold compared with that in nonexposed brain (both P < .0001). Contrast-enhanced MR imaging indexes correlated with bevacizumab concentration (r = 0.748-0.857) in vivo. Focused ultrasound-enhanced bevacizumab delivery significantly retarded glioma progression, with a significantly increased median survival (median increase in survival time = 135% in the group treated with bevacizumab and focused ultrasound, P < .0001; as compared with 48% in the group treated with bevacizumab alone, P = .0002).

Focused ultrasound-enhanced bevacizumab delivery can provide an antivascularization normalization effect to suppress glioma [21].

A separate area focuses on the enhancement of the permeability of the blood brain barrier to various substances driven by focused ultrasound. The possibilities of enhancing the permeability to chemotherapeutic agents, immune drugs, and other substances are being investigated in laboratories. A large number of studies focus on treatment of Alzheimer disease. clinical trials aimed at enhancing the permeability of the blood-brain barrier to chemotherapeutic agents have been initiated. Reversible neuromodulating, stimulating, and inhibiting effect of focused ultrasound on the nervous system structures is another non-destructive effect, which is currently being actively investigated in animals. Furthermore, laboratory studies demonstrated the ability of focused ultrasound to destroy blood clots and thrombi. Transcranial focused ultrasound provides numerous unique possibilities for scientific and practical medicine. Large-scale research is required prior to the widespread clinical implementation. Nevertheless, we can already state that implementation of this technique will significantly enhance diagnostic and therapeutic potential of neurosurgery and neurology [22].

Huang et al developed and test a protocol in preparation for a clinical trial on opening the blood-brain barrier (BBB) with magnetic resonance (MR) imaging-guided focused ultrasound for the delivery of chemotherapy drugs to brain tumors. Materials and Methods The procedures were approved by the institutional animal care committee. A trans-human skull porcine model was designed for the preclinical testing. Wide craniotomies were applied in 11 pigs (weight, approximately 15 kg). A partial human skull was positioned over the animal's brain. A modified clinical MR imaging-guided focused ultrasound brain system was used with a 3.0-T MR unit. The ultrasound beam was steered during sonications over a 3 × 3 grid at 3-mm spacing. Acoustic power levels of 3-20 W were tested. Bolus injections of microbubbles at 4 µL/kg were tested for each sonication. Levels of BBB opening, hemorrhage, and cavitation signal were measured with MR imaging, histologic examination, and cavitation receivers, respectively. A cavitation safety algorithm was developed on the basis of logistic regression of the measurements and tested to minimize the risk of hemorrhage. Results BBB openings of approximately 1 cm3 in volume were visualized with gadolinium-enhanced MR imaging

after sonication at an acoustic power of approximately 5 W. Gross examination of histologic specimens helped confirm Evans blue (bound to macromolecule albumin) extravasation, and hematoxylin-eosin staining helped detect only scattered extravasation of red blood cells. In cases where cavitation signals were higher than thresholds, sonications were terminated immediately without causing hemorrhage.

With a trans-human skull porcine model, this study demonstrated BBB opening with a 230-kHz system in preparation for a clinical trial [23].

A study took advantage of the ability of low-intensity focused ultrasound (FUS) to transiently disrupt the blood-brain barrier (BBB) to deliver a neurotoxin with poor BBB permeability (quinolinic acid [QA]) in a guided manner to a target region in the brain parenchyma. Ten male Sprague-Dawley rats were divided into two groups receiving the following treatments: (i) magnetic resonance-guided FUS + microbubbles + saline (n = 5), or (ii) magnetic resonance-guided FUS + microbubbles + QA (n = 5). Systemic administration of QA was well tolerated. However, when QA and microbubbles were systemically administered in conjunction with magnetic resonance-guided FUS, the BBB was disrupted and primary neurons were destroyed in the targeted subregion of the hippocampus in all QA-treated animals. Administration of vehicle (saline) together with microbubbles and FUS also disrupted the BBB but did not produce neuronal injury. These findings indicate the feasibility of non-invasively destroying a targeted region of the brain parenchyma using low-intensity FUS together with systemic administration of microbubbles and a neurotoxin. This approach could be of therapeutic value in various disorders in which disturbances of neural circuitry contribute to neurologic disease [24].

Spine

A work introduces usage of an ex-vivo Thiel embalmed human tissue model for preclinical verification of MRgFUS on intervertebral discs or bone metastases within the spinal body.

Thiel embalmed human cadaver was subjected to FUS sonication of the vertebra (with energies 250J, 420J, 600J) and the intervertebral disc (with energies 310J, 610J, 950J) of the lumbar spine for 20s of sonication under MR guidance.

For the vertebra, maximum temperatures were recorded as 38 °C, 58.3 °C, 69 °C. The intervertebral disc reached maximum temperatures of 23.7 °C, 54 °C, 83 °C. The temperature measurements showed that the spinal canal and adjacent organs were not heated > 0.1 °C.

A heating pattern that can induce thermal ablation was achieved in the vertebral body and the intervertebral disc. Adjacent structures and nerves were not heated in lethal levels. Thus, the Thiel embalmed human cadaver can be a safe and efficient model for preclinical study of application of MRgFUS on the upper lumbar spine [25].

Transcranial magnetic resonance-guided focused ultrasound for dystonia

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