Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Focused Ultrasound

Evidence Summary

FUS at appropriate power can efficiently lesion tissue, enhance BBB permeability, and potentially modulate neuronal activity. The clinical effects of BBB permeability and neuromodulation are unknown.

Neuroprotective Benefit: Based on preclinical and clinical research, FUS can transiently open the BBB and modulate neuronal activity. The effects of these activities, especially long-term effects, are not yet fully understood.

Aging and related health concerns: FUS can offer non-invasive tumor destruction for certain cancers and may also provide relief for some kinds of chronic pain. However, many applications of this technology are new and still under investigation.

Safety: Safety varies based on type of FUS and target tissue. Burns, pain, and fever have been reported as adverse events for high intensity FUS. Lower intensity FUS in the brain has not caused alarming adverse events, but significant research is still needed.

Availability: Approved for certain clinical uses; under development for other indications.	**Dose**: The most efficient dosing parameters have not yet been identified.
Half-life: High intensity FUS: permanent lesion. Medium intensity FUS for BBB opening: BBB opening typically closes within 24 hours based on available data. Low intensity FUS: unknown.	**BBB**: Not Applicable
Clinical trials: Varies based on indication. For high intensity FUS: one meta-analysis included 7,393 patients. For medium/low intensity FUS in AD, multiple small trials of ~5-10 subjects, for a total of approximately 100 individuals.	**Observational studies**: Varies based on indication. For high intensity FUS: largest identified study included 1,381 patients.

What is it?

As reviewed by Fishman and Frenkel, 2017, Tyler et al., 2018, and the Focused Ultrasound Foundation, sound moves as a pressure wave through a medium, including gases and liquid, and can be measured by its amplitude and/or frequency. Ultrasound is defined as waves with a frequency of more than 20 kilohertz (kHz), and the name ultrasound is used as it is above the range of detectable sound for humans. As ultrasound is a non-invasive, non-ionizing imaging modality, it is used in a variety of medical settings. Like other energy waves, ultrasonic waves can be focused onto a single small area when used with special equipment. The focus area receives a relatively higher amount of energy, whereas the intervening tissues receive relatively lower amounts of energy. This technique is called focused ultrasound (FUS). When targeted appropriately, such as with MRI guidance, the target tissue can be as small as a grain of rice, and the surrounding tissue is relatively unaffected.

The intensity of ultrasounds – that is, the power it delivers to the area of interest – often determines the exact application. High intensity FUS typically involves an intensity of 100 W/ cm^2 or greater. This intensity results in tissue heating, which ultimately results in tissue destruction. Real-time monitoring of

tissue temperature is often used to ensure the intensity is appropriate. Other mechanisms of action of high intensity FUS are possible, such as mechanical disruption of tissue. This modality is FDA approved for indications where tissue destruction is desirable, such as for ablation of prostate cancer, bone metastases, and treatment of uterine fibroids. High intensity FUS is also approved for treatment of movement disorders such as Parkinson's disease and essential tremor to lesion part of the brain to provide symptomatic relief. The technique is also in clinical trials for a variety of other conditions, including treatment of atrial fibrillation and neuropathic pain (Fishman and Frenkel, 2017, Tyler et al., 2018, Elhelf et al., 2018, Focused Ultrasound Foundation).

Intensities less than100 W/ cm^2 can be used for different purposes, such as for enhancing blood-brain barrier (BBB) permeability and for neuromodulation. Typically, these intensities are significantly under the 100 W/ cm^2 threshold. The nomenclature of the intensity varies; some papers differentiate between medium and low intensity ultrasound based on application, and others do not delineate between intensities under the high intensity FUS threshold. For this report, use of FUS specifically to enhance BBB permeability will be called medium intensity FUS and use of FUS that seeks to leave the BBB intact and only modulate neuronal activity will be called low intensity FUS. For reference, these intensities are above that of diagnostic ultrasound which typically has a very low intensity (below 0.1 W/cm^2) (Elhelf et al., 2018). Both medium and low intensity FUS are thought to act through mechanical means; they are not meant to involve any substantive increase in temperature. Real-time monitoring of temperature and other parameters are often used to help ensure safety and appropriate application (Fishman and Frenkel, 2017).

There are numerous variations on FUS techniques. MRI guidance is common for targeting and can be accomplished using an all-in-one machine where the patient receives an MRI and the FUS session in the same device (ExAblate MRgFUS, InSightec) or frameless systems where targeting is performed using neuronavigation systems based on prior MRIs (NaviFUS). There is an implantable device known as SonoCloud (Carthera) that can be used for brain applications. MRI can also be used to assess the efficacy of the procedure; for instance, when the desired application is opening of the BBB, MRI using non-BBB penetrant contrast can indicate whether there was successful BBB opening. Microbubbles can also be used in conjunction with FUS. Microbubbles are both an imaging contrast agent and can also have therapeutic utility ranging from acting as drug delivery systems to a tool for real-time monitoring and titrating of appropriate ultrasonic intensity through monitoring of cavitation, which is a physical response of the microbubbles to the ultrasonic waves. Cavitation can be important to monitor as stable

cavitation can have clinical utility by providing mechanical pressure onto nearby cells, but unstable cavitation leads to bubble explosion which can damage nearby tissue (Lee et al., 2017, Song et al., 2023).

The FUS protocol also has a number of parameters that need to be optimized for the desired application or individual patient, including amplitude of the wave, frequency of the wave, the pulse on and off time, the total length of the FUS session, the total number of FUS sessions, and the time in between sessions. These variables are particularly relevant for medium and low intensity FUS.

While high intensity FUS is FDA approved, most medium and low intensity FUS is still under development. Many of the variables above are still being tested and optimized for efficacy in humans (Song et al., 2023).

Neuroprotective Benefit: Based on preclinical and clinical research, FUS can transiently open the BBB and modulate neuronal activity. The effects of these activities, especially long-term effects, are not yet fully understood.

Types of evidence:

- 10 open-label studies in humans
- 9 reviews

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

There are no completed in-human studies of the effects of FUS in preventing dementia, decline, or improving cognitive function. There are two ongoing trials that are exploring whether FUS can improve cognitive function (see "Research Underway" section for more details).

Human research to suggest benefits to patients with dementia:

High intensity FUS is approved for use in patients with Parkinson's disease (PD) and essential tremor to treat motor symptoms. This approach involves unilateral lesioning of brain regions involved in motor behavior: either the thalamus for tremor or globus pallidus for PD motor symptoms and dyskinesia. High intensity FUS and deep brain stimulation (DBS) are different routes to similar symptomatic relief and are

often discussed as alternatives to one another. High intensity FUS has the benefit of being non-invasive and doesn't require adjustment; however, the lack of permanence is also a benefit of DBS, in that the device can be adjusted for symptomatic relief and isn't permanent (Fishman and Frenkel, 2017, Moosa et al., 2019, Michael J. Fox Foundation).

Several small trials utilizing medium or low intensity FUS in people with neurodegenerative diseases have been completed and published, though the efficacy is not yet clear. Given the recency of the publications, long-term effects of FUS are also unknown. Most of these trials found that FUS does indeed transiently open the blood-brain barrier as intended and did not observe serious adverse events, but also found no or only small effects of FUS on AD-relevant clinical measures such as cognition or aggregate load as measured by Aβ PET. Most of these studies are also not controlled, making it difficult to assess these clinical measures.

Lipsman and colleagues describe an open-label study of ExAblate MRgFUS with microbubbles to modulate the BBB. This was the first study of opening the BBB in humans; their primary aim was to establish whether this technique was feasible, as well as to collect initial safety data. Their secondary aims were to explore whether there was any effect on cognition or amyloid beta deposition, as preclinical work has shown benefits in both measures after FUS treatment. The study enrolled 5 participants with early to moderate stage AD. After an MRI to properly target the superior frontal gyrus white matter of the dorsolateral prefrontal cortex (DLPFC), microbubble contrast was administered and the FUS was performed. One month later, the procedure was repeated. The subjects also received fMRI imaging, PET scans for amyloid beta, and tests for cognitive and daily functioning. The outcomes of the study were safety assessments as well as the technical feasibility of opening the BBB. Safety was assessed through physical exams as well as radiographic imaging to check for adverse events such as edema or hemorrhage. There was a follow-up visit one month after the second scan and FUS session. The authors found that the BBB did open transiently; there were no changes on PET or on measures of cognition (Lipsman et al., 2018).

In a follow-up paper that examined changes in fMRI, the authors reported transient, immediate decreases in connectivity in the hemisphere targeted by FUS following the treatment session, as measured by fMRI. This decrease did not persist; by one day post-treatment, it had disappeared. They also compared the changes in functional connectivity over time in the trial participants to matched control from the Alzheimer's disease Neuroimaging Initiative (ADNI). The authors did not observe any difference in change from baseline to three-month follow-up visit between the study subjects and ADNI

controls. This report is evidence for neuromodulation following BBB-opening FUS, but it remains to be seen what the clinical effects are of these changes (Meng et al., 2019a).

The same group also published the results of a small open-label trial in ALS patients. The trial enrolled 4 participants. The study design was similar to that described by Lipsman in 2018, but this study targeted the primary motor cortex and used fMRI to help identify the region of interest. The subjects also underwent just one session of FUS instead of two. Like their study in AD patients, they found that BBB permeability was transiently increased, as assessed by MRI with contrast. There were no serious adverse events. There were no clinically significant changes in any cognitive or ALS-specific measure, or differences on EEG or laboratory values (Abrahao et al., 2019).

A 2019 open-label study from Nicodemus and colleagues investigated the effects of bilateral FUS in 11 patients with AD and 11 patients with Parkinson's disease (PD). This group is also interested in the effects of slow-wave sleep on aggregate load, so this study performed the FUS while participants were asleep. The researchers targeted different brain regions for the two patient populations - the temporal lobe for AD patients and the substantia nigra for PD patients. Participants received weekly hour-long sessions for 8 weeks, along with assessments of motor and cognitive functions. The authors reported that 62.5% of participants showed improvement on at least one cognitive measure, though 27.5% showed decline on at least one cognitive measure, and on most measures most patients did not show any changes. It is particularly difficult to interpret the findings in this study, as there is no control group (Nicodemus et al., 2019).

Two papers from the same group detail the results of an initial clinical trial using ExAblate MRgFUS to transiently open the BBB unilaterally in the hippocampus / entorhinal cortex in 6 patients with AD. Participants received the FUS treatment every other week for a total of 3 sessions. Neurological exams and MRI were performed immediately after FUS for both safety and to assess extent of BBB opening, and patients were followed for up to 15 months post treatment. Patients also received Aβ PET scans at baseline and after the end of treatment. The authors report that the FUS treatment did induce transient increased BBB permeability; this permeability resolved within 24 hours (Rezai et al., 2020). The researchers found decreases in Aβ PET signal in the treated hemisphere as compared to the untreated hemisphere, though they did not run statistical analyses on the results (D'Haese et al., 2020).

Karakatsani et al., 2023, primarily discussed preclinical work, but also reported very preliminary data from a single patient in their ongoing open-label study investigating FUS and microbubble treatment on

BBB opening (NCT04118764; see "Research Underway" section for more details). The participants received an injection of microbubbles at the same time as the 2-minute FUS treatment began. The researchers then performed MRI to check for any imaging abnormalities that might indicate safety concerns like edema or hemorrhage as well as to confirm BBB opening. Aβ PET was also performed at baseline and then 3 week and 3 months after treatment. The authors report that this one patient appeared to not have any safety signals on the MRI scans taken on the same day as FUS treatment. They also report a 1.8% reduction in PET signal at 3 weeks after treatment as compared to baseline, and then a 5.9% increase in PET signal at 3 months after treatment (Karakatsani et al., 2023).

Park et al., 2021 also report a small open-label study using ExAblate MRgFUS to enhance BBB permeability. The study enrolled 6 participants with moderate to severe AD, though only 5 were able to complete the study, as one patient was unable to complete the MRIs needed for the trial. Four of the five patients who completed the study were APOE4 carriers. The participants received 2 MRgFUS sessions three months apart. MRI, Aβ PET, and cognitive assessments were also performed. The results confirmed that the BBB was opened. Compared to baseline, there was a statistically significant decrease in Aβ PET in the brain region that contained the sonication target three months after the procedure. There was also a transient improvement from baseline in neuropsychiatric symptoms two weeks after the second FUS session, though this improvement disappeared by the three month follow-up (Park et al, 2021).

Jeong et al., 2021 details a small open-label study of FUS with microbubble ultrasound contrast, but purposefully utilized a sonication protocol that was below the threshold for BBB opening. The researchers enrolled 4 subjects with moderate or severe AD. MRI and CT imaging was performed for sonication targeting. Participants also received cognitive testing before and after the procedure, along with FDG PET to assess glucose metabolism. Results confirmed that the BBB was not disrupted. The authors report significant increases in glucose metabolism as indicated by the 2-week post-treatment FDG PET in the target region as compared to baseline. There were also mild improvements in global cognitive tests, though the authors did not perform statistical analyses on these tests (Jeong et al., 2021).

The above studies all involve external machinery that directs FUS through the skull. A 2022 paper from Epelbaum and colleagues details their trial of an implantable FUS device in 9 patients with mild AD. Twice a month for 3.5 months, participants received FUS along with microbubble infusions for a total of seven sessions. PET, MRI, and cognitive assessments were also performed at baseline, 4 months, and 8

months. The authors reported a trend towards decrease Aβ PET signal, but this was not statistically significant. There were no changes in cognition or on FDG PET compared to non-sonicated brain region (Epelbaum et al., 2022).

There is also a study on transcranial pulse stimulation (TPS) in AD patients. TPS is considered distinct from focused ultrasound. TPS involves a single ultrasound pulse, whereas FUS involves periodic waves. Proponents of TPS cite benefits such as better skull penetration and absence of potential side effects such as tissue heating and wave interactions in comparison to FUS. TPS is currently being explored as a method for neuronal stimulation rather than for BBB opening. Beisteiner and colleagues described a pilot trial of TPS in 10 healthy controls and then 35 patients with AD. The portion of the study with AD patients involved 3 TPS sessions a week for 2-4 weeks. TPS was targeted to AD relevant brain regions, and targeting was guided by individual patient MRIs. fMRI and cognitive testing were also performed. Results included safety and cognitive outcomes. Headache and mood deterioration were reported in 4% and 3% of the participants, respectively. The authors report improvement in measures of cognition such as memory, though some participants showed decreases in performance on visuospatial tasks. While the authors also report changes in fMRI that correlated to cognitive changes, as this trial was not controlled, it is difficult to assess whether it was specifically due to the TPS treatment (Beisteiner et al., 2020).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

The primary mechanism of action of high intensity FUS for PD and essential tremor is tissue lesioning through increased tissue temperature, a process called coagulative necrosis (Fishman and Frenkel, 2017).

The main mechanism of action of medium FUS is thought to be BBB opening, though it can also include neuromodulation. Neuromodulation will be discussed below in the context of low intensity FUS. BBB opening is typically achieved using FUS and intravenous administration of microbubbles. The application of FUS causes the microbubbles in blood vessels to rhythmically expand and contract, a phenomenon known as cavitation. Cavitation applies mechanical pressure to the cells that make up the BBB, leading to membrane permeability. Care must be taken to ensure that cavitation remains stable to prevent bursting of the microbubbles and damage to surrounding tissue (Fishman and Frenkel, 2017).

There are a number of hypotheses about the potential benefits of BBB opening. Modulation of the innate immune system is thought to be a main benefit. FUS activates the innate immune system, including microglia. It should be noted that transient sterile inflammation has been reported after FUS-mediated BBB disruption, and inflammation can be a double-edged sword, and more research will likely be needed to fully understand and appropriately regulate the consequences of the inflammatory response. There is preclinical evidence that BBB opening reduces the load of Aβ and tau aggregates (Fishman and Frenkel; 2017 Wu et al., 2021; Karakatsani et al., 2023; Song et al., 2023). Karakatsani and colleagues also reported enhanced cognitive function in not just animal models of AD but also in wild-type mice.

Based on preliminary findings in pilot studies, Meng and colleagues suggest that glymphatic clearance of aggregates may also be a mechanism of action in FUS (Meng et al., 2019b). Opening the BBB also allows for drug delivery of molecules that otherwise have more limited BBB penetrance. This can be done in a very region-specific manner with FUS (Fishman and Frenkel, 2017).

Low intensity FUS is typically used to modulate neuronal activity without causing BBB disruption. Neuromodulation is thought to occur through mechanical effects of the ultrasonic waves on ion channels and membrane permeability that then can lead to changes in neuronal activity. Increased neurogenesis and changes in brain activity have been reported in animal models, and changes in brain activity have also been reported in humans (Tyler et al., 2014; Fishman and Frenkel, 2017; Jeong et al., 2021).

Some preclinical evidence indicates that non-high intensity FUS may also have other neuroprotective mechanisms of action, such as increase in neurotrophic factor release and expression, reducing ROS production and oxidative stress, and promoting neuronal repair (Zhong et al, 2023).

APOE4 interactions:

Whether there is an interaction between FUS and APOE4 status has not yet been studied and/or published. One preclinical study reported changes in gene expression related to cholesterol handling, which may provide a theoretical basis for interaction between FUS and APOE4 status (Karakatsani et al., 2023). However, this is very speculative. Significant work remains to be done to assess whether APOE4 carriers could receive additional benefit, or conversely, increased risk of adverse events, from this technique.

Aging and related health concerns: FUS can offer non-invasive tumor destruction for certain cancers and may also provide relief for some kinds of chronic pain. However, many applications of this technology are new and still under investigation.

Types of evidence:

- 1 meta-analyses or systematic reviews
- 2 systematic reviews
- 1 clinical trial
- 1 observational study
- 6 reviews

FUS is currently approved for use in several cancers for tumor destruction, as well as for ablation of uterine fibroids. FUS is also under clinical investigation for a variety of other conditions, including neuropathic pain, chronic pain, atrial fibrillation, depression, obsessive compulsive disorder. There are many other applications of FUS that are still at a preclinical stage, such as for atherosclerosis, stroke, wound healing, and diabetes. A comprehensive list of indications and state of research can be found at the Focused Ultrasound Foundation.

Cancer: APPROVED FOR USE, BENEFIT FOR CERTAIN SUBTYPES

FUS is an FDA approved modality for treatment of several tumor types, including prostate cancer and bone metastases, and is being investigated for others such as pancreatic cancer, breast cancer, and glioblastoma. Typically, this treatment involves high intensity FUS to raise the temperature in target tissue and destroy that tissue. It is also thought that FUS may have other mechanisms of action, such as destruction of tissue through cavitation, activation of the immune system, and/or improved drug delivery (Diaz-Alejo et al., 2022; Hersh et al., 2022; Focused Ultrasound Foundation

Chronic Pain and Neuropathic Pain: BENEFIT FOR CERTAIN PATIENTS

Both high intensity and medium/low intensity FUS have been investigated for use in treating chronic pain. High intensity FUS to ablate tissue in the thalamus to alleviate chronic neuropathic pain is an approved treatment in some countries, though it has not yet been approved in the US. High intensity FUS is also being investigated as a potential treatment for pain such as through tumor ablation or

lesioning of specific brain areas. Medium and/or low intensity FUS is being investigated for a variety of other applications for treatment of pain, such as increased delivery of medication through BBB opening, neuromodulation, or direct treatment of osteoarthritis (di Biase et al., 2021; Taranta et al., 2023).

Safety: Safety varies based on type of FUS and target tissue. Burns, pain, and fever have been reported as adverse events for high intensity FUS. Lower intensity FUS in the brain has not caused alarming adverse events, but significant research is still needed.

Types of evidence:

- 1 Cochrane meta-analysis
- 1 systematic review and meta-analysis
- 1 systematic review
- 8 open label studies
- 1 observational studies
- 1 review

The safety profile of FUS depends on the precise application. Skin burns are possible for most if not all applications, particularly with high intensity FUS. Other potential adverse events are more tissue specific. For instance, urinary incontinence is a potential adverse event in treatment of prostate cancer with high intensity FUS; this is also an adverse event in other treatment strategies of this cancer (He et al., 2020). Pain in the treated area, skin burns, and fever have been reported when using high intensity FUS for treatment of pancreatic cancer (Qian et al., 2023). Local pain, skin burns, nausea and vomiting, fever, and shoulder pain have been observed in trials in patients with breast cancer (Zulkifli et al., 2023).

Several small studies of medium and/lor low intensity FUS have been completed. The safety results of those that aimed to open the BBB or provide neuromodulatory stimulation in patients with neurodegenerative diseases are discussed here. These trials are largely uncontrolled.

Lipsman et al., 2018 discusses the results of a trial of MRgFUS in 5 patients with AD. The authors reported no serious adverse events, and the MRI images indicated that BBB closed within 24 hours. One patient reported a headache following the procedure (Lipsman et al., 2018). The group also performed a similar protocol targeting a different brain region in ALS patients. Three of the four subjects reported moderate headache during the procedure. There was also mild pain, swelling, and/or bruising

associated with the procedure itself. The researchers also report one instance of transient and asymptomatic imaging hyperintensity known as fluid-attenuated inversion recovery (FLAIR) signal that appeared the day after the FUS treatment and resolved by Day 7 (Abrahao et al., 2019).

Epelbaum et al., 2022 reported the results of an open-label study of 9 patients with mild AD. The participants received FUS plus microbubbles every other week for a total of 7 sessions. The authors reported adverse events during treatment or up to 30 days after the end of the sessions. Most were mild, and included headache, fatigue, asymptomatic low blood pressure, abdominal pain, and diarrhea. There was one more serious adverse event: two days after the second treatment, a patient experienced delirium for 2 hours secondary to bleeding from a previously existing microbleed. The bleed was 5 cm from the FUS target region. An Independent Data Safety Monitoring Board concluded it was unlikely that this adverse event was related to the study intervention; the patient continued to participate in the trial. This patient did not experience any other adverse events after they resumed participation (Epelbaum et al., 2022).

Nicodemus et al., 2019, Rezai et al., 2020, Jeong et al., 2021, and Park et al, 2021 all reported no adverse events.

There are known dangers of FUS that can be mitigated if not avoided all together. When performing FUS with microbubbles, the goal is to use an ultrasonic frequency that results in stable cavitation of microbubbles – that is, expansion and contraction that does not lead to bursting. If the microbubbles burst, it can cause damage to the surrounding tissue, including edema or hemorrhage; these can be particularly dangerous for someone on anticoagulants. Ramp testing, which is applying increasing ultrasonic power to the target region until subharmonic acoustic feedback is observed and then scaling back power, can help ensure stable cavitation. Certain settings of FUS can also result in tissue heating. Using instruments with real-time temperature and acoustic feedback, as well as protocols like ramp testing, can help avoid these dangers. MRI guided FUS can also help ensure that the appropriate brain region is targeted (Lipsman et al., 2018).

Other potential dangers are more difficult to avoid and may require more rigorous studies to fully characterize. For instance, opening the BBB is thought to activate the innate immune system. Immune system activation can be both beneficial and destructive, and optimizing factors like timing and dose of microbubbles if applicable are necessary for appropriate inflammatory regulation. It remains to be seen whether the inflammatory responses are net beneficial or net detrimental under specific conditions.

Opening the BBB also poses a potential infection risk; this risk could theoretically be heightened in someone with an active infection (Song et al., 2023).

There are potentially fewer adverse events of neuromodulation, as the BBB remains intact. This application of the technology is very new, and there is much we don't know- for instance, what regions should be targeted, what FUS protocols achieve the desired technique, what the ideal frequency of sessions is or what could be the ideal number of sessions.

Drug interactions:

As FUS often requires MRI for ideal targeting, FUS is contraindicated for anyone who cannot receive an MRI, such as someone with a pacemaker. High intensity FUS should also not be used in other patient populations, including those with advanced kidney disease, unstable heart conditions, severe hypertension, substance abuse disorders, history of abnormal bleeding or blood clotting disorders, stroke, or brain tumors. High intensity FUS or any US modality where bleeding is a concern should not be used in patients taking anticoagulants (FDA).

Research underway:

There are more than 200 registered clinical studies on clinicaltrials.gov that involve focused ultrasound. The trials are for a variety of conditions, ranging from cancer to depression and anxiety to chronic pain to noninvasive fat reduction. Approximately 23 of these studies focus on neurodegenerative diseases or cognitive function.

There are 8 ongoing trials of FUS in AD patients. Half of these trials focus on low intensity FUS with the goal of neuromodulation or neurostimulation, and the other half of the trials focus on blood-brain barrier (BBB) opening.

Focused ultrasound with the goal of BBB opening:

- NCT04118764 is an open-label study of 6 patients with AD. This study will test MRI-guided focused ultrasound in conjunction with microbubbles to induce BBB opening. MRI scans performed before and after treatment will confirm BBB opening and closing. Amyloid PET will also be performed before and after the treatment to assess change in uptake of PET tracer. The outcomes will include whether the BBB is opened successfully, adverse events, change in

amyloid PET signal, and change in cognition as assessed by MMSE. This study has reached primary completion.

- NCT03739905 and NCT03671889 are both open-label studies of repeated BBB opening using the ExAblate MR-guided focused ultrasound in AD patients; the former is recruiting in Canada, and the latter is recruiting in the US. Both studies plan to recruit up to 30 participants, and all participants will receive 3 sessions of FUS under MRI guidance. The outcome measures for both studies are adverse events related to the device and procedure, as well as whether the BBB is opened and subsequently closed. The Canadian study also plans to assess cognitive changes at baseline and at six months, as well as change in uptake of an amyloid tracer.

- NCT05469009 is another study that plans to assess the use of the ExAblate MR-guided focused ultrasound device in patients with MCI or mild AD. This open-label study will specifically test BBB opening in the context of aducanumab therapy. The trial aims to recruit 5 patients who are eligible for aducanumab therapy and will involve administering aducanumab every 4 weeks followed by FUS to transiently open the BBB. The outcomes include incidence of adverse events, change in amyloid PET signal, and cognitive performance as measured by ADAS-Cog and MMSE.

Low intensity focused ultrasound:

- NCT03347084 is a small study of low intensity focused ultrasound pulsation (LIFUP) that has reached primary completion. The study aimed to enroll 8 patients with MCI or mild AD. The participants were randomized to one of two sonication paradigms – one that they believe will excite and one to inhibit hippocampal neuron activity. Both paradigms involved four treatments of 30 seconds each, with two-minute intervals between treatments, with fMRI data collection throughout treatment. Neuropsychological testing was performed at baseline, immediately after the LIFUP protocol, and then one week after the treatment. Outcomes include changes in fMRI, cognition, and a measure of anxiety.

- NCT05417555 is a study from the same group as the above trial. This study investigates the use of low intensity focused ultrasound pulsation (LIFUP) in the entorhinal cortex – an AD relevant region. The study intends to enroll 144 patients with amnestic MCI. The participants will be randomized into one of four groups who will receive different LIFUP 'doses: 0, 1, 2, or 3 doses of a 6 minute sonication session. Each pulse will be 30 seconds on, 30 seconds off. There will be two sessions two weeks apart. MRI will be performed to ensure targeting, and fMRI data will be

collected during sonication to assess cerebral blood flow. Cognitive testing will be performed before and after the sessions, culminating in a final memory testing 2 weeks after the last LIFUP session. Outcomes include change in cerebral blood flow and functional connectivity as measured by fMRI and changes in learning and memory scores. Post-hoc analyses will also be completed to assess whether APOE4, plasma Aβ 42/40 ratio, or plasma p-tau predict efficacy.

- NCT05997030 plans to enroll 15 patients with MCI. This single-arm study will assess safety and tolerability of low intensity focused ultrasound (LIFU). It appears that the study will involve a single LIFU session targeting a particular brain region. Outcomes include adverse events in the 7 days following the procedure, cognitive changes as assessed by ADAS-Cog, and changes in fMRI and/or PET.

- NCT05910619 is a study of transcranial pulse stimulation (TPS) using a device called Neurolith TPS. This instrument also uses acoustic pulses, but they are fundamentally different from ultrasonic waves; ultrasound involves continuous waves, whereas TPS involves a 'single pressure pulse followed by a tensile wave of lower amplitude' (Storz Medical). This technology is outside the scope of this report, but in brief, this study aims to enroll 20 patients with mild AD and randomize them to either TPS treatment or sham treatment. Patients will receive treatment or sham treatment three times a week for four weeks. MRI and cognitive testing will be performed both before and after the treatment. Outcome measures include measures of cognition and changes in cerebral blood flow.

There are 16 trials of FUS in patients with Parkinson's disease (PD) or related disorders. Six of these trials (NCT02246374, NCT02252380, NCT02347254, NCT04991831, NCT05539196, NCT03100474,) are assessing the safety and efficacy of using high intensity FUS to lesion a brain region to provide symptomatic relief. The other studies utilize low or medium intensity FUS.

Several studies aim to use FUS as neuromodulation.

- NCT05475340 is an open label study hoping to enroll 50 participants with tremor, whether from PD or essential tremor. The patients will receive 8 sessions of 10–30-minute transcranial ultrasound targeting the hypothalamus. MRI will be used as targeting guidance. The outcomes are measures of tremor, PD severity, and fine motor skills.

- NCT05499429 is a randomized controlled trial that aims to enroll 20 patients with mild Lewy body dementia, a dementia with pathology similar to PD. The intervention group will receive a low intensity FUS with the goal of modulating neuronal activity, and the control group will receive sham treatment. Participants will receive 20–30-minute treatments three times a week for 3-12 weeks. EEG, MRI, PET, and cognitive assessments will be administered at baseline and after completion of treatments. The outcomes of the study include any changes in clinical symptoms, EEG, and fMRI.

- NCT05965960 is a study that focuses more on uncovering mechanisms of action of transcranial ultrasound stimulation (TUS) on neurons in patients with implanted deep brain stimulators (DBS). The researchers will enroll 25 participants with movement disorders who have had a DBS device for at least 1 month. The subjects will all receive both a sham session and an active session of TUS. The DBS system will be used to record activity before, during, and after the stimulation. The main goal of this study is to characterize the neural correlates of TUS in these patients; secondary outcomes include assessments of movement disorder severity as well as adverse events.

- NCT04593875 is a randomized double-blinded trial that seeks to enroll 30 participants with PD. The study will involve receiving either two sham treatments or two low intensity FUS sessions of the putamen, which is a PD relevant brain area. Both groups will receive MRI and fMRI measurements before and after the sessions. The primary outcomes are measures of PD severity; the secondary outcomes are measures of blood flow before and after the treatments.

- NCT03981055 is a randomized and blinded study of 40 participants with PD and is investigating whether transcranial ultrasound + transcranial direct current stimulation and physical therapy can improve postural instability. The treatment sessions and physical therapy will happen three times a week for two weeks in this phase of the trial. The outcomes include measures of postural stability and overall motor function, as well as severity of PD.

Two studies from InSightec, the company that manufactures the ExAblate MRI guided FUS system, propose using FUS to open the BBB for drug delivery.

- NCT05565443 is a study of 14 patients with PD, half of whom have idiopathic PD and half of whom have a mutation in the *GBA* that codes for the glucocerebrosidase (GCase). The open-

label trial involves all participants receiving three cycles of IV infusion of GCase followed by MRI-guided FUS for BBB opening in the putamen. The outcomes of the study are safety and feasibility, as measured by adverse events and MRI with contrast to assess the extent of BBB opening.

- NCT04370665 is a similar study of 4 patients with PD. The participants will receive three biweekly doses of Cerezyme, an analogue of GCase, followed by MRI-guided FUS into the putamen. The outcome measures include the extent of BBB opening, adverse events, and exploratory measures of the activity of GCase and cognitive function as assessed by MMSE. This trial is listed as active, not recruiting, though it was estimated to be completed in late 2022.

Finally, two trials are exploring the effects of low intensity FUS and cognition.

- NCT05303428 aims to enroll 80 healthy adult volunteers and explore the cognitive effects of low intensity focused ultrasound (LIFU) with the goal of modulating neuronal activity. The LIFU will be targeted to brain regions of interest; active sham regions will also be used in the same patients. Participants will receive MRI and CT scans, and then fMRI after LIFU treatment to assess differences in brain activity in resting state and during structured tasks. The primary outcome is change in fMRI signal during cognitive tasks in a brain region of interest. Other outcome measures include performance on executive function testing and any changes in physiological measures such as heart rate or blood pressure during testing.

- NCT03717922 is a study examining the effects of low intensity focused ultrasound pulsation (LIFUP) on learning and memory in 40 adults 35 to 65 years of age. This crossover blinded design will entail participants receiving short and long LIFUP sessions as well as sham sessions. Participants will receive an MRI for targeting of LIFUP to the entorhinal cortex. They will then receive their assigned treatment(s). Participants will also complete learning and memory tasks and fMRI data will be collected before and after sonication. The outcomes of this study include performance on a learning and memory task and changes in cerebral blood flow as assessed by fMRI during and after the sonication protocol.

Search terms:
Pubmed, Google: focused ultrasound

- Dementia, Alzheimer's, APOE4, cancer, neuropathic pain, pain, Parkinson's

Websites visited for focused ultrasound:

- Clinicaltrials.gov
- WebMD.com: High intensity focused ultrasound for prostate cancer
- Cafepharma: FUS for uterine fibroid ablation

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