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Review article

Therapeutic use of transcranial ultrasound for epilepsy: A review

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ABSTRACT

Up to 40 % of people with epilepsy (PwE) suffer from drug-resistant epilepsy (DRE). Despite the approval of novel anti-seizure medication (ASM), a significant treatment gap persists, emphasizing the need for alternative therapies. Transcranial delivery of ultrasound waves or focused ultrasound (FUS) is a promising novel non-invasive technique for PwE, capable of targeting deep brain regions at millimeter resolution. High-intensity Focused Ultrasound (HiFU) is used for focal ablation and Low-intensity Focused Ultrasound (LiFU) for non-invasive neuromodulation. Transcranial delivery of ultrasound waves can also be used for targeted drug delivery by either transiently opening the blood-brain barrier (BBB), or increasing focal drug uptake without BBB opening, through mechanisms such as reducing plasma protein binding or drug uncaging. An update on the current state of the art of LiFU, HiFU and ultrasound waves for targeted drug delivery in epilepsy is timely in view of recently performed clinical trials. We provide scientific background and discuss its added value for PwE. The limitations are addressed, and the technique is discussed in the context of currently available therapies for DRE.

1. Introduction

Epilepsy is a highly prevalent chronic neurological disorder affecting 0.5–1% of the population globally. Up to 40 % of people with epilepsy (PwE) do not respond to treatment with anti-seizure medication (ASM) and develop drug-resistant epilepsy (DRE). While several novel ASM have been approved in the past decade, the number of patients with DRE remains high, and a notable treatment gap still exists [1].

Patients with DRE should be referred to a specialized epilepsy center for advanced diagnostics and treatment, where suitability for other therapies can be evaluated. In several patients, the origin of the disorder is located deep within brain tissue requiring highly invasive treatments. These treatments are associated with a significant risk such as the overlap with eloquent cortex, making these treatments not suitable for all patients with DRE [2–4]. More recently, less invasive techniques have been described, including laser interstitial thermal therapy (LITT), radiofrequency ablation and stereotactic radiosurgery. Apart from resective neurosurgery, invasive neuromodulation techniques such as Vagus Nerve Stimulation (VNS) and Deep Brain stimulation (DBS) are available for the treatment of DRE [5,6]. Several non-invasive neuromodulation techniques that use electric or magnetic fields have been investigated in PwE with limited success [7]. The spatial resolution of both transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) is too low, cortical effects vary greatly among subjects, and targeting deeper brain regions remains a challenge [8–12]. TMS and

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tDCS are currently not part of the therapeutic armamentarium for DRE. The development of novel approaches with the ability to non-invasively target structures in various locations in the brain is highly needed.

Ultrasonic waves, delivered at frequencies beyond human hearing (>20 kHz), can be focused to transfer energy to a target with a high spatial resolution and are compatible with other modalities, including MRI and EEG [9]. Focused ultrasound waves can pass through human tissue and penetrate deep into the body. The safety and utility of focused ultrasound have been extensively analysed for many indications, and it is widely used in systemic disorders, including uterine fibroids, bone cancer pain, disorders of the prostate, and nephrolithiasis [13]. While ultrasound, especially at high frequencies, is absorbed and scattered by bone tissue, lower frequencies (e.g., < 1 MHz) have higher penetration depths and can still be effectively focused through the skull, allowing transcranial applications. Frequencies close to 1 MHz have been found to be the most useful for heat deposition [14]. More recently, the technique is also under investigation for the treatment of neurological and psychiatric disorders, including brain tumours, Alzheimer's dementia, Parkinson's disease, neuropathic pain, and obsessive-compulsive disorder [15,16]. Transcranially delivered focused ultrasound waves can be applied in different ways, all minimally invasive, whereby the acoustic energy of the ultrasound waves can interact with human tissue by thermal and mechanical mechanisms [17,18]. High-intensity Focused Ultrasound (HiFU) is used for heating and tissue ablation. Low-intensity Focused Ultrasound (LiFU) has been designed for neuromodulation [19]. Other low to moderate frequencies, ranging from 0.2 to 1.5 MHz, can be used to open the blood-brain barrier (BBB) or enhance focal drug uptake without BBB opening. This is achieved through mechanisms such as reducing plasma protein binding or drug uncaging for targeted CNS drug delivery [20–22]. This review will provide an overview of the potential clinical applications of these various approaches for treating epilepsy, examine clinical trial data, and discuss current limitations of the technique and areas in need of further investigation.

2. Materials and methods

Although this study does not follow the formal criteria of a systematic review, it was conducted in a systematic manner. No review protocol was registered for this study. A comprehensive literature search was performed using the electronic databases PubMed, Embase, and Web of Science. Studies were included if they met the following eligibility criteria: investigated transcranial ultrasound delivery in human studies related to epilepsy, were published from 2022 onwards (using a publication date filter) as the aim was to provide an update on recent developments, addressed at least one of the following aspects: safety, efficacy, or cost-benefit considerations, included any focused ultrasound modality, and no language restrictions were applied. All publication types (e.g., conference abstracts, editorials, and reviews) were considered to ensure a comprehensive assessment of the available research. The full search strategy, including search terms, is provided in Table 1.

Titles and abstracts of all identified records were screened by one reviewer to determine eligibility. Studies that did not meet the inclusion criteria were excluded. Full texts of the remaining manuscripts were retrieved and reviewed in detail. Additional relevant studies were identified through pearl growing, utilizing references from included studies and review articles. Articles unrelated to the topic were excluded.

A standardized data charting form was developed to extract relevant information. Data collection was performed by one reviewer using Microsoft Excel. Extracted data included study characteristics (e.g., authors, year of publication, study design, sample size, patient characteristics, and target area), device details (e.g., ultrasound modality and sonication protocol), outcome measures (e.g.,

Table 1
Search strategy for each database, including the specific search terms used.

Database	Search terms
Pubmed	("focused ultrasound" OR LIFU* OR HIFU OR FUS OR TUS OR FUN OR "transcranial ultrasound stimulation" OR "focused ultrasound therap*" OR "focused ultrasound treatment*" OR "transcranial focused ultrasound" OR "low intensity focused ultrasound" OR "high-intensity focused ultrasound ablation"[Mesh] OR "high-intensity focused ultrasound" OR "Ultrasonic Therapy"[Mesh] OR "ultrasonic therap*") AND ("Epilepsy"[Mesh] OR epilepsy OR "drug resistant epilepsy" OR "refractory epilepsy" OR mechan* OR cavitation OR therm* OR "ion channel*" OR neuromod* OR "Pharmacology"[Mesh] OR "Chemical Actions and Uses"[Mesh] OR "Neurons"[Mesh] OR mechanotransduction OR bioeffect OR "therapy effect")
Embase	('focused ultrasound therapy'/exp OR 'focused ultrasonic ablation' OR 'focused ultrasonic irradiation' OR 'focused ultrasound' OR 'focused ultrasound therapy' OR 'focused ultrasound treatment' OR 'transcranial ultrasound stimulation'/exp OR 'transcranial pulse stimulation'/exp OR 'transcranial focused ultrasound'/exp OR 'transcranial low intensity ultrasound') AND ('epilepsy'/exp OR 'acute epilepsy' OR 'attack, epileptic' OR 'cerebral seizure, epileptic' OR 'chronic epilepsy' OR 'comitial disease' OR 'convulsion, epileptic' OR 'convulsive epilepsy' OR 'epilepsia' OR 'epilepsy' OR 'epilepsy, convulsive OR 'epileptic' OR 'epileptic attack' OR 'epileptic convulsion' OR 'epileptic disorder' OR 'epileptic fit' OR 'epileptic insult' OR 'epileptic seizure' OR 'epileptic seizure, cerebral' OR 'epileptic syndrome' OR 'epileptic syndromes' OR 'falling sickness' OR 'fit, epileptic' OR 'seizure, epileptic' OR 'sickness, falling' OR 'tardy epilepsy' OR 'refractory epilepsy'/exp OR 'drug refractory epilepsy' OR 'drug resistant epilepsy' OR 'intractable epilepsy' OR 'intractable seizure' OR 'medication resistant epilepsy' OR 'pharmaco-refractory epilepsy' OR 'pharmaco-resistant epilepsy' OR 'pharmacorefractory epilepsy' OR 'pharmacoresistant epilepsy' OR 'pharmacotherapy-resistant epilepsy' OR 'refractory epilepsy' OR 'therapy resistant epilepsy' OR 'treatment resistantepilepsy' OR 'physiology'/exp OR 'drug effect'/exp OR 'mechanism of action' OR 'thermal modulation' OR bioeffect OR 'therapy effect'/exp OR 'ion channel' OR 'pharmacology'/exp OR 'drug mechanism' OR pharmacology OR temperature OR 'mechanotransduction'/expOR neuromodulation OR cavitation OR 'nerve cell'/exp) OR mechanosensitivity)
Web of Science	("focused ultrasound" OR FUS OR TUS OR "transcranial ultrasound stimulation" OR LIFU OR HIFU OR MRgFUS OR "low intensity focused ultrasound" OR "high intensity focused ultrasound" OR "therapeutic ultrasound" OR "High-Intensity Focused Ultrasound Ablation" OR "transcranial focused ultrasound" OR "pulsed ultrasound") (All Fields) AND (epilepsy OR "refractory epilepsy" OR DRE OR "drug-resistant epilepsy" OR neuromodulation OR neuromodulate OR "mechanism of action" OR "therapeutic effect" OR cavitation OR "ion channel" OR mechanic OR mechanotransduction OR bioeffect OR pharmacology OR thermal OR temperature OR mechanosensitivity) (All Fields)

efficacy, reported side effects, radiographical follow-up), and follow-up duration. Data were synthesized qualitatively. This search was supplemented with additional information on available devices obtained from the Focused Ultrasound Foundation's website.

3. Results

3.1. High-intensity Focused Ultrasound or HiFU for ablation

When high intensity ultrasound beams are focused to converge at an intracranial target, e.g., an epileptogenic focus or a network, tissue can be ablated in a minimally invasive way. HIFU thus has a controlled lesioning effect achieved through thermal heating of brain tissue at the target [14] (Fig. 1A). The high intensity acoustic pulses may induce a non-thermal, mechanical effect leading to the formation of bubbles which cause shear stress to cells. This can lead to unintended tissue damage, called unstable cavitation [14]. The goal temperature at the target is set at 56°C–60 °C, heating known to create immediate thermal ablation, but below the level of internal cavitation induction [23,24]. The HiFU procedure is typically performed using a helmet formation incorporating >1000 ultrasonic emitters in a hemispheric phased array, combined with real-time MR guidance to repeatedly evaluate the lesion location and monitor intracranial temperature. The procedure can be safely repeated since there is no total dosage limit, due to its non-cumulative and localized energy delivery system, in contrast to other therapies such as radiation or laser treatments [14,22,25,26].

Only one device is currently FDA approved for HiFU (Insightec Neuro Exablate system, Haifa, Israel) and no device has received a CE mark yet. HiFU has been FDA-approved for lesioning of the ventral intermediate nucleus of the thalamus in essential tremor and Parkinson's disease since July 2016 and December 2018, respectively. The safety of HiFU has been investigated in several psychiatric disorders and no major complications have been reported [27,28]. Clinical trials investigating the safety and efficacy for treating brain tumours are ongoing [29].

HiFU ablation of an epileptic focus or network has been performed in a few small clinical trials. In total, eight PwE underwent HiFU to the (para)hypothalamic hamartomas, the hippocampus, and the anterior nucleus of the thalamus (ANT), primarily to investigate safety (Table 2) [23–25,30,31]. Follow-up in these patients ranged from 7 to 43 months [24,25]. Regarding efficacy, these cases and small series with HiFU showed notable reductions in seizure frequency. The first patient with HiFU was treated in 2020 and underwent one sonication procedure intending to disconnect a parahypothalamic hamartoma. Multiple regions at the boundary were targeted, leading to seizure freedom and the EEG showed no remaining spikes at one-year follow-up [25]. In a second patient with temporal lobe epilepsy (TLE) the ipsilateral hippocampus was targeted. One month after the procedure, the patient first experienced a 60 % increase in seizures, followed later at 12 months by a reduction in seizures of >90 % [24]. Treatment in these two patients allowed a reduction of ASM dosages [24,25]. Two years later, HiFU-induced ablation of a hypothalamic hamartoma was performed in a case series of three patients, leading to reductions in seizure frequency varying from 90 % to complete seizure freedom [23].

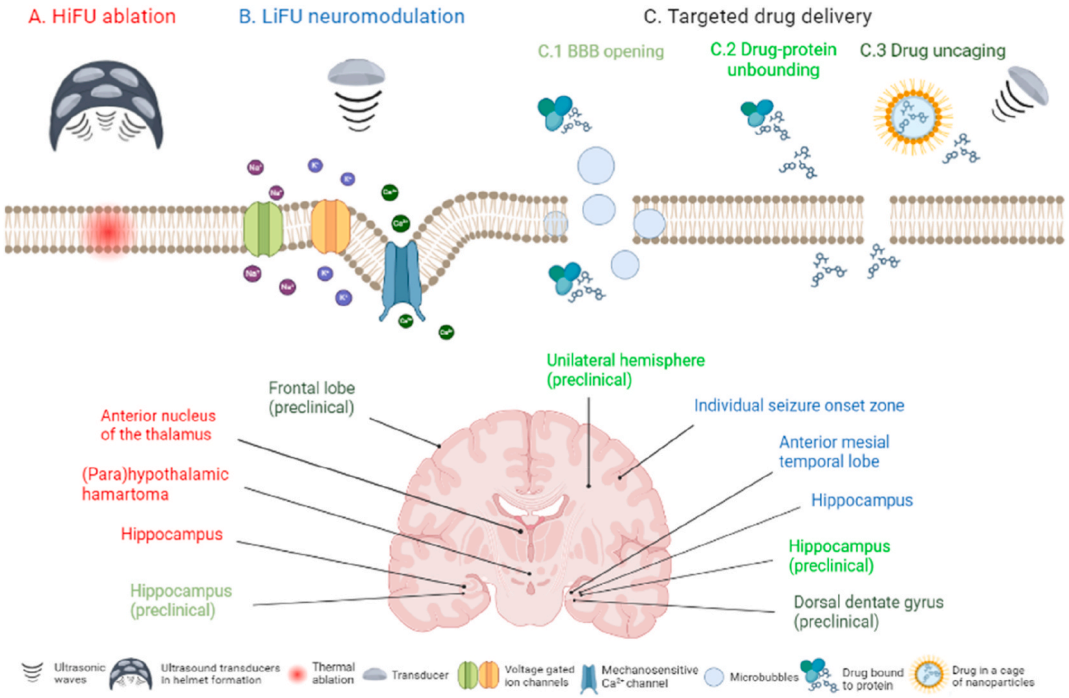

Fig. 1. Schematic figure depicting the different mechanisms of focused ultrasound and potential targets in epilepsy. Legend: red: ablative HiFU targets in humans (A), blue: neuromodulatory LiFU targets in humans (B) and green: targets for three types of drug delivery in rodents (C) (created with Biorender).

Table 2
Overview of clinical trials with HiFU (ExAblate, Insightec, Haifa, Israel). Legend: NS: not specified, d: day, m: months, CBZ: carbamazepine, FOS: focal onset seizures, LEV: levetiracetam, NR: not reported, GTCS: generalized tonic-clonic seizure, FF: fundamental frequency, Fa: female a, Fb: female b, Ma: male a, Mb: male b, ANT: anterior nucleus of the thalamus.

Publication	Patient characteristics	Target	Sonication protocol	Radiographical follow-up	Efficacy	(Sub)acute side effects	Chronic side effects	Follow-up (m)
Yamaguchi et al. (2020) [25]	N = 1 (M, 26 yrs) gelastic seizures	parahypothalamic hamartoma	6 sonications (NS), 50–53 °C	- MRI 1d after HiFU: oval-shaped lesion at target - FDG-PET 3m after HiFU: increase metabolism bilateral inferior frontal lobe and temporoparietal lobe - MRI 12m after HiFU: faint hypointense zone in ablated area	– 12m after HiFU: seizure free, spike free EEG – 87 % reduction dosage CBZ - improvement memory and concentration	nausea and vomiting during procedure	none	12
Abe et al. (2020) [24]	N = 1 (F, 36 yrs) FOS with impaired awareness	left-sided (ipsilateral), hypometabolic hippocampus	12 sonications of 10–20s, 42–44 °C	- MRI day 0 + 1m after HiFU: no lesion or oedema at target - FDG-PET (time point NR): increase in metabolism in left lateral temporal lobe, bilateral striata and frontal bases, left and posterior cingulate gyrus, decrease hypometabolism in left medial temporal tip	- 1m after HiFU: 60 % increase seizure frequency – 12m after HiFU: significant reduction seizure frequency (NS) + 50 % reduction dosage LEV	scalp heating, dizziness and headache during procedure	none	12
Tierney et al. (2022) [23]	N = 3 (1M, 2F, 18–22 yrs) **Fa**: gelastic seizures **Fb**: gelastic seizures, absences and GTCS **M**: hypnopompic seizures	hypothalamic hamartoma	FF 650 kHz, power up to 1500W, max 54–59 °C	**M**: MRI day 0 after HiFU: target coverage, no off-target ablation, no haemorrhage - MRI 12m after HiFU: sustained changes **Fa**: MRI day 0 after HiFU: complete target coverage, gliosis, no off-target ablation, no haemorrhage - MRI 12m after HiFU: earlier signal changes decreased **Fb**: MRI day 0 after HiFU: target coverage, no haemorrhage - MRI 12m after HiFU: sustained changes	**M**: 24m after HiFU: overall 90 % seizure reduction **Fa**: immediately seizure free up to 9m follow-up, recurrence seizures while off medication **Fb**: 30m after HiFU: 95 % reduction GTCS, seizure free for gelastic seizures and absences **Fb, M**: attenuation of neuro-cognitive and behavioural problems	**M**: intraoperative scalp heating	none	12–43
Krishna et al. (2023) [30]	N = 2 (M, 39–57 yrs) FOS	ipsilateral (**Ma**) or contralateral (**Mb**) ANT	NR	**Ma**: MRI 1d after HiFU: target coverage, no off-target ablation, no haemorrhage **Mb**: MRI 1d after HiFU: target coverage	**Ma,b**: immediate seizure reduction **Ma**: 12m follow-up: 95 % seizure reduction **Mb**: 1m after HiFU: seizure free up to 12m after HiFU + reduced doses ASM	**Ma**: postprocedure decline verbal memory **Mb**: postprocedure transient headache lasting few hours	**Ma**: decline verbal memory, stable up to 12m **Mb**: 3m after HiFU: decline verbal fluency, attention- and verbal memory, stable up to 12m	12 ± 1
Galimova et al. (2024) [31]	N = 1 (F, 32 yrs) gelastic and dacryocystic seizures, focal hypomotor seizures with impaired awareness, GTCS	type II hypothalamic hamartoma	9 sonications of 15–25s, T 52–58 °C, 10.000–22.000 J	MRI day 0 after HiFU: mild swelling along edge HH and focal necrosis at target sites, no haemorrhage	- immediate seizure reduction - 6m after HiFU: significant reduction epileptiform activities on video-EEG - 7m after HiFU: seizure free for gelastic and dacryocystic seizures, GTCS once a month, and attenuation of social and professional activities	nausea, feelings of temperature change during procedure	none	7

In 2023, Krishna et al. reported on two patients with focal onset epilepsy who underwent HiFU targeted to the ANT. In the first patient, with a hypothesised seizure onset located in the left frontal region involving Broca's area, the ipsilateral ANT was ablated. The second patient suffered from TLE with a cavernous malformation on the right side, believed to be the seizure onset zone. In the latter, the contralateral ANT was ablated, since the ipsilateral ANT was atrophic. Both patients showed an immediate reduction in seizure frequency and became seizure-free one month after the intervention. The first patient reported a reoccurrence of the seizures but had experienced a reduction in monthly seizure frequency of 95 % at 12 months follow-up. An earlier treatment with ANT deep brain stimulation had already resulted in a seizure frequency reduction of 65 %. The second patient, in whom the contralateral ANT was targeted, remained seizure free at 12 months follow-up. The MRI tractography had shown extensive bilateral connections of the ANT to the cingulate, frontal, and temporal regions [30].

More recently, Galimova et al. published the case of a patient who received nine sonications to a hamartoma and became immediately free from gelastic and dacryocystic seizures for up to seven months post-intervention. However, she still experienced monthly bilateral tonic-clonic convulsions. A comparison of video-EEG monitoring before and six months after HiFU showed a significant decrease in epileptiform discharges in the right temporal region [31]. Apart from seizure improvements in these eight initial PwE, several other positive observations were noted. The first patient treated with HiFU showed improvement in memory and concentration [25]. Tierney et al. observed attenuation of neuro-cognitive and behavioural difficulties [23]. Galimova et al. reported positive changes in social and professional activities [31].

In this initial series of patients treated with HiFU, only mild to moderate acute side effects were observed during sonication, including transient nausea and vomiting [25,31], feeling cold or hot [31], headache, and dizziness [23,24]; which were probably attributed to skull heating. In two patients, the sonication procedure was paused due to the detection of acoustic cavitation. Pausing for a cooling period resulted in no further cavitation events [23]. Only in the two patients who received ANT HiFU long-term side effects were reported. One of them reported a postprocedure decline in verbal memory and fluency. The neurophysiological examination was stable at 12 months. Delayed free recall did worsen at 12 months follow-up compared to three months. The other patient experienced a headache for a few hours after HiFU and a delayed decline in verbal memory, attention, and working memory, observed three months after the sonication of the left ANT. The neuropsychological examination remained compromised, but without worsening, at 12 months. This patient's self-reported depression score also worsened, which may have impacted performance in other cognitive domains [30].

Besides intra-operative MR monitoring, i.e. thermography, post-intervention MRI was performed in all eight patients immediately following the intervention or one day later. MR images revealed no unexpected abnormalities, and the intended target coverage was seen in 7/8 patients [23,25,31]. In the remaining patient, the targeted temperature increase had not been reached during the procedure. The maximal permitted energy could not generate the desired temperature, possibly due to the relatively small number of transducer elements [24]. Five out of eight patients received a second MRI at a later time point during their follow-up, respectively after one month in one patient and after 12 months in the remaining four [23–25]. In the patient without target coverage immediately post-intervention, the 1-month follow-up MRI remained unchanged. In one other patient, the target coverage (that was described earlier) and the gliosis (indicating the lesion) had diminished after 12 months [23]. In these two patients in whom no thermal ablation was achieved, pre-and post HiFU FDG-PET comparison did demonstrate an increase in metabolism in the focus and surrounding regions. The authors suggested that despite the absence of a visible lesion, the clinical effects might be caused by neuromodulatory rather than lesional mechanisms. Another possibility was that the changes in the hippocampal structures were not visible on MR imaging [24,25]. Currently, HiFU is being trialed via thalamotomy and for seizure focus ablation (Clinicaltrials.gov with identifiers: NCT03417297, NCT05032105, NCT02804230).

3.2. *Low-intensity Focused Ultrasound or LiFU for neuromodulation*

LiFU can produce reversible neuromodulatory effects in a region-specific manner when ultrasonic waves are focused at the area of interest (Fig. 1B). While the highest level of focality can be achieved with hemispheric arrays, such as the ones used for HiFU, smaller transducers can still effectively focus through the skull, albeit with a larger, more elongated focus. The transducers often have a bowl-shaped surface or an acoustic lens, leading to a geometric focus, with electronic control over array elements to allow steering of the focus. Transducers can be handheld or worn in a headset and are connected to a power output of which various parameters can be modified to deliver acoustic energy at specific pulsing schemes [32]. Important sonication parameters include the fundamental frequency, peak intensity, the pulse duration, the pulse repetition frequency, and the duration of the pulse train or sonication [33–35]. At focus, selective alteration of neural activity, including neural inhibition or activation can be achieved, leading to circuit-level neuromodulation [36]. Different hypotheses on the mechanism of action of LiFU have been proposed to acknowledge its potential for various applications in neuromodulation. Possible mechanisms include modulation of neuronal activity by activation of mechanosensitive calcium channels and voltage-gated ion channels, which is comparable to the working mechanism of some ASM [17,35,37,38] (Fig. 1B). Additionally, the regulation of thalamic GABAergic inhibitory neurons may play a role in reducing epileptic activity. Unlike HiFU for tremor, LiFU is an emerging neurotechnology and has not yet received FDA approval or CE marking. Initially, the safety and efficacy of LiFU to manipulate activity in many brain areas were investigated in healthy human populations and in animals [19,39–46], and recently an international expert consensus on the biophysical safety of LiFU has been proposed [47].

The profile and incidence of adverse effects are comparable to other forms of non-invasive brain stimulation. Adverse effects were mild to moderate and transient and included neck pain, muscle twitches, anxiety, scalp tingling, and headache [48]. LiFU has also been investigated in patients with neuropathic pain and neuropsychiatric disorders such as depression and anxiety [13]. If found to be effective, LiFU may provide a unique non-invasive neuromodulatory alternative for PwE, since current neuromodulatory options for

DRE involve permanently implanted electrostimulation devices.

Earlier preclinical data demonstrated that LiFU was able to suppress epileptiform activities and seizures in rodents and monkeys [49–56]. Following this, three human studies investigating safety as a primary outcome have been conducted (Table 3) [57–60]. In 2021, the first case series demonstrated histopathologic safety after delivery of a single session of LiFU to the anteromesial temporal lobe in eight patients who were planned to undergo temporal lobectomy epilepsy surgery [60,61]. Two prospective pilot trials, each including six PwE, were then performed with a maximum follow-up ranging from 28 days to 6 months [57,58]. In the first prospective trial in 2022, Lee et al. delivered 10 min LiFU targeting the presumed seizure onset zone in patients undergoing invasive EEG recording for presurgical evaluation [57]. Two out of three patients from whom seizures could be recorded within 72 h after LiFU, had a decrease in seizure frequency. One patient had no change in clinical seizures but was found to have an increase in subclinical seizures observed on SEEG. After LiFU delivery, the time to seizure recurrence ranged from 4 h to 5 months [57]. Four out of six patients showed some form of decrease in interictal epileptiform discharges, whereas two patients had a transient increase [57]. Changes in spectral power were observed during and after the sonication. During treatment, the spectral power increased in five out of six patients in at least one of the four frequency bands. Ten minutes after LiFU, in three patients a significant decrease was seen in all frequency bands of signals recorded from the target electrodes, while this was not significant in the wider areas. Two of these patients showed a significant decrease in power from the delta to beta bands. No correlation between significant short-duration changes in spectral power analysis and subsequent seizure control was found. One patient received a second treatment after a pause, which led to a more significant decrease in spectral power of the delta band on SEEG compared to the first session. Therefore, a dose-dependent effect of the treatment was suggested based on the SEEG analysis [57].

Bubrick et al. delivered serial treatments of LiFU to the anterior hippocampus (4 mm apart) in six patients with TLE. A total of six sessions of 140s were delivered per target, twice a week over three weeks with a gradually increasing intensity [58]. An average seizure frequency reduction of 50 % was found. Five out of six patients had an important seizure reduction during the six-month follow-up period. One patient remained seizure free for over a year. In the other four patients, the duration of frequency reduction varied from weeks to several months [58]. In a subset of three patients who underwent resting-state functional MRI (rs-fMRI) before and after LiFU, two showed improvements in functional brain connectivity, while the other subject who had very little reduction in seizures, did not [58].

In Stern et al., several sonication protocols with different parameters were investigated. Four out of eight patients underwent two pulsing protocols and had a small decrease in verbal memory on neuropsychological testing immediately after the sonication. Comparison with patients receiving another protocol was impossible due to the small number of patients [60]. These eight patients underwent resective surgery, and the brain specimens showed no histological complications due to sonication in 7 out of the 8 patients. The tissue did not show necrosis, vascular damage, acidophilic or ischemic neurons, or extravasation. In one patient, acidophilic neurons and extravasation in the sonicated tissue were evident, but this was also observed in unsonicated regions, which made these results inconclusive [60].

In the two prospective pilot trials only mild, acute effects were reported [57,58]. In Lee et al., during treatment, a mild headache and transient scalp heating were reported in three and one out of six patients, respectively. An impairment in naming and memory performance was found between days 4 and 11 following LiFU in one other patient. This was resolved within three weeks [57]. In the study by Bubrick et al., one patient experienced a habitual seizure at the end of the first sonication. Reducing the duty cycle from 50 % to 18.3 % for the remaining subjects resulted in no additional clinical epileptic events. The association with the procedure of LiFU delivery remained uncertain and no other patient reported adverse events during or after the procedure. No significant problems in memory or mood were observed during, or 1 month post-treatment [58]. In none of the patients, structural changes were seen on the MRI post-LiFU, performed after two weeks in the series of Lee et al. and after one month in Bubrick et al. [57,58]. A subgroup analysis of four patients in the first study who underwent contrast imaging demonstrated no contrast leakage, indicating that the BBB remained intact [57]. One patient underwent surgery of the identified epileptic zone after two months, and indications of gliosis were found without any other cortical or sub-cortical changes on histological analysis [57]. A number of trials using LiFU to target the temporal lobe and individual seizure onset zone in epilepsy patients are currently ongoing (Clinialtrials.gov with identifiers: NCT05947656, NCT02151175, NCT04999046, NCT06492720, NCT06388707).

3.3. Targeted drug delivery

Ultrasound waves can enhance drug delivery to the central nervous system (CNS) by different mechanisms (Fig. 1C). The BBB permeability can be transiently and focally increased in a specific brain region to promote the transport of drugs that are, under physiological conditions, unable to cross the BBB. It was first demonstrated that HiFU increased the permeability of the BBB, but this was associated with brain damage. In 2001, Hynynen et al. introduced a technique whereby LiFU is combined with a peripheral intravenous injection of microbubbles [34]. These microspheres of gas covered by a shell of lipid or proteins oscillate in response to sonication and in this way facilitate BBB opening. This effect is called stable cavitation and occurs only in the targeted region (Fig. 1C1) [21]. The delivered energy accumulates inside the blood vessel and generates a mechanical effect on the vascular wall, which leads to a transient and localized opening of the BBB [22,62–64]. The used intensity lays mostly between 100 and 200W/cm^2 [33]. A few hours later, the BBB closes again, and normal cerebral functions are observed [62].

Both preclinical and clinical studies have investigated this technique and have found it to be non-invasive and safe. In view of the high spatial resolution of this approach, the risk of side effects is limited and can be repeated multiple times without tissue damage [22,62,65]. In 2016, the first-in-human BBB opening study was performed using a transducer surgically implanted in the epidural space, above the tumour in patients with recurrent glioblastoma [66]. The device used was SonoCloud (CarThera, France), which has

Table 3
Overview of clinical studies with LiFU. Legend: yrs: years old, TLE: temporal lobe epilepsy, w: weeks, FF: fundamental frequency, PRF: pulse repetition frequency, SD: sonication duration, ISI: interstimulus interval, DC: duty cycle, ISPTA: intracranial spatial-peak temporal-average intensity, PT: pulse train, NR: not reported, FOS: focal onset seizure, secondary generalization, PW: pulse width, RAVLT = Rey Auditory Verbal Learning Test, BVMT-R = brief visuospatial memory test-revised, NS: not specified, BL: burst length, MI = mechanical index, d: days, SEEG: stereo-EEG, m: months, h: hours, BRP: burst repetition duration, DMN: default mode network.

Publication	Patient characteristics	Target	Sonication protocol	Device	Main outcome measurements/results	Side effects	Follow-up
Lee et al. (2022) [57]	N = 6 (4M, 2F, 26–42 yrs) undergoing SEEG FOS (type NS)	SOZ: left fusiform gyrus (N = 1), left premotor gyrus (N = 1), right frontal operculum (N = 1), left body of hippocampus (N = 1), right superior border of insula (N = 1), left anterior cingulate (N = 1)	FF NR, PRF 100 Hz, ISPTA <2.8 W/cm2, BL 3 ms, MI 0.75, DC 30 %, PT: 600s	NaviFUS (NaviFUS Corporation, Taipei City, Taiwan) + neuronavigation	**seizure frequency** up to 14d after LiFU: – 72h after LiFU: 2/3 decrease seizure frequency, 1/3 increase in seizure frequency (subclinical seizures) - time to seizure reoccurrence range from 4h to 5m **interictal epileptiform discharges** 72h after LiFU SEEG: 4/6 patients decrease in epileptic discharges, 2/6 increase **spectral analysis** from target electrode 10min prior, during and 10min after LiFU: - during LiFU: 5/6 patients increase in spectral power in at least ¼ frequency bands - after LiFU: 3/6 decrease in spectral power, 2/3: significant decrease in power from delta to beta band **MRI** 14d after LiFU: in 6/6 patients no changes, in 4/4 no contrast leakage **histology** 2m after LiFU (N = 1): gliosis without other cortical or sub-cortical changes	- during sonication scalp heating in 1/6, headache in 3/6 - transient impairment in naming and memory in 1/6 between 4d and 11d after LiFU, up to 3w	28d
Bubrick et al. (2023) [58]	N = 6 (5M, 1F, 23–73 yrs) unilateral TLE (N = 5) bilateral TLE (N = 1)	4 hippocampal targets: ipsilateral (N = 5), left side (N = 1)<	6 sessions (2/w for 3w), for each target: FF 548 kHz, PRF 500 Hz, DC 18–50 %, BRP = 7s, ISPTA = 0.50–1.1 W/cm2, PNP = 0.14–0.42 MPa, PT 140s	custom made device + neuronavigation	**seizure frequency** up to 6m after LiFU: - seizure reduction in 6/6, significant reduction in 5/6, seizure free >1 year in 1/6 **neuropsychological tests** (NS) prior, during and 1m after LiFU: no significant worsening in mood or memory, minimal improvements **MRI** 1m after LiFU: no structural changes **rs-fMRI** 1m after LiFU (N = 3): 2/3 significant improvement DMN organization, 1/3 no changes	During first sonication session: habitual seizure in 1/6	6m

(*continued on next page*)

Table 3 (*continued*)

Publication	Patient characteristics	Target	Sonication protocol	Device	Main outcome measurements/results	Side effects	Follow-up
Stern et al. (2021) [60]	N = 8 (5F, 3M, 22–65 yrs) planned epilepsy surgery for TLE FOS with impaired awareness (N = 7), FOS + SG (N = 1)	anterior mesial temporal lobe to be resected	2 treatment protocols: - suppression: 2 sonications, FF 650 kHz, SD 30s, PW 0.5 ms, PRF 100Hz, DC 5 %, intensity 720 mW/cm^2 - activation: 8 sonications, FF 650 kHz, SD 0.5s, PW 2 ms, PRF 250 Hz, DC 50 %, intensities ranging from 720 mW/cm^2–5760m>/cm^2	BX Pulsar 1002 (BrainSonix Inc., Sherman Oaks, California, USA) MR guided + neuronavigation	**neuropsychological testing** (RAVLT and BVMT-R) prior and day 0 after LiFU: decrease in verbal memory on RAVLT in group receiving suppression + activation (N = 4) **MRI** prior, during and after LiFU: results NR **fMRI** during LiFU: results NR **histology** resected tissue 1w after LiFU: no apoptosis, no necrosis, no vascular damage, no extravasation in 7/8, acidophilic neurons and extravasation in both sonicated and unsonicated regions in 1/8	After LiFU: decrease in verbal memory (N = 4)	NR

received FDA approval to perform a clinical trial for this indication. Recently, a phase I/II clinical trial with the same device showed promising results regarding the ultrasound device combined with carboplatin [67]. Several groups have since investigated non-invasive BBB opening in patients with brain tumours as a means of targeted central nervous system (CNS) delivery of chemotherapeutic agents [66]. This BBB opening strategy is also being studied for the treatment of Alzheimer's disease. It is considered safe en holds promising effects [68]. Rezai et al. conducted a first-in-human clinical trial in Alzheimer's disease and reported the results of three patients who received repetitive antibody infusions immediately followed by LiFU, targeting specific brain regions, including the frontal lobe, the temporal lobe, or the hippocampus where high levels of amyloid-beta were present. There were no adverse events, and the procedure led to a measurable reduction of amyloid-beta on an 18F-florbetaben PET [69].

Focused ultrasound-induced BBB opening for targeted CNS drug delivery in epilepsy has been accomplished in rodent models and showed the ability to reduce epileptic activity [70–72] (Fig. 1C1). This technique has not yet been investigated in PwE. Targeted drug delivery enhancement can also be achieved without BBB disruption using drugs that can penetrate the BBB. When these drugs are highly bound to plasma proteins, the concentration that passes the BBB is low. This is the case for some ASM. Even ASM that can cross the BBB do so diffusely, which can result in global or off-target side effects, such as drowsiness. Delivery to specific brain regions can be enhanced by increasing the local concentration of available unbound drug by reducing the level of the plasma protein binding (PPB) [73]. LiFU applied targeted to a specific region of the brain can temporarily reverse drug PPB in a spatially selective manner (Fig. 1C.2).

The mechanical effects are sufficient to overcome the binding forces involved in PPB, leading to an increased level of unbound drug at the target region, thereby limiting side effects [74,75]. Preclinical research in two rodent studies reported that the anti-epileptic efficacy of intraperitoneal phenytoin was enhanced when used in combination with LiFU applied to one hemisphere and the hippocampus [73,76].

This idea was further developed and evolved in the approach where a drug is dislodged by LiFU from injected engineered nanoparticles (e.g. liposomes) with selective drug affinity, thereby allowing BBB crossing of a targeted drug only at the sonicated region (Fig. 1C.3) [77–79]. This process is known as "drug uncaging" and builds on previously validated approaches using light-dependent release of a drug in a closed-loop system [80]. Previous studies have demonstrated that liposomes are capable of releasing drugs for up to one week after sonication [79].

Two preclinical studies have been conducted: one demonstrated the attenuation of epileptiform activity following sonication of the frontal lobe, while the other found that bilateral sonication of the dentate gyrus was effective in treating a rat model of status epilepticus [77,79]. This research highlights the potential of choosing a pharmacological agent to be delivered focally to the brain and using LiFU to uncage it only in the area of interest. This approach could have potentially transformative utility in treating epileptogenic areas of the brain both in the outpatient setting in DRE as well as in status epilepticus. Much of the morbidity and mortality seen in attempting to treat status epilepticus results from the large number and high doses of ASM required to cross the BBB and abort the seizures. The ability to ensure the rapid delivery of a drug of choice (e.g. propofol) only to the seizure focus could transform how we treat status epilepticus and possible other neurologic emergencies [77,79].

4. Discussion

Early trials of therapeutic delivery of ultrasound waves to the brain have shown promise in treating patients with DRE, with its high

spatial selectivity and capability of reaching deep brain regions [12]. Despite its potential as a minimally invasive technique, the number of completed and ongoing clinical trials for epilepsy remains limited. Phase-I trials are ongoing in epilepsy, and objective outcomes have been only sparsely studied [25,31,57]. Therefore, further research is needed to confirm safety and evaluate efficacy.

Assessment indicates a favourable safety profile of transcranial ultrasound stimulation with mild side effects, consistent with earlier reviews. However, impairment in naming and memory performance has been reported in more recent reports, the etiology of which remains unclear due to small sample sizes, comorbidities, and benzodiazepine use in exploratory studies [30,57,60]. Implementing safety measures, akin to those used in laser ablation, could mitigate risks associated with skull heating during treatment with HiFU [81]. No signs of overheating were found in studies with LiFU supporting its safety also for repeated sessions [82]. LiFU also induces sustained changes in synaptic connectivity through biomechanical effects without significant thermal changes, with side effects comparable to other non-invasive neuromodulation techniques [39,83,84].

HiFU has been more extensively researched than LiFU, yet its superiority in seizure control and safety over standard surgical procedures remains uncertain. Initial trials suggest promising subjective efficacy of HiFU, with immediate effects ranging from a 95 % reduction in seizure frequency to seizure freedom. Epilepsy surgery yields seizure freedom rates ranging from 50 % to 80 % and is considered cost-effective with improved seizure control and quality of life compared to medical treatment alone [2,85,86]. However not all patients with DRE are suitable candidates due to risks associated with proximity to eloquent cortex and the invasiveness of surgery [2–4]. In comparison, HiFU offers a promising alternative by targeting deep, localized brain structures in a minimally invasive manner. Under real-time MRI guidance, HiFU can achieve definitive lesions and disconnections, with low morbidity and complication rates [27,81]. Although costly, HiFU may reduce overall expenses by decreasing the need for operating rooms, hospital stays, anesthesia, and complication management. Laser interstitial thermal therapy of hypothalamic hamartoma's has shown seizure freedom in up to 93 % of patients. Stereotactic radiosurgery has seizure control rates between 60 and 66 % with minimal adverse events [87]. Unlike radiosurgery, which requires time for the biological mechanisms to take effect, HiFU provides immediate clinical and electrographic efficacy without a latent period. Additionally, HiFU allows for prompt retreatment if the desired effect is not achieved, due to its non-cumulative, localized energy delivery system, which eliminates the risk of damaging healthy tissue [14,23,25,26,31].

Emerging techniques are anticipated to shift the focus of epilepsy surgery from targeting single focal points to disrupting entire epileptogenic networks. However, the high spatial precision of HiFU and its capacity for creating only small lesions, it may still be insufficient for effectively addressing broader epileptogenic networks and larger targets [27,81]. Failure to achieve desired temperatures due to the risk of cavitation induction can further limit efficacy [23]. Nevertheless, studies suggest that the effects of HiFU may not solely result from lesioning. Abe et al. observed seizure frequency reductions without obvious lesions on follow-up imaging. Targeting the contralateral thalamus demonstrated superior efficacy in seizure reduction compared to ipsilateral targeting and Krishna et al. did report a delayed effect. This emphasizes the importance of target selection but also the possibility of non-ablative neuromodulatory effects induced by HiFU [24,30].

In DRE, the epileptogenic zone or network is often highly intertwined with important normal brain functions such as memory and emotion [88–90]. A non-lesioning, non-invasive neuromodulatory intervention via acoustic energy may herald the potential to affect the typical excitation and inhibition disbalance present in the epileptogenic brain without the destruction of normal neuronal networks. LiFU for neuromodulation offers the ability to modulate brain targets non-invasively while preserving neural tissue. Although there are no comparative trials between the different neurostimulation modalities available for DRE, long-term follow-up with VNS or DBS shows a a reduction in seizure of 50%–60 % [91–95]. No more than 10 % of patients become seizure free [86]. Available reports show that LiFU demonstrates a relatively rapid onset effect on seizure frequency observed in the days following treatment similar to findings with HiFU [57,58]. Seizure reductions vary between individuals, lasting from weeks to months, and even achieving seizure freedom for over a one-year period. As epilepsy is a chronic disorder, this potential long-term inhibitory effect seems promising [50,96]. Both DBS and VNS involve implantation, making them invasive techniques that increase the risk of perioperative complications [5].

Multifocal and bilateral targeting may also be feasible, which has been investigated in several areas of the brain [97]. In certain areas of the skull, such as the temporal window—a relatively thin segment of cortical bone—ultrasonic waves can pass through with minimal absorption and dispersion. This might be interesting, especially in cases where hippocampal sclerosis is the cause of TLE, where surgery has been the gold standard of treatment [98]. In other segments of the skull, especially thicker segments with trabecular bone, transmission and wave dispersion become severely limiting, even more so when aiming for a small focus using higher fundamental frequencies (e.g. 750 kHz). Overcoming this requires absorption and aberration correction as achieved through acoustic lensing or phased-array wave-front shaping. The required corrections can be based on individualized skull imaging with computed tomography (CT) or MR sequences sensitive to bone content, such as ultra-short or zero echo time imaging (UTE/ZTE) [99,100]. An alternative approach is to use the ultrasound wave itself, for example, based on the full-transmit signal measured with a second transducer array, and correcting accordingly [101].

The potential for targeted drug delivery in PwE remains largely unexplored, with only preclinical studies conducted so far. To be viable as an outpatient therapy for seizure prevention, the effects of a single administration must be long-lasting. The practicality of this approach in outpatient settings, especially with standard ASM and daily treatment, remains uncertain and requires further investigation [73,79].

As in many epilepsy trials, objective clinical outcome data is limited. Only one report examined treatment effects on epileptiform activities using EEG, revealing inconsistent patterns, despite overall reductions in epileptic discharges. Rs-fMRI may serve as a means to confirm target engagement and evaluate the neuromodulatory effects of LiFU [58].

Transcranial ultrasound stimulation might be considered next to other non-invasive and minimally invasive modalities with a similar adverse event profile [81]. The utility of LiFU or HiFU in the treatment of epilepsy has not yet been fully explored. Clinical

trials, incorporating control groups and standardized outcome parameters will be required before this technique can be applied in clinical practice. Furthermore, clinicians require clear guidelines on treatment strategies and safety measures. To ensure safety, comprehensive monitoring using MRI, fMRI and concurrent EEG before, during, and after treatment is advisable [83].

Up till now, patients eligible for focused ultrasound treatment for epilepsy are typically those with drug-resistant focal epilepsy that have not responded to conventional treatments such as medications or surgery. Ideal candidates often have well-defined, localized seizure foci such as the hippocampus or hypothalamic hamartomas, which can be accurately targeted using HiFU [102]. This non-invasive approach is particularly suitable for patients who are not ideal candidates for surgery due to high risks like bleeding, cognitive impairment, or for those with relative contraindications for VNS or DBS. It is also an option for patients who prefer to avoid invasive procedures.

HiFU is effective for creating irreversible lesions in localized epileptogenic zones, while LIFU offers reversible modulation of neuronal activity, making it suitable for more diffuse or complex seizure origins or when targeting of epileptogenic hubs in an epileptogenic network such as the thalamus is the therapeutic strategy. Although FUS is minimally invasive and generally safer compared traditional surgery, risks such as off-target thermal effects potentially associated with neurological complications may still be present and should be further investigated. Therefore, careful patient evaluation, imaging compatibility, and precise procedural planning are crucial to ensure safety and optimize outcomes [103].

Advancing the field of FUS for epilepsy requires a deeper understanding of physical parameters and their impact on bioeffects in humans and clinical populations [83]. This includes physical parameters, such as the optimal intensity, pulsing shape and frequency, but also clinical parameters, such as the number and frequency of treatment sessions that will be required to suppress seizures in DRE. A dose-dependent effect is suggested with potential for multiple treatment sessions in clinical practice [57,58]. Parameter optimization requires an integrative approach bridging across all levels, from biophysics to cellular biomechanisms, to circuit-level neurophysiology, to the human brain and behaviour, and to clinical outcomes.

Epilepsy research in HiFU and LiFU studies is limited and sonication protocols have been reported inconsistently. Key parameters were often incomplete or missing. For HiFU, the fundamental frequency was reported only once (650 kHz). When reported, sonication duration ranged from 10 to 25 s, with 6–12 sonications, temperatures of 42–59 °C, and power up to 1500 W or 10,000–22,000 J. In LiFU studies, when specified, the fundamental frequency ranged from 548 to 650 kHz, pulse repetition frequency from 100 to 500 Hz, and duty cycle from 5 to 50 %. Sonication duration varied from 140 to 600 s. Tables 2 and 3 summarize the reported parameters, though few studies provided complete data.

As seen before, the choice of parameters can have an important influence on the outcomes [34]. For instance, the efficiency of dual HiFU depends on the specific parameters, with different pulse parameters producing varied lesion types [104]. Higher frequency stimulation allows for higher spatial resolution but is also associated with increased attenuation through the skull. In humans, 250–650 kHz is most commonly used [34]. Studies with LIFU have shown that shorter sonication and lower duty cycles tend to produce inhibitory effects, while duty cycles above 20 % are more likely to result in neurons' excitation [41]. An increased pulse repetition frequency may lead to excitation, but does not significantly affect inhibition [34].

Earlier studies reviewed parameters from research in neurology and psychiatry and highlighted their wide variation. Several brain regions including the primary motor cortex, sensory cortex, visual cortex, thalamus and centro-parietal regions were most commonly studied [33,34,46]. Parameters that led to inhibition in earlier human studies had a fundamental frequency of 500 kHz, duty cycles ranging from 5 to 50 %, pulse repetition frequencies of 1 kHz (one study used 10Hz) and sonication durations of 100 ms-30 s. Protocols that led to excitation had fundamental frequencies ranging from 250 to 500 kHz, duty cycle of 36–50 %, pulse repetition frequencies of 500Hz-1kHz and sonication durations of 300–500 ms [33,34,46]. These inhibitory protocols might be useful for people with epilepsy, however the full impact of various parameters and protocols has yet to be revealed. Importantly, FUS can have different, even opposing, effects on individual levels. Ultrasound can facilitate calcium influx and spiking activity at the membrane level, exciting the stimulated neurons [105]. However, some pulsing protocols show selectivity for GABA-ergic inhibitory neurons, leading to circuit-level inhibition. Protocols can lead to both excitatory and inhibitory effects, depending on the level of description [33,46]. Similarly, at the level of clinical outcome, we can differentiate between acute and delayed effects. Different parameter sets are likely required to induce acute effects, such as immediate seizure suppression upon detection of pre-ictal activity, and those to induce delayed effects, such as the early-phase and persistent long-term depression leading to a sustained shift in the excitation/inhibition balance. Earlier studies found that protocols with higher intensities and higher duty cycles are more likely to lead to effects that outlast the sonication procedure [106,107]. The wide variability in parameters across studies, populations, and brain regions underscores the complexity of FUS research.

Indeed, studies of parameter testing and optimization at the cellular and circuit levels should be pursued in parallel and close translational alignment with studies into clinical efficacy, with clear consideration of acute modulatory and delayed neuroplasticity effects. More research is required to resolve the remaining challenges. Enhancing comparability across studies necessitates standardized reporting of LiFU parameters [39]. In this context, the International Transcranial Ultrasonic Stimulation Safety and Standards Consortium (ITRUSST) has published a consensus on reporting guidelines [32]. These guidelines include a checklist comprising six aspects of a LiFU protocol that should be reported: the transducer and driving system, drive system settings, free field acoustic parameters, pulse timing parameters, in situ estimates of exposure parameters in the brain, and intensity parameters. This suggestion could be a significant initial step towards standardized reporting.

5. Conclusion

The successful management of DRE requires the development of novel minimally invasive therapies to close the existing treatment

gap. The early observations in this field indicate that focused ultrasound, with its myriad of potential applications, holds promise as a therapeutic intervention for epilepsy. The available evidence, predominantly in the form of case series, suggests favourable outcomes, demonstrating advantages over pharmacologic approaches or alternative non-invasive interventions. Key benefits include its ability to target deep brain regions with a high spatial resolution. Clinical trials incorporating control groups and standardized outcome parameters will be imperative before this technique can be applied in clinical practice. Despite the promise of focused ultrasound as a non-invasive technique, the number of currently ongoing trials is still limited. Standardization and repetition of earlier methodologies and parameters are imperative since the true impact of focused ultrasound, optimal brain targets, and patient selection remain to be elucidated. Development of protocols that help to increase knowledge on safety and efficacy and especially help to identify optimal focused ultrasound treatment paradigms may truly impact the lives of people living with epilepsy. Before the technique can be integrated into clinical practice, further translational neuroscientific research is necessary to bridge the existing knowledge gaps.

CRediT authorship contribution statement

Lara Hogeveen: Writing – original draft, Visualization, Methodology. **Paul Boon:** Writing – review & editing, Supervision, Conceptualization. **Ann Mertens:** Writing – review & editing. **Lennart Verhagen:** Writing – review & editing. **Kristl Vonck:** Writing – review & editing, Supervision.

Data availability statement

All gathered data including search strategy that support the findings of this study are available in the article.

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Declaration of competing interest

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