Focused Ultrasound for Brain Diseases: A Review of Current Applications and Future Perspectives

Focused Ultrasound for brain diseases: a review of current applications and future perspectives

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1. Background

The non-invasive treatment of intra-cranial targets, either consisting of pathological processes or malfunctioning physiologic structures, has always been an established priority. Other than pharmacological solutions, a variety of technologies have been developed in the last few centuries, encompassing radiotherapy and radiosurgery, electroconvulsive therapy and deep brain stimulation[1,2]. Focused Ultrasound (FUS) technology represents a rather novel endeavor, albeit its roots go back to the first half of the 20th century[3,4]. Focused Ultrasound, with respect to the other strategies proposed to non-invasively treat intra-cranial targets, has the advantage of being a non-invasive, extracorporeal, and non-ionizing treatment modality.

The idea of using focused ultrasound to induce thermal ablation dates back to the 1940s when John G. Lynn was the first to propose that ultrasound could be focused to produce lesions in tissue and successfully managed to produce lesions deep in bovine liver without damaging surrounding tissue.[5] However, the first attempts at translating this technology to the central nervous system (CNS) were hindered by the presence of the skull bone, shielding the parenchyma from the penetration of US waves;[4] indeed, the Fry brothers in 1955 had to resort to a craniotomic access to perform the very first ablation of basal ganglia by means of a 4-tranducers array[6]. In 1987, Tobias proposed to increase the penetrance of therapeutic ultrasound in the brain via the substitution of a part of the cranial vault with a biocompatible material that would both protect the brain and allow for ultrasound hyperthermal therapy, overcoming the attenuation artefact discussed above. The Authors evaluated the efficacy of 4 different plastic materials; the best performing material (HDPE, allowing 88% of energy transmission) was then tested on animals to assess the feasibility for ultrasound hyperthermal therapy *in vivo*. The results were encouraging with stable increase in temperature at the target site without neurological damage; but for some reasons this study did not prompt any enthusiasm towards the possibility of ultrasound-translucent implants for human use.[7]

The introduction of MR-guided treatments in 1993[8] was a pivotal moment for the technology and the term Magnetic Resonance Imaging-guided FUS was coined (MRgFUS); indeed, not only does MRI provide excellent spatial resolution of intracranial structures, but nowadays also allows the detection of real-time temperature changes with high accuracy, in order to avoid unwanted surrounding tissue damage[9]. However, the first neurosurgical applications were delayed until the early 2000s, due to the unsolved problem of the skull acoustic attenuation[8,10]. Only in 2004 was this obstacle overcome, when phased-array transducers and distortion-corrective algorithms were introduced[11].

Nowadays, FUS treatments may be applied through different approaches and devices:[4] undoubtedly, MRI-guided suites are the most employed and complete systems, as they provide the highest precision as well as real-time monitoring of thermal effects of US waves.[12,13] MRgFUS surely is the mainstay of current US-based treatments, notwithstanding the obvious limitations represented by the need for a whole MRI suite, long treatment times and restricted target volume; however, in the last few years the FUS community has developed new concepts and approaches to US-based therapies: navigated FUS transducers, as an example, represent a more agile and readily-available device, that do not need an operating room with an intra-operative MRI to

function. This is possible because the focused ultrasound beam is guided by neuro-navigation systems which are routinely used in neurosurgical practice. [14,15]In addition, navigated FUS mounts a phased-array transducer comparable to the one employed in MR-guided systems. This allows navigated FUS systems to perform accurate steering and focusing to reach precise targets without moving the ultrasound probe , as well as phase correction of skull aberrances.

In addition to MR-guided and navigated FUS devices, another system was developed for neuro-oncological purposes, specifically to perform US-mediated the blood-brain barrier (BBB) opening, to transiently increase the permeability of the brain to substances, such as chemotherapeutics. The strategy to avoid the aforementioned attenuation effect exerted by the skull on US waves, is to implant the US-transducer into the calvarium[16–18]. The device was developed to perform BBB-opening on patients harboring brain tumors; hence, even if it has to be implanted with a surgical procedure, usually this is done during the surgical debulking of the tumor. If there is no indication to tumor debulking surgery, the device can be implanted during a dedicated surgical procedure in an ambulatory fashion under local anesthesia. Once the device is in place, to activate the device, a transdermal needle connection device is connected to the implant and plugged into a proprietary external radiofrequency (RF) generator. However, an initial surgical procedure is necessary for device implantation, and the treatment radius is fixed and not adjustable, thus it is only optimal for single and superficial lesions, whereas extracranial devices may be employed for multiple and deep targets[19]. A recent trial (NCT02253212) reported the safety and efficacy of an implantable, pulsed US device with microbubble injection to disrupt the blood-brain barrier in association with carboplatin administration in 21 patients with recurrent GBM. Interestingly, within the endeavor of implantable devices lies a rather innovative concept of therapeutic US, which encompasses an unfocused beam of US waves in combination with intravenous injection of a microbubble agent to achieve diffuse mechanical and biological effects rather than focused to pinpoint targets.

Most recently, a novel approach has been proposed to perform repeated FUS-based treatments with real-time US guidance for intracranial lesions, which maintain the advantages of implantable devices while overcoming the aforementioned limitations[20–22]: indeed, the idea of an implantable acoustic window to perform ultrasonic therapies -and specifically ablation of deep-seated pathologies- dates back to 1987[7]. However, the recent introduction in the neurosurgical practice of intraoperative ultrasonography with its latest technological advancements, and the consequent development of a cerebral US semeiology[23,24], has opened the possibility of performing both imaging and therapy through cranioplastic implants, as long as the employed materials are proven to produce only minimal distortion of the US beams. Alongside commonly used materials, such as PEEK or PMMA, recent studies proposed novel low-porosity and low-density materials specifically designed to allow the unhindered penetration of US waves[20,25].

Such approach, by decoupling the implanted device from the transducer, may improve the adaptability of the treatment to the evolution of the pathology, being also theoretically compatible to any external device, such a

navigation-based one. Moreover, trans-prosthesis US multimodal imaging may provide a new instrument for non-invasive and less cumbersome guidance of ultrasonic treatments.

Over the course of the years, FUS has found its way for the treatment of a wide range of brain pathologies, ranging from tumors to functional and psychiatric disorders, in both an ablative and non-ablative fashion according to the mechanisms of action discussed in the following paragraphs[26].

1.1. High intensity FUS

High intensity FUS (HIFU) takes advantage of its heat generating properties to perform thermal ablation to the target volume. Thermal ablation is the direct consequence of the frictional molecular vibration caused by US waves; on a smaller scale, non-linear wave propagation is another source of heat. Therefore, protein denaturation, metabolic arrest and cell death occur, leaving however a well-defined border between target and non-target cells. The temperature rise in the affected tissue occurs in a matter of seconds, depending on the intensity of the US beam, on the acoustic absorption coefficient of the tissue and on the treatment duration. [27,28] A single application may be sufficient for small volumes, however larger lesions may require repeated treatments of overlapping areas.[29] Depending on the temperature reached in target tissues different biological effects can be observed, the threshold is usually set at 55°C. At energy doses that yield a temperature lower than 55°C, hyperthermia leads to increased cellular permeability, increasing the delivery of nanoparticles via thermally modulated carrier molecules.[30] At higher energy doses resulting in a temperature that exceeds the threshold, coagulative necrosis can be observed; this state of necrotic cell death is useful in tumor ablative therapies. [30] For this reason, it is important to differentiate between hyperthermia (HT) and thermal ablation (TA). HT, as a general concept, refers to the procedure of rising tissue temperature to 40-45°C for various lengths of time (up to 60 minutes) (Hurwitz and Stauffer 2014). HT has been extensively studied and has been demonstrated to increase the efficacy of chemotherapy and radiation therapy in a plethora of solid tumors. On the other hand, TA occurs at higher temperature values (< 55°C) and is a procedure used to create ablative lesions in punctuate areas of tissue. Recent FUS systems are able to cause both HT and TA; regarding brain applications of FUS, the modality that yielded most results is FUS-induced thermal ablation.

The procedure is usually executed under MRI guidance (MRgFUS) in order to obtain real time temperature and volume monitoring. As previously discussed, MR-guided systems can achieve great precision at the cost of being expensive and time-consuming; hence the procedure must follow specific steps to be successful. First, a CT scan is performed prior to treatment to assess the inconsistencies of bone thickness that may impact the US beam trajectory. In particular, the Skull Density Ratio (SDR) is measured to correct the transducers' phase, improving the accuracy of the US waves reaching the target. The SDR is defined as the overall ratio in Hounsfield units between the spongy and the compact component of the skull bone. It ranges between 0 and 1, with values approaching 1 corresponding to less discrepancies and vice versa; values above 0.4 are preferable for the treatment, since higher SDRs are more likely to achieve high temperatures in target tissues.[31] The CT scan may also identify structures which can hinder US waves passage, such as frontal sinuses, choroid plexuses, falx, and pineal gland. If found, these structures are then marked in the planning software as no-pass

regions.[32] The patient is also subjected to a preoperative MRI scan to study the target volume. Once shaved, as the hair prevents optimal US delivery, the patient's head is placed in a stereotactic frame, specifically customized to be compatible with the transducer and the MRI. The transducer features multi phased-array systems that allow a superior versatility when it comes to targeting the volume area, and to adjusting the focus in real time, which is a desirable trait in larger target volumes. In addition, phased-arrays provide the possibility of correcting the US beam according to the SDR. [33] To achieve so, another MRI is performed, and the images are overlapped with the preoperative CT, so that correct sonication is achieved through SDR-correcting algorithms. [32]

Treatment is divided into 3 steps: alignment, target confirmation and sonication. The alignment is achieved through low-energy FUS in order to create a thermal rise between 40C and 45C that can be spotted via 2D MR thermography. Anterior-posterior, medial-lateral and superior-inferior orientations are checked. If the zeroing is off, the transducer can be shifted via the software. Once optimal alignment is reached, target confirmation is ensured by increasing temperature to values slightly above 50°C and monitoring potential neurological changes due to sonication of the affected area. Finally, thermal ablation may begin by exceeding the threshold value of 55°C that was previously discussed.[32] During the procedure, MRI imaging provides real time information on the affected area, which are crucial to prevent heat-related damage and unwanted cavitation to the surrounding healthy tissues[27,34]. At the end of the sonication protocol, a final MRI acquisition is performed to confirm a successful ablation, which appears as a T2 hyperintense spot. [32] Possible complications include intraoperative head pain, unwanted damage and cavitation, inability to achieve high temperatures and patient movement.

HIFU mediated theramal-ablation is mainly used in neuro-oncology and functional neurosurgery settings. Regarding its application in neuro-oncology, the primary objective of tumor ablation is the focused destruction of malignant parenchyma while avoiding any unwanted damage to the surrounding tissues.[2] In 2006, MRgFUS was used for the first time in an attempt to ablate a glioblastoma multiforme (GBM), although with limited success due to power restrictions. [35] In 2014, a recurrent GBM was successfully treated for the first time, without neurological deficits or side effects.[36] There are two main limitations when using MRgFUS: the bone acoustic attenuation still represents an obstacle and skull base or superficial lesions are still not targetable; additionally, while a focused beam enhances precision, the target volume is limited and subsequent sonication protocols may be required for larger lesions.[29] US contrast agents (USCA), in the form of microbubbles, may be used alongside MRgFUS to reach a better postoperative result. It has been shown that administration of microbubbles-based US contrast agent lowers the wave energy threshold to cause lesions in rabbit brains. As a matter of fact, FUS induced microbubbles act as cavitation nucleation sites and they may enhance tissue damage and favor tissue heating, thus lowering the time frame and overcoming skull heating.[37] There are currently three ongoing trials (NCT03028246, NCT00147056, NCT01473485) to prove MRgFUS as a safe and effective treatment option for brain tumors. One trial (NCT01698437) is concluded, but results are not available yet.

In functional neurosurgery, HIFU-mediated thermal ablation can be applied to different clinical scenarios, such as essential tremor (ET), Parkinson's disease (PD), obsessive-compulsive disorder (OCD), major depressive disorder (MDD) and neuropathic pain.

MRgFUS-mediated thalamotomy on the ventralis intermediate nucleus (VIM) as an alternative treatment for severe ET was first described in a 2013 pilot study by Elias et al, with marked improvement in every patient enrolled in the study.[38] The same result was achieved later in a randomized controlled trial by Elias et al, comparing MRgFUS-mediated thalamotomy with a sham procedure[39]. A recent meta-analysis[40] compared unilateral MRgFUS to unilateral and bilateral DBS. Results showed that while bilateral DBS is significant superior both to unilateral DBS and MRgFUS ($p<0.001$), no significant difference between MRgFUS and unilateral DBS ($p<0.198$) was found, and MRgFUS achieved a significantly better postoperative quality of life improvement than DBS ($p<0.001$). A more recent Japanese multicenter clinical trial[41] confirmed its efficacy and safety.

For refractory PD, deep brain stimulation (DBS) is a valid option targeting the VIM, subthalamic nucleus (STn) and globus pallidus pars interna (GPi)[42]. Thermal ablation with MRgFUS on the same targets has been proposed as an alternative option. A 2017 study[43] showed the results of MRgFUS VIM ablation in 9 PD patients and 3 PD-ET patients: tremor disappearance occurred in 100% of the cases after the procedure; in the 2 years of follow-up, tremor reappeared in 2 PD patients and 2 PD-ET patients, albeit in a much lesser extent and with overall QoL improvement. An open-label pilot study[44] showed the efficacy of MRgFUS STn ablation. while a 2021 meta-analysis[45] comparing MRgFUS and DBS on PD tremor confirmed that MRgFUS is a safe, efficacious and non-inferior to DBS option to improve parkinsonian tremor.

Functional ablation with MRgFUS in psychiatric disorders is also under investigation: MRgFUS targeting the anterior limb of the interior capsule (ALIC) has been recently proposed as an alternative non-invasive option for the treatment of OCD and MDD. In a 2020 phase I trial[46], 6 MDD patients and 6 OCD patients underwent MRgFUS bilateral capsulotomy. No severe side effects were reported. At the 6 months follow-up, 4 OCD patients and 2 MDD patients achieved treatment response. Another study[47] with 5 MDD and 5 OCD patients reached stable or improved results at 12 months in all subjects. Together, these findings suggest that MRgFUS-AC is a safe treatment option for patients with refractory OCD or MDD.

Chronic neuropathic pain is another common condition under scrutiny. In 2009, Martin et al.[48] were the first to use MRgFUS to treat chronic neuropathic pain. Nine patients underwent central lateral thalamotomy (CLT) via MRgFUS and they reported immediate pain relief. A 2020 study[49] demonstrated the safety and the efficacy of MRgFUS-CLT in 8 patients with treatment resistant trigeminal neuralgia (TN), with postoperative pain relief occurring in 78% of the subjects and postoperative paroxysms in 63% of the patients, but with a much lesser intensity.

1.2. Medium and low intensity FUS

While HIFU technology mainly allows to perform ablative treatments, medium and low-intensity focused ultrasound (LIFU) employ mechanical energy of US beams to produce cavitation and acoustic streaming within target tissues without significant temperature raises.

Ultrasound induces pressure variations in a liquid medium that can in turn cause a void, or bubble, to form and subsequently collapse; this process is defined as cavitation. Acoustic cavitation refers generally to the interaction between sound waves and bubbles in liquids, and can be broadly divided into stable and inertial. Inertial cavitation takes place at high pressure amplitudes in the form of bubble formation and collapse, the latter resulting in high temperatures within the bubble, shock wave formation, the emission of light (sonoluminescence) and the formation of fluid jets and turbulent flow.[50,51] In comparison, stable cavitation results in stable oscillation of the bubble size under the influence of the ultrasound field, with microstreaming and shear stresses in the surrounding liquid.[52] The mechanical index (MI) is an approximation of the inertial cavitation threshold: high-MI sonications cause inertial cavitation while low-MI sonications cause stable cavitation. [28,53]

In 2001 Hynynen et al. applied this concept for opening the blood-brain barrier (BBB) in rabbits to allow easier delivery of therapeutics to the CNS.[54] HIFU was used in the first studies, achieving BBB opening but also causing local inflammation and microhemorrhage to the surrounding tissues. The solution was to employ microbubble-based UCAs along with LIFU: microbubbles helped to concentrate the cavitation effect to the intraluminal side of the endothelial wall, and combined with lower energy US, they reduced collateral effects to the local healthy parenchyma.[53,55] Several preclinical studies have demonstrated the enhanced delivery of trastuzumab, anti-amyloid antibodies, liposomal doxorubicin, temozolomide and DNA for gene therapy.[3,56,57] A multicentric trial (NCT03712293) on six GBM patients confirmed that multiple BBB openings along with temozolomide is a safe procedure without short or long-term (15 months) complications, and with a certain degree of increased survival.[58] The disruption of the BBB may not only be employed to enhance the penetration of therapeutics to the CNS[59]: indeed, recent studies have highlighted the possibility to allow the clearance of toxic substances from brain parenchyma, which could be pivotal in both the prevention and long-term treatment of neurodegenerative diseases like Alzheimer disease[60–62]. These concept, which has shown interesting results in preclinical models, is currently under investigation for human subjects.

Liquid biopsy (LB) of intracranial masses represents another potential application of US-induced BBB disruption. Brain tumor-specific DNA and proteins can be isolated in the circulating blood, but the BBB limits the passage and thus the detection of such molecules. It has been theorized that LIFU-induced BBB disruption may increase the circulating levels of such molecules. Preclinical studies have shown that MRgFUS enhances tumor-mRNA levels in murine GBM models.[63] A first-in-human proof of concept study has demonstrated that LIFU can significantly amplify the signal of circulating brain-derived proteins, DNA, and extracellular vesicles, proving the potential of this technology to promote LB for brain tumors.[64]

Sonodynamic therapy is a novel technique that couples LIFU sonication with non-toxic sonosensitizers, substances that enhance the therapeutic effects of ultrasound in tissues. Both ultrasound and sonosensitizers

per se are not able to induce relevant effects, that are only evident when the two components are combined. The most accredited mechanism through which SDT exerts its cytotoxic effects in target tissues is through generation of reactive oxygen species (ROS) which are able to cause damage at the DNA level that leads to cellular apoptosis. Evidence suggests that ROS generation is caused by ultrasound induced cavitation phenomena that release a considerable amount of energy, that in the presence of oxygen and water elicits the formation of reactive oxygen species. [65–67] Some sonosensitizers are tumor-specific, such as 5-aminolevulinic acid (5-ALA) that is routinely used in neurosurgical practice to identify gliomas intraoperatively, thus making sonodynamic therapy particularly effective for neuro-oncological purposes. [34]

Although still unclear, also anti-angiogenetic, enhanced anti-tumor immune response and sonoluminescence effects have been observed [68–71]. Recently a trial evaluating the safety and feasibility of SDT in patients with newly diagnosed cerebral glioblastomas has started recruiting. In this trial patients will be subjected to SDT with 5-ALA before undergoing to the surgical excision of the tumor, the secondary aim of the trial is to evaluate the efficacy of the procedure in terms of tumor regression and degree of cellular necrosis/apoptosis. ((NCT04845919). An additional clinical trial evaluating the safety and efficacy of SDT with 5-ALA in patients harboring recurrent high-grade gliomas is currently recruiting (NCT04559685).

In mammalian subjects, including humans, various studies have described a neuromodulating effect, in particular suppression of somatosensory and visual evoked potentials, EEG activity, seizures. Such results are probably due to the interaction between the FUS-generated mechanical effects and ion channels, enzymes activity and the cell membrane itself, leading to alterations of the neuronal firing rate. Although in a much lesser extent compared to HIFU, slight temperature changes may play a role in the alterations of neuron action potentials. Additionally, these events have been shown to be completely reversible and to be clear of any pathological findings on histological examination.[72] Several trials on the potential therapeutic benefit of LIFU-mediated neuromodulaton for Alzheimer's disease (NCT03347084), epilepsy, Parkinson's disease (NCT01615718) and diseases of consciousness (NCT02522429) are ongoing, but the results are yet to be published. On the other hand, a double-blind study revealed significant anti-nociceptive effects in healthy adults after LIFU sonication on the anterior nuclei of the thalamus.[73] As a matter of fact, in murine models, low-intensity pulsed FUS has been shown to significantly decrease seizure activity that was induced by intraperitoneal injection of pentylenetetrazol.[74] There are two clinical trials currently undergoing: NCT02151175 on LIFU induced suppression of temporal lobe epilepsy; NCT02804230 for the suppression of cortical lob epilepsy. Neuromodulation has also been studied for mood disorders: a double-blind study using EEG-guided FUS targeting the right ventrolateral prefrontal cortex (rVLPFC) showed an increase self-reported mood in healthy adults compared to the baseline. [75]

Several clinical and preclinical studies have proved that FUS, with or without microbubbles, enhances the immune response to brain tumors via multiple mechanisms. Thermal ablation causes necrosis and release of danger molecules, such as ATP, and tumor antigens. Hyperthermia leads to heat-shock-proteins (HSPs) upregulation: HSPs act as intracellular chaperones, being able to bind tumor antigens which are then

endocytosed by antigen-presenting cells (APCs), such as dendritic cells (DCs). Cavitation opens the BBB, facilitating leukocyte extravasation and permeability to inflammatory cytokines, and it disrupts cell membranes, releasing further antigens. The newly released antigens and HSPs are recognized by DCs, leading to the activation and migration of cytotoxic T-lymphocytes and tumor suppression.[27,28,34] These inflammatory molecules were also the subject for a potential immunogenic hepatocellular carcinoma vaccine in murine models: following its administration, an increased DCs, APCs and T-lymphocytes cells activity was reported; additionally, it would elicit a protective effect in naïve models against a tumor challenge.[76] Moreover, FUS-induced hyperthermia increases blood flow and oxygen delivery, boosting malignant cells metabolic activity. As a direct consequence, cells are more susceptible to both chemotherapy and radiotherapy. Additionally, FUS (i) may revert eventual drug-acquired resistances enhancing therapeutic response, and (ii) cause a hyperthermic cytotoxic effect in S-phase cells, which are naturally more resistant to radiotherapy.[77] Along with immunomodulation, this potential option opens the door for another area that may see MRgFUS in a future clinical setting.[34,78]

2. CONCLUSIONS

Despite being quite novel compared to other treatment modalities, focused ultrasound technology is witnessing an exponential growth in the last few years, gaining interest due to its versatility and its potentially wide range of applications, from radical ablative procedures to complex neuromodulation. Although major obstacles have already been surpassed, the greater part of FUS applications are in their clinical or preclinical infancy, and more investigations and clinical trials are needed in order to establish them within clinical practice; however, as the interest in this new technology spreads around the world, their number is expected to grow, and FUS might represent the key for non-invasive treatments of brain pathologies in the near future.

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