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The Therapeutic Potential of Focused Ultrasound in Patients with Alzheimer's Disease

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Alzheimer's disease (AD) is a common progressive neurodegenerative disease characterized by abnormal deposition of β-amyloid (Aβ) and hyperphosphorylated tau protein. Despite the fact that biomarkers and methods of treating AD are currently under active investigation, there is still no therapy that can significantly reduce the progression of this disease. Seeking therapeutic disease-modifying strategies is therefore becoming increasingly popular. One such strategy is MRI-guided focused ultrasound (FUS) using a contrast agent (microbubbles). Low-intensity FUS produces a temporary increase in the permeability of the blood–brain barrier (BBB), which is the main obstacle to the effective delivery of therapeutic compounds to the brain, imposing size limits and biochemical restrictions on the passage of molecules. AD is associated with BBB dysfunction, so studies of the use of FUS in patients with AD is of considerable interest. Studies in animal models of AD have provided evidence indicating the effectiveness of FUS. Researchers attribute the effectiveness of the method to an increase in BBB permeability induced by FUS and a decrease in the number of amyloid plaques. FUS has also been shown to be able to facilitate the delivery of therapeutic drugs to the brain. FUS can therefore be regarded as a contemporary noninvasive treatment method. Further studies are needed to evaluate the effectiveness of FUS in patients with AD.

Keywords: Alzheimer's disease, focused ultrasound, blood–brain barrier, β-amyloid, tau protein, treatment.

Alzheimer's disease (AD) is a progressive neurodegenerative disease and is one of the most common causes of dementia, which leads to social, professional, and domestic maladjustment of patients. Due to the fact that dementia is most common in older people, the continuing rapid increase in the proportion of older people in the population has led to an increase in the prevalence of AD [1, 2].

AD is diagnosed mainly in the late stages of the disease, which is probably due to lack of awareness in the population and medical specialists regarding the symptomatology of this disease and the lack of a widely used neuropsychological screening method to assess the presence of cognitive decline, which is the main clinical manifestation of AD. Early diagnosis of AD may be the key to the effective treatment of AD. Methods for diagnosing and treating this disease are therefore being improved by research seeking accessible biomarkers of AD and therapeutic targets. Drugs used in AD include acetylcholinesterase inhibitors aimed at eliminating neurotransmitter imbalance and making up for neurotransmitter deficiencies; another is the reversible NMDA receptor blocker memantine, which reduces the formation of β-amyloid (Aβ) and senile plaques by regulating the metabolism of amyloid precursor protein (APP), inhibiting Aβ aggregation, reducing the level of insoluble Aβ, and accelerating its degradation [3, 4].

Unfortunately, the use of drugs with cholinergic and neuroprotective effects does not provide long-lasting effects. Research seeking disease-modifying strategies for the treatment of AD is therefore being pursued. The main goal of this work is to influence the pathological deposition of Aβ and hyperphosphorylated tau protein. However, the development of drugs based on the inhibition of Aβ production (acting on β and γ secretases) has come up against a number of problems, in particular, significant side effects such as blindness [5].

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Another area under development is the use of monoclonal antibodies aimed at binding and removing Aβ. Studies using monoclonal antibodies showed dose-dependent decreases in Aβ accumulation and a slight slowing of the progression of cognitive impairment. However, monoclonal antibody titration schemes have not yet been developed sufficiently to achieve higher doses without adverse events (microbleeding, cerebral edema). Among the various drawbacks of therapy using monoclonal antibodies, a particular issue is that of their poor penetrating ability – only 0.1% crosses the blood–brain barrier (BBB) [6].

The BBB is a major obstacle to the efficient delivery of therapeutic compounds to the brain, operating by imposing size and biochemical restrictions on the passage of molecules. The BBB actively and passively prevents molecules from crossing the boundary between the blood and the cerebral parenchyma. Endotheliocytes are the main structural element of the BBB, and its structure also includes pericytes and astrocytes., Endotheliocytes, pericytes, and astrocytes of BBB neuroglia are separated by smaller spaces than cells in other tissues [7].

The main functions of the BBB are to protect neurons and maintain a tightly regulated internal environment in the brain, which is required for proper synapse and neuron functioning. Damage to the BBB promotes entry of neurotoxic blood products, cells, and pathogens into the brain and is associated with inflammatory and immune responses able to initiate neurodegenerative processes. Researchers regard pathological changes to BBB function as a possible mechanism underlying the occurrence of AD [8].

It has been suggested that AD is caused by an imbalance between the production and clearance of Aβ. Decreased Aβ clearance may be partly due to progressive dysfunction of the cerebral vessels and the BBB. Different data have been obtained in relation to BBB permeability and its relationship with AD pathology. On the one hand, some authors have described high BBB permeability as an early sign of AD [9, 10]. On the other, decreased BBB permeability for Aβ can lead to impaired release of protein from brain tissues into the blood [11]. Studies on animal models and in patients with AD have shown that improvements in BBB permeability due to short-term increases in permeability (opening) allow endogenous antibodies and blood proteins to penetrate into the brain, which can help reduce Aβ accumulation and improve cognitive functions [11–14]. Focused ultrasound (FUS) was used in these studies as a noninvasive approach to producing temporary opening of the BBB.

Ultrasound has a variety of biological effects, mediated via thermal/non-thermal, mechanical, or electrophysiological interactions with biological tissues, and these can be used for therapeutic effects [15].

FUS is a medical technology consisting of targeted and noninvasive transcranial focusing of ultrasound energy in local areas of the brain with constant monitoring of the process by MRI. High-intensity and low-intensity variants of FUS are discriminated. Thermal tissue destruction procedures are performed using high-intensity (>100 W/cm^2) FUS, while nonthermal actions producing temporary opening of the BBB are obtained using low-intensity FUS [16]. Previously published work has shown that noninvasive opening of the BBB, alone or in combination with therapeutic agents, may be a potential treatment option for patients with AD. Most published data on the effects of FUS were obtained in animal models of AD, while there are few data on the use of FUS in AD patients. Thus, further research on the use of FUS in patients with AD, is a promising direction, as is study of the pathology of BBB functioning.

The aim of the present review is to analyze data on the use of FUS in animal models of AD and in AD patients.

FUS Technology and Its Application. FUS technology has been under development for more than 70 years. High-intensity FUS has been used in neurosurgery. However, a number of shortcomings significantly complicating implementation of the procedure were found. One of these was the need for craniotomy, due to the fact that the bones of the skull reduce conduction of the ultrasound wave and undergo heating. This problem was solved in the late 1990s by applying multiple ultrasound sources evenly over the cranial vault [17, 18]. Additionally, FUS is delivered using waves at a frequency of <1 MHz (frequencies used in diagnostic ultrasound are 1–15 MHz), which reduces heating of the skull bones.

An important event in the development of the technology was the creation of the ExAblate Neuro transcranial system by the Israeli company InSightec in 1999. The current model of this system is a helmet (containing 1024 ultrasound sources; frequency 650 kHz), which is positioned on the MRI table (using a 1.5- or 3-T MRI scanner) [19]. Before FUS is carried out, a CT brain scan is used to construct a virtual spatial model of the skull and bone thickness is assessed. The ultrasound energy parameters are then adjusted to ensure passage through the skull bones [20]. FUS technology uses multiple synchronized ultrasound sources to guide the ultrasound wave. The target area is addressed using brain MRI integrated with FUS. MRI also provides real-time feedback, with determination of the location of the zone of action and the temperature within it (MRI thermometry and construction of temperature maps). Primary exposure begins with a series of short (10–30 sec) activations of the ultrasound sources, increasing the power level with each successive activation. There are breaks between series, during which the scalp and skull cool down. The breaks are also used for assessment of the presence of a clinical effect or the appearance of complications resulting from the procedure. An obligatory stage consist of a non-destructive ultrasound exposure (heating to 41–45°C) trial in the area in which damage is to be produced, with assessment of neurological status. The trial application of FUS leads to inactivation of the treatment zone without forming a necrosis zone (reversible tissue damage), so the position of the

exposure focus can be adjusted during FUS as necessary. The final destructive treatment, applied after obtaining convincing positive clinical effect in the trial, is carried out at a temperature of 51–64°C and leads to necrosis of the affected area. Lesioning of the selected local area is completed when a sufficient temperature is reached, when the clinical effect appears, if complications appear, and on the basis of the brain MRI [18–20].

The greatest progress in the use of FUS for therapeutic purposes has been achieved in functional neurosurgery for Parkinson's disease, essential tremor (ET), pain syndromes, and obsessive-compulsive disorder [21–26]. The most studied and best confirmed treatment for these pathologies is high-intensity FUS with ablation (thermal action forming thermal destruction zones). Thus, a prospective, uncontrolled, single-center study involving six patients showed that unilateral FUS ablation of the cerebellothalamic tract was effective in reducing contralateral hand tremor in ET [24].

It should be noted that the use of FUS has come up against a number of complications. Thus, Jung et al. [27] found a lack of clinical effect of ultrasound thalamotomy of the ventral intermediate nucleus of the thalamus (Vim-thalamotomy) in four of 17 patients with ET. It has been suggested that limitations are associated with the ratio of the thicknesses of the compact and cancellous bones of the skull above the intercommissural line, as well as with the shape of the skull. One solution proposed for this problem consists of introduction of an ultrasound contrast agent (microbubbles) into the bloodstream, which decreases the size of the thermal energy release zone and, thus, expands the exposure window [28–30].

The effects of low-intensity transcranial FUS (a module operating at 230 kHz) are also under active study; this is a novel brain stimulation method able to excite or inhibit neuron activity in a reversible and noninvasive manner without increasing tissue temperature. This type of FUS is based on the cavitation effect: ultrasound and the resultant tissue stretching forms vapor or gas bubbles in areas of reduced interstitial pressure. Continuing ultrasound exposure produces oscillatory movements of these bubbles, accompanied by the occurrence of tissue fluid microflows. These processes result in transient damage to cell membranes and uncoupling of the intercellular connections of endotheliocytes, followed by a temporary local increase in BBB permeability. Stability of cavitation is required for this effect to be obtained, and this is achieved by introducing microbubbles as contrast agent for FUS. Recovery of the BBB is seen within a day following FUS [20].

Possible mechanisms for increases in BBB permeability have been described by Sheikov et al. [31]. These authors studied morphological changes in endotheliocytes on exposure to FUS in rabbits using electron microscopy and immunocytochemical studies to determine endogenous immunoglobulin G (IgG). After low-power (0.55 W) ultrasound exposure, capillaries showed increased numbers of vesicles and vacuoles, formation of fenestrations and channels, as well as opening of some tight junctions. Damage to the cellular ultrastructure was not seen in these areas. However, passage of IgG through defects in the endothelial lining was noted after ultrasound exposure at a power of 3 W, The data showed that there were several possible mechanisms by which such ultrasound exposure might increase capillary wall permeability: 1) transcytosis, 2) formation of cytoplasmic openings in endotheliocytes, i.e., fenestration and channel formation, 3) opening of some tight connections, and 4) free passage through damaged endothelium (at higher ultrasound power, i.e., >3 W) [31].

Another effect of low-intensity FUS is non-destructive neuromodulation, i.e., FUS has a reversible neuromodulatory (stimulating and inhibitory) effect on the nervous system. This is evidenced by previous studies. Thus, Kim et al. [32] demonstrated initiation of outward movement of the eyeball on stimulation of the abducens nerve in rats using FUS. Lee et al. [33] demonstrated inhibition of motor or sensory spike conduction along the sciatic nerve in rats on exposure to FUS. In particular, the neuromodulatory effect is likely to result from cavitation within the lipid bilayer of the neuron membrane [34]. Some evidence suggests that exposure to FUS causes direct neuron activation with synaptic vesicle release, while other results suggest that exposure to FUS does not directly activate neurons, but rather increases their excitability. Neurochemical changes also play an important role. Exposure to FUS has been shown to be able to modulate the levels of various neurotransmitters [35]. Thus, Min et al. [36] observed a significant increase in extracellular dopamine and serotonin concentrations in rats subjected to a FUS procedure (targeting the thalamus), as compared with the reference group not exposed to ultrasound.

As noted above, BBB pathology can play a role in the development and progression of AD, so a large number of studies on the use of low-intensity FUS address the possibilities of treating this disease. Also, given that AD is based on neurotransmitter disorders, in particular cholinergic insufficiency, research into the effects of FUS on pathology such as AD is of great interest.

Use of FUS in Animal Models of Alzheimer's Disease. Studies in animal models of AD have shown that the use of MRI-guided FUS in combination with i.v. microbubbles temporarily promotes the opening of the BBB and reduces the pathological accumulation of Aβ and tau protein. FUS has been used in transgenic mouse models of AD to deliver anti-Aβ and anti-tau antibodies, producing significant reductions in pathology and positive effects on memory. In addition, BBB opening itself has an anti-amyloid effect. Several preclinical studies have demonstrated that FUS-mediated opening of the BBB can improve neuroplasticity processes and have positive effects on cognitive functions [37–40].

Nisbet et al. [41] investigated the effectiveness of a new 2N tau isoform-specific single chain antibody fragment (RN2N) delivered by passive immunization in the pR5

P301L transgenic mouse model with human tau protein. RN2N was found to reduce anxiety behavior and tau phosphorylation. When RN2N administration was combined with FUS in scanning mode (scanning ultrasound), RN2N delivery to the brain and its neuronal uptake increased markedly, and treatment effectiveness increased significantly [41]. The immunotherapy of AD is based on administration of antibodies against toxic Aβ, which circulate in the bloodstream and remove Aβ from the brain. Studies in mouse models of AD have shown that anti-Aβ antibodies delivered to the brain with FUS can reduce the pathological accumulation of Aβ four days after FUS [42].

Another study, also in a mouse model of AD, demonstrated that transcranial FUS resulted in a significant reduction in Aβ plaques four days after a single session of FUS, and endogenous Ig was found associated with Aβ plaques. Immunohistochemical analysis and Western blotting showed an increase in endogenous Ig in the cerebral cortex area targeted by FUS. Subsequently, microglia and astrocytes in areas of the cortex exposed to FUS showed signs of activation. Increased glial activation correlated with increased internalization of Aβ (uptake from the extracellular space) in microglia and astrocytes. Taken as a whole, these data demonstrate that FUS improves endogenous Ig bioavailability and leads to transient activation of glial cells, suggesting antibody-dependent and glio-dependent mechanisms of FUS-mediated reductions in Aβ plaques [11].

Another study in mice with AD showed a decrease in the number of Aβ plaques after FUS, which contributed to improvements in cognitive performance. Mice performed better in a Y-maze routing test, recognizing new objects, and actively avoiding a specific place [43]. Repeated exposures to FUS improved spatial memory. The mice were exposed to FUS targeting the hippocampal region on both sides weekly. Spatial memory was tested using a Y-shaped maze at one month. After FUS, mice spent 61% less time learning a new branch of the Y-maze than mice not exposed to FUS ($p < 0.05$). Behavioral changes correlated with reductions in the number and size of Aβ plaques in FUS-treated animals ($p < 0.01$). In addition, application of FUS was followed by an increase in the number of newly formed neurons in the hippocampus by 250% ($p < 0.01$) [37].

This effect of FUS exposure has been observed in other studies. Thus, work in rats showed that exposure to FUS led to an increase in neurogenesis in the hippocampus. Rats subjected to FUS-mediated opening of the BBB displayed significant increases in the concentrations of brain-derived neurotrophic factor (BDNF; $p < 0.05$), transcription factor 1 protein (EGR1) ($p < 0.01$), hippocampal neurogenesis ($p < 0.01$), and acetylcholinesterase activity in the frontal cortex ($p < 0.05$) and hippocampus ($p < 0.01$) [44]. A study on rabbits showed that a single dose of antibodies to Aβ reduced the area of amyloid plaques from 200 to 170 cm^2, while combined use of FUS and antibodies decreased it from 200 to 78 cm^2. Repeated FUS led to a decrease in Aβ plaques [45]. In contrast, a study in dogs showed no significant reduction in Aβ plaques following exposure to FUS [46].

One study aimed to evaluate whether the use of FUS-mediated BBB opening could enhance delivery of a glycogen synthase kinase 3 (GSK-3) inhibitor in transgenic AD mouse models, as this might contribute to an additive effect on Aβ clearance and reduce its synthesis. The procedure was performed unilaterally, using the contralateral hemisphere for comparison. Immunohistochemical investigations showed that GSK-3 inhibitors reduced GSK-3 activity by up to 61.3% with FUS, while autoradiographic studies showed a significant decrease in Aβ [39].

Treatment of the hippocampus with FUS has been shown to have a neuroprotective effect in dementia. Mice with two types of dementia were studied: vascular dementia and AD dementia. FUS therapy significantly improved cognitive performance (testing in a Y maze and/or a passive avoidance test) and cerebral blood flow in both models [47].

The effects of mono- and combination therapy of FUS using gastrodin (GAS) were studied in mouse models of AD. Gastrodin is a phenolic glycoside extracted from the plant *Gastrodia elata* and has been reported to be a potential therapeutic agent for the treatment of AD. Mice were divided into five groups: controls, untreated, GAS, FUS, and FUS + GAS. Combined treatment (FUS + GAS) resulted in improved memory while monotherapy (GAS or FUS) did not. The Aβ and tau protein contents in the hippocampus (the target) decreased. Increases in BDNF, synaptophysin (SYN), and postsynaptic density protein 95 (PSD-95) were noted in the FUS + GAS group [48].

Aspartic endopeptidase (AEP) inhibitors are among the potential drugs for the treatment of neurodegenerative diseases mediated by tau and Aβ, though no method for targeted intracerebral delivery of AEP inhibitors has as yet been developed. A study was conducted in which ultrasound-sensitive nanobubbles were fabricated to be loaded with the AEP inhibitor RR-11a. Opening of the BBB with FUS was followed by selective penetration of RR-11a molecules into the AD brain, with selective binding to damaged neurons and a resultant significant decrease in amyloid plaque deposition in the hippocampus. Cognitive functions in the mice improved significantly [49]. The number of FUS procedures performed may be important for the effectiveness of the treatment of AD. This was demonstrated using in vivo two-photon fluorescence microscopy to monitor changes in the size of Aβ plaques in AD mice. Single applications of FUS were found to reduce the size of existing Aβ plaques, the effect being maintained for two weeks. Three to five FUS treatments once every two weeks resulted in a more significant reduction in Aβ plaques [50].

Thus, studies in animal models have shown that FUS promotes reversible opening of the BBB and can facilitate the delivery of therapeutic drugs into the brain, such that it can be regarded as a potential noninvasive treatment for patients with AD.

Use of FUS in Patients with Alzheimer's Disease. Although preclinical studies have shown promising therapeutic effects with low-intensity FUS in animal models of AD, its efficacy and safety in humans remain unclear. Results from the first study were published in 2018 and showed successful opening of the BBB in patients with AD. Lipsman et al. [51] demonstrated that primary and repeat BBB opening were safe in patients with AD. The study included five patients with AD. Mean age was 66.2 years; there were three men and two women, and the mean Mini Mental Status Examination (MMSE) score was 22.8. The following scales were used for the neuropsychological examination: MMSE, an AD evaluation scale (ADAS-Cog), the Neuropsychiatric Inventory (NPI-Q), the ADCS-ADL to assess the activities of daily living, and the Geriatric Depression Scale (GDS). Initially, the BBB was successfully opened in all patients who underwent FUS to the white matter of the right frontal lobe. The average maximum FUS power was 4.6 W. Opening was achieved at about 50% power. At 24 h post-procedure, the BBB was completely closed. No serious adverse events were identified in any of the patients during the study. One patient demonstrated a transient increase in NPI-Q scores. The study results showed that reopening of the BBB did not lead to serious clinical or radiological adverse events. There were no statistically significant changes in cognitive performance at three months as compared with baseline. Aβ levels were measured prior to FUS exposure using positron emission tomography (PET) with ^{18}F-florbetaben to confirm Aβ deposition in the area of interest. The analysis results showed no changes at the group level after application of FUS [51].

Results from another study demonstrated the safety of opening the BBB in the hippocampus and entorhinal cortex. The hippocampus is one of the key targets for new therapeutic agents and plays an important role in the development of AD. A study by Rezai et al. [52] showed that FUS can safely provide noninvasive, temporary, and focal induction of BBB opening in the hippocampus and entorhinal cortex in humans. Six patients with AD underwent a total of 17 FUS procedures without adverse effects or deterioration in cognitive or neurological function. Closing of the BBB was noted at 24 h [52].

None of these studies showed any significant improvements in cognitive functions, so the effectiveness of FUS in patients with AD continues to be studied, as do the effects of FUS on patients' cognitive status and pathological Aβ deposition. Thus, D'Haese et al. [53] demonstrated FUS-mediated BBB opening affects Aβ plaques in 2020. Six patients with AD underwent PET scans with ^{18}F-florbetaben at baseline and one week after completion of a third course of FUS (with a 60-day interval). Analysis of PET results (comparison of the hippocampus and entorhinal cortex in the FUS-treated and -untreated hemispheres) revealed a decrease in ^{18}F-florbetaben binding. The decrease in the standard uptake value ratio (SUVr) was 2.7–10%, mean 5.05 ± ± 2.76%, which indicates a decrease in Aβ plaques [53].

In a 2020 open-label prospective study from South Korea (n = 6), patients with AD underwent FUS-mediated BBB opening targeting bilateral areas of >20 cm^3 in the frontal lobes. FUS was performed twice with an interval of three months. FUS targeted a mean volume of 21.1 ± ± 2.7 cm^3. PET data demonstrated a decrease in Aβ three months after FUS. The Neuropsychiatric Inventory score (CGA-NPI) two weeks after the second procedure decreased significantly from baseline (2.2 ± 3.0 points versus 8.6 ± 6.0 points, p = 0.042), but recovered at three months (5.2 ± 5.8 points versus 8.6 ± 6.0 points, p = 0.89). There were no changes in measures on the Korean version of the MMSE or other neuropsychological tests (Seoul Neuropsychological Screening Battery, Digit Span Backward, Boston Naming Test, Rey–Osterrieth Complex Figure Test, Seoul Verbal Learning Test, phonemic Controlled Oral Word Association Test (COWAT), semantic COWAT, Stroop Color Reading Test, Clinical Dementia Rating (CDR) scale, CDR Sum of Boxes (CDR-SOB), and Korean Instrumental Activities of Daily Living). No side effects were observed. The study confirmed that repeated and extensive opening of the BBB in the frontal lobe is safe for AD patients. Importantly, previous studies reported small-scale opening (<3 cm^3), while this work confirmed the safety of large-scale opening of the BBB, >20 cm^3 [54]. Thus, simple opening of the BBB, even without any additional anti-amyloid treatment, was shown to be able to affect Aβ clearance. It seems likely that this may be due to endogenous antibodies able to penetrate into the cerebral parenchyma and act on Aβ plaques.

In addition, several other clinical trials are currently ongoing or have been completed: NCT03119961 (France, BOREAL1, *Open Single-Arm Monocentric Study Evaluating the Tolerance and Interest of Transient Opening of the Blood–Brain Barrier by Low Intensity Pulsed Ultrasound with the SONOCLOUD® Implantable Medical Device in Mild Alzheimer's Disease Patients*) and NCT04118764 (USA, *Neuronavigation-Guided Focused Ultrasound-Induced Blood–Brain Barrier Opening in Alzheimer's Disease Patients*, addressing the safety and feasibility of FUS using a neuronavigation-guided single-element transducer and evaluating changes in Aβ levels in treated brain areas during FUS and its potential impact on cognitive function in patients with BA) [54, 55].

Meng et al. [56] demonstrated that FUS affects functional connectivity. The study analyzed changes in bilateral frontoparietal networks on functional MRI brain scans at rest in five patients after opening of the BBB in the right frontal lobe. A temporary decrease in functional connections was seen only in the ipsilateral frontoparietal network, which was restored the next day. In addition, comparison of initial levels with the level at three months did not reveal any significant differences between AD patients and the control group [56].

Data showing that positive effects in relation to cognitive functions and cerebral metabolism can be recorded

on exposure to FUS even without opening the BBB are of interest. Thus, a pilot study conducted in South Korea and published in 2021 showed the effect of low-intensity FUS on the rate of cerebral regional glucose metabolism and cognitive functions in patients with AD. Four AD patients (mean age 78.8 ± 3.3 years; three women) underwent FUS to the right hippocampus immediately after intravenous injection of a microbubble ultrasound contrast agent. Low-intensity FUS was used at a pressure level below the threshold for BBB opening. As expected, there were no signs of active BBB opening on dynamic MRI with contrast enhancement in T1 mode. The regional rate of cerebral glucose metabolism increased after exposure to FUS in the superior frontal ($p < 0.001$), middle cingulate ($p < 0.001$), and fusiform ($p = 0.001$) gyri. Patients showed slight improvements in post-FUS cognitive parameters: memory, executive functions, and integrative assessment of cognitive status. No adverse events were reported either after the procedure or one year after it [57].

The main drawback of these studies is sample size, which prevents generalization of the results. Further studies on larger samples are therefore required. In addition, the effectiveness of opening the BBB with FUS depends on a number of procedural and technical variables. Determining optimal power using a linear test is the first step to achieving uniform opening of the BBB. Other factors include microbubble size and dose, target tissue volume and type, and coordination between sonication and microbubble injection [51].

It can be suggested that monitoring of the spatial position of the target area by real-time imaging with submillimeter resolution will allow the BBB to be opened in areas with complex anatomy, such as the hippocampus and other cortical and subcortical structures. These first findings in AD patients are of value in developing FUS as a platform for drug delivery to pathologically altered brain tissues and its use for noninvasive neuromodulation.

Conclusions. Research over the past decade has revealed the great potential of FUS. Unlike other methods, FUS-mediated opening of the BBB is both noninvasive and targeted. Local action, combined with circulation of intravenous microbubbles, initiates biological effects limited only to vessel walls and seen only in the target area of the brain. Noninvasive opening of the BBB alone or in combination with therapeutic agents may be a potential treatment option for patients with AD.

Studies in animal models have yielded promising results in terms of reducing the severity of pathologies such as AD, though there are few reports on the use of FUS in humans and larger studies are needed. Studies in AD patients have demonstrated the safety and reversibility of BBB opening. In this regard, the relevance of further study of FUS as a new strategy for the treatment of patients with AD is confirmed.

The authors declare no conflict of interest.

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