Applications of focused ultrasound in the brain: from thermoablation to drug delivery

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Abstract | Focused ultrasound (FUS) is a disruptive medical technology, and its implementation in the clinic represents the culmination of decades of research. Lying at the convergence of physics, engineering, imaging, biology and neuroscience, FUS offers the ability to non-invasively and precisely intervene in key circuits that drive common and challenging brain conditions. The actions of FUS in the brain take many forms, ranging from transient blood–brain barrier opening and neuromodulation to permanent thermoablation. Over the past 5 years, we have seen a dramatic expansion of indications for and experience with FUS in humans, with a resultant exponential increase in academic and public interest in the technology. Applications now span the clinical spectrum in neurological and psychiatric diseases, with insights still emerging from preclinical models and human trials. In this Review, we provide a comprehensive overview of therapeutic ultrasound and its current and emerging indications in the brain. We examine the potential impact of FUS on the landscape of brain therapies as well as the challenges facing further advancement and broader adoption of this promising minimally invasive therapeutic alternative.

Ultrasound is one of the safest and most versatile diagnostic modalities in medicine. Focused ultrasound (FUS) refers to ultrasound that is focused via a curved transducer, lens or phased array, such that the pressure is highest at a small target and minimal elsewhere. Although its therapeutic potential has been known for decades, the thermal and mechanical effects of FUS have only recently been recognized as clinically important. FUS has been approved for the treatment of a range of conditions, including uterine fibroids and breast, prostate and liver lesions[1,2]. Brain applications have traditionally been hampered by the skull, which attenuates and distorts ultrasound transmission; however, technical, imaging and medical advances in the past two decades have led to a surge of interest in FUS as an important brain intervention, influencing brain structure and function while obviating the need for specific cranial access.

These advances are occurring in the context of an urgent and growing need for safe and effective approaches to the most common brain disorders. In 2016, the WHO estimated that one-third of the global population is affected by psychiatric or neurological conditions at some point in their lives. Alzheimer disease (AD) alone is predicted to cost the worldwide economy an estimated US$2 trillion by 2030, potentially overwhelming the health and social care system[3]. New treatments for brain diseases, from AD to brain tumours, have lagged behind our improved understanding of the genetics, biology and pathology of these conditions. The reasons for this lag include the limitations of preclinical models to accurately reflect human pathology, the heterogeneous nature of the diseases themselves and the restrictions to potential therapies that are imposed by the blood–brain barrier (BBB)[4,5]. Furthermore, some currently established therapies, such as open surgical approaches or brain implants for AD and Parkinson disease (PD), carry inherent operative risks[6].

FUS is a promising alternative to surgery, whereby unique thermal or mechanical effects can be harnessed to non-invasively and precisely intervene in key circuits that underlie common brain conditions. Recent trials have led to the clinical adoption of FUS for some movement disorders, with budding applications in psychiatry, chronic pain, epilepsy and other conditions[7,8]. In addition to its widespread use for thermoablation, the potential ways in which FUS can interact with brain tissue, from BBB opening (BBBO) to neuromodulation, have led to substantial interest in its use as a safe therapeutic option.

In this Review, we provide a comprehensive overview and update of the applications of therapeutic ultrasound in the brain[9], with an emphasis on current and emerging clinical indications. We review the principles and mechanisms of FUS as well as the relevant preclinical literature

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Key points

- Recent advances have led to a surge of interest in focused ultrasound (FUS) as a non-invasive, potentially disruptive tool for the most intractable neurological conditions.
- Magnetic resonance-guided FUS thermoablation has been approved for the treatment of essential tremor and tremor-dominant Parkinson disease and is being investigated in psychiatric applications as well as in chronic pain and epilepsy.
- Transient opening of the blood–brain barrier for drug delivery is a burgeoning field, with early human studies demonstrating a favourable safety profile as well as versatility across and scalability within a range of clinical indications.
- Future studies will investigate the delivery of established pharmaceuticals and novel therapies in combination with FUS blood–brain barrier opening.
- Emerging applications are also harnessing the myriad of ways in which FUS can interact with the CNS, including immune modulation and neuromodulation.

that has provided the rationale for clinical translation. With rapid developments in the field, our focus is on clinical and human studies that have been published in the past 5 years, highlighting both the promise and the challenges of this treatment modality.

Historical and mechanistic perspective

The principal attraction of therapeutic FUS is the ability to exert biological effects through the intact skull. Capitalizing on reduced tissue trauma, inflammation and pain, minimally invasive interventions are generally associated with lower surgical risks and shorter recovery compared with more invasive procedures[10]. However, bone strongly attenuates, reflects and distorts ultrasound, resulting in inefficient delivery and off-target effects. The skull also varies widely in thickness and density between individuals[11]. The presence of hair, which introduces air, additionally reduces and distorts the delivery of ultrasound by up to 80%, although the effects vary considerably depending on factors such as the characteristics of the hair and the ultrasound frequency[12].

In the 1950s, Russell Meyers, Peter Lindstrom and William and Francis Fry, among others, led the initial trials of FUS to treat movement and psychiatric disorders and brain tumours[13,14]. Lars Leksell also wrote on CNS applications of ultrasound and was said to be particularly interested in treating psychiatric disorders with FUS[15], before developing ionizing radiation for non-invasive ablation[16]. These early attempts to administer FUS to the brain required a craniectomy and sonication was performed in the operating room before replacing the skull bone. A skin flap over a craniectomy created a window for repeated FUS hyperthermia treatments[17] and thermoablation of tumours[18].

Several advances have led to an acceleration of research activity in the field of FUS over the past two decades. Transcranial FUS was made feasible by the implementation of phased array transducers and real-time MRI thermometry monitoring around the turn of this century[19] (FIG. 1). Individual adjustments to the phase and amplitude of transducer elements can correct for aberrations introduced by the skull during ultrasound propagation[20,21]. These corrections can be calculated from patient-specific information such as head CT scans or acoustic measurements[20,22]. Magnetic resonance (MR) coupling further enabled real-time monitoring of the lesion and temperature during sonication, thereby overcoming some of the limitations of established techniques such as radiofrequency and stereotactic radiosurgery[23,24]. The skull can also be circumvented by direct placement of the transducer on the dural surface via a small craniotomy[25] (FIG. 2). For some low-power applications, lens-based aberration correction, whereby an ultrasound beam from a single transducer is focused by a patient-specific acoustic lens[26], could be a cost-effective approach.

Two principles, temperature elevation and cavitation, are essential to understanding the biological effects of ultrasound. With high-intensity FUS, ultrasound absorption in the targeted medium can cause localized thermal necrosis within seconds[27]. Temperatures of >56 °C typically cause rapid tissue necrosis[28] — the dominant biological effect when high-intensity FUS is used for thermoablation (FIG. 3).

Cavitation refers to the oscillation of bubbles in response to pressure waves. In stable cavitation, bubbles oscillate without collapse but can cause mechanical stress on the vessel walls that comprise the BBB. Exogenously introduced microbubbles can facilitate stable cavitation at reduced power, enabling a biological effect such as BBBO to be achieved without mechanical or thermal injury to the vessel or parenchyma[29]. In inertial cavitation, bubbles expand during the low-pressure phase of the wave and begin to contract during the high-pressure phase, eventually resulting in collapse and producing immense local heating and shockwaves, which are damaging and undesirable. Histotripsy is an emerging method to control this type of cavitation, allowing rapid mechanical ablation with high-energy ultra-short ultrasound pulses[30].

Thermoablation

Ablative procedures have been practised since the early days of neurosurgery for a wide range of indications, ranging from psychiatric to neurological disease. Whether using direct means (for example, leucotomy), radiofrequency or implanted radioactive seeds, the goal of ablative surgery was to interrupt pathological brain circuits that drive troublesome symptoms. With the development of deep brain stimulation (DBS), in which implanted leads are used to deliver an electric current, a non-ablative option emerged, providing the ability to titrate clinical effects and create reversible effects[31]. For some disorders, including PD, DBS has become the standard of care[32]. However, DBS is highly resource intensive, can only be offered at specialized centres and is associated with the attendant risks of a brain operation, including haemorrhage, infection and device malfunction.

MR-guided FUS (MRgFUS) is an incisionless image-guided procedure in which FUS is delivered transcranially and with stereotactic precision. To date, the only FDA-approved neurological indications for MRgFUS are thalamotomy for essential tremor (ET) and tremor-dominant PD (TDPD), using the high-frequency ExAblate 4000 system (InSightec, Haifa, Israel). Early attempts in neuro-oncology failed to achieve sufficient temperature increases owing to technical limitations[33].

Blood–brain barrier
(BBB). A structural and functional border along the capillaries in the brain that tightly regulates paracellular and transcellular transport.

Craniectomy
A surgical procedure in which a piece of the skull is removed and the overlying skin flap is replaced to create a window for ultrasound propagation.

Sonication
The active delivery of ultrasound. Currently, each typical sonication lasts ~0.5 min for thermoablation and ~1 min for blood–brain barrier (BBB) opening. A rest period allows scalp cooling in thermoablation and systemic clearance of microbubbles in BBB opening.

Cavitation
The change of a liquid to a gas state when subjected to reduced pressures and/or interactions of ultrasound with gas bubbles.

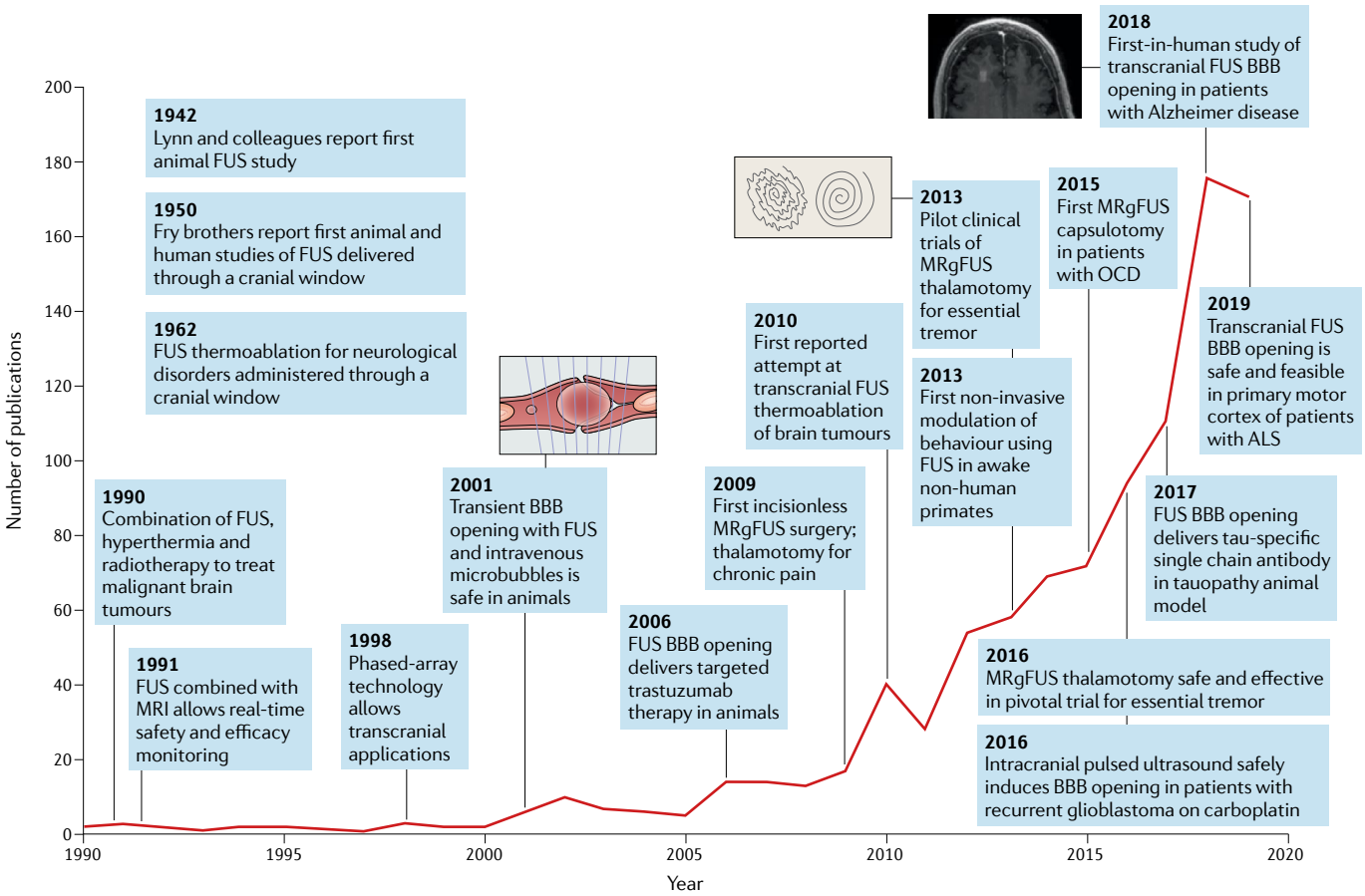

Fig. 1 | **The FUS literature.** The graph shows publications per year on focused ultrasound (FUS) in the brain since 1990 (red line) with major milestones in the field superimposed. ALS, amyotrophic lateral sclerosis; BBB, blood–brain barrier; MRgFUS, magnetic resonance-guided FUS; OCD, obsessive–compulsive disorder. The MRI scan in the inset was adapted from REF.[122], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Although subsequent work demonstrated successful partial ablation of a centrally located tumour[34], the mixed results overall underscore the importance of achieving broader treatment envelopes and larger ablation volumes for effective ablative tumour treatment.

Small, centrally located targets that require a high degree of anatomical precision, such as those used in functional neurosurgery (for example, thalamotomy, pallidotomy or subthalamotomy), seem to be best suited to high-intensity MRgFUS. Central targets minimize the ultrasound incidence angles at the skull, allow more economical utilization of the hemispheric array and, ultimately, provide a more efficient on-target temperature increase and less skull heating[35]. This less invasive approach to lesioning has led to a resurgence of interest in ablative procedures in functional neurosurgery, beginning with ET (FIG. 1).

Essential tremor

ET is one of the most common movement disorders, characterized by postural and kinetic action tremor frequently isolated to the upper extremities. ET affects ~1% of the population worldwide, with a strong genetic component. First-line treatment is medical, most commonly with propranolol or primidone, but as many as half of the patients do not benefit from and/or tolerate pharmacotherapy[36]. The disability that results from ET substantially compromises the quality of life of patients. The pathophysiology of ET is still emerging, although the condition is known to be highly heterogeneous and is likely to be a syndrome rather than a specific disease[37]. The anatomical underpinnings of ET, by contrast, have been well established through imaging, electrophysiology, investigation of stroke syndromes and neurosurgical interventions[38,39]. In treatment-refractory ET, ablation or stimulation of the ventral intermediate nucleus (VIM) of the thalamus (a relay structure between the cerebellum and the motor cortex) is the standard of care. Ablation of the VIM stops the pathological oscillations that are responsible for the tremor, providing excellent clinical benefits[40].

On the basis of the well-established safety and efficacy profile of thalamotomy for ET, two pilot trials using MRgFUS were conducted in patients with medically refractory ET[41,42]. Both trials established the safety, technical feasibility and potential efficacy of unilateral lesions in the VIM. A subsequent randomized, sham-controlled pivotal trial in 76 patients demonstrated significant between-group differences in tremor at 3 months, with a 47% relative tremor reduction in the treated patients at this time[7]. An analysis of adverse events revealed paraesthesia (14%) and gait disturbance

Treatment envelopes
The spatial extent of the brain regions where the desired biological effect (for example, thermoablation) can be successfully achieved with FUS.

Beta frequency
Sustained beta frequency oscillations (12.5–30 Hz) in the cortex and subthalamic nucleus are a characteristic of Parkinson disease and related motor impairments.

(9%) at 12 months. Quality-of-life measures improved following MRgFUS, both in this pivotal trial and in subsequent trials in other cohorts[43]. Open-label long-term follow-up showed a relative tremor improvement of 43% and 56% in two separate cohorts, supporting the longevity of the treatment effect for ET[44,45]. A subset of 12 patients showed a tremor reduction of 56% at 4 years[46]. Some patients in whom the clinical benefit has waned over time might benefit from retreatment[47].

The safety profile of MRgFUS thalamotomy has been comprehensively reviewed[48]. Of 443 adverse events in 186 patients, 79%, 20% and 1% were mild, moderate and severe, respectively. Sonication-related adverse events (for example, headache), paraesthesia and imbalance were the most common. Of the five severe adverse effects, two were sonication-related and self-limiting within days of the procedure and three were ataxia. The rate of serious adverse events is lower than would be expected for more invasive procedures, in which surgical complications, such as infection and intracranial haemorrhage, are material risks. Although a larger lesion size is associated with greater tremor reduction, lesion volume also correlates with the risk of adverse events such as gait imbalance[45,49,50]. Studies using advanced structural imaging, such as lesion mapping relative to key anatomical pathways, have helped to enhance the spatial accuracy of targeting and to identify targeting approaches that improve outcomes[49,51,52].

In 2019, the American Society for Stereotactic and Functional Neurosurgery endorsed the clinical practice of MRgFUS thalamotomy for ET[53]. Several cost–utility comparisons of MRgFUS, medical therapy and DBS have all found MRgFUS to be a cost-effective health-care technology and treatment for ET[54,55]. The safety and efficacy of bilateral MRgFUS thalamotomy, performed in a staged manner, is also being evaluated in a single-arm, open-label study (NCT0346576 and NCT04112381). In addition, the role of MRgFUS thalamotomy for patients with focal dystonia (ventro-oral thalamotomy) and non-ET tremor is currently under investigation[56–58].

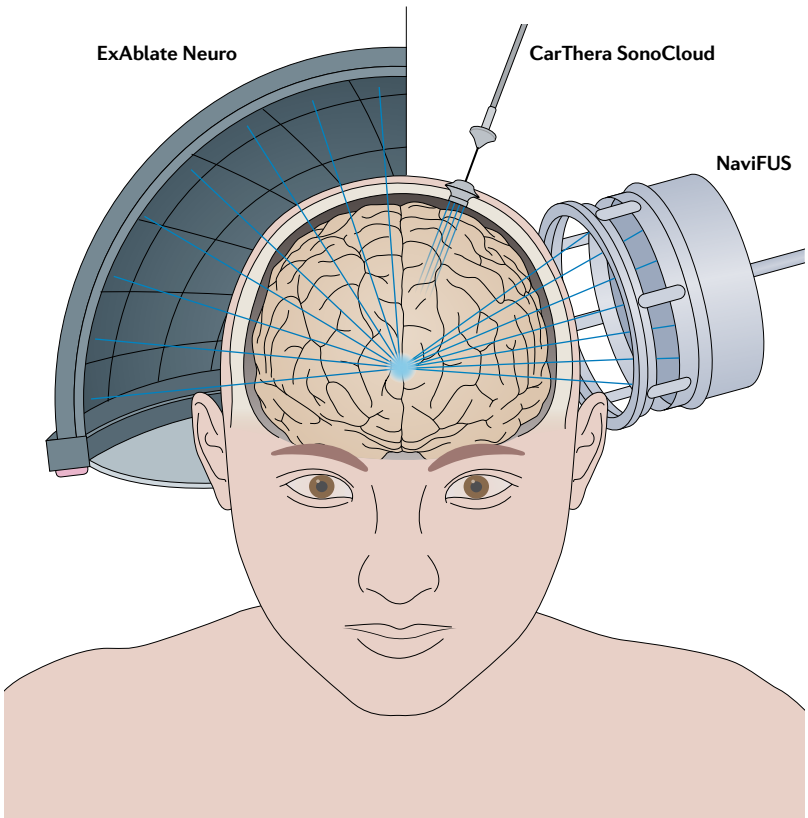

Fig. 2 | **Current therapeutic ultrasound devices for brain applications.** The ExAblate Neuro system comprises a phased array of transducers coupled to an MRI system. The elements line the concave inner surface of a helmet that is placed close to the scalp with intervening degassed water. NaviFUS is another transcranial system. Like ExAblate Neuro, NaviFUS is multi-channelled but with fewer elements on a smaller surface area. Navigation of the device is based on pre-procedure imaging. The CarThera SonoCloud implanted ultrasound device is powered through a bipolar needle introduced through the skin for each treatment. The ExAblate Neuro systems are employed for both thermoablation and blood–brain barrier opening whereas NavFUS and CarThera SonoCloud are currently being investigated for blood–brain barrier opening.

Parkinson disease

PD is the second most common neurodegenerative condition, affecting >3% of people over the age of 80 years[59]. PD is marked by progressive loss of nigrostriatal dopaminergic neurons and current treatments are generally aimed at replacing dopamine or mimicking its action. Both ablative surgery and DBS are options for patients who cannot tolerate medical therapy or whose symptoms, despite optimized medical treatment, are inadequately controlled. The globus pallidus interna (GPi) and subthalamic nucleus (STN) are two common targets for the treatment of cardinal motor features and motor fluctuations, with the GPi being favoured for levodopa-induced dyskinesias[60]. The VIM is a target for patients with TDPD, which comprises 7% of all PD cases. Additional targets have been explored for subsets of patients, for example, pedunculopontine nucleus or spinal cord stimulation for postural instability, but these approaches remain investigational[61,62].

Leveraging the early experience with MRgFUS VIM lesions, a randomized controlled trial (RCT) was conducted in 27 patients with TDPD[8]. Patients experienced an improvement of 62% in the on-medication Clinical Rating Scale for Tremor score at 3 months from unilateral thalamotomy, compared with an improvement of 22% from sham procedures ($P = 0.04$). No differences in Montreal Cognitive Assessment and Beck Depression Inventory II scores were observed between the two groups. Three severe treatment-related adverse events were reported, two of which were persistent mild hemiparesis, suggesting that the safety profile might be affected in a more vulnerable patient population such as those with complex conditions or comorbidities.

The STN is the most common surgical target in PD and subthalamotomies are among the oldest ablative procedures in functional neurosurgery. The role of the STN in the circuitry underlying PD was established through research in preclinical models and neurophysiological studies that linked synchronous neuronal firing in the beta frequency band to PD symptoms[63]. In a prospective open-label study of ten patients with asymmetric PD, eight responded with a >30% reduction in both off-medication and on-medication Unified PD Rating Scale part III scores for the treated hemibody

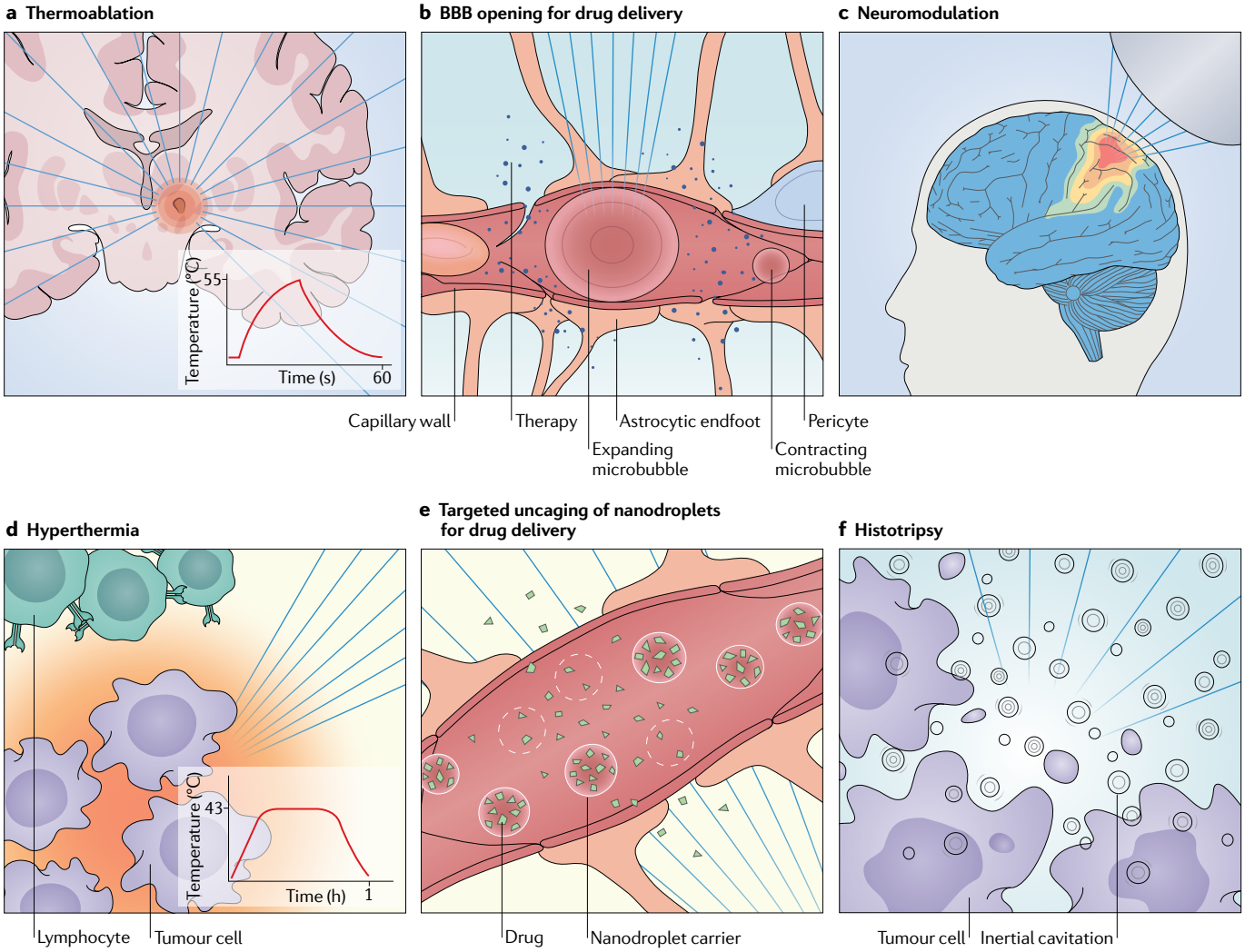

Fig. 3 | **Biological effects of FUS.** The diverse biological effects of focused ultrasound (FUS) on tissue can be categorized as predominantly thermal or mechanical. The top panels illustrate the effects that have been demonstrated so far in humans. High-intensity FUS delivered through the intact skull creates a coagulative necrotic lesion with millimetric precision for incisionless neurosurgery (part **a**). Stable cavitation of intravascular microbubbles under FUS induces mechanical forces on the blood–brain barrier (BBB) that transiently increase its permeability for drug delivery (part **b**). FUS neuromodulation potentially offers higher spatial and temporal resolution than existing techniques, with the ability to non-invasively target deep brain regions (part **c**). The bottom panels illustrate emerging FUS effects that are at more preliminary stages of development. Hyperthermia to increase radiosensitivity and immunogenicity of tumour cells (part **d**). Ultrasound-responsive drug carriers for targeted delivery (part **e**). Histotripsy for non-invasive mechanical fractionation of large volumes of tissue or blood clot (part **f**).

6 months after unilateral MRgFUS subthalamotomy[64]. The response was immediate on completion of FUS treatments. Transient adverse events included ataxia (60%), facial asymmetry (10%) and mild-to-moderate disinhibited behavioural changes (20%), with no significant differences on cognitive assessments. Two patients had postoperative dyskinesia but improved with time or medication adjustments. Results from a larger RCT (NCT03454425) are expected to be published soon.

Lesioning of the GPi, also known as pallidotomy, is another established ablative treatment for PD. However, the GPi is located more laterally than the STN or the VIM and, hence, achieving a sufficiently high temperature for coagulative necrosis via MRgFUS can be challenging. In a non-blinded study, MRgFUS pallidotomy was successful in eight of ten participants, with statistically significant reductions of 32.2% and 39.1% in off-medication Unified PD Rating Scale part III scores and of 52.7% and 42.7% in the Unified Dyskinesia Rating Scale at 6 and 12 months, respectively[65]. One individual experienced severe off-target effects in the internal capsule, manifesting as dysarthria and grade III hemiparesis. An RCT to compare MRgFUS pallidotomy against sham is under way (NCT03319485). Unilateral pallidothalamic tractotomy in a case series of patients with PD showed promising safety and efficacy outcomes; however, this will also require further comparisons with other targets and modalities in RCTs[66].

Adverse events have been recognized for all types of bilateral lesions; therefore, staged bilateral procedures

should be evaluated only after establishing a favourable safety and efficacy profile with unilateral procedures[67]. Feasibility testing of staged bilateral MRgFUS subthalamotomies is under way (NCT03964272). Ongoing work also includes utility and cost comparisons of MRgFUS and DBS in PD to determine how to integrate MRgFUS into the current treatment algorithm[68]. For patients who do not want or cannot undergo open surgery, such as elderly individuals with comorbidities, MRgFUS might be the recommended option. In patients who live far from specialized neuromodulation centres or who do not want an implanted device, a less invasive option may be more attractive. The cost of implants, battery replacements and associated maintenance are additional important considerations.

OCD and major depression

Obsessive–compulsive disorder (OCD) is one of the most common anxiety disorders, affecting ~2% of the general population[69]. OCD is characterized by unwanted anxiogenic repetitive thoughts and behaviours that can render patients incapacitated, leading to reductions in quality of life and high rates of morbidity and suicidality[69]. First-line treatment consists of cognitive behavioural therapy or selective serotonin reuptake inhibitors, in particular clomipramine. Despite treatment, 20–30% of patients have intractable illness and might benefit from surgical options[70].

An imbalance of excitatory and inhibitory pathways in the corticostriatal–thalamocortical circuit is thought to form the neural substrate of OCD symptoms. Neuroimaging studies in people with OCD have consistently found hyperactivity in the orbitofrontal cortex, caudate and anterior cingulate cortex[71,72]. Surgical targets for DBS include the ventral striatum, the subthalamic nucleus, the anterior limb of the internal capsule and the anterior cingulate cortex; the latter two regions have also been targeted for ablation[73]. Level I evidence has been obtained for surgery in patients with severe refractory OCD[74]. Between 40% and 60% of these individuals will respond to surgical treatment, regardless of modality, with patient and treatment centre-specific factors often influencing the choice of approach[75,76]. Although lesioning obviates the need for a permanent implant, battery replacement and regular programming, the efficacy and safety of this intervention relative to DBS has yet to be established in OCD. A meta-analysis of DBS in people with OCD showed that 20% of patients experienced transient worsening of anxiety during programming[77]. Conversely, problems with executive function have been reported in patients after capsulotomy[76].

MRgFUS capsulotomy targeting the centrally located anterior limb of the internal capsule was investigated in a pilot study involving four patients with treatment-refractory OCD. The participants showed a mean improvement of 33% on the Yale Brown Obsessive Compulsive Scale (YBOCS) at 6 months[78]. Two of the four patients were classed as responders (>35% improvement in YBOCS score). A 2-year follow-up study with the addition of seven more patients showed a mean reduction of 37.8% in YBOCS score, with seven patients being categorized as responders and six considered to be in remission (YBOCS score ≤12)[79]. No appreciable behavioural adverse events or changes in neuropsychological functioning were reported, contrary to the historical experience with other ablative techniques[80]. These improvements might be related to the generation of smaller, more precise lesions, which is made possible with real-time imaging guidance and thermographic feedback. In a separate open-label trial of MRgFUS capsulotomy in six patients with refractory OCD, four patients were treatment responders at 6 months. The treated patients showed stable neuropsychological performance as well as widespread metabolic reductions on ^{18}F-FDG PET, in agreement with the previous capsulotomy literature[81].

Major depressive disorder (MDD) affects ~6% of the general population and shows a high degree of overlap with other psychiatric and medical disorders, including OCD[82]. About one-third of patients with MDD are treatment refractory despite pharmacotherapy and psychotherapy. Multiple structural and functional brain circuit alterations that have been implicated in MDD are targets for neuromodulation, including MRgFUS thermoablation[82]. A patient who underwent MRgFUS bilateral anterior capsulotomy to treat MDD showed a significant improvement (from 26 to 7) on the Hamilton Depression Rating Scale, with no reported physical or cognitive adverse effects[83]. In an open-label trial of MRgFUS capsulotomy in six patients with refractory MDD, two of the participants were treatment responders at 6 months[81]. The safety profile of the intervention was favourable and no adverse neuropsychological or cognitive effects were reported.

Chronic pain

Chronic pain is defined as persistent or recurrent pain lasting ≥3 months[84]. The emergence of the opioid epidemic has brought the health and socioeconomic burden of pain into sharp focus, leading to calls for research into different management options beyond medical therapy[85]. Chronic pain is also associated with high rates of depression and anxiety. Targets for ablative therapies for chronic neuropathic pain include the thalamus, anterior cingulate, brainstem, spinal cord and pituitary gland[86]. However, the quality of evidence to date is poor, consisting mainly of case series without blinding or placebo control, which is problematic given the large placebo effect in this population.

In one study, the bilateral central lateral thalamic nuclei were targeted with MRgFUS thermoablation in nine patients with chronic neuropathic pain of various aetiologies. Pain relief of >50% was reported in six patients at 3 months and in five patients at 1 year following surgery[24,87]; another open-label study (NCT03111277) is ongoing. The level of evidence is currently low, although MRgFUS does provide an opportunity for placebo-controlled studies. Indeed, a randomized, double-blinded study of MRgFUS bilateral thalamotomy for chronic trigeminal pain is actively recruiting (NCT03309813). Outside the CNS, MRgFUS ablation of the stump neuroma is being investigated in an open-label trial to treat chronic phantom limb pain (NCT03255395). Other studies (for example,

P-glycoprotein
A member of the ATP-binding cassette transporter B subfamily that pumps a wide range of foreign substances out of cells and is important in multidrug resistance.

NCT04283643) are adopting a neuromodulation approach, using low-intensity FUS[88].

Blood–brain barrier opening

The BBB is composed of tight junctions and membrane transporters, receptors and channels (for example, ATP-binding cassette transporters) that tightly regulate the passage of systemically circulating substances into the brain parenchyma[89]. The BBB plays a crucial role in CNS homeostasis by regulating interstitial fluid composition, peripheral and central cellular signalling, and immunity[90,91]. Dysfunction of the BBB has been implicated in numerous brain diseases, including multiple sclerosis, AD and amyotrophic lateral sclerosis (ALS)[89]. Even when partial breakdown is evident, such as within the malignant tumour environment, the BBB presents a critical obstacle to achieving sufficient bioavailability of therapeutics in the brain[92,93].

The BBB restricts a wide range of therapeutic agents from entering the CNS[94]. Even for small molecules, penetration can be suboptimal, requiring large doses that increase the risk of systemic adverse effects and incur high costs[95,96]. As a result, the possibility of incorporating various methods to circumvent the BBB, including FUS, into treatment workflows is currently being explored (BOX 1).

BBBO is one of the most extensively investigated FUS applications, with the safety and efficacy of FUS BBBO having been validated in hundreds of preclinical studies, from rodents to non-human primate models, as well as in both health and disease[97]. The use of FUS in combination with microbubbles increases BBB permeability, which manifests as enhanced intracellular and paracellular transport. Mechanical forces from stable microbubble cavitation induce structural and functional disruption of the tight junctions, decreased expression of P-glycoprotein and increased formation of caveolae[98]. The temperature rise induced by FUS BBBO is negligible and the power employed to achieve BBBO is typically at least three orders of magnitude below what is necessary for thermoablation[99,100]. In addition, cerebral vessels are resilient to the mechanical stress imposed by stable microbubble cavitation, allowing BBB integrity to be restored without haemorrhagic or ischaemic complications after BBBO.

The consequences of exposure of brain tissue to blood constituents, such as fibrinogen, after BBBO include a transient inflammatory response involving the elevation of pro-inflammatory cytokine levels and microglial activation[100]. The impact of chronic FUS BBBO treatment continues to be elucidated, although several studies indicate that the inflammatory response is mild and short lived (<2 weeks), even after repeated administration[101–104]. No long-term complications, such as persistent BBB dysfunction, were observed. Furthermore, behavioural, neuroimaging and morphological characteristics were preserved even after biweekly BBBO over 4 months in non-human primates or 6 months in rats[105,106].

The degree of BBBO is modulated by transducer frequency, ultrasound pressure amplitude, exposure duration, burst parameters, microbubble size and dosage[107–109]. FUS BBBO has enabled dextran molecules of up to 2,000 kDa to be delivered safely to the brain[110]. By comparison, therapeutic antibodies have a molecular weight of ~150 kDa with a brain penetration of <1% of the injected dose and thus should be amenable to delivery via FUS BBBO[95]. Indeed, FUS has been shown to dramatically enhance the bioavailability of antibodies such as trastuzumab in the brain[107]. In addition to antibodies[111–114], other successful deliverables include chemotherapeutics[115,116], viral constructs (for example, adeno-associated virus serotype 9)[117] and cells[118–120]. Furthermore, evidence exists that FUS can be targeted to achieve BBBO in a wide range of different brain regions with varying vasculature and structural properties, including cortical targets[111], hippocampus[117], striatum[117,121] and brainstem[115].

Several FUS BBBO devices are currently under development and active investigation, including ExAblate Neuro 4000 220 kHz (InSightec, Haifa, Israel)[122], NaviFUS (NaviFUS, Taipei, Taiwan)[123] and SonoCloud-9 (CarThera, Paris, France)[124] (FIG. 2). The former two systems employ extracranial FUS phased array transducers that can correct for skull-induced distortions. The geometric focus of the transducer array is mechanically positioned to the target through a system that combines intraoperative MRI and head fixation (ExAblate) or preoperative MRI and optical neuronavigation (NaviFUS). The devices further electronically scan a smaller target volume around the geometric focus. ExAblate uses real-time image guidance with the patient in the MRI scanner, whereas NaviFUS treatment is administered outside the MRI environment.

SonoCloud is an ultrasound device that is surgically implanted in a hole in the skull bone. The latest iteration, SonoCloud-9, has nine emitters and generates larger BBBO volumes than previous SonoCloud devices, which

Box 1 | FUS BBB disruption and other current BBB technologies

Approaches to breaching the blood–brain barrier (BBB) can be categorized as biological or physical. Biological methods include the coadministration of a drug that improves transcellular or paracellular transport (for example, mannitol or elacridar)[198], re-engineered drugs for receptor-mediated uptake (for example, transferrin receptor[199] or LRP1-targeting peptide[200]) and drug carriers (for example, nanoparticles). Physical methods include radiation therapy[201], localized therapy with drug-embedded biomaterials[202,203] and convection-enhanced delivery (CED). CED has been used in clinical trials to treat diffuse intrinsic pontine glioma and Parkinson disease[95].

CED is a familiar technique to neurosurgeons but the drug delivery is localized and invasive. By comparison, focused ultrasound (FUS) BBB opening is non-invasive and temporary and can be applied to focal yet distributed brain regions. FUS can also be combined with other therapies without further drug modifications, although it might modify drug–target interactions and thus drug safety and efficacy profiles. Parameters such as ultrasound and microbubble dosing can be adjusted to achieve an appropriate level of BBB opening[129,148,215].

After successful completion of initial phase I trials, identifying the optimal FUS–therapy combination and dosage is the next step. One approach is to repurpose existing therapeutics that are effective for systemic pathology (for example, immunotherapy for melanoma or breast cancer or enzyme replacement therapy for neuronopathic Gaucher disease or Parkinson disease associated with *GBA* mutations) for CNS conditions. Gene therapy and gene editing are other promising approaches that could potentially be combined with FUS. FUS-aided gene therapy delivery has been extensively studied in rodent models[130,149,216]. Studies in large animal models, such as non-human primates, will be crucial for ensuring the safety of these modalities. Additionally, industry and academic partnerships will be needed to scale up efforts to large multicentre trials.

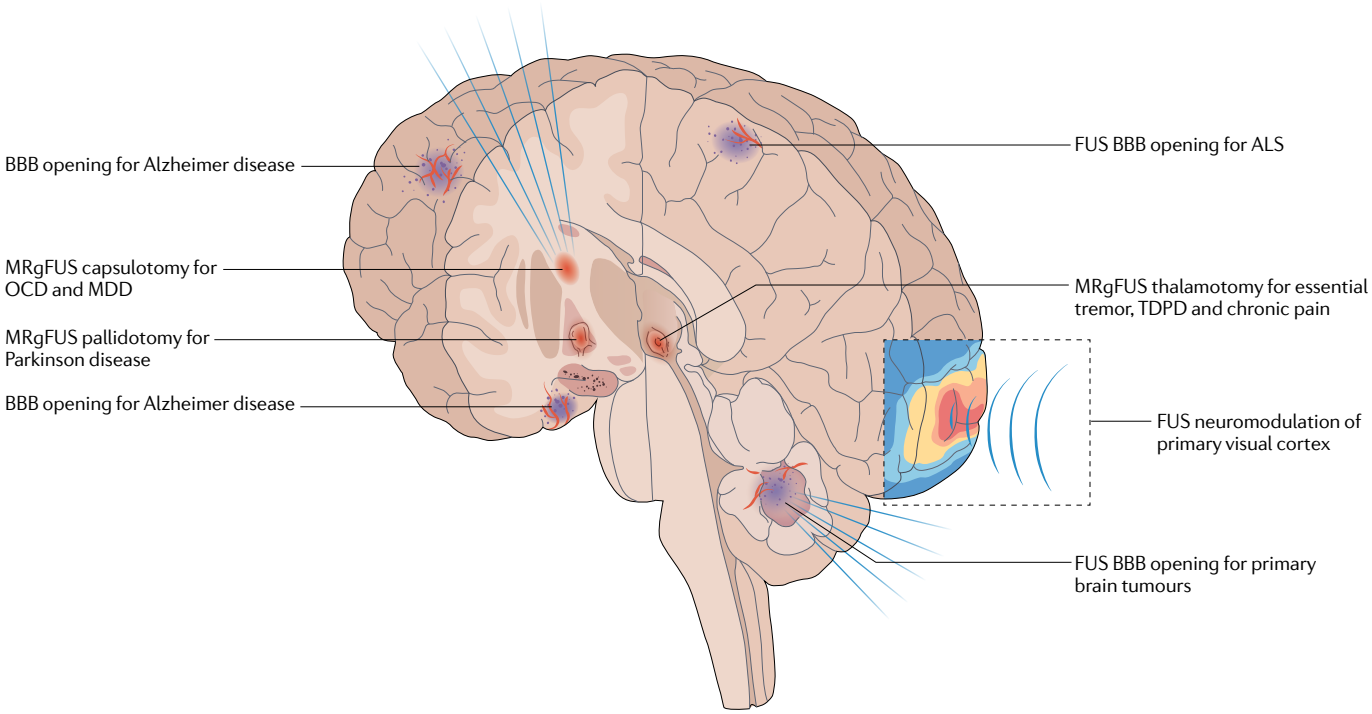

Fig. 4 | **Intracranial applications of FUS in humans.** ALS, amyotrophic lateral sclerosis; BBB, blood–brain barrier; FUS, focused ultrasound; MDD, major depressive disorder; MRgFUS, magnetic resonance-guided FUS; OCD, obsessive–compulsive disorder; TDPD, tremor-dominant Parkinson disease.

had a single emitter[125]. At each treatment session, the device is powered through a subcutaneous port, requiring piercing through the skin. This system is intuitive for the clinician and practical for the patient in terms of mobility and ease of multiple treatments. However, the possible trade-offs include the inability to change the target during treatment and to cover large, irregular or multiple lesions, as in the case of large tumours.

Neurodegenerative diseases

Alzheimer disease. AD is the most common neurodegenerative disorder and its prevalence is projected to triple by 2050 (REF.[126]). AD is characterized by progressive cognitive decline resulting from widespread neurodegeneration and is associated with considerable morbidity and mortality[127]. Numerous therapeutics to address one of the pathological hallmarks of AD, that is, the accumulation of amyloid-β (Aβ) in the brain, have been investigated over the past two decades with little success[128]. In trials of approaches such as passive immunotherapy, an important consideration is whether sufficient amounts of an agent have crossed the BBB to achieve therapeutic levels in the brain.

The urgent need for disease-modifying therapy underlies a strong research interest in developing FUS-mediated drug delivery for AD. Early animal experiments with passive amyloid and tau immunotherapies and neurotrophic factors showed that FUS enhanced the clearance of pathological proteins from the brain[111,114,129,130]. Notably, BBBO alone reduced the amyloid plaque load and improved memory performance in transgenic models[102,131–133]. The extravasation of endogenous immunoglobulin (for example, IgG and IgM) and clustering of activated microglia around amyloid plaques suggested a role for immune recognition in generating this effect[102]. FUS BBBO also reliably induces neurogenesis in rodents, which might be secondary to activation of the pro-survival AKT–GSK3β pathway[134,135].

Based on this body of work, a pilot study in people with AD was launched using the transcranial MRgFUS (ExAblate Neuro 220 kHz) device with $5 \times 10 \times 7\ mm^3$ target volumes in the right frontal lobe[122] (FIG. 4). Five patients with mild-to-moderate AD were enrolled and underwent the procedure twice over a period of 1 month. Immediately upon sonication, the sonicated regions became hyperintense on contrast T1-weighted MRI, indicating increased permeability to gadolinium. No serious adverse events, clinically significant changes in neurocognitive scores or adverse effects on serial MRI (for example, haemorrhage or oedema) were detected. Although BBB dysfunction has been reported in people with AD, in this study, the integrity of the BBB recovered by ~24 h after treatment in all participants[136]. Furthermore, the Aβ load, as measured by ^{18}F-florbetaben PET, remained stable at the 1-month time point.

A recent study demonstrated the safety and feasibility of transient BBBO within the hippocampus in people with early AD[137]. The favourable safety profile of this approach has prompted worldwide efforts to test larger-volume BBBO across multiple brain regions (NCT03739905 and NCT03671889) as well as early-phase studies with different devices

(NCT04118764 and NCT03119961). Establishing an excellent safety profile sets the stage for drug delivery trials, which are in active development. Preclinical and early clinical experience will guide the selection of therapeutics to be delivered with FUS. The pathophysiology of AD, in particular the contribution of Aβ to the clinical picture, remains an area of active investigation and debate. The next phase of clinical trials of FUS in AD will need to combine BBBO with the most promising therapeutic agents to directly address AD pathology[138].

Amyotrophic lateral sclerosis. ALS is a relatively rare neurodegenerative disease that shows rapid progression[139], with an average survival time of ~2–4 years following diagnosis. Patients with ALS experience muscular weakness, wasting and spasticity resulting from upper and lower motor neuron degeneration. Various cellular and microenvironmental abnormalities, including oxidative stress, protein handling defects, excitotoxicity and neuroinflammation, have been identified in ALS[140,141]. The success of translating initially promising therapies from the bench to the bedside has been limited, with only two drugs (riluzole and edaravone) having shown modest benefit on disease progression[142,143]. One of the theories of motor neuron degeneration involves the cortical hyperexcitability that is detected early in ALS[144]. Evidence from preclinical studies suggests that targeting of neuroprotective or neuroregenerative strategies, such as growth factors or gene or cell therapies, to the primary motor cortex via FUS BBBO could be an effective approach[145,146].

In a single-arm, open-label study, transient BBBO using FUS was tested in the non-dominant primary motor cortex of four patients with ALS who had severe leg or arm weakness[147]. Two patients were on stable doses of riluzole and one patient was receiving edaravone. Sonication of the eloquent cortex was asymptomatic, and no serious procedure-related adverse events were detected on clinical, radiological and laboratory examinations, including EEG. Transient adverse effects included mild-to-moderate discomfort from aspects of the procedure such as immobilization or the stereotactic frame. FUS BBBO did not result in the acceleration of disease progression, as determined through motor power, functional measurements and cognitive testing.

Parkinson disease. Gene therapy has generated considerable interest as a potential treatment for PD but the opportunities remain to be realized. Convection-enhanced delivery (CED) has been used to deliver viral constructs expressing neurotrophic factors to the striatum in preclinical models and patients with PD[148]. The hurdles to this approach include achieving sufficient distribution of the infusion volume past the catheter tip and providing justification to implement invasive neuroprotective strategies at early disease stages before substantial neurodegeneration has taken place. In rodent models, various biological therapies have been explored in combination with FUS, including the delivery of neurotrophic factors, gene therapy and vector-based short hairpin RNA for gene silencing[149–151].

Clinical protocols for striatal BBBO, with or without therapeutic agents, are being developed globally. An ongoing pilot study (NCT03608553) is targeting the parietal lobe of patients with PD dementia. Of all the potential therapeutics, gene therapy, with a minimal dosing regimen, is arguably optimally suited to FUS. If these early clinical trials show target engagement, then FUS technology, which is less invasive than CED, will lower the threshold for enrolment into surgical trials and should enable the treatment of patients at earlier stages of the disease.

Neuro-oncology

High-grade glioma, in particular glioblastoma, remains one of the most intractable and fatal of all cancers[4]. No real progress has been made in extending life expectancy since the adoption of the protocol by Stupp et al. in 2005 (REF.[152]). An expert panel has identified the failure of drugs to penetrate the BBB to any clinically meaningful extent as an important reason for poor treatment response[4]. Two open-label studies, one using the ExAblate device combined with systemic temozolomide and the other using the SonoCloud device combined with systemic carboplatin, demonstrated that transient BBBO was safe, well tolerated and technically feasible in 5 patients with high-grade glioma and in 19 patients with recurrent high-grade glioma, respectively[25,153,154]. In addition, a phase I dose-escalation study to test the NaviFUS system in patients with recurrent glioblastoma (NCT03626896) has been completed and publication of the results is pending.

In the ExAblate study described above, no adverse events grade 3 or higher according to the Common Terminology Criteria for Adverse Events were reported. Surgical tissue specimens did not reveal increased temozolomide concentrations in the brain, although delays in sampling (resections were performed ~24 h after FUS BBBO) might have limited the reliability of this outcome measure[153]. No survival data were reported for this study. In a follow-up report of all 21 patients in the SonoCloud study, grade 3 and 4 adverse events were mostly linked to carboplatin toxicity or underlying illness in patients with recurrent glioblastoma[154]. One patient required reoperation following device malfunction, one developed a subdural hygroma and another developed a transient facial palsy. Presumably owing to the enhanced bioavailability of carboplatin, median progression-free survival was 4.11 months in patients with clear BBBO, compared with 2.73 months in patients with no or poor BBBO.

The immunosuppressive glioblastoma microenvironment, along with the BBB, enables tumour cells to evade the systemic immune system[4,155]. By breaking the immune-privileged status of the CNS, FUS BBBO could be beneficial for tumour cell detection and initiation of an antitumour immune response[156]. The immunological impact of FUS is a fascinating area of research and preclinical studies have demonstrated the feasibility of FUS-based immunomodulation of brain and systemic cancers[120,156,157]. Therefore, the combination of FUS BBBO and immunotherapies could have a synergistic antitumour response. However, potential additive risks, such as autoimmune encephalitis, will need to be

Stereotactic frame
A stereotactic frame is fixed to the head to provide a reference for precise targeting. Common examples include the Leksell (polar coordinate) and Cosman–Roberts–Wells (Cartesian coordinate) frames.

Common Terminology Criteria for Adverse Events
The Common Terminology Criteria for Adverse Events allows the standardized classification of adverse events with condition-specific severity designations. Generally, grade 1 denotes a mild adverse event and grade 5 denotes death.

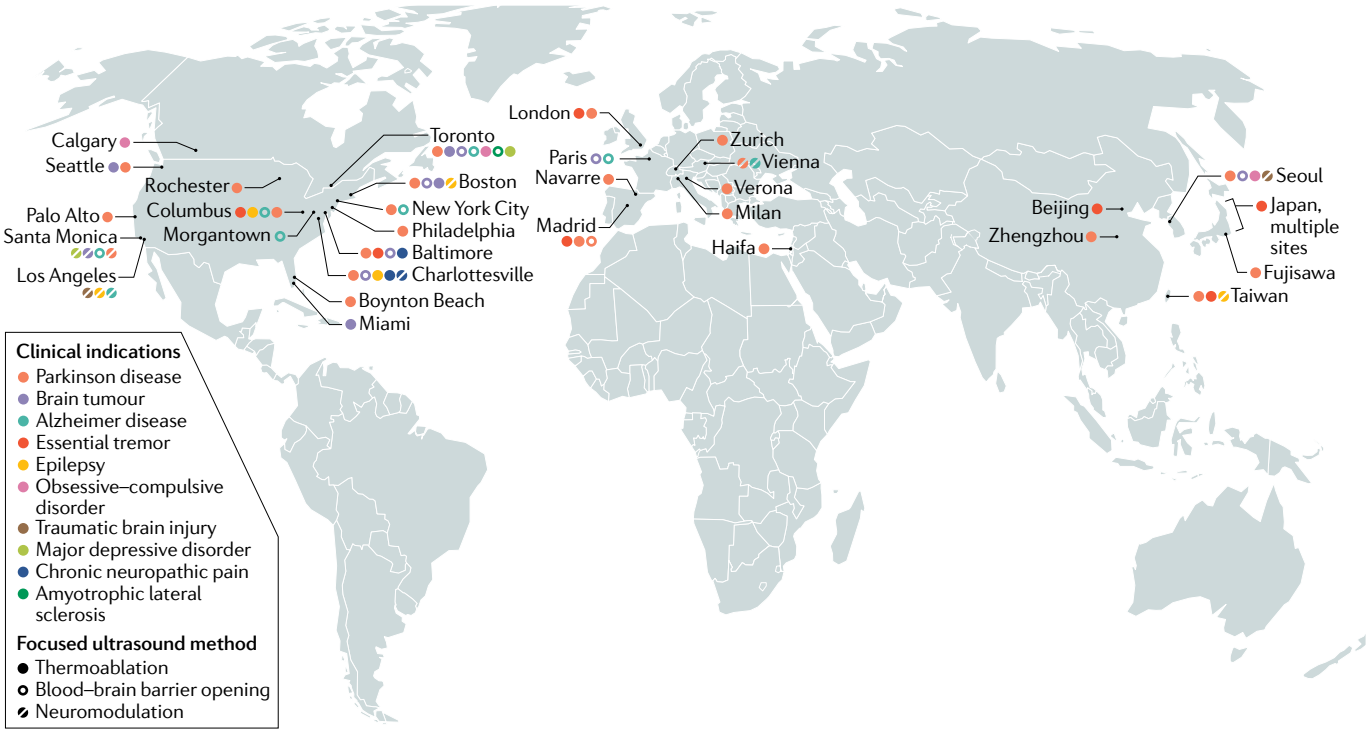

Fig. 5 | **The global landscape of human focused ultrasound clinical trials.** The figure shows trials that are registered and active at ClinicalTrials.gov, spanning diverse neurological indications and biological mechanisms. For more detailed information, see Supplementary Table 1.

considered when designing trials of this approach[158,159]. FUS BBBO might also be useful for visualizing the structure and function of the human glymphatic system, which provides a conduit for immune surveillance and waste clearance in the CNS[160,161].

Numerous clinical investigations combining FUS and chemotherapy in patients with new and recurrent primary brain tumours are ongoing[107,162] (FIG. 5; Supplementary Table 1). Recently, Park et al. described the feasibility and safety of repeated FUS BBBO in patients with glioblastoma who were undergoing standard maintenance temozolomide chemotherapy[163]. Although temozolomide is already known to penetrate the BBB and has an excellent systemic safety profile, this study is notable in establishing patient acceptability of repeated procedures, providing the catalyst for combinations with other antitumour therapies. For instance, compelling evidence of tumour response in xenograft HER2 brain tumours after FUS plus trastuzumab is driving forward phase I clinical testing in patients with metastatic breast cancer (NCT03714243). Another early trial, SONIMEL01 (NCT04021420), is using the SonoCloud system to deliver nivolumab to the brains of patients with melanoma brain metastases. Diffuse pontine intrinsic glioma, a devastating cancer in children, is also of pressing interest given the difficulty of safe surgical access and the dearth of available effective treatments and clinical trials are under active development[115]. Finally, the ability to breach the blood–spinal cord barrier, though nascent, will be an important area of research in the near future, with potential implications for the treatment of spinal cord injury and tumours[164].

Other mechanisms and applications

Neuromodulation

The appeal of neuromodulation lies in the ability to restore or prevent functional decline by 'fine-tuning' the pathological circuits underlying brain disorders. Examples of transformative neuromodulation include DBS for PD and transcranial magnetic stimulation (TMS) for MDD[31,165]. Another example is the discovery of optogenetics, which has unleashed the potential to interrogate and understand the neural substrates of behaviour in the laboratory[166].

FUS neuromodulation has several potential advantages over these existing modalities. In contrast to transcranial direct current stimulation and TMS, FUS can target deep brain regions with millimetric spatial resolution[7,167,168]. Compared with DBS, FUS is less invasive, eliminating surgical risks and permitting versatility in serial and repeat treatments. A range of brain regions, including the hippocampus, frontal lobe, motor cortex, putamen and substantia nigra, can be sonicated by repositioning or steering the transducers[122,137,147,169]. The technical feasibility of sonicating multiple diffuse structures in a single sitting is currently being tested in the context of BBBO (NCT03739905 and NCT03671889).

Preclinical studies using various assays, including immunohistochemistry, electrophysiology, in vivo calcium imaging, neuroimaging and behavioural tests, have confirmed that low-intensity pulsed FUS can both inhibit and enhance neural activity in superficial and deep brain regions[168,170–172]. Although the initial results are promising, several factors have impeded clinical translation of this technology. These factors include the

Optogenetics
A neuromodulation technology that uses specific wavelengths of light to excite or inhibit neurons through light-sensitive ion channels, which can be introduced through viral transfection.

large variability in transducer design and parameters as well as a lack of consensus on the mechanisms of action and robustness of the effects. The in vivo pressure fields that dictate the biological effects will differ substantially according to species, age and sex, partly owing to variations in skull shape and properties[173]. For example, in rodents where the head dimension is comparable to ultrasound wavelengths, complex pressure distributions can form within the skull, sometimes leading to activation of the auditory pathway and a related startle response[174–176]. According to a simulation analysis of experimental conditions from selected studies, increases in temperature could be another confounder[177].

Efforts over the past 2 years are rapidly moving towards filling the translational gap. These experiments focused on identifying effective parameters for neuromodulation with equipment and animal models that better resemble those in human studies (for example, 250 kHz transducers, non-human primates)[167,168,171,172,178,179]. Using modern laboratory techniques, major advances were made in elucidating the mechanisms of FUS neuromodulation, including inhibition via transient hyperthermia and excitation via effects on membrane-bound mechanosensitive receptors (for example, astrocytic TRPA1), synaptic transmission, and postsynaptic regulation[167,180–182]. Intravascular microbubbles can also augment the mechanical effects of ultrasound or transiently open the BBB, thereby aiding neuromodulation[183–186]. Another key discovery was the offline effect of FUS on the basal forebrain, anterior cingulate cortex and amygdala up to 2 h post-stimulation[168,171,172].

With these recent translational studies and a well-established safety profile, low-intensity FUS is poised for human studies. The potential impact will be determined by initial testing in patients with epilepsy, neurodegenerative disease and psychiatric disorders[169,182,187] (FIG. 5; Supplementary Table 1). A study in healthy individuals showed that sonication of the primary visual cortex could elicit phosphenes concurrent with activation of this region on blood oxygen level-dependent functional MRI[188]. Another study using functional MRI suggested that the spatial resolution of FUS stimulation is superior to that of TMS[189]. Low-intensity FUS was found to be safe in patients with PD or AD but target engagement of the hippocampus and substantia nigra has yet to be demonstrated[169,190]. NEUROLITH (Storz Medical AG, Tägerwilen, Switzerland) is a clinical prototype designed for neuromodulation that uses an optical tracking system for navigation. Randomized sham-controlled trials of NEUROLITH in AD and PD are ongoing.

Other applications of FUS neuromodulation include the delivery or triggering of optogenetic and chemogenetic constructs, peripheral nerve stimulation and targeted delivery of psychoactive agents[191–197]. Vagus nerve stimulation can activate cholinergic anti-inflammatory pathways, which might be beneficial in inflammatory and autoimmune conditions[191]. Ultrasound-responsive nanodroplet carriers can be loaded with lipophilic psychoactive drugs, such as propofol and barbiturates, and local release results in reliable neural inhibition[192,196]. The delivery of GABA with or without BBBO has also been proposed and proof-of-concept studies have been conducted in rodent and primate models[193,198]. This approach combines the flexibility of FUS with the reliable and robust effects of pharmacological agents that are already approved for human administration, thereby providing a clear pathway for clinical translation.

Emerging approaches

Emerging applications are harnessing the myriad of ways in which FUS can interact with the CNS. Indeed, few modalities have as diverse an array of biological effects on tissue as ultrasound. Although thermoablation and BBBO are the most common approaches, additional FUS mechanisms, including hyperthermia, sonodynamic therapy, sonothrombolysis and histotripsy, are under active investigation.

Hyperthermia therapy, in which the temperature of the target tissue is raised to 40–45 °C, can enhance tumour cell chemotherapy uptake, radiosensitivity and immunogenicity[199,200]. In preclinical glioblastoma models, the addition of hyperthermia before radiotherapy impaired DNA repair, survival pathway activation and glioma stem cell proliferation in vitro and in vivo[201]. Hyperthermia therapy is one of the most potent radiosensitizers and has the potential to improve treatment outcomes and reduce radiation toxicity in people with brain tumours. However, to date, clinical studies have focused predominantly on systemic cancers[202]. Only one brain application, using a single element transducer through a cranial window, has been reported in patients with glioblastoma[17]. Although the current generation of devices are non-invasive and allow unprecedented flexibility and precision, hyperthermia therapy with FUS remains challenging owing to excessive skull heating when large and off-centre targets are treated.

Another potential FUS approach in neuro-oncology is sonodynamic therapy, which involves the use of ultrasound to generate reactive oxygen species from sonosensitizers. Sonodynamic therapy is similar in principle to photodynamic therapy but is less invasive and has shown promise in controlling tumour growth in vivo[203].

Sonothrombolysis is the dissolution of intravascular thrombus, using ultrasound alone or with microbubbles, to treat ischaemic stroke. A Cochrane meta-analysis published in 2012 found that the addition of pulsed ultrasound to tissue plasminogen activator within 12 h of symptom onset significantly decreased the rate of failure to recanalize (OR 0.28) and the rate of death or disability at 3 months (OR 0.50) without an increased risk in intracranial haemorrhage[204]. However, a larger multicentre, double-blind phase III RCT, CLOTBUST-ER, did not find a difference in modified Rankin scale scores between ultrasound plus alteplase and alteplase alone groups 90 days after acute ischaemic stroke[205]. Owing to the success of endovascular thrombectomy, which emerged during the study period, the results were reanalysed, excluding centres with a biased randomization of patients to endovascular thrombectomy trials. This post hoc analysis found that the addition of ultrasound to the treatment protocol was associated with an increased rate of functional independence[206]. The widespread adoption of endovascular techniques could hamper the further development of sonothrombolysis to treat ischaemic stroke[206].

However, because the ultrasound device employed is non-invasive, operator independent and potentially less costly than endovascular treatment, its efficacy might still be evaluated in specific clinical scenarios, rural communities or as an adjunct to current standards.

Histotripsy is a technique in which high-intensity, microsecond-range ultrasound pulses fractionate tissue within seconds to minutes by means of cavitation. Applications include rapid non-thermal tissue ablation or liquefaction of clots to facilitate the minimally invasive removal of intracranial haemorrhages[30,207]. Data on the safety of histotripsy are still preliminary, particularly in the context of transcranial applications. Histotripsy ablation via a craniectomy seems to be feasible in vivo, with negligible off-target tissue injury being observed on histology[30,208]. If successful, histotripsy will dramatically expand the treatment envelope and volume of tissue ablated by FUS and will provide a powerful addition to the minimally invasive surgical armamentarium.

Challenges and future directions

Despite the rapid progress in therapeutic FUS over the past decade, considerable scope remains for technical and clinical advancement. Currently, high-intensity FUS thermoablation is inefficient for peripheral brain regions, large lesions and in patients with unfavourable skull morphology such as a low skull density ratio (SDR)[209]. A SDR of <0.45 is a relative contraindication to MRgFUS thermoablation owing to reduced efficiency of ultrasound propagation. Although large datasets show that MRgFUS thalamotomy is feasible with a SDR of <0.45, considerable heat deposition in the skull bone can be intolerably painful and result in injuries to the bone marrow[210,211]. Furthermore, for lesions close to the skull base, sensitive neurovascular structures (for example, the optic nerve) are at risk. Technical advancements that are anticipated in the coming years include optimized ultrasound focusing and correction, patient-specific ultrasound arrays[212], and microbubble-mediated non-thermal ablation to minimize heating and expand the treatment envelope down to the skull base[213]. Currently, clinical efforts in FUS thermoablation are aimed at improving tolerability (for example, through the use of shorter procedure times and neuroimaging adjuncts) and uncovering new indications for FUS, including subcortical lesions that cause epilepsy such as hypothalamic hamartoma and tuberous sclerosis lesions (NCT02804230).

The development of less invasive devices will help to address practical and ethical challenges in surgical trials. The decreased surgical risks associated with non-invasive modalities can render randomization, blinding and sham surgeries more practical and less ethically controversial[214]. In addition, minimally invasive modalities are likely to be more acceptable to patients and referring clinicians. However, any new technology must be evaluated in the appropriate cultural and ethical context, for example, to ensure equitable distribution of resources and access to participation in clinical research. Frequent and active engagement of all stakeholders, including scientists, clinicians, patients, funders and industry, should be encouraged to proactively define and explore the most important issues.

Many questions remain unanswered with regard to FUS BBBO; for example, how much drug passes through the BBB? What is the optimal therapeutic for a given disease indication? What is the safety profile of chronic BBBO? The immediate objective of the field is to establish direct measures of therapeutic delivery and target engagement in humans. To achieve the ultimate goal of improved clinical outcomes, broad interdisciplinary collaborations will be required, for example, to source radiopharmaceuticals or tissue or cerebrospinal fluid samples (NCT03714243). The identification of optimal therapeutics to cross the BBB could be guided by previous trials involving CED and intrathecal injections. In the case of intracranial metastatic diseases, for instance, antitumour therapies that are efficacious against systemic lesions but do not cross the BBB offer an economical approach to this problem. The success of FUS BBBO will hopefully unlock exciting opportunities to deliver nanoparticle drug carriers and viral constructs, although these agents are still in the early stages of development and will require systemic administration. Studies in large animal models, such as non-human primates, and judicious conduct of appropriately designed clinical trials that aim to capture valid outcomes are necessary to bridge the translational gap.

Over the next two decades, we will undoubtedly see many of these questions answered, as existing pharmaceuticals are revisited and novel therapies are explored in combination with FUS delivery. To achieve these objectives and make an impact on the most intractable conditions affecting humanity, a global, concerted effort through research networks and consortia is needed.

Conclusions

The current generation of FUS represents the culmination of decades of research and lies at the convergence of global expertise in medical physics, engineering, imaging, biology and neuroscience (FIG. 5). The past 5 years have seen a surge in innovation and global productivity in FUS clinical efforts, with the demonstration of a favourable safety profile as well as versatility across and scalability within several clinical indications. Following regulatory approval of MRgFUS thalamotomy for ET and tremor-dominant PD, thermoablation has gone from experimental treatment to standard of care. Efficacy data for drug delivery via FUS BBBO are anticipated over the next 2 years, probably within the neuro-oncology field initially. Additionally, a growing number of registered trials are addressing the application of FUS neuromodulation in epilepsy, AD, PD, depression and traumatic brain injury (Supplementary Table 1).

Over the next decade, we expect to see a continued increase in our understanding of FUS mechanisms and more widespread coupling of FUS with promising therapeutics. However, many challenges remain and the role of FUS in the treatment of brain disease will continue to be explored in this highly dynamic and exciting field. Only through continued collaboration and global efforts can progress be made in developing safe and effective therapies for the most challenging brain conditions.

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Skull density ratio (SDR). The ratio of cancellous to cortical bone density in the skull.

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Y.M. researched data for the article. Y.M. and N.L. wrote the article. All authors made substantial contributions to discussions of the content and reviewed and/or edited the manuscript before submission.

Competing interests
K.H. is an inventor on intellectual property owned by Brigham and Women's Hospital in Boston, MA, USA, and Sunnybrook Research Institute in Toronto, Canada, related to intracranial focused ultrasound technology. N.L. has received an honorarium from the Focused Ultrasound Foundation, a not-for-profit funding agency, for serving on an expert steering committee on focused ultrasound in Alzheimer disease. Y.M. declares no competing interests.

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