



A systematic review of preclinical and clinical transcranial ultrasound neuromodulation and opportunities for functional connectomics

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ABSTRACT

Background: Low-intensity transcranial ultrasound has surged forward as a non-invasive and disruptive tool for neuromodulation with applications in basic neuroscience research and the treatment of neurological and psychiatric conditions.

Objective: To provide a comprehensive overview and update of preclinical and clinical transcranial low intensity ultrasound for neuromodulation and emphasize the emerging role of functional brain mapping to guide, better understand, and predict responses.

Methods: A systematic review was conducted by searching the Web of Science and Scopus databases for studies on transcranial ultrasound neuromodulation, both in humans and animals.

Results: 187 relevant studies were identified and reviewed, including 116 preclinical and 71 clinical reports with subjects belonging to diverse cohorts. Milestones of ultrasound neuromodulation are described within an overview of the broader landscape. General neural readouts and outcome measures are discussed, potential confounds are noted, and the emerging use of functional magnetic resonance imaging is highlighted.

Conclusion: Ultrasound neuromodulation has emerged as a powerful tool to study and treat a range of conditions and its combination with various neural readouts has significantly advanced this platform. In particular, the use of functional magnetic resonance imaging has yielded exciting inferences into ultrasound neuromodulation and has the potential to advance our understanding of brain function, neuromodulatory mechanisms, and ultimately clinical outcomes. It is anticipated that these preclinical and clinical trials are the first of many; that transcranial low intensity focused ultrasound, particularly in combination with functional magnetic resonance imaging, has the potential to enhance treatment for a spectrum of neurological conditions.

1. Introduction

Ultrasound has been established as one of the safest and most versatile diagnostic tools since its first medical applications in the 1950s. At higher intensities, ultrasound – typically focused with an acoustic lens or transducer array – can also induce a range of therapeutic effects which have been leveraged to achieve compelling treatment options that have been clinically approved for a range of conditions [1] including uterine fibroids [2], as well as prostate [3], liver [4], pancreatic [5], breast [6], and bone [7] lesions.

Until recently, brain applications have been hindered by the high acoustic attenuation, large specular reflections, and aberrations caused by the skull [8–10]. However, recent advances have led to a surge of

interest in transcranial focused ultrasound as a transformative tool for neurological conditions. The advantages of focused ultrasound, namely its ability to elicit profound effects non-invasively and precisely in deep brain regions, have resulted in its widespread clinical approval for movement disorders (essential tremor, Parkinson's), with trials and limited approval for neuropathic pain and psychiatric disorders of depression and obsessive-compulsive disorder [1]. In addition to the aforementioned applications, which utilize high intensity focused ultrasound (HIFU) for thermo-ablation, promising clinical trials of focused ultrasound and exogenous microbubble contrast agents for transient blood-brain barrier opening (BBBO) for drug delivery have emerged, demonstrating safe mechanical interaction of ultrasound with brain tissue [11]. Most recently, low-intensity focused ultrasound has been

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applied for neuromodulation (non-lesional), referred to as transcranial ultrasound stimulation (TUS), in research studies that aim to examine basic neuroscience questions on brain function, as well as to prevent or restore functional decline by modulating the underlying neural circuits.

Neuromodulation (Fig. 1) has traditionally been achieved with electromagnetic techniques such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS). Each of these approaches has advantages and has played a key role in research and therapy (as reviewed in Ref. [12]). However, these approaches are of limited precision and are restricted to more superficial targets unless invasively implanting electrodes for deep brain stimulation (DBS). Electromagnetic methods are also affected by changes in conductivity in the brain, which may be altered in pathological cases making individualized targeting difficult [13]. In contrast, TUS is unaffected by conductivity changes and provides non-invasive, selective, and focal (mm-scale) deep brain stimulation. Indeed, preclinical and clinical studies utilizing electrophysiology, neuroimaging, behavioural testing, microscopy, immunohistochemistry, and histology have demonstrated the ability of TUS to safely either inhibit or enhance neural activity in both superficial and deep brain regions, eliciting positive effects in a variety of cohorts of neurodegenerative and psychiatric disorders [11,14].

In this systematic review, we first outline the principles and mechanisms of TUS neuromodulation. We then provide a comprehensive overview and update of preclinical and clinical TUS and the accelerating breadth of potential for non-invasive brain stimulation. Potential confounds and mitigation strategies are discussed. Finally, we highlight the emerging role of functional brain mapping in conjunction with ultrasound neuromodulation and emphasize the opportunities that brain connectomics brings to better understand and predict patient outcomes.

2. Methods

This review follows the standards established in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [15]. Web of Science and Scopus databases were queried using search parameters ultrasound-AND-neuromodulation-AND-transcranial, and ultrasound-AND-neuromodulation-AND-fMRI, and ultrasound-AND-fMRI with the latest updated search in December 2023. References were imported for screening with Covidence [16], a systematic review management tool. For inclusion, studies had to utilize transcranial ultrasound for neuromodulatory purposes, be performed in human or animal subjects (*in vivo*), and be written in the English language. Abstracts were screened for relevance, and relevant articles were then assessed for eligibility by reading their full texts. Additional articles were sought by checking the received citations of the included studies. For each study, extracted variables included bibliographic data, subject cohort,

ultrasound device, ultrasound parameters, sonication target, outcome assessment methods, and summary of results.

Search queries resulted in 971 studies (Fig. S1). After the removal of 307 duplicates, 664 studies were screened for relevance. 229 studies were found to be relevant, and their full texts were assessed for eligibility. 57 studies were deemed ineligible and were excluded: 23 were preprints or abstracts published prior to the complete study; 17 were not transcranial or were not assessing neuromodulation; 10 were not *in vivo*, 7 were reviews. The remaining 172 studies were found eligible. After screening the citations of the included papers, 15 additional papers were included for a total of 187 papers in the systematic review.

3. Principles and mechanisms of ultrasound neuromodulation

3.1. Parameters

TUS protocols are defined by the fundamental frequency, pulse repetition frequency, duty cycle, duration, and intensity [17]. The fundamental frequency is the number of oscillations of the ultrasound wave per unit time and is important for spatial targeting. Higher frequencies result in a tighter focus but are more attenuated by the skull; <700 kHz has been shown to be optimal for transcranial transmission [18,19]. The pulse repetition frequency (PRF) determines the rate at which pulses are delivered, and the duty cycle (DC) describes the ultrasound-on portion of each cycle. It is worth noting that some studies report pulse duration (PD) instead of DC (DC = PD x PRF). Some studies employ continuous wave paradigms, but pulsed delivery has a lower risk of heating [20] and has been used more frequently in the literature. Pulse train duration (PTD) describes the total time from the onset of the first pulse to the end of the last pulse. TUS protocols also typically include pulse train repetitions over several sessions with their own pulse repetition interval (PRI_{pulse train repeat}). Protocols are also characterized by the intensity, which is proportional to the square of the pressure, and is inversely related to the density and speed of sound in the medium. Intensity is often reported through the spatial-peak temporal average (I_{spta} ; the average intensity during the PTD), or the spatial-peak pulse average (I_{sppa} ; the average intensity over the PD). Alternative measures include the pressure or the mechanical index (MI), which is the peak negative pressure divided by the square of the fundamental frequency and provides an estimation of the likelihood of destructive inertial cavitation. A wide range of protocols have been used, and it has been found that even small variations can profoundly affect neuromodulatory outcomes (see Table S1, Table S2); while beyond the scope of this review, there is a dire need to discuss best practices moving forward; while select studies do assess the impact of changes in parameters (e.g. Ref. [21]), it is difficult to fully uncouple all of the protocol parameters to clearly elucidate the physiological implications and biological effects

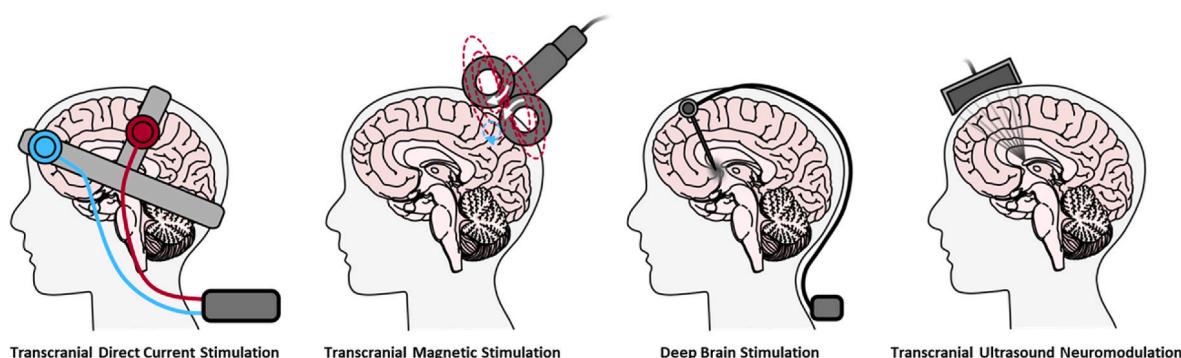


Fig. 1. Methods of neuromodulation. Concept illustrations of current methods of neuromodulation, including transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), deep brain stimulation (DBS), and transcranial ultrasound neuromodulation. tDCS and TMS are notably limited to superficial targets and are of limited precision. DBS can reach deep brain sites, but is invasive. Transcranial ultrasound stimulation (TUS) neuromodulation, the topic of this review, provides non-invasive and focal stimulation of both superficial and deep brain targets.

thereof. A significant aid to the field moving forward would be standardized reporting of TUS parameters, following the recently published guidelines from the International Transcranial Ultrasonic Stimulation Safety and Standards Consortium [17].

3.2. Mechanisms

Acoustic waves can interact with the neuronal membrane in various ways, modifying its state (Fig. 2). Here we outline proposed mechanisms by which TUS can result in the subsequent triggering of action potentials and thereby modulate neural activity [22].

3.2.1. Membrane conformational state and flexoelectricity

Mechanical ultrasound waves can change the neuronal membrane's mechanical properties in a localized manner, yielding changes in the membrane conformational state or relative displacements between lipids modifying electrostatic interactions. These conformational changes and flexoelectric effects have been shown to alter the transmembrane potential and induce capacitive currents, thereby modulating

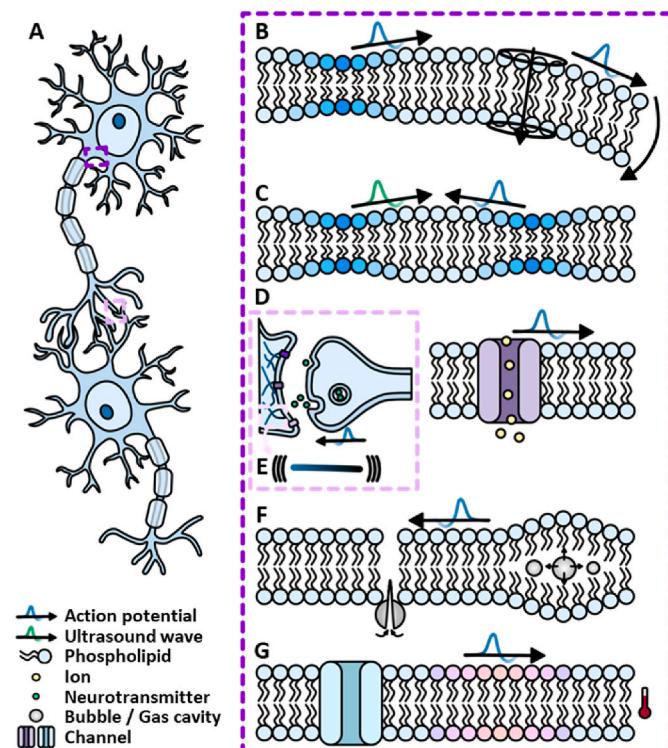


Fig. 2. Mechanisms of TUS neuromodulation. (A) Neurons, with dashed line boxes indicating a zoomed-in location to illustrate various proposed mechanisms in the membrane (purple) and at synapses (pink). (B) **Membrane conformational state and flexoelectricity:** ultrasound waves cause changes in the neuronal membrane's mechanical properties, yielding a mechanical strain gradient and changing the membrane conformational state. (C) **Thermodynamic membrane waves:** interactions of the acoustic pressure wave with interface waves can result in generation or suppression of an action potential. (D) **Mechanosensitive channels and synaptic vesicles:** ultrasound has been found to disrupt chemical synapses (left), and various membrane channels have exhibited mechanosensitivity and can thus be triggered by mechanical ultrasound waves (right). (E) **Microtubule resonance:** microtubules in the synapse cytoskeleton can resonate at ultrasonic MHz frequencies, influencing synaptic plasticity. (F) **Cavitation:** ultrasound can lead to the creation of pores in the membrane by inducing a lipid phase transition or micro-cavitation. (G) **Thermal modulation:** ultrasound can yield thermal changes in biological tissue, which can trigger thermosensitive ion channels and affect neural activity. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

neural activity. For example, Muratore et al. reported that acoustic radiation forces can reversibly deform cells [23]. Prieto et al. measured changes in membrane capacitance in an artificial bilayer upon TUS, reporting that changes in pressure caused by ultrasonic radiation forces disrupt the balance between bilayer tension and hydrostatic pressure, making the fluid membrane oscillate [24]. It has also been proposed that ultrasound can modify the viscoelastic properties of neuronal membranes to alter membrane conductance [25]. Recently, Chen et al. demonstrated that TUS can induce an action potential by the direct flexoelectric effect (generation of an electric polarization response under a mechanical strain gradient), and further explain that if perturbations are sufficiently compressive the resulting currents are excitatory, and if dilatational, the subsequent currents are inhibitory [26].

3.2.2. Thermodynamic membrane waves

Nerve impulses have been associated with interface waves that propagate along the axon or plasma membrane, similar to a propagating sound wave [27,28]. When an acoustic wave interacts with that cellular membrane, a pressure wave forms. Linear and nonlinear interactions of the waves can then lead to chemical and electrical processes resulting in an action potential (or suppression thereof) [29–32].

3.2.3. Mechanosensitive channels and synaptic vesicles

Ultrasound waves interacting with axonal membranes can induce reversible changes in ion transport mechanisms, which can induce cell depolarization [33]. Indeed, many ion channels are mechanosensitive and sensitive to ultrasound, including two pore domain potassium (K_{2P}) channels (such as TREK-1, TREK-2, TRAAK) [34,35], voltage-gated sodium (Na^+) and calcium (Ca^{2+}) channels [36], voltage-activated sodium channels (Nav1.5) [35], piezo-type channels (Piezo1 [37–39] and Piezo2 [40]), and transient receptor potential channels in astrocytes (TRPA1 – where ultrasound induces glutamate-releasing Best1 as a mediator of glia-neuron interaction [41], TRP4 [42], and TRPM7 [43]). Ultrasound can also disrupt chemical synapses, which can involve increased neurotransmitter release, synaptic cleft widening, and altered synaptic densities [44–47], or synaptic vesicle exocytosis [36].

3.2.4. Microtubule resonance

Microtubules are a key cytoskeleton component, and thus have an important role in synapse regulation. The MHz frequencies employed in TUS are in the range of the resonance frequencies of intra-neuronal microtubules [48,49]. Hameroff et al. therefore hypothesized that TUS may cause microtubules to vibrate, influencing synaptic plasticity and modulating synaptic potential [50].

3.2.5. Cavitation

Ultrasound waves interacting with bilayer leaflets can lead to the creation and collapse of nanobubbles in the intramembrane space [51]. Indeed, the cavitation threshold decreases with exogenous microbubble contrast agents, an approach that has also been applied in the context of focused ultrasound to create physical pores in the lipid bilayer membrane to transiently increase permeability [11,52]. This can be due to ultrasound interfacing with the conformational state of the lipids leading to a phase transition, or micro-cavitation [53]. Neurostimulation has also been found to be increased with the addition of microbubbles [38, 43], though cavitation agents are not typically used in conventional TUS protocols.

3.2.6. Thermal modulation

In addition to mechanical effects, ultrasound can yield thermal effects. While most TUS protocols do not induce any notable temperature rise ($<1\text{ }^\circ\text{C}$), stimulating at higher intensities or for sustained periods can. Temperature changes on the order of a few degrees can affect neural activity, altering neuronal membrane capacitance, as well as the amplitude and kinetics of synaptic potentials [54–58]. Certain ion channels also exhibit thermosensitivity [59], further contributing to a

potential thermal mechanism.

It should be noted that while the above interactions are expected to occur for as long as ultrasound is delivered, sustained or repeated exposure has sometimes been found to yield plastic effects in excitability without microstructural damage, with synaptic potentials outlasting the stimulation [60–64]. The mechanisms behind sustained yet reversible neuromodulatory effects of ultrasound are currently unclear. Such

plastic effects, however, are the main target for developing protocols, though achieving this has been difficult as effects are highly dependent on the stimulation parameters as well as the target tissue [65]. In general, however, while nerve impulses are electrical, they can involve mechanical-, chemical-, and thermal-induced changes, resulting in a variety of proposed mechanisms to date. There is overlap in how these mechanisms occur and a wide variety of parameters employed, and thus

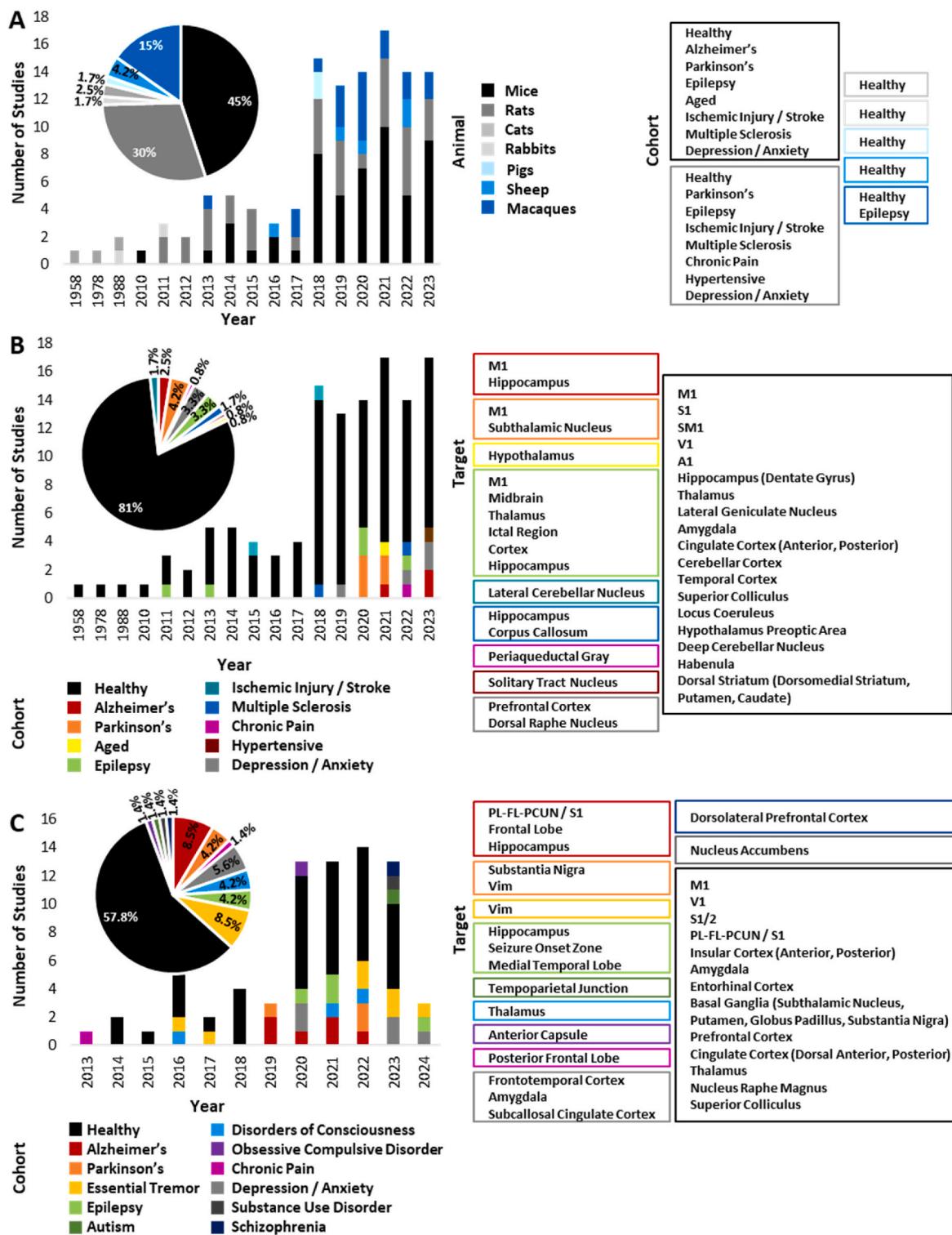


Fig. 3. Preclinical and clinical TUS neuromodulation landscape. (A) Preclinical TUS neuromodulation study overview, by animal and corresponding cohort. (B) Preclinical TUS studies organized by cohort and corresponding targets (for all animal species). (C) An overview of clinical TUS studies, organized by cohort and corresponding target.

it is likely that a combination of these mechanisms (and potentially others) provides the basis for TUS neuromodulation.

4. Preclinical and clinical ultrasound neuromodulation

Several studies have leveraged the above effects to modulate behaviour, perception, and neurophysiological responses in preclinical (115 studies) and clinical (71 studies) works (Fig. 3, Fig. S1). Preclinical studies have included both small (mice, rats, cats, rabbits) and large (pigs, sheep, macaques) animals, covering a range of models (healthy, Alzheimer's disease, Parkinson's disease, aged, epilepsy, ischemic injury, multiple sclerosis, chronic pain, hypertension, depression, and anxiety) and various targets. Clinical studies have addressed similar cohorts (healthy, Alzheimer's disease, Parkinson's disease, essential tremor, epilepsy, Autism, disorders of consciousness, obsessive compulsive disorder, chronic pain, depression, anxiety, substance use disorder, and schizophrenia) and similarly targeted regions. Here we describe highlights and milestones of TUS within an overview of the broader landscape, comment on potential confounds, and discuss outcome readouts and measures used to date.

4.1. Milestones of TUS neuromodulation

The earliest study of *in vivo* low-intensity TUS neuromodulation was conducted in 1958 by Fry et al., demonstrating the ability to temporarily suppress components of the electrical response (electroencephalogram; EEG) upon stimulation of the visual cortex in cats [66]. This sparked an array of works from the 1960s [67–69] and onwards [14,70] seeking to investigate the mechanism of action, establish the safety and efficacy of stimulation parameters, and demonstrate neuromodulatory outcomes for a range of cohorts and patient populations (with milestones provided in Fig. 4). In 2011, Min et al., provided the first evidence that TUS can alter the concentration of neurotransmitters in healthy rats, with the potential to modulate their local release, uptake, or degradation [71].

That same year, Min et al., also experimented with the first disordered cohort (a rat epilepsy model) and demonstrated that TUS could significantly decrease the occurrence of epileptic EEG bursts [72]. It was also shown at this time by Yoo et al. in healthy rabbits that TUS could modulate brain activity bimodally (i.e. stimulate or suppress) in a safe manner, depending on stimulation parameters [63]. This study further presented the first use of functional magnetic resonance imaging (fMRI) as a neural readout in the context of TUS [63].

Soon after, TUS was first demonstrated in humans in 2013 with improvement in mood and pain scores after sonication of the posterior frontal lobe in patients with chronic pain [50]. It was later demonstrated that S1 stimulation in healthy humans could elicit sonication-specific evoked potentials and produce phantom tactile sensations [73]. The first fMRI-ultrasound clinical studies emerged in 2016: Ai et al., demonstrated that TUS of M1 and the caudate nucleus in healthy subjects can induce changes in blood oxygen-level dependent (BOLD) signals [74], and Jang et al. showed that MRI-guided focused ultrasound (MRgFUS) ventral intermediate nucleus (Vim) thalamotomy (ablative HIFU) regulates interactions over the motor network via symptom-related connectivity changes [75]. That same year, Monti et al. published a case report of thalamic TUS in a patient with a traumatic brain injury who later demonstrated a marked clinical improvement [76].

The next few years saw various milestones in both preclinical and clinical contexts. In 2017, Downs et al. sonicated the putamen of healthy macaques, demonstrating that TUS could have a sustained positive impact on the performance of cognitive tasks [77]. This was mirrored by Legon et al. in healthy humans in 2018, where it was shown that M1 stimulation could confer a motor performance advantage [78]. 2018 also introduced new cohorts into the preclinical landscape: Baek et al. stimulated the lateral cerebellar nucleus in a mouse stroke model, and elicited significantly enhanced sensorimotor recovery that was maintained for 4 weeks following treatment [79]. The same study also found decreased levels of brain edema in the affected hemisphere, indicating a

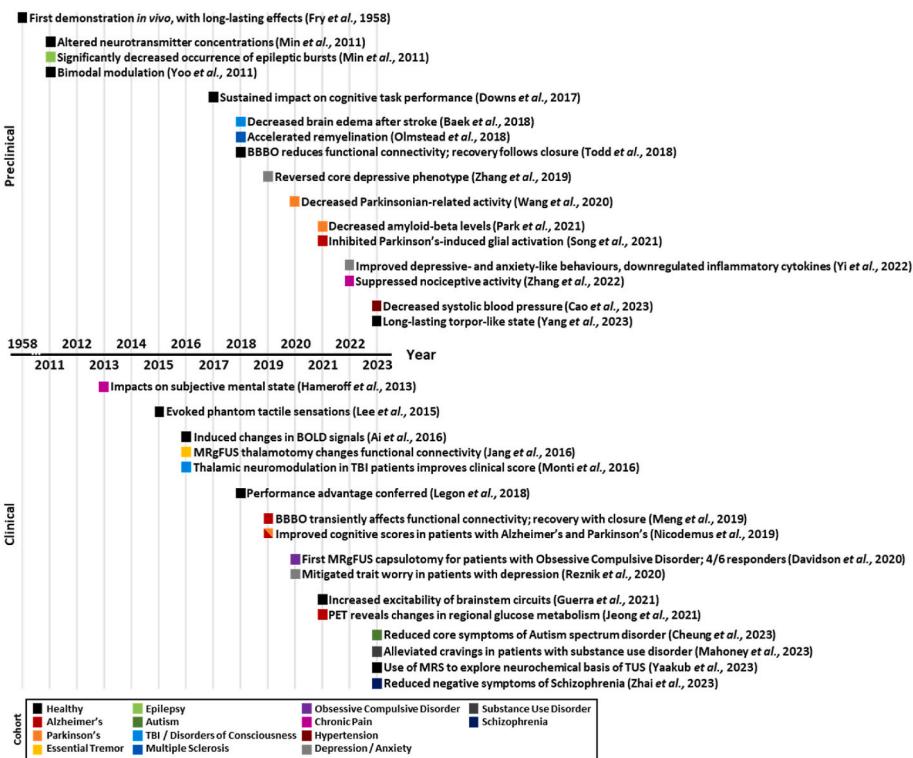


Fig. 4. Milestones in TUS neuromodulation, in both the preclinical (top) and clinical (bottom) contexts. Highlighted studies report the first instance of neuromodulation for a specific cohort, or a particularly important insight or outcome. BBBO: blood-brain barrier opening; BOLD: blood oxygenation level dependent; MRgFUS: magnetic resonance guided focused ultrasound; MRS: magnetic resonance spectroscopy; PET: positron emission tomography; TBI: traumatic brain injury.

possible TUS-induced anti-inflammatory response [79]. Olmstead et al. targeted the corpus callosum in a multiple sclerosis mouse model, resulting in significantly accelerated remyelination [80]. Both of these cohorts have received little attention in clinical ultrasound neuro-modulation studies to date, but the preclinical results point to optimistic future possibilities. The first study of possible neuromodulatory changes following ultrasound-mediated BBBO was conducted by Todd et al. in 2018 [81]. They found that BBBO caused a reduction in functional connectivity, though this recovered following closure [81]. This was mirrored in human patients with Alzheimer's the following year by Meng et al., who concurred [82].

While BBBO studies included Alzheimer's patients, 2019 saw the first inclusion of Alzheimer's and Parkinson's patients in the context of TUS neuromodulation trials, where Nicodemus et al. demonstrated improved cognitive and motor scores [83]. The following two years brought the first preclinical Parkinson's animal model use in TUS neuromodulation, where stimulation of M1 reduced Parkinsonian-related neural activity in mice [84], and stimulation of the right hemisphere in rats significantly reduced Parkinson's-induced glial activation and the phosphorylation of nuclear factor-kB p65 in the substantia nigra pars compacta [85]. The first preclinical Alzheimer's animal model use in TUS was also demonstrated around this time, with a study by Park et al. reporting decreased amyloid-beta levels after ultrasound in the pre- and infra-limbic cortex, and hippocampus in mice [86]. The first inclusion of depression was also in 2019 and 2020 in preclinical and clinical studies, respectively: Zhang et al. applied TUS to the prelimbic cortex of depressed rats, resulting in a reversed core depressive phenotype [87], while Reznik et al. stimulated the fronto-temporal cortex in a cohort of patients suffering from depression, yielding a decrease in trait worry and improvement in Global Affect [88]. The first ultrasound study with obsessive-compulsive disordered patients was also presented in 2020 (in the context of HIFU capsulotomy), with 4/6 responders and where fMRI revealed voxel clusters significantly associated with the eventual clinical response [89].

The most recent years (2021–2024) saw widely varying applications. Preclinically, pain models began to be assessed, where Zhang et al. demonstrated analgesia upon stimulation of the periaqueductal gray in a rat pain model [90]. Depression and anxiety were also assessed with more rigour in mice, where TUS of the prefrontal cortex was found to improve depressive- and anxiety-like behaviours, and inflammatory cytokines were significantly downregulated [91]. Induced hypothermia and hypometabolism was also achieved for the first time, with Yang et al. demonstrating a long-lasting (>24-h) torpor-like state in mice upon TUS of the hypothalamus preoptic area [92]. In clinical studies, brainstem excitability was modulated in healthy subjects [93], and positron emission tomography (PET) was employed for the first time with TUS to assess cerebral glucose metabolism in patients with dementia [94]. It is also noteworthy that the neurochemical basis of TUS neuromodulation has begun to be evaluated leveraging magnetic resonance spectroscopy (MRS) in clinical studies [95]. Most recently the newest applications of TUS emerged in clinical trials: Cheung et al. presented a double-blind, randomized, sham-controlled trial demonstrating significant clinical improvements in treated children with Autism [96]; Zhai et al. demonstrated the reduction of negative symptoms and improved cognitive performance in patients with Schizophrenia [97]; and Mahoney et al. showed alleviated cravings in patients with substance use disorders [98]. 2024 is likewise off to a promising start, with TUS clinical trial efforts in the treatment of epilepsy [99], depression [100], and essential tremor [101].

4.2. General results, neural readouts and outcome measures

The above studies represent particular milestones in TUS research; they contributed to the foundation for – and themselves built upon – a wider array of preclinical and clinical achievements. A complete list of studies can be found in Table 1 (preclinical) and Table 2 (clinical), organized chronologically by objective or response (expanded versions

Table 1

Preclinical studies of TUS neuromodulation. Summary of preclinical studies of low-intensity TUS neuromodulation, organized chronologically by response (motor/sensory, cognition/mood, consciousness, blood-brain barrier opening, direct neural effect). Note that the category of blood-brain barrier opening (BBBO) involving higher intensity ultrasound was included only when neuro-modulatory or connectivity changes were assessed with fMRI. (*) denotes the use of fMRI for targeting purposes only. (**) denotes the use of fMRI where connectivity results were reported. An expanded version of the table including study size, ultrasound details, and key results can be found in the Supplementary Information, in Table S1.

Author, Year	Cohort/Target	Read-Out
Motor/Sensory		
Fry et al., 1958 [66]	Cats (healthy)/V1	EEG + histology
Foster et al., 1978 [108]	Cats (healthy)/Right temporal cortex	EEG
Velling et al., 1988 [235]	Cats (healthy), rabbits (healthy)/M1	EEG
Tufail et al., 2010 [102]	Mice (healthy)/M1, Hippocampus	EMG + LFP + behavioural + histology + immunohistochemistry
Yoo et al., 2011 [63] **	Rabbits (healthy)/S1, V1	EEG + EMG + MRI + fMRI + histology
Kim et al., 2012 [236]	Rats (healthy)/Abducens nerve	Visual tracking of motor response + histology
Deffieux et al., 2013 [174]	Macques (healthy)/Frontal eye field	Visual tracking of motor response + behavioural
Kim et al., 2013 [157]	Rats (healthy)/M1	Visual tracking of motor response + FDG-PET + MRI + histology
King et al., 2013 [125]	Mice (healthy)/M1	EMG
Younan et al., 2013 [237]	Rats (healthy)/M1	Visual tracking of motor response
Kim et al., 2014 [158]	Rats (healthy)/Thalamus	Visual tracking of motor response + 18 F-FDG PET
Kim et al., 2014 [21]	Rats (healthy)/M1	EMG + histology
King et al., 2014 [126]	Mice (healthy)/M1	EMG
Mehic et al., 2014 [238]	Mice (healthy)/M1	Visual tracking of motor response + histology
Kamimura et al., 2015 [127]	Mice (healthy)/Hippocampus, locus coeruleus, superior colliculus	Visual tracking of motor response + EMG + histology
Kim et al., 2015 [239]	Rats (healthy)/V1	EEG
Kamimura et al., 2016 [128]	Mice (healthy)/SM1, superior colliculus, locus coeruleus, hippocampus	Visual tracking of motor response + EMG + histology
Lee et al., 2016 [109] *	Sheep (healthy)/SM1, V1	EEG + EMG + MRI + fMRI + behavioural + histology
Li et al., 2016 [129]	Mice (healthy)/M1	Visual tracking of motor response + EMG + histology
Gulick et al., 2017 [130]	Rats (healthy)/M1	EMG
Wattiez et al., 2017 [103]	Macaques (healthy)/Frontal eye field	Visual tracking of motor response + EEG + LFP (single-unit monitoring) + behavioural
Baek et al., 2018 [79]	Mice (stroke)/Lateral cerebellar nucleus	EMG + behavioural + histology
Dallapiazza et al., 2018 [110]	Pigs (healthy)/Somatosensory thalamus, ventrolateral thalamus	EEG + MRI + histology
Daniels et al., 2018 [111]	Rats, pigs (healthy)/Inferior colliculus	EEG + MRI + histology
Fisher et al., 2018 [154]	Mice (healthy)/S1	Ca+2 imaging + immunohistochemistry
Han et al., 2018 [155]	Mice (healthy)/M1	Visual assessment of motor response + Ca+2 imaging + histology
Lee et al., 2018 [240]	Rats (healthy)/M1	Visual assessment of motor response + histology + immunohistochemistry
Li et al., 2018 [131]	Rats (healthy)/M1	EMG

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Table 1 (continued)

Author, Year	Cohort/Target	Read-Out
Sato et al., 2018 [132]	Mice (healthy)/V1, cochlea	EMG + Ca+2 imaging
Yang et al., 2018 [160] **	Macaques (healthy)/S1	MRI + fMRI
Yoo et al., 2018 [112]	Rats (healthy)/S1	EEG
Xie et al., 2018 [104]	Mice (healthy)/M1	EMG + LFP
Cui et al., 2019 [133]	Mice (healthy)/M1	EMG + histology + immunohistochemistry
Kim et al., 2019 [134]	Mice (healthy)/M1	EMG
Kim et al., 2019 [173]	Mice (healthy)/S1	Near-infrared spectroscopy
Mohammadjavadi et al., 2019 [135]	Mice (deaf)/Auditory pathway	EMG
Verhagen et al., 2019 [62] **	Macaques (healthy)/Supplementary motor area, frontal polar cortex	MRI + fMRI + histology
Wang et al., 2019 [136]	Mice (healthy)/M1	TMS + EMG
Yoon et al., 2019 [113] *	Sheep (healthy)/M1, thalamus	EEG + EMG + MRI + fMRI + behavioural + histology + immunohistochemistry
Gaur et al., 2020 [241]	Sheep, macaques (healthy)/V1, lateral geniculate nucleus	MRI + histology
Pouget et al., 2020 [175]	Macaques (healthy)/Frontal eye field, supplementary eye field, cortical motor and visual cortex	MRI + behavioural
Qiu et al., 2020 [137]	Mice (healthy)/Cerebral cortex or dorsomedial striatum	EMG + Ca+2 imaging + immunohistochemistry
Wang et al., 2020 [84]	Mice (Parkinson's)/M1	LFP
Wang et al., 2020 [105]	Mice (healthy)/M1	LFP
Xu et al., 2020 [176]	Mice (Parkinson's)/M1	Behavioural + histology + immunohistochemistry
Yuan et al., 2020 [106]	Mice (healthy)/M1	EMG + LFP + laser speckle contrast imaging + visual assessment of motor response
Yuan et al., 2020 [242]	Mice (Parkinson's)/M1	Behavioural
Aurup et al., 2021 [138]	Mice (healthy)/M1	EMG
Baek et al., 2021 [139]	Mice (healthy)/Cerebellum	EMG + MRI + histology + immunohistochemistry
Kim et al., 2021 [140]	Mice (healthy)/M1, habenula	EMG + visual assessment of motor response + immunohistochemistry
Lu et al., 2021 [114]	Rats (blind)/V1	EEG
Yang et al., 2021 [161] **	Macaques (healthy)/S1	MRI + fMRI
Cheng et al., 2022 [115]	Mice (healthy)/V1	EEG + Ca+2 imaging
Kim et al., 2022 [141] *	Sheep (healthy)/M1, thalamus	EMG + MRI + fMRI + behavioural + histology
Munoz et al., 2022 [162] **	Macaques (healthy)/Putamen, caudate	MRI + fMRI + behavioural
Ramachandran et al., 2022 [142]	Rats (healthy)/S1	EMG
Xie et al., 2022 [107]	Mice (healthy)/M1	EMG + LFP
Yang et al., 2022 [163] **	Macaques (healthy)/S1	MRI + fMRI
Zhang et al., 2022 [90]	Rats (pain)/Periaqueductal gray	LFP + histology
Chu et al., 2023 [143]	Rats (healthy)/M1	TMS + EMG + CA+2 imaging + histology + immunohistochemistry
Hesselink et al., 2023 [144]	Mice (healthy)/M1	EMG + contact microphone
Xu et al., 2023 [156]	Mice (paroxysmal kinesigenic dyskinesia)/Cerebellar cortex	Ca+2 imaging + histology

Table 1 (continued)

Author, Year	Cohort/Target	Read-Out
Zhu et al., 2023 [145]	Mice (healthy)/M1	EMG + visual assessment of motor response + immunohistochemistry
Cognition/Mood		
Min et al., 2011 [71]	Rats (healthy)/Thalamus	Microdialysis + HPLC
Downs et al., 2017 [77]	Macaques (healthy)/Putamen	MRI + behavioural
Zhang et al., 2019 [87]	Rats (depression)/Prelimbic cortex	Behavioural + histology + immunohistochemistry
Bongioanni et al., 2021 [184] **	Macaques (healthy)/Medial frontal cortex	MRI + fMRI + behavioural
Pang et al., 2021 [190]	Mice (healthy, aged)/Hypothalamus	Behavioural + histology + immunohistochemistry
Yi et al., 2022 [91]	Mice (depression, anxiety)/Prefrontal cortex	Behavioural + histology + immunohistochemistry
Webb et al., 2023 [179]	Macaques (healthy)/Lateral geniculate nucleus	EEG + MRI + behavioural
Zhu et al., 2023 [191]	Mice (depression)/Dorsal raphe nucleus	Behavioural + LCMS + histology + immunohistochemistry
Consciousness		
Min et al., 2011 [72]	Rats (epilepsy)/Thalamus	EEG + behavioural + histology
Kim et al., 2013 [193]	Rats (chronic mesial temporal lobe epilepsy)/Ictal region	EEG + histology + immunohistochemistry
Guo et al., 2015 [198]	Rats (ischemic injury)/Cortex	Laser speckle imaging + behavioural + histology + immunohistochemistry
Airan et al., 2017 [194]	Rats (acute seizure)/Midbrain	EEG + MRI + histology
Chen et al., 2020 [195]	Rats (epilepsy)/Cortex, hippocampus, thalamus	EEG + behavioural + histology + immunohistochemistry
Zou et al., 2020 [196]	Macaques (epilepsy)/Prefrontal motor cortex	EEG + MRI
Wang et al., 2023 [192]	Mice (Alzheimer's, sleep-disordered)/M1, hippocampus	LFP + EMG
Yang et al., 2023 [92]	Mice, rats (healthy)/Hypothalamus preoptic area	Metabolism monitoring + MRI + immunohistochemistry
Choi et al., 2024 [203]	Rats (epilepsy)/Anterior thalamic nuclei	EEG + cerebral blood volume + immunohistochemistry + microdialysis
BBBO		
Scarcelli et al., 2014 [232]	Mice (healthy)/Hippocampus	MRI + histology + immunohistochemistry
Chu et al., 2015 [220] **	Rats (healthy)/S1	MRI + fMRI + EEG + histology + immunohistochemistry
Todd et al., 2018 [81] **	Rats (healthy)/S1	MRI + fMRI + histology
Todd et al., 2019 [223] **	Rats (healthy)/S1	MRI + fMRI + histology
Todd et al., 2019 [222] **	Rats (healthy)/S1	MRI + fMRI + histology
Constans et al., 2020 [221]	Macaques (healthy)/V1	EEG + MRI
Lea-Banks et al., 2021 [233]	Rats (healthy)/M1	MRI + behavioural + histology + immunohistochemistry
Liu et al., 2023 [224] **	Macaques (healthy)/Dorsal striatum	MRI + fMRI
Kline-Schoder et al., 2023 [234]	Mice (Alzheimer's)/Hippocampus	MRI + immunohistochemistry
Neural Effects		
Yang et al., 2012 [214]	Rats (healthy)/Thalamus	HPLC + histology
Kim et al., 2017 [212]	Mice (healthy)/Cortex	Optical intrinsic signal imaging
Olmstead et al., 2018 [80]	Mice (Multiple sclerosis)/Corpus callosum	EEG + MRI + histology

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Table 1 (continued)

Author, Year	Cohort/Target	Read-Out
Folloni et al., 2019 [64] **	Macques (healthy)/Amygdala, anterior cingulate cortex	MRI + fMRI
Huang et al., 2019 [215]	Rats (healthy)/Hippocampus	Histology + immunohistochemistry
Li et al., 2020 [243] **	Macques (healthy)/Posterior cingulate cortex	MRI + fMRI
Asan et al., 2021 [204]	Rats (healthy)/Cerebellum	LFP (Single-unit activity)
Hou et al., 2021 [213]	Mice (healthy)/Ventral tegmental area	Ca+2 imaging + histology + immunohistochemistry
Huang et al., 2021 [216]	Mice (healthy)/Cortex, hippocampus	Histology + immunohistochemistry
Park et al., 2021 [86]	Mice (Alzheimer's)/Whole brain	EEG, histology, immunohistochemistry
Song et al., 2021 [85]	Rats (Parkinson's)/Right hemisphere	Histology + immunohistochemistry
Yu et al., 2021 [205]	Rats, mice (healthy)/S1	EEG + LFP (single-unit activity) + histology
Zhou et al., 2021 [217]	Mice (Parkinson's)/Subthalamic nucleus	Behavioural + histology + immunohistochemistry
Dong et al., 2022 [206]	Mice (healthy)/Hippocampus	LFP
Mohammadjavadi et al., 2022 [210]	Sheep (healthy)/Lateral geniculate nucleus	EEG + MRI
Murphy et al., 2022 [159]	Mice (epilepsy)/Hippocampus	LFP + PET + fiber photometry
Nguyen et al., 2022 [207]	Rats (healthy)/Hippocampus	LFP
Niu et al., 2022 [208]	Rats (depression)/Hippocampus	LFP (Field excitatory post synaptic potentials)
Yang et al., 2022 [218]	Rats (Multiple sclerosis)/Hippocampus	Immunohistochemistry
Cao et al., 2023 [211]	Rats (hypertensive)/Solitary tract nucleus	ECG + histology + immunohistochemistry
Yuan et al., 2023 [209]	Mice (healthy)/Midbrain	LFP + optical intrinsic signal imaging

can be found in [Table S1](#) and [Table S2](#), respectively). Objectives and responses were categorized as motor/sensory, cognition/mood, consciousness, general neural effect, BBBO, or ablative.

The majority of TUS studies have been conducted with the aim of eliciting functional (motor/sensory) responses. While such investigations have generally been performed in healthy subjects, they have the potential to treat movement disorders, alleviate chronic pain, etc. These studies typically employ structural MRI for targeting (indeed most ultrasound neuromodulation studies are performed under post-scanning MRI guidance) and then electrophysiological recordings as the primary readout including local field potential (LFP) [84,90, 102–107], EEG [61,63,66,73,103,108–124], and electromyographic (EMG) [21,63,78,79,93,102,104,106,107,109,113,125–153] readings to assess the enhancement or suppression of evoked potentials accompanying elicited movement. It should be noted, however, that while direct motor responses from TUS have been captured in small animals, they have not been observed in large mammals or humans. It is also worth noting that many clinical studies of TUS have also applied TMS, and thus one must be cautious in attributing responses solely to TUS when being combined online with another form of neuromodulation. A complementary tool used in motor/sensory ultrasound neuromodulation studies has been calcium imaging, which does not record the finely time-resolved spiking activity capable with electrophysiology but does capture a view of activity across a large neuron population [115, 132,137,143,154–156]. Another modality is PET, bringing the ability to spatially monitor glucose metabolism [157–159]. PET has contributed to providing proof-of-principle of the spatial selectivity of TUS. Similarly, fMRI has been applied in preclinical [62,63,109,113,141, 160–163] and clinical [74,99,100,118,152,164–170] studies to measure brain activity and connectivity, typically with the blood oxygenation

Table 2

Clinical studies of TUS neuromodulation. Summary of clinical studies of low-intensity TUS neuromodulation, organized chronologically by response (motor/sensory, cognition/mood, consciousness, blood-brain barrier opening, ablative). Note that categories of blood-brain barrier opening (BBBO) and ablative responses involving higher intensity ultrasound were included only when neuro-modulatory or connectivity changes were assessed with fMRI. (*) denotes the use of fMRI for targeting purposes only. (**) denotes the use of fMRI where connectivity results were reported. An expanded version of the table including study size, ultrasound details, and key results can be found in the Supplementary Information, in [Table S2](#).

Author, Year	Cohort/Target	Read-Out
Motor/Sensory		
Hameroff et al., 2013 [50]	Chronic pain/Posterior frontal lobe	Clinical score
Legon et al., 2014 [116]	Healthy/S1	EEG + behavioural (sensory discrimination task)
Mueller et al., 2014 [117]	Healthy/S1	EEG
Lee et al., 2015 [73] *	Healthy/S1	EEG + fMRI
Ai et al., 2016 [74] **	Healthy/M1, caudate nucleus	MRI + fMRI
Lee et al., 2016 [118] **	Healthy/V1	EEG + MRI + fMRI
Lee et al., 2016 [164] *	Healthy/S1/2	MRI + fMRI
Legon et al., 2017 [165] **	Healthy/M1	fMRI
Ai et al., 2018 [166] **	Healthy/M1	MRI + fMRI + behavioural (finger tapping task)
Gibson et al., 2018 [146]	Healthy/M1	TMS + EMG
Legon et al., 2018 [78]	Healthy/M1	TMS + EMG + behavioural (stimulus response reaction time task)
Legon et al., 2018 [119]	Healthy/Thalamus	EEG + behavioural (two-point discrimination task)
Badran et al., 2020 [167] *	Healthy/Thalamus	MRI + fMRI
Braun et al., 2020 [120]	Healthy/V1	EEG + questionnaire (auditory testing)
Fomenko et al., 2020 [147]	Healthy/M1	TMS + behavioural (visuo-motor task)
Lambert et al., 2020 [121]	Healthy/S1	EEG
Legon et al., 2020 [244] **	Healthy/M1	Questionnaire (follow-up safety study)
Schimek et al., 2020 [245]	Healthy/V1	TMS + questionnaire (visual percept reporting)
Cain et al., 2021 [168] **	Healthy/Globus pallidus	MRI + fMRI
Guerra et al., 2021 [93]	Healthy/Substantia nigra, nucleus raphe magnus, superior colliculus	EMG + behavioural (blink reflex)
Johnstone et al., 2021 [246]	Healthy/Inion	Questionnaire (auditory reporting)
Liu et al., 2021 [122]	Healthy/S1	EEG + MRI + behavioural (sensory discrimination task)
Xia et al., 2021 [148]	Healthy/M1	TMS + EMG
Yu et al., 2021 [123]	Healthy/M1	EEG + behavioural (foot pedal task)
Zeng et al., 2021 [149]	Healthy/M1, V1	TMS + EMG + behavioural (visuo-motor task)
Zhang et al., 2021 [150]	Healthy/M1	TMS + EMG + behavioural (stop signal reaction time task)
Butler et al., 2022 [169] *	Healthy/Human visual motion processing cortex	MRI + fMRI + EEG + behavioural (visual stimulus task)
Heimbuch et al., 2022 [151]	Healthy/M1	TMS + EMG
Matt et al., 2022 [170] **	Healthy/S1	MRI + fMRI + behavioural (tactile, sensorimotor function)

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Table 2 (continued)

Author, Year	Cohort/Target	Read-Out
Nakajima et al., 2022 [152] **	Healthy/FDI-M1, basal ganglia, prefrontal cortex	TMS + EMG + MRI + fMRI + behavioural (stop-signal task)
Park et al., 2022 [177]	Healthy/Dorsolateral prefrontal cortex	Electrooculography + behavioural (anti-saccade task)
Samuel et al., 2022 [153]	Healthy/M1	TMS + EMG + behavioural (motor task)
Zhang et al., 2022 [178]	Healthy/M1	EMG + behavioural (finger tapping task)
Legor et al., 2023 [124]	Healthy/Anterior insula, posterior insula	MRI + CT + EEG + physiological recordings + questionnaire
Riis et al., 2024 [101]	Essential tremor/Vim	MRI + behavioural (task) + accelerometer (tremor measure)
Cognition/Mood		
Nicodemus et al., 2019 [83] *	Alzheimer's, Parkinson's/Hippocampus (AD), substantia nigra (PD)	MRI + fMRI + clinical score
Beisteiner et al., 2020 [185] **	Healthy, Alzheimer's/PL-FL-PCUN/S1	MRI + fMRI + behavioural (memory task) + clinical score
Reznik et al., 2020 [88]	Depression/Fronto-temporal cortex	Clinical score
Sanguinetti et al., 2020 [186] **	Healthy/Right inferior frontal gyrus	fMRI + clinical score
Jeong et al., 2021 [94]	Alzheimer's/Hippocampus	MRI + FDG-PET + clinical score
Popescu et al., 2021 [187] **	Alzheimer's/PL-FL-PCUN/S1	MRI + fMRI + clinical score
Dorl et al., 2022 [188] **	Alzheimer's/PL-FL-PCUN/S1	MRI + fMRI + clinical score
Kim et al., 2022 [180]	Healthy/Medial prefrontal cortex	EEG + MRI
Cheung et al., 2023 [96]	Autism/Right tempoparietal junction	MRI + questionnaire + clinical score
Forster et al., 2023 [181]	Healthy/Inferior frontal gyrus of the lateral prefrontal cortex	EEG + behavioural (go/no-go task, internal shift task)
Forster et al., 2023 [182]	Healthy/Lateral prefrontal cortex	EEG + behavioural (learned helplessness task)
Kuhn et al., 2023 [189] **	Healthy/Amygdala, entorhinal cortex	MRI + fMRI
Mahdavi et al., 2023 [247]	Anxiety disorder/Amygdala	MRI + questionnaire + clinical score
Mahoney et al., 2023 [98]	Substance use disorder/Nucleus accumbens	MRI + questionnaire (visual analog scale) + clinical score
Riis et al., 2023 [100] **	Depression/Subcallosal cingulate cortex	fMRI + clinical score
Yaakub et al., 2023 [95] **	Healthy/Cingulate cortex (dorsal anterior, posterior)	MRI + MRS + fMRI
Zhai et al., 2023 [97]	Schizophrenia/Dorsolateral prefrontal cortex	Clinical score
Ziebell et al., 2023 [183]	Healthy/Prefrontal cortex	EEG + behavioural (virtual T-maze task), questionnaire (mood)
Riis et al., 2024 [248]	Depression/Subgenual cingulate cortex, ventral striatum	Questionnaire + clinical score
Consciousness		
Monti et al., 2016 [76]	TBI, disorder of consciousness/Thalamus	MRI + clinical score
Brinker et al., 2020 [202]	Epilepsy/Hippocampus (seizure onset zone)	Clinical score
Cain et al., 2021 [199]	TBI, disorder of consciousness/Thalamus	Clinical score
Lee et al., 2021 [197]	Epilepsy/Hippocampus (seizure onset zone)	EEG
Stern et al., 2021 [200] *	Epilepsy/Medial temporal lobe	MRI + fMRI + clinical score + histology
Cain et al., 2022 [201] **	Disorder of consciousness/Thalamus	MRI + fMRI + clinical score
Bubrick et al., 2024 [99]	Epilepsy/Medial temporal lobe	MRI + fMRI + clinical score
BBBO		
Meng et al., 2019 [82] **	Alzheimer's/Anterior right frontal lobe	MRI + fMRI

Table 2 (continued)

Author, Year	Cohort/Target	Read-Out
Ablation		
Jang et al., 2016 [75] **	Essential tremor/Ventral intermediate nucleus of the thalamus (Vim)	MRI + fMRI + clinical score
Park et al., 2017 [225] **	Essential tremor/Vim	MRI + fMRI + clinical score
Davidson et al., 2020 [89] **	Obsessive compulsive disorder, major depressive disorder/Bilateral anterior capsule	MRI + fMRI + 18 F-FDG PET + clinical score
Lu et al., 2022 [226] **	Essential tremor/Vim	MRI + fMRI + clinical score
Stanziano et al., 2022 [227] **	Parkinson's/Vim	MRI + fMRI + clinical score
Xiong et al., 2022 [229] **	Essential tremor/Vim	MRI + fMRI + clinical score
Xiong et al., 2022 [228] **	Parkinson's/Vim	MRI + fMRI + clinical score
Kato et al., 2023 [230] **	Essential tremor/Vim	MRI + fMRI + clinical score
Pae et al., 2023 [231] **	Essential tremor/Vim	MRI + fMRI + clinical score

level-dependent (BOLD) contrast technique to provide an indirect measure of neuronal activity; BOLD reflecting a combination of changes in regional cerebral blood flow, volume, and oxygen consumption [171, 172]. fMRI has contributed to our understanding of the large-scale effects of ultrasound neuromodulation, assessing the impact on coupling between the targeted area and other distant regions that form a neural network to serve specific functions. Optical methods have also been used to assess blood oxygenation (near-infrared spectroscopy [173]) and flow (laser speckle contrast imaging [106]). To examine whether these neuromodulatory effects are coupled to intended behavioural or clinical outcomes, studies have also employed behavioural (task) testing in preclinical [79,102,103,106,162,174–176] and clinical [78,101,116, 119,122,123,147,149,150,152,153,166,169,170,177,178] scenarios, and clinical scores [50]. In general, preclinical studies of TUS on the motor and somatosensory cortices have assessed induced muscle contractions and movement, or evoked sensory responses mimicking tactile or visual stimuli; clinical studies have seen modulations of cortical activity (but no movement), associated changes in motor performance, and in some cases elicited tactile sensations with TUS.

Other studies have assessed the effects of TUS on cognition or mood, with the intention to treat mood disorders (depression, anxiety) or disorders of cognitive function (dementia, autism). Along with EEG [179–183], PET [94], fMRI [83,95,184–189], behavioural testing [77, 87,91,179,181–184,190,191], and clinical scores [83,88,94,96, 185–188], studies in this category have also performed molecular and biochemical analyses to assess changes in monoamine neurotransmitter concentrations and changes in inflammatory cytokine expression [71, 87,91,95,190,191]. These studies have generally achieved improvements in cognitive performance and global affect. A small group of studies has assessed the impact of TUS on consciousness (epilepsy, TBI, disorders of consciousness). While only a limited number of reports in this category have been made, outcome measures have included LFP [192], EEG [72,193–197], EMG [192], molecular and biochemical analyses [92,195,198], fMRI [199–201], laser speckle imaging [198], behavioural testing [72,195,198], and clinical scores [76,199–202]. Such studies have successfully elicited improvements in behavioural responsiveness, modulated sleep states, and decreased epileptic activity. For example, in a recent preclinical study, Choi et al. used TUS in a rat model of drug-induced acute epilepsy and demonstrated a bidirectional modulation of epileptic seizures depending on the duration, intensity, and timing of the sonication [203]. In addition to EEG and cerebral blood volume measurements to measure seizure suppression or enhancement, they measured glutamate and GABA levels in interstitial

fluid obtained via microdialysis. This study demonstrates the clinical translation potential of TUS in epilepsy as well as other neurological diseases with excitatory/inhibitory imbalances.

The most diverse category is that of general neural effects, where a collection of preclinical studies has focused on general changes in neural activity following TUS, investigating neurotransmitter expression levels, protein expression, glial cell activation, and myelination. This category has also used the most diverse outcome measures including LFP [159, 204–209], EEG [80, 86, 205, 210], electrocardiogram [211] measurements, optical intrinsic signal imaging [209, 212], fiber photometry [159], calcium imaging [213], molecular and biochemical analyses [85, 86, 214–218], behavioural testing [217], and histology. Indeed, most preclinical studies include histologic and immunohistochemical analyses as a measure of the safety of the treatment approach, sometimes coupled with adverse behavioural performance. In clinical studies, safety is assessed via behavioural changes and subject questionnaires. In general, studies indicate a favourable safety profile for low-intensity TUS neuromodulation (in-depth assessments of safety can be found in Refs. [14, 219]).

Categories of BBBO and ablation were also assessed here. Ablation uses HIFU, and is notably a form of irreversible neuromodulation, in that it alters neural activity via intentional thermal damage (lesioning) to change brain function. BBBO also alters normal brain function with lower intensities than ablative procedures but higher (effective) intensities than typical low-intensity TUS studies (with the use of exogenous microbubbles), albeit temporarily and unintentionally. These studies have employed structural MRI (for targeting and BBBO verification), EEG [220, 221], fMRI [75, 81, 82, 89, 220, 222–231], PET [89], immunohistological analyses [232–234], behavioural testing [233], and clinical scores [75, 89, 225–231] as outcome measures. It should be noted that these studies were included specifically only when they also reported assessment of neuromodulatory or connectivity changes (with fMRI).

4.3. Potential confounds

An area of caution is the potential for experimental confounds in TUS neuromodulation studies. A majority of preclinical studies employ anesthesia, which can modulate membrane excitability in many ways that overlap with the potential mechanisms underlying TUS [22]. Isoflurane, dexmedetomidine, and propofol have all been found to affect functional connectivity, spontaneous firing rate, and spiking patterns, generally resulting in an overall depression of neural activity [249–251]. Ketamine has been shown to block cortical neuron activity, which can suppress ultrasound-elicited motor responses [155], and isoflurane likewise suppressed motor-evoked potentials in a dose-dependent manner [252]. Most studies have utilized isoflurane, and in more recent studies reduce the concentration to 0.1 % to effectively render the animals semi-aware [125].

Another potential confound is the involvement of auditory pathways upon TUS, impacting both preclinical and clinical studies, particularly with semi-aware or awake subjects. Note that while the fundamental frequency is well above the audible range for humans, the pulsing rate is not. Some studies have reported neuronal activity along the auditory pathway [108], as well as other auditory artifacts and audible buzzing upon TUS which can elicit a startle response in animals [132, 253] and impact placebo control testing in humans [78, 116, 117] – calling into question the fidelity of neuromodulatory responses to ultrasound. Recently, Mohammadjavadi et al. demonstrated that the ultrasound modulation envelope can be modified to attenuate or eliminate audible components and auditory brainstem responses, and that the responses then match those in deaf knockout mice [135]. It has also been shown that propagation of ultrasound shear waves and subsequent skull vibrations occur at the PRF of the ultrasound incident wave [120, 254], and that altering the PRF to avoid skull vibrations [144] or applying a masking sound at that frequency [120] can minimize auditory

confounds. Thus, while auditory components of pulsed ultrasound waveforms and anesthesia can contribute to responses, TUS neuromodulation can also occur independent of these effects, though proper controls or mitigations should be implemented to address such confounds.

5. Opportunities of fMRI and connectomics

As MRI is often combined with TUS for high precision targeting purposes (using MR techniques to capture skull anatomy and composition [255]; along with neuronavigation [70] and consideration of acoustic simulations for safe treatment planning [256]), a natural extension has seen a growing number of studies utilizing fMRI as a neural readout of TUS neuromodulation. The basic concept underlying fMRI is that an increase in local neuronal activity is a metabolically demanding process requiring increased blood flow to deliver glucose and oxygenated blood via the neurovascular coupling mechanism [171]. The blood flow response exceeds the oxygen consumption increase and this results in a decreased concentration of deoxygenated venous blood, leading to an increase in the fMRI BOLD signal [257, 258]. Combining fMRI neuroimaging with TUS allows for detailed causative inferences of neural activity and provides insights into the function and interactions of specific brain regions and networks, and by extension, their relation to behavioural and cognitive outcomes [70]. Here we discuss reported studies of TUS utilizing fMRI, current limitations, and a future outlook of the opportunities that this combination can provide.

5.1. Combining fMRI neuroimaging with TUS neuromodulation

17 preclinical studies have combined fMRI with TUS neuromodulation: 3 used fMRI for targeting [109, 113, 141] (and will not be discussed further), 5 in the context of BBBO [81, 220, 222–224], and 9 for low-intensity TUS neuromodulation [62–64, 160–163, 184, 243] (Table 3, Table S3). Clinically, 33 studies have applied fMRI: 6 for targeting [73, 83, 164, 167, 169, 200], 10 with BBBO [82] or ablative HIFU [75, 89, 225–231], and 17 with low-intensity TUS neuromodulation [74, 95, 99, 100, 118, 152, 165, 166, 168, 170, 185–189, 201, 244] (Table 4, Table S4).

For BBBO studies, fMRI revealed a suppressed BOLD response and reduced functional connectivity in preclinical studies [81, 220, 222–224] that recovered within 24-h [81, 222]. This was mirrored in a clinical trial of BBBO in Alzheimer's patients, where BBBO transiently decreased functional connectivity in the ipsilateral frontoparietal network with recovery by the next day consistent with BBB closure [82]. Following ablative ultrasound (HIFU), fMRI has revealed both decreasing and increasing functional connectivity following thalamotomy or capsulotomy. Thalamotomy was performed for the treatment of essential tremor in 6 studies, where functional connectivity patterns have been proposed as a possible predictive factor for clinical outcomes. Specifically, pre-operative functional connectivity was found to be decreased in the sensorimotor network, primary visual network, and visuospatial networks compared to healthy controls; post-operative functional connectivity was generally reduced in motor-related areas, but increased in the cerebellar network with augmented connectivity in the sensorimotor and visuospatial networks that persisted for at least 3- [75, 225, 231] or 6- [226, 229, 230] months post-treatment. Thalamotomy was also performed to treat tremor dominant Parkinson's in 2 trials: Stanziano et al. found that good responders (>50 % tremor improvement) showed reduced functional connectivity between the bilateral supplementary motor area, between the interpositus nucleus of untreated cerebellum and Lobe VI of treated cerebellum, and between the untreated supplementary motor area and contralateral putamen, where the clinical tremor score at 3-months correlated with the post-treatment decrease in functional connectivity [227]. Xiong et al. assessed the fractional amplitude of low-frequency fluctuations (fALFF) in the BOLD signal and found that the fALFF decreased significantly in the left occipital cortex at

Table 3

Preclinical TUS neuromodulation studies with fMRI. Summary of preclinical studies of low-intensity TUS neuromodulation where fMRI connectivity changes were reported, organized chronologically by response (motor/sensory, cognition/mood, BBB, neural effects). Further information about these studies can be found in the Supplementary Information, in Table S1 (cohort size, ultrasound details, read-outs, general findings) and Table S3 (fMRI-specific findings).

Author, Year	Cohort/Target	Key fMRI Finding
Motor/Sensory		
Yoo et al., 2011 [63]	Rabbits (healthy)/S1, V1	- TUS can transiently modulate brain activity bimodally.
Yang et al., 2018 [160]	Macaques (healthy)/S1	- TUS can induce stronger BOLD changes than natural tactile stimulation, suggesting a different neural hemodynamic coupling mechanism.
Verhagen et al., 2019 [62]	Macaques (healthy)/Supplementary motor area, frontal polar cortex	- TUS can lead to focal changes in the stimulated region's connectivity profile for up to 2-h.
Yang et al., 2021 [161]	Macaques (healthy)/S1	- TUS modulatory effects on active and resting neurons differ.
Munoz et al., 2022 [162]	Macaques (healthy)/Putamen, caudate	- Applying TUS to the dorsal striatum can positively impact motivational and cognitive aspects of decision making.
Yang et al., 2022 [163]	Macaques (healthy)/S1	- TUS yields distinct state-dependent and dose-response curves.
Cognition/Mood		
Bongioanni et al., 2021 [184]	Macaques (healthy)/Medial frontal cortex	- TUS to the medial frontal cortex resulted in a significant reduction in the integration coefficient.
BBBO		
Chu et al., 2015 [220]	Rats (healthy)/S1	- TUS suppressed BOLD responses in a pressure-dependent manner.
Todd et al., 2018 [81]	Rats (healthy)/S1	- Ultrasound BBBO yields reduced functional connectivity that recovers with BBB closing.
Todd et al., 2019 [223]	Rats (healthy)/S1	- Ultrasound BBBO with and without GABA reduces BOLD response (to a greater extent with GABA co-administration).
Todd et al., 2019 [222]	Rats (healthy)/S1	- Ultrasound BBBO altered the state of local brain neurovascular physiology in a way that hinders its ability to respond to demands for increased blood flow to the region.
Liu et al., 2023 [224]	Macaques (healthy)/Dorsal striatum	- Different alteration patterns in functional connectivity for low-intensity TUS compared to ultrasound BBBO in several cortical areas.
Neural Effects		
Folloni et al., 2019 [64]	Macaques (healthy)/Amygdala, anterior cingulate cortex	- TUS of the amygdala and anterior cingulate cortex altered connectivity in the targeted regions for 10s of min, but sonication of each did not affect the other.
Li et al., 2020 [243]	Macaques (healthy)/Posterior cingulate cortex	- TUS of the posterior cingulate cortex increased the BOLD signal.

12-months post-thalamotomy, correlating with tremor improvement [228]. Bilateral capsulotomy was applied in 1 study: Davidson et al. found that 4/6 patients with obsessive compulsive disorder and 2/6 patients with major depressive disorder responded to treatment, and responders could be distinguished from non-responders based on pre-operative connectivity (between the right central striatum and right posterior hippocampus, and between the left dorsal putamen and left occipital cortex as well as the left postcentral gyrus) [89]. At 6-months post-treatment, responders and non-responders could no longer be

Table 4

Clinical TUS neuromodulation studies with fMRI. Summary of clinical studies of low-intensity TUS neuromodulation where fMRI connectivity changes were reported, organized chronologically by response (motor/sensory, cognition/mood, consciousness, blood-brain barrier opening, ablative). Further information about these studies can be found in the Supplementary Information, in Table S2 (cohort size, ultrasound details, read-outs, general findings) and Table S4 (fMRI-specific findings).

Author, Year	Cohort/Target	Key fMRI Finding
Motor/Sensory		
Ai et al., 2016 [74]	Healthy/M1, caudate nucleus	- Detectable BOLD activation at 3T and 7T.
Lee et al., 2016 [118]	Healthy/V1	- TUS elicited associated efferent sensory perception in the form of phosphene, with a similar activation pattern to control photonic stimulation.
Legon et al., 2017 [165]	Healthy/M1	- Variable BOLD response at the individual level; no significant activation at the group level.
Ai et al., 2018 [166]	Healthy/M1	- Spatially selective increased activation volume during TUS, without effects in the downstream motor network.
Legon et al., 2020 [244]	Healthy/M1	- Follow-up safety study: 7/64 subjects reported transient mild to moderate symptoms, but no serious adverse events.
Cain et al., 2021 [168]	Healthy/Globus pallidus	- General decrease in relative perfusion throughout cerebrum following TUS.
Matt et al., 2022 [170]	Healthy/S1	- TUS increased both functional and structural coupling with plastic changes.
Nakajima et al., 2022 [152]	Healthy/FDI-M1, basal ganglia, prefrontal cortex	- TUS resulted in a significant impairment of stopping performance, with BOLD activation in anterior putamen during response inhibition.
Cognition/Mood		
Beisteiner et al., 2020 [185]	Healthy, Alzheimer's/PL-FL-PCUN/S1	- Clinical scores improved significantly after TUS for up to 3-months, correlated with upregulation of memory network.
Sanguinetti et al., 2020 [186]	Healthy/Right inferior frontal gyrus	- TUS increased global affect and resulted in a positive shift in mood.
Popescu et al., 2021 [187]	Alzheimer's/PL-FL-PCUN/S1	- Memory areas that respond functionally to TUS also respond morphologically.
Dorl et al., 2022 [188]	Alzheimer's/PL-FL-PCUN/S1	- TUS did not stimulate important visuo-constructive network nodes, and global efficiency of the network decreased along with functional connectivity.
Kuhn et al., 2023 [189]	Healthy/Amygdala, entorhinal cortex	- TUS spatially selectively increased cerebral perfusion in targeted region, and not in contralateral homolog or either bilateral control region.
Riis et al., 2023 [100]	Depression/Subcallosal cingulate cortex	- TUS decreased BOLD signals at the target, coupled with resolution of the patient's depressive symptoms within 24-h for 44-days.
Yaakub et al., 2023 [95]	Healthy/Cingulate cortex (dorsal anterior, posterior)	- TUS of the posterior cingulate cortex increased functional connectivity of the dorsal anterior cingulate cortex but not vice versa, indicating a possible state- or location-dependence.
Consciousness		
Cain et al., 2022 [201]	Disorder of consciousness/Thalamus	- Thalamus increased its connectivity with two clusters—one in the ipsilateral

(continued on next page)

Table 4 (continued)

Author, Year	Cohort/Target	Key fMRI Finding
Bubrick et al., 2024 [99]	Epilepsy/Medial temporal lobe	pre- and post-central gyrus and one subsuming portions of the contralateral opercular and insular cortex—while decreasing connectivity with the ipsilateral frontal polar cortex (associated with behavioural responsiveness). - TUS reduced seizure frequency for at least 6-months, with significantly improved default mode network organization 1-month post-treatment.
BBBO Meng et al., 2019 [82]	Alzheimer's/Anterior right frontal lobe	- Ultrasound caused a transient functional connectivity decrease that recovered at 1-day and remained unchanged at 3-months post-treatment.
Ablation Jang et al., 2016 [75]	Essential tremor/Ventral intermediate nucleus of the thalamus (Vim)	- HIFU thalamotomy regulates interactions over the motor network via symptom-related connectivity changes, but have transient, symptom-unrelated diaschisis in the global brain network.
Park et al., 2017 [225]	Essential tremor/Vim	- Changes in effective connectivity predicted changes in clinical motor-symptom scores. - fMRI revealed voxel clusters significantly associated with eventual clinical response.
Davidson et al., 2020 [89]	Obsessive compulsive disorder, major depressive disorder/Bilateral anterior capsule	- Changes in fALFF, regional homogeneity, and functional connectivity values were correlated with tremor relief.
Lu et al., 2022 [226]	Essential tremor/Vim	- Correlation between disease duration and functional connectivity increase at 3-months.
Stanziano et al., 2022 [227]	Parkinson's/Vim	- Increased activity in sensorimotor cortex and decreased activity in posterior cingulate cortex, significantly correlated with concurrent tremor improvement.
Xiong et al., 2022 [229]	Essential tremor/Vim	- fALFF in left occipital cortex significantly decreased at 1-year, correlating with hand tremor improvement. Visual area relevant to tremor improvement after thalamotomy suggests distant effect of thalamotomy and involvement of visuomotor networks in tremor control in Parkinson's.
Xiong et al., 2022 [228]	Parkinson's/Vim	- Increase in connectivity in cerebellar network following HIFU thalamotomy.
Kato et al., 2023 [230]	Essential tremor/Vim	- Functional connectivity pattern may be predictive factor.
Pae et al., 2023 [231]	Essential tremor/Vim	

distinguished based on the prior connections [89].

fMRI has also provided unique inferences in the context of low-intensity TUS neuromodulation studies. Preclinically, fMRI has been performed following TUS in healthy animals and has revealed that ultrasound can modulate brain activity and connectivity bimodally, and in a spatially-specific (with downstream effects sometimes assessed [62, 64]) and dose-dependent manner. These effects were often transient but

could be sustained for tens of minutes [64] or for up to 2-h [62]. The studies were generally performed in a resting-state (i.e. in the absence of external stimuli or the demands of an imposed task), though occasionally ultrasound effects were assessed while under simultaneous tactile stimulation [160,161] or upon a task [162,184]. For example, Munoz et al. found that applying TUS to the dorsal striatum could positively impact motivational and cognitive aspects of decision-making in a visuomotor decision-masking task with rewards, at the cost of a lower reaction time [162]. This correlated with significant changes in functional connectivity between the sonicated caudate and multiple cortical regions [162]. Bongioanni et al. showed that TUS of the medial frontal cortex resulted in reduced BOLD signal, and a significantly compromised decision-making ability in making new inferential choices [184]. It should be noted, however, that in all studies, stimuli or tasks were either performed simultaneously with TUS but not with fMRI, or with fMRI but with TUS being performed ‘offline’ (not during fMRI).

In clinical low-intensity TUS neuromodulation studies, fMRI likewise revealed that ultrasound can both enhance or reduce connectivity in a localized (with some effects in higher-order networks) manner, with changes that could last from 20-min [186] to 7-days [170]. Of note is that most fMRI-TUS studies were performed in healthy subjects, however a subset assessed cohorts of Alzheimer's [185,187,188] and disorders of consciousness [199]. The studies performed in Alzheimer's patients found an increased BOLD response in the hippocampus, parahippocampal cortex, parietal cortex, and precuneus that correlated with improved clinical scores [185]. The neuropsychological improvement was further found to be accompanied by an increase in cortical thickness in Alzheimer's disease-critical brain regions; i.e. memory areas that responded functionally also responded morphologically [187]. When applied to patients with disordered consciousness, TUS was found to decrease connectivity between the targeted thalamus and regions in the frontal lobe, and increase connectivity between the targeted thalamus and regions throughout the contralateral motor cortex, the parietal and temporal lobes, and the occipital cortex [201]. These connectivity changes were also found to correlate with increased recovery in patients assessed over a 7-day period [201]. Given the association between functional connectivity changes and patient outcomes, the application of fMRI in the context of TUS studies is expected to become more prevalent moving forward.

It should be noted that, similar to the preclinical literature, clinical studies were also generally performed with resting-state fMRI with only 3 studies being task-based [152,166,185]. For example, Ai et al. assessed fMRI during a finger-tapping task and found that TUS increased the BOLD activation volume [166]. This study, however, did not reveal changes in downstream functionally connected regions [166]. Nakajima et al. studied fMRI during a stop-signal task and demonstrated that TUS to the basal ganglia resulted in a significant impairment of stopping performance [152]. Beisteiner et al. performed task-based fMRI during a face-name encoding task and found an increase in activity in the bilateral hippocampus after TUS [185]. However, as in the preclinical studies, the clinical task-based assessments were also conducted with TUS offline. Perhaps in the future, more studies will assess how TUS alters task-based BOLD responses and associated cognitive processes, and it is hoped that further technological advances will enable truly simultaneous TUS neuromodulation and fMRI.

5.2. Current limitations

While simultaneous fMRI with TUS can bring exciting opportunities, there are limitations to be aware of. From a mechanistic standpoint, it should be noted that ultrasound pressure-mediated effects on the vasculature may give rise to direct flow-mediated BOLD signals in addition to, or instead of, neuronal-mediated BOLD effects [118,259]. Care should thus be taken when analyzing BOLD fMRI data, as interpretation exclusively in terms of neuronal activity may provide an incomplete view and thus motivate quantitative fMRI methods that can

specifically measure both hemodynamic and metabolic responses [172]. From a technological perspective, the logistical and technical device compatibility also needs further improvement, particularly for clinical translatability and adoption. While there are currently ultrasound transducers that are compatible with MRI, the complexity and materials of most standard transducers, as well as the presence of water (for coupling and cooling) induce magnetic field inhomogeneities that reduce image quality and introduce artifacts. The dimensions of the transducer and fit inside MRI coils also need to be considered, as do the coils themselves in terms of optimization of signal and compatibility for transducer positioning. While some dedicated head coils have been developed for transcranial MRgFUS ablative surgeries [260–263], a majority of MRgFUS studies employ a body coil due to space constraints; the lower signal-to-noise ratio of the body coil and low scan acceleration capabilities limit the spatial and temporal resolution and available fMRI sequences. While low-intensity TUS studies have greater flexibility as they can use smaller footprint transducers, fMRI is still subject to greater noise and thus higher SNR and resolution capabilities are essential. Dedicated head coils for simultaneous fMRI and TUS are currently being explored [243,264] but have not yet reached widespread adoption, with TUS to date being performed ‘offline’ rather than concurrently with fMRI. Continued investigation and further development of MRI-compatible ultrasound transducers and/or dedicated head coils, as well as of optimal MRI acquisition parameters and pulse sequence selection will contribute to our future ability to perform simultaneous fMRI and TUS neuromodulation.

5.3. Future outlook and opportunities of fMRI in TUS neuromodulatory studies

Neuroimaging advances have led to the recognition that the brain is a complex network of functionally and structurally connected and interacting regions. fMRI has brought the ability to visualize and map these networks (the ‘functional connectome’ [265]). Combining fMRI neuroimaging with ultrasound thereby brings unprecedented opportunities to understand the physiological effects of TUS neuromodulation, tailor treatment for improved individualized efficacy, and advance our understanding of brain function in health and disease [266]. As seen above, fMRI has already provided insight into which brain networks are activated upon TUS of various targets and how network connectivity changes. This can lend insight into the pathological features of underlying disorders, the therapeutic mechanism of action of TUS neuromodulation, and may in future provide predictions of clinical outcomes prospectively. Understanding connectivity between the stimulation site and network nodes in healthy individuals and those with various neurological and psychiatric conditions can also help predict clinical response via prior reports in the literature of other neuromodulatory modalities and studies. For example, referring to the wider fields of DBS and TMS, which have been combined with fMRI more often, may provide insight into whether TUS will also be effective when applied to a particular target or individual. Further, regardless of whether the same target is chosen, consulting studies that have targeted different locations to treat the same diseases is useful in general, as fMRI studies have shown that different targets used to treat the same disorders are often nodes within the same network [267]. Symptoms for the same disorders can also be heterogeneous and may map to different networks; understanding these networks can help guide symptom-specific, and more personalized treatment plans. Thus, one might imagine future studies in which aberrant functional connectivity in an individual patient is characterized via fMRI scanning and comparison to normative and disease-specific databases. One or more nodes in an affected network could then be precisely targeted with excitatory or inhibitory TUS inside the MRI and acute network modulations observed with fMRI in real time. This could be an iterative and personalized process with the goal being to renormalize network function. Identified targets and stimulation protocols could then be used in repeated sessions that aim to induce

lasting network changes. In some cases, targets might also be identified for permanent lesioning using HIFU. Similarly, while TUS has been found to be safe with few reports of adverse events, fMRI may help to identify and avoid connections and networks associated with unwanted side effects. Indeed, inhibitory TUS might also be integrated in functional neurosurgery workflows whereby potential lesions are first interrogated for efficacy and safety before lesioning. While normative connectomes made up from >1000 datasets provide the highest resolution information, individualized connectivity data can further improve guidance and efficacy of neuromodulation treatments. While perhaps facing obvious practical challenges, fMRI acquisitions on a patient-by-patient basis to guide subsequent treatment holds potential for individualized and optimized precision treatment. Groups have already begun to compare results of normative and patient-specific connectomes in the context of DBS [268] and TMS [269], and have noted better predictive performance with individualized data. Beyond predicting and guiding particular clinical outcomes, applying fMRI to study changes to the functional connectome during TUS can improve our general understanding of the brain. In this way, we can explore novel targets and gain a better understanding of brain pathophysiology.

6. Conclusion

TUS has the potential to be a non-invasive, transformative tool for the study of the brain in health and disease and for the treatment of a range of neurological and psychiatric disorders. This review outlined the principles and mechanisms of TUS neuromodulation, highlighted pre-clinical and clinical milestones within an overview of the broader landscape of reports to date, and discussed the breadth of potential offered by combining TUS with fMRI. In particular, combining fMRI with TUS brings exciting opportunities to understand the physiological effects of neuromodulation and better predict treatment outcomes.

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CRediT authorship contribution statement

Carly Pellow: Writing – review & editing, Writing – original draft, Visualization, Investigation, Conceptualization. **Samuel Richardson:** Writing – review & editing, Supervision. **G Bruce Pike:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2024.06.005>.

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