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Editorial

Low-intensity focused ultrasound for the treatment of brain diseases: safety and feasibility

Giada Toccaceli[1], Giuseppe Barbagallo[2], Simone Peschillo[3] ✉

1. Endovascular Neurosurgery, Università di Catania, Catania, Italy
2. Neurosurgery Department, Università di Catania, Catania, Italy
3. Endovascular Neurosurgery, Policlinico Umberto I, Rome, Italy

✉ Corresponding author: Simone Peschillo, M.D., Ph.D., s.peschillo@policlinicoumberto1.it; simone.peschillo@gmail.com

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Abstract

The use of focused ultrasound (FUS) as a tool for blood-brain barrier (BBB) permeabilization is opening new ways for the treatment of several pathologies, in particular brain tumors and neurodegenerative diseases. However, even if there are promising results in these fields, the efficacy and safety of this technique is unknown in long-term follow-up. The study of Blakmore et al. [17] evaluated the long-term effects of FUS on brain parenchyma in aged mice with Alzheimer's disease. This is the first study which applied a multimodal analysis to demonstrate the safety of FUS in aged brain in view of a potential introduction of this technique in common clinical practice in the future.

Key words: focused ultrasounds, brain, neurodegenerative diseases, Alzheimer's diseases

Focused ultrasound (FUS) represents a non-invasive therapeutic strategy that is currently used for the treatment of several disorders. In the field of neuroscience, magnetic resonance imaging (MRI)-guided FUS (MRIgFUS) is commonly used for treating essential tremor, chronic neuropathic pain, parkinsonism, and Parkinson's disease. Moreover, MRIgFUS has been successfully tested for the ablation of deep intracranial tumors, for acute ischemic stroke, and for specific psychiatric disorders. All of these applications utilize the thermoinducing and thermoablative properties of FUS which are able to reach high temperatures (>55 °C) in non-surgical sites (deep or eloquent encephalic zones), leading to coagulative necrosis, protein denaturation and cell apoptosis.

Recently, the potential of FUS has been experimentally expanded by exploiting its ability to temporarily alter the permability of the blood-brain barrier (BBB) . As a result, it is possible to not only deliver drugs or genetic material in targeted brain areas but also activate and modulate specific functional areas [1].

The permeabilization of BBB can be performed through FUS as well as microbubbles (MB) and/or nanoparticles (NP) that serve as carriers and vectors for drugs, including immunotherapydrugs, or genetic material. These are released directly into cells or into the brain interstitial system [2].

This new perspective of using FUS could be useful to treat a large number of pathologies in the neurological and neurosurgical fields. Presently, MRIgFUS has already been used in several clinical trials for the treatment of cerebral tumors (e.g., NCT02343991, NCT03551249, NCT03616860, NCT03712293, and NCT03714243), epilepsy (e.g., NCT03657056 and NCT02151175), consciousness disorders in acute brain injury (e.g., NCT02522429), as non-invasive option to deep brain stimulation (e.g., NCT02382965, NCT03717922, and NCT03347084), and as a method to improve the reuptake of β-amyloid in patients affected by Alzheimer's disease (e.g., NCT02986932).

MRIgFUS also offers another therapeutic strategy for neurodegenerative diseases. The transient permeabilization of the BBB could increase the

clearance of β-amyloid plaques in an animal model of Alzheimer's disease, improving the bioavailability of endogenous antibodies and activating glial cells [3,4].

After the study of Raymond et al. [5], which demonstrated that FUS can make the delivery of immuno-therapeutic agents in transgenic mice with Alzheimer's disease more effective, a more recent work demonstrated that the association of MRIgFUS and endovenous administration of BAM-10 anti-Ab antibodies can mitigate β-amyloid plaque development. The anti-amyloid effect is confirmed by other studies that showed a significant improvement of cognitive tasks in tested animals and, at the same time, a reduction in β-amyloid plaques and an improvement of neurogenesis in the sonicated brain areas [6, 7, 8, 9].With reference to the neuroinducing and neuroprotective effects of FUS, Scarcelli et al.[10] assumed that they could positively induce the endogenous regulation of Brain-Derived Neurotrophic Factor (BDNF) expression. In the same way, many studies investigated the potential to promote neurogenesis and angiogenesis using FUS with pulse repetition frequency, which seems to increase the BBB permeability better than FUS with set pressure strategy, or using microbubbles as a way to amplify these effects, opening the door to several therapeutic solutions in neurology and psychiatry [11, 12, 13].

However, despite the fact that FUS may be used in multiple fields, there are only a few studies that have investigated the long-term risk of potential brain damage. In 2015, Downs et al. [14] first analyzed the clinical and neuroradiological (MRI) changes that FUS might lead to in primates subjected to multiple sessions of sonication. The follow-up was performed at 20 months and did not reveal the presence of any permanent neurological damage. Similarly, other studies were conducted with the purpose of detecting issues related to repeated sonication of specific brain areas. O'Reilly et al. [15], by means of MRI scans and histological analysis, examined the safety and short-term effects of FUS in canine models with β-amyloid plaques. This work assessed the safety and efficacy of FUS, but did not highlight the possible effects that it might have on an aged brain or on a brain affected by a neurodegenerative disease. Moreover, Kovacs et al. [16] have recently analyzed the histological and neuroradiological changes that repeated sessions of FUS + MB might induce on a murine model. In this work, the steryl inflammation that FUS usually promotes seemed to be linked to persisting alterations of BBB, signs of vascular damage, inflammation, and neurodegeneration. All of these factors are common in traumatic brain injury.

In this context, the study of Blackmore et al. [17] has added data to our knowledge of secondary long-term effects of the permeabilization of BBB by SUS (scanning ultrasound) in aged animals.

In this work, the authors tested 12-month old mice with multimodal analysis and then exposed them to six weekly SUS treatments and compared the results with a case control group. Subsequently, several features concerning spatial memory, metabolic and cell function shifts (detected by measuring changes in brain volume), and tissue microstructure (evaluated by diffusion tensor imaging, DTI) were analyzed in vivo. Then, the synaptic level of activity was evaluated both functionally by electrophysiology and morphologically by analyzing the structural anatomy of neurons. Each of these analyses demonstrated experimentally that SUS is not only a safe treatment (in long-term follow-up) but also shows a neuroprotective effect, especially in an aged brain. This work, even with the limitations already highlighted by the authors, reveals the advantage of utilizing a multimodal approach in the analysis of histological and functional characteristics of sonicated tissues.

Alzheimer's disease and other dementias are serious conditions and common causes of mortality and morbidity among the elderly population for which there are no effective therapies available. For these reasons, it is, therefore, advisable to continue to develop FUS in order to verify its safety and fully strengthen its potential in clinical practice. New and important data could be deduced from recent clinical studies concerning the use of FUS in neurodegenerative diseases.

Abbreviations

BBB: Blood Brain Barrier; BDNF: Brain-Derived Neurotrophic Factor; DTI: diffusion tensor imaging; FUS: focused ultrasounds; MB: microbubbles; MRIgFUS: MRI guided focused ultrasounds; NP: nanoparticles.

Competing Interests

The authors have declared that no competing interest exists.

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