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Focused ultrasound–mediated blood-brain barrier opening in Alzheimer's disease: long-term safety, imaging, and cognitive outcomes

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OBJECTIVE MRI-guided low-intensity focused ultrasound (FUS) has been shown to reversibly open the blood-brain barrier (BBB), with the potential to deliver therapeutic agents noninvasively to target brain regions in patients with Alzheimer's disease (AD) and other neurodegenerative conditions. Previously, the authors reported the short-term safety and feasibility of FUS BBB opening of the hippocampus and entorhinal cortex (EC) in patients with AD. Given the need to treat larger brain regions beyond the hippocampus and EC, brain volumes and locations treated with FUS have now expanded. To evaluate any potential adverse consequences of BBB opening on disease progression, the authors report safety, imaging, and clinical outcomes among participants with mild AD at 6–12 months after FUS treatment targeted to the hippocampus, frontal lobe, and parietal lobe.

METHODS In this open-label trial, participants with mild AD underwent MRI-guided FUS sonication to open the BBB in β-amyloid positive regions of the hippocampus, EC, frontal lobe, and parietal lobe. Participants underwent 3 separate FUS treatment sessions performed 2 weeks apart. Outcome assessments included safety, imaging, neurological, cognitive, and florbetaben β-amyloid PET.

RESULTS Ten participants (range 55–76 years old) completed 30 separate FUS treatments at 2 participating institutions, with 6–12 months of follow-up. All participants had immediate BBB opening after FUS and BBB closure within 24–48 hours. All FUS treatments were well tolerated, with no serious adverse events related to the procedure. All 10 participants had a minimum of 6 months of follow-up, and 7 participants had a follow-up out to 1 year. Changes in the Alzheimer's Disease Assessment Scale–cognitive and Mini-Mental State Examination scores were comparable to those in controls from the Alzheimer's Disease Neuroimaging Initiative. PET scans demonstrated an average β-amyloid plaque of 14% in the Centiloid scale in the FUS-treated regions.

CONCLUSIONS This study is the largest cohort of participants with mild AD who received FUS treatment, and has the longest follow-up to date. Safety was demonstrated in conjunction with reversible and repeated BBB opening in multiple cortical and deep brain locations, with a concomitant reduction of β-amyloid. There was no apparent cognitive worsening beyond expectations up to 1 year after FUS treatment, suggesting that the BBB opening treatment in multiple brain regions did not adversely influence AD progression. Further studies are needed to determine the clinical significance

ABBREVIATIONS AD = Alzheimer's disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–cognitive; ADNI = Alzheimer's Disease Neuroimaging Initiative; AE = adverse event; ApoE = apolipoprotein E; BBB = blood-brain barrier; EC = entorhinal cortex; FUS = focused ultrasound; MMSE = Mini-Mental State Examination; SAE = serious AE; SUVr = standard uptake values ratio.

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of these findings. FUS offers a unique opportunity to decrease amyloid plaque burden as well as the potential to deliver targeted therapeutics to multiple brain regions in patients with neurodegenerative disorders.

Clinical trial registration no.: NCT03671889 (ClinicalTrials.gov)

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KEYWORDS Alzheimer's disease; focused ultrasound; FUS; blood-brain barrier opening; BBB; β-amyloid plaque; surgical technique

Alzheimer's disease (AD) is the most common form of dementia marked by progressive memory and cognitive decline. The incidence of AD is increasing worldwide, with enormous healthcare costs and human suffering.[1,2] AD treatments have modest effects despite decades of research and extensive clinical trials involving medications, immunotherapy, gene therapy, and other disease-modifying or biological therapeutic agents.[3–7]

A significant challenge to developing effective therapies for neurodegenerative disorders such as AD is limited access to target brain regions due to the blood-brain barrier (BBB). More than 99% of all AD therapies do not implement strategies to increase the transfer of the therapeutic agents across the BBB.[8] To overcome the restrictions posed by the BBB, transarterial diuretic infusion and stereotactic neurosurgical procedures are used for direct intracranial infusion.[9,10] Not only do these procedures involve considerable risk, but also neither direct infusion from a catheter tip nor targeting through a vascular distribution allows conformal delivery of agents to precise, anatomically defined complex brain regions. Recently, MR-guided low-intensity focused ultrasound (FUS) technology has emerged as a safe and noninvasive technology to reversibly open the BBB with precise and focal targeting.[11–14] Low-intensity FUS does not result in an increase in temperature or brain lesions. When combined with intravenous microbubble infusion, low-intensity FUS creates acoustic cavitation precisely at the target tissue and not beyond, resulting in a conformal, transient, and reversible disruption of the capillary wall tight junctions, thereby increasing BBB permeability—i.e., BBB opening.[15,16] Experimental studies have shown a safe, noninvasive, and focal delivery of genetic vectors and cells after BBB opening.[11,17–19] In humans, BBB opening is used to deliver chemotherapy to brain regions believed to harbor malignant cells.[20]

Preclinical studies in animal models of AD have demonstrated that administration of low-intensity FUS results in safe, focal, and reversible BBB opening,[11–13] with reduction of β-amyloid plaque, increased neurogenesis, and memory improvement. Given the potential of FUS-mediated BBB opening to reduce β-amyloid plaques and the possibility of facilitating noninvasive, conformal delivery of biological agents and other disease-modifying therapeutics, we previously performed an initial safety and feasibility study of FUS BBB opening limited to the hippocampus and entorhinal cortex (EC) in patients with mild AD.[21,22] Given that pathology in most patients with AD extends beyond these 2 brain regions and that there is equipoise regarding both safety and feasibility of widespread BBB opening in human neurodegenerative diseases, we expanded this study to include multiple cortical and subcortical areas of the frontal and parietal lobes. We now report the feasibility and outcomes in 1 year—including safety, cognitive performance, imaging, and β-amyloid PET scans—among participants with mild AD treated with FUS BBB opening.

Methods

This study was an open-label, prospective clinical trial conducted in participants with mild AD undergoing focal FUS-mediated BBB opening. This study was registered with the ClinicalTrials.gov database (http://clinicaltrials.gov), and its registration no. is NCT03671889. The trial was conducted at two institutions (West Virginia University Rockefeller Neuroscience Institute and Weill Cornell Medical College) with FDA investigational device exemption and institutional review board approvals. The protocol we followed adheres to the US Code of Federal Regulations and the World Medical Association Declaration of Helsinki principles.

The primary objective was to evaluate the safety and feasibility of repeated FUS-mediated BBB opening in participants with mild AD. We assessed the procedure's safety through analysis of BBB opening and closure, adverse events (AEs) including abnormalities on MRI, and clinical and cognitive outcomes. The secondary objectives of this study were to quantify the extent of BBB opening and β-amyloid plaque burden measured with ^{18}F-florbetaben PET imaging.

Participant Population and Enrollment Criteria

Persons eligible to participate in this study were 50–85 years of age, with a diagnosis of probable AD according to the National Institute of Aging–Alzheimer's Association criteria,[23] with the presence of β-amyloid plaques on ^{18}F-florbetaben PET scan and no evidence of other CNS disease. Additionally, a baseline Mini-Mental State Examination (MMSE) score of 18–26 was required, as was ≥ 3 months on a stable dose of medication (e.g., donepezil, memantine). Participants were excluded from enrollment if they could not undergo MRI, if they had significant medical comorbidities (e.g., cardiac and vascular conditions), or if they had the presence of apolipoprotein E (ApoE) ε4 allele homozygosity, due to the potential for an increased rate of vascular complications. Complete inclusion/exclusion criteria are available in the Supplemental Material. Informed consent was obtained from all participants. Figure 1 shows the enrollment process for participants in this protocol.

Treatment and Follow-Up Measures

Figure 2 indicates the overall treatment and follow-up schedule for all safety and outcome measures reported in

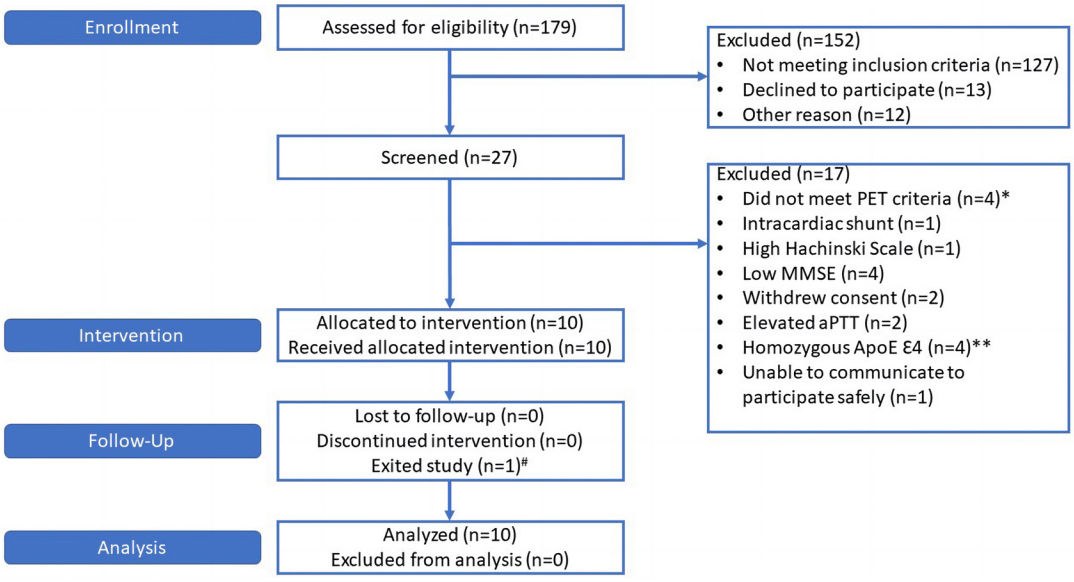

FIG. 1. Clinical trial flow diagram showing the enrollment process for participants in this protocol. *One patient was found to have an intracardiac shunt as well as an ineligible PET scan and is reported in both categories. **One patient was found to have a high Hachinski score as well as homozygous ApoE Ɛ4 and is reported in both categories. #One patient died of pancreatic adenocarcinoma 44 weeks after study enrollment (36 weeks after completion of FUS treatment). aPTT = activated partial thromboplastin time. Figure is available in color online only.

this study. Eligible participants who had given informed consent underwent baseline history, physical examination, and imaging followed by 3 separate FUS treatment sessions, each 2 weeks apart. Outcome evaluations were conducted on days 7, 8, 180, and 365 after the last FUS treatment.

FUS Treatment Protocol

The FUS treatment protocol has been published previously by our group.[21,22,24] MR-guided FUS technology involves a transducer helmet array comprising more than 1000 ultrasound transducers precisely converging on a defined focal point in the brain.[13,14] Briefly, participants

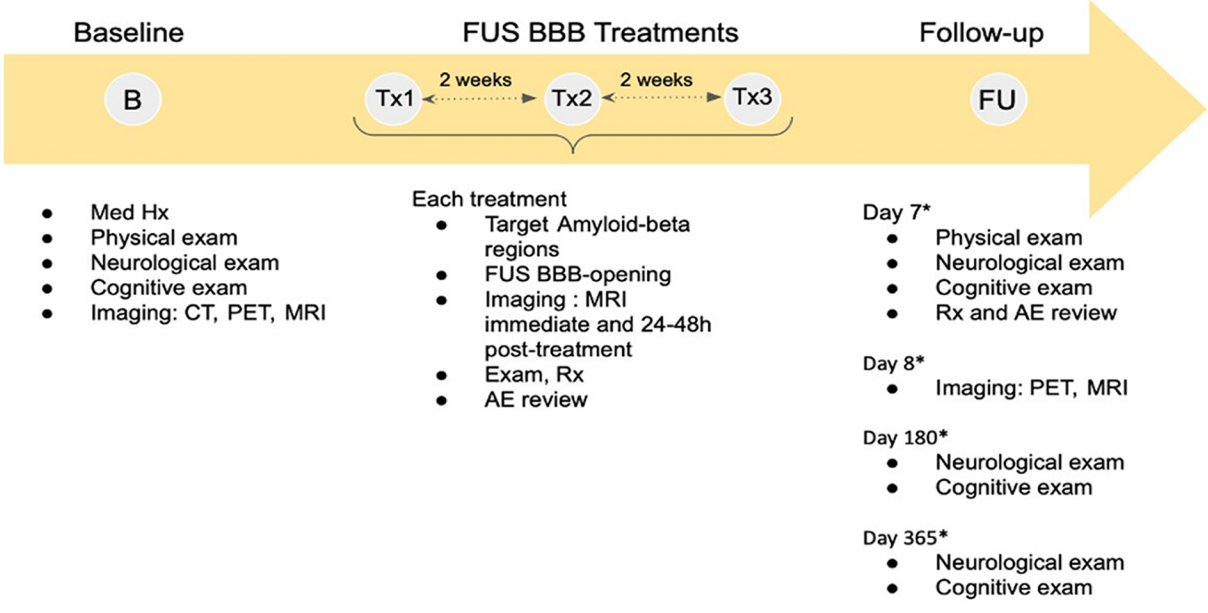

FIG. 2. Clinical trial timeline and evaluations showing the overall treatment and follow-up schedule for all safety and outcome measures reported in this study. AEs are evaluated continuously. *Time period after third treatment. Med Hx = medical history; Rx = prescription; Tx = treatment. Figure is available in color online only.

underwent MR-guided, low-intensity FUS treatment at 220 kHz (ExAblate Neuro Type 2; INSIGHTEC) with concomitant intravenous administration of microbubbles (Perflutren; Lantheus Medical Imaging). Initial FDA approval for the study was limited to the hippocampus and EC in the first 6 participants, and was expanded for increased volume and additional targeting of frontal and parietal lobes in the subsequently enrolled participants.

Imaging and BBB Opening Assessment

Brain MRI was performed on a 3T GE (Architect 3T) and Siemens (Prisma 3T) scanner at baseline, during sonication/treatment (as part of the FUS treatment session), immediately following each sonication/treatment, and at designated times following treatment. Standard MRI sequences included T2* gradient recalled echo imaging, T2 FLAIR, 3D T1 spoiled gradient recalled acquisition, MPRAGE, and T1 with Gd contrast (0.1 mmol/kg intravenous gadobutrol). Brain MRI with and without contrast was performed to assess and document both BBB opening and closure. BBB opening was evaluated by the presence of contrast enhancement within the targeted brain parenchyma on immediate post-FUS MRI following completion of the entire sonication session on each of the 3 treatment sessions.[21,24] A second MRI session with and without contrast was performed 24 hours post-FUS treatment to assess and document BBB closure. If needed, based on the results of the 24-hour images, additional MRI was performed at 48 hours or later to verify BBB closure. PET images were obtained after intravenous injection of ^{18}F-florbetaben[25] to identify and quantify β-amyloid presence at baseline and 1 week after the third FUS treatment.

Imaging Analysis

The MRI studies were reviewed and interpreted by experienced neuroradiologists and neurosurgeons to detect infarction, hemorrhage, edema, and gliosis. In addition, these investigators quantified the BBB opening and closure via evaluation of contrast enhancement volumes by manually segmenting the regions presenting parenchymal contrast, with subsequent comparisons to the planned target regions.

To evaluate the impact of FUS on β-amyloid in the target areas, PET images were coregistered with MR images to allow alignment of β-amyloid to the MR images used for FUS targeting and to evaluate the impact of FUS on β-amyloid in the target areas. Segmentation of brain regions permitted quantified assessments of contrast enhancement and β-amyloid. Segmentation was achieved using an MRI 3D T1-weighted sequence and an automated brain segmentation algorithm incorporating machine learning methods validated in the previous studies.[21,26] The uptake of β-amyloid markers obtained from PET imaging was aligned to the segmented brain regions identified on MRI by using a rigid registration method.[27] To track focal β-amyloid changes associated with FUS-mediated BBB opening within the targets, we computed the standard uptake values ratio (SUVr)[21] and the Centiloid scale for quantifying β-amyloid PET[28–32] in the FUS-treated regions. The Centiloid scale was developed to standardize quantitative amyloid imaging–based reported outcomes in AD. The approach quantifies the outcomes of a particular analysis method and amyloid tracer according to a 0–100 scale, anchored by young controls (≤ 45 years of age) and AD-positive patients. To assess the impact of the therapy, we calculated the average β-amyloid change in the FUS therapy zone. Although all participants were required to be β-amyloid positive as part of the inclusion criteria in the study, we used the commonly accepted SUVr cutoff value of 1.4[33–35] for amyloid positivity for the quantitative calculation in the focal targeted regions.

Participant Outcome Measures

Clinical AEs

A complete standard neurological examination was performed by a board-certified neurologist at baseline, immediately prior to and after FUS treatments, and on days 7, 180, and 365 following the third (i.e., last) FUS treatment. Additional assessments were performed as needed based on any safety concerns.

Cognitive Outcomes

Cognitive assessments were performed at baseline and on days 180 and 365 following the third (i.e., last) FUS treatment. Cognitive tests included (MMSE,[36] range 0–30) and the Alzheimer's Disease Assessment Scale–cognitive (ADAS-Cog,[37] range 0–70).

The cognitive performance (MMSE and ADAS-Cog) scores of our treatment cohort were compared to age- and sex-matched patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership led by Principal Investigator Michael W. Weiner, MD. The primary goal of the ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early AD. We selected age- and sex-matched ADNI participants who had been diagnosed with AD at baseline and who had been assessed with both the MMSE and ADAS-Cog at baseline, at 6-month follow-up, and at 12-month follow-up, with no missing data. Given the small number of participants, descriptive statistics are presented.

Results

Participants

Ten participants with mild AD, aged 55–76 years, mean age 66.6 years, were enrolled at West Virginia University Rockefeller Neuroscience Institute (8 participants) and Weill Cornell Medical College (2 participants) (Table 1).

BBB Opening

All 10 participants completed 3 FUS BBB opening procedures for a total of 30 distinct treatment sessions. Immediate BBB opening of the FUS target region was demonstrated by parenchymal contrast enhancement in

TABLE 1. Characteristics of 10 participants with AD

Case No.	Study Site	Age (yrs)	Sex	MMSE Score	ADAS-Cog Score	ApoE
1	WVU-RNI	61	F	23	19	ε3/ε3
2	WVU-RNI	73	F	23	12	ε3/ε3
3	WVU-RNI	73	F	23	10	ε3/ε4
4	WCMC	71	F	22	26	ε3/ε4
5	WVU-RNI	68	M	22	19	ε3/ε3
6	WCMC	55	F	26	14	ε3/ε4
7	WVU-RNI	55	F	19	24	ε3/ε3
8	WVU-RNI	63	M	24	17	ε3/ε4
9	WVU-RNI	70	M	22	15	ε3/ε4
10	WVU-RNI	76	F	25	17	ε3/ε4

WCMC = Weill Cornell Medical College; WVU-RNI = West Virginia University Rockefeller Neuroscience Institute.

all participants and sessions. The BBB opening, which was determined by contrast enhancement, was confined to the FUS target region and did not occur in other brain regions. The MRI-based segmental volumetric analysis demonstrated BBB opening involving an average of 82% (range 53%–99%) of the FUS-treated brain region as assessed by 3 experts (1 neurosurgeon and 2 neuroradiologists). All BBB openings were transient, and BBB closure occurred within 24–48 hours in all targeted brain regions of all participants (Fig. 3).

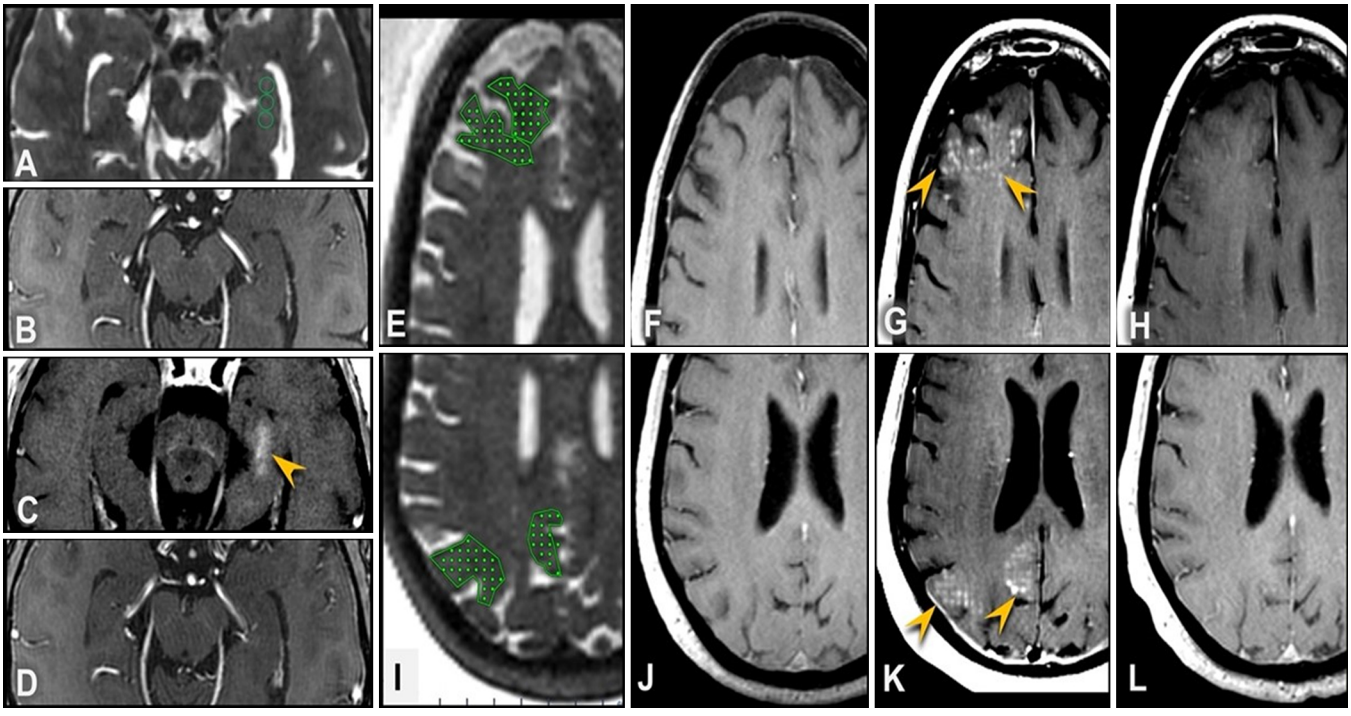

FIG. 3. MRI evidence of BBB opening and closure in the hippocampus, frontal lobe, and parietal lobe. **A:** Axial T2-weighted MR image shows 3 target sites (*green circles*) in the left hippocampus. **B–D:** Baseline (B), immediate post-FUS (C), and 24 hours post-FUS (D) contrast-enhanced axial T1-weighted MR images show parenchymal contrast enhancement at targeted hippocampal sites (*arrowhead*, C), indicating BBB opening and resolution of enhancement at 24 hours following repeat contrast administration, indicative of BBB closure. **E:** Axial T2-weighted MR image shows target sites (*green dots*) in the right frontal lobe. **F–H:** Baseline (F), immediate post-FUS (G), and 24 hours post-FUS (H) contrast-enhanced axial T1-weighted MR images show parenchymal contrast enhancement at targeted right frontal lobe sites (*arrowheads*, G), indicating BBB opening, and resolution of enhancement at 24 hours following repeat contrast administration, indicative of BBB closure. **I:** Axial T2-weighted MR image shows target sites (*green dots*) in the right parietal lobe. **J–L:** Baseline (J), immediate post-FUS (K), and 24 hours post-FUS (L) contrast-enhanced axial T1-weighted MR images show parenchymal contrast enhancement at targeted right parietal lobe sites (*arrowheads*, K), indicating BBB opening, and resolution of enhancement at 24 hours following repeat contrast administration, indicative of BBB closure. Figure is available in color online only.

TABLE 2. Cognitive outcome in 10 patients and 33 controls with AD

Scoring System & Participants*	Baseline	6 Mos, n = 10	1 Yr, n = 7	Mean Relative Change From Baseline†	
				6 Mos	1 Yr
MMSE					
FUS group	22.9 (1.9)	22.6 (2.7)	20.3 (3.5)	–0.3 (3.1)	–2.6 (4.1)
ADNI group	23.2 (2.3)	22.1 (3.7)	19.3 (4.6)	–1.1 (2.7)	–3.9 (4.0)
ADAS-Cog					
FUS group	17.3 (5.0)	17.1 (2.7)	21.9 (8.8)	–0.2 (5.7)	4.1 (6.8)
ADNI group	21.1 (6.9)	22.8 (6.9)	27.6 (9.8)	1.7 (5.6)	6.5 (6.8)

Values are expressed as the mean (± SD).
* Control group (n = 33, mean age 67.9 years, sex matched to each FUS participant) was obtained from the ADNI database. For MMSE, lower scores denote worse performance. For ADAS-Cog, higher scores denote worse performance.
† Values represent the average of each individual change score from baseline.

Safety

Participants tolerated the procedure well, with no procedure-related serious AEs (SAEs). No new neurological findings were present on examination at any time point. All participants were discharged from observation within 24 hours of each of the 30 procedures. T2* MRI immediately following FUS treatment and at subsequent follow-up did not indicate any overt hemorrhage. One participant had small transient edema in the hippocampus that resolved in 72 hours, with no associated clinical significance. There was no indication of infarction or gliosis in the targeted areas, as indicated by persistent increases on T2-weighted FLAIR imaging. Two of the study participants had SAEs unrelated to the study. One male participant was diagnosed with pancreatic adenocarcinoma and died 3 weeks after this diagnosis; his death occurred 44 weeks after his enrollment in the study, and 36 weeks after completion of the final treatment. A female participant was diagnosed with bilateral ovarian cancer involving the peritoneum and colon. She underwent surgical removal of the mass followed by chemotherapy. Subsequently, she had a recurrence and completed a second round of chemotherapy, which was complicated by renal failure and increased depression.

Cognitive Outcomes

Ten participants completed 6-month assessments, and 7 completed 1-year follow-up assessments (see Table 2). At the 6-month follow-up (n = 10), cognitive function was stable compared to baseline. At the 1-year follow-up (n = 7), cognition showed a decline in the overall group, similar to what was observed in the ADNI cohort. As a group, all FUS participants are within 2 SDs of the change on the MMSE and ADAS-Cog scores at the 6- and 12-month follow-ups compared to the matched group (age, sex) of ADNI participants. No individual FUS participant showed greater decline than the greatest individual decline observed in the ADNI-matched comparison group. Finally, no individual FUS-treated participant demonstrated change greater than 2 SDs from the mean scores for the MMSE and ADAS-Cog of the ADNI comparison group.

PET Outcomes

Table 3 shows the focal β-amyloid PET analysis results for all 10 participants. We observed an average reduction in SUVr of 5% (± 4%) in the focal FUS target zone, which corresponds to a reduction of 14% (± 14%) on the Centiloid scale from baseline (before FUS) compared to after the third FUS treatment (approximately 8 weeks). These values are expressed as the mean (± SD). Although all the participants were eligible for enrollment per the qualitative global uptake positivity criteria on β-amyloid PET, 3 participants (cases 4–6) had a baseline SUVr lower than the cutoff value of 1.4 in AD within the FUS target region. These 3 participants were thus removed to be consistent with published cutoff values for comparative analysis.

Discussion

FUS is a noninvasive outpatient procedure that allows for conformal and reversible BBB opening. We and others have reported initial safety and feasibility of FUS-mediated focal BBB opening targeting limited brain volumes in a single brain region among a small group of patients with mild AD, with no longer-term outcomes.[22,38,39] We now report FUS-mediated BBB opening in multiple brain locations, comprising far larger brain volumes than previously described. We progressively expanded the target volume from 5 cm^3 in one brain target (hippocampus/EC)[22] to 30 cm^3, covering additional areas in the frontal and parietal lobe associated with cognition, executive function, behavior, and spatial orientation.[40] Importantly, 12-month cognitive outcomes after FUS treatment were similar to those reported in the ADNI cohort, suggesting that FUS treatment does not accelerate cognitive decline in early AD. All 10 participants had safe and reversible BBB opening across 30 separate treatment sessions, with no procedure-related SAEs.

Although this study targeted FUS to larger brain volumes and multiple locations, the accuracy and efficiency of BBB opening within all targeted areas was precise and conformal. BBB opening was reversed within 24–48 hours after each FUS treatment. Quantitative analysis of BBB opening showed an average of 82% opening of the targeted region. This suggests that FUS can be used to open the BBB safely, repeatedly, and reproducibly in multiple cortical and subcortical regions and in larger volumes in patients with AD.

We observed an average focal reduction of β-amyloid in the FUS-targeted regions of 5% SUVr and 14% Centiloid

TABLE 3. Focal β-amyloid PET results in 10 patients with AD

Case No.	Regions	Baseline SUVr	Post-FUS SUVr	SUVr Change (%)	Baseline Centiloid Units	Post-FUS Centiloid Units	Change in Centiloid Units (%)
1	Hipp/EC	1.79	1.57	–0.22 (–12%)	146	97	–49 (–34%)
2	Hipp/EC	1.47	1.39	–0.08 (–6%)	76	57	–19 (–25%)
3	Hipp/EC	1.80	1.77	–0.03 (–2%)	148	141	–7 (–5%)
4*	Hipp/EC	1.00	0.99	–0.01 (–1%)	–28	–30	–2 (–7%)
5*	Hipp/EC	0.91	0.91	0.00 (0%)	–49	–49	0 (0%)
6*	Hipp/EC	1.27	1.05	–0.22 (–17%)	31	–17	–49 (–158%)
7	Hipp/EC, parietal	4.36	4.03	–0.32 (–7%)	398	336	–62 (–16%)
8	Hipp/EC, parietal, frontal	5.63	5.45	–0.18 (–3%)	442	406	–36 (–8%)
9	Hipp/EC, parietal, frontal	4.73	4.71	–0.02 (–0.4%)	264	261	–3 (–1%)
10	Hipp/EC, parietal, frontal	6.49	6.27	–0.22 (–3%)	617	572	–45 (–7%)

Hipp = hippocampus.

Results from the β-amyloid PET focal analysis reported per participant as the sum value of SUVr and the SUVr normalized to the standard Centiloid scale for targeted region of the hippocampus/EC, parietal lobe, and frontal lobe. Results are reported at baseline and post-FUS (1 week after the third FUS treatment, approximately 60 days after baseline assessment); also reported are their change in raw value and Centiloid units.

* Patients in cases 4–6 showed a baseline SUVr lower than 1.4 in the target region and were therefore excluded from the comparative analysis.

scale after 3 BBB openings (approximately 8 weeks post-baseline). This agrees with the preclinical studies demonstrating a reduction in β-amyloid with BBB opening.[11,17,41] The exact mechanism of FUS-mediated β-amyloid reduction is unknown and is an area of active investigation. Possible mechanisms include activation of microglia and focal inflammation linked to the clearance of β-amyloid protein.[41,42] We recently demonstrated increased perivenous permeability and possible increased glymphatic-mediated clearance after FUS BBB opening.[24] Our observation of β-amyloid reduction needs to be confirmed with a larger sample size. In addition, the clinical significance of β-amyloid reduction in AD needs to be further investigated. Although our current study evaluated changes in β-amyloid with FUS BBB opening, it is plausible that other biomarkers/mediators of the AD pathogenesis, such as Tau proteins, may also be impacted by FUS-mediated BBB opening.

This study addressed several critical issues that are necessary for developing FUS as a viable method for therapeutic intervention in AD and other neurodegenerative disorders. Demonstration of reliable targeting of BBB opening and rigorous follow-up are essential given the potential confounding effects of progressive atrophy and brain structure changes observed in AD and other neurodegenerative conditions.[43,44] A matter of concern in the population of patients with neurodegenerative disorders is the potential for immune-mediated worsening of brain pathology, because there is increasing evidence that immune mechanisms may potentiate pathology and possibly even be primary pathogenic causes of neurodegenerative disease.[45] Although BBB opening could aid in the clearance of β-amyloid, it could also disrupt the relative brain immune privilege resulting from an intact BBB. Exposing the brain to the immune system could result in enhanced inflammation that may exacerbate neurodegenerative conditions, manifesting as a progressive worsening of neurological decline over time compared with the natural history of the disease.

We did not observe evidence of clinically significant inflammation or encephalitis in our study with up to 1 year of follow-up. Moreover, our study did not demonstrate an acceleration of cognitive decline among FUS-treated participants compared to the ADNI control cohort. This suggests that the relatively brief BBB opening following FUS, even in a large volume of brain tissue encompassing multiple at-risk regions, did not adversely impact pathogenesis or worsen the natural history of the disease. However, short-term follow-up in patients with a neurodegenerative disorder may be insufficient to thoroughly evaluate the safety of this technique; therefore, additional participants, larger treatment volumes, longer-term follow-up periods, and a randomized sham-controlled study are necessary for definitive conclusions to be made.

Although FUS-mediated BBB opening alone can reduce β-amyloid and potentially be of therapeutic benefit, the possibility of additional targeted delivery of therapeutic or disease-modifying agents has important implications for AD and other neurological conditions. In this context, we have demonstrated efficient and focal delivery of Gd-based contrast into the hippocampus/EC, and into the temporal, frontal, and parietal lobes after BBB opening in patients with AD. Furthermore, a recent AD preclinical study has demonstrated enhanced focal aducanumab delivery with FUS BBB opening,[46] and a clinical study has demonstrated safe monoclonal antibody delivery to the brain following FUS-mediated BBB opening in metastatic brain cancer.[47] Coupling the on-demand noninvasive BBB opening with precision-targeted, conformal delivery of medications, immunotherapy, gene therapy, and cell therapy provides new opportunities to advance disease-modifying treatments in patients with neurodegenerative disorders while minimizing the risks associated with invasive surgery that are often particularly concerning in these populations.

Conclusions

We have shown that FUS provides a safe, noninvasive, and reversible focal opening of the BBB across substantial volumes of multiple brain regions in 10 patients with mild

AD. Clinical efficacy and impact on β-amyloid and other biomarkers can be further determined with future studies that include larger sample sizes, larger brain volume treatment, and longer follow-up. FUS combined with medications, antibodies, or other therapeutics offers a unique opportunity for investigations in a focused and targeted approach. The FUS technology has evolved since the enrollment of our first AD study participant in October 2018. Current technology now provides for frameless procedures and no longer requires the head to be shaved, which is likely to enhance patient comfort and the acceptability of the procedure. These and other innovations should significantly expand the adoption and widespread use of this technology and should lower the barrier for multiple treatments.

Appendix

Data used in preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Disclosures

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