Biomedical Engineering Letters (2024) 14:407–438
https://doi.org/10.1007/s13534-024-00369-0

REVIEW ARTICLE

A review of functional neuromodulation in humans using low-intensity transcranial focused ultrasound

Kyuheon Lee[1,2] · Tae Young Park[1,3] · Wonhye Lee[1,4] · Hyungmin Kim[1,3]

Received: 31 December 2023 / Revised: 17 February 2024 / Accepted: 23 February 2024 / Published online: 2 March 2024

Abstract

Transcranial ultrasonic neuromodulation is a rapidly burgeoning field where low-intensity transcranial focused ultrasound (tFUS), with exquisite spatial resolution and deep tissue penetration, is used to non-invasively activate or suppress neural activity in specific brain regions. Over the past decade, there has been a rapid increase of tFUS neuromodulation studies in healthy humans and subjects with central nervous system (CNS) disease conditions, including a recent surge of clinical investigations in patients. This narrative review summarized the findings of human neuromodulation studies using either tFUS or unfocused transcranial ultrasound (TUS) reported from 2013 to 2023. The studies were categorized into two separate sections: healthy human research and clinical studies. A total of 42 healthy human investigations were reviewed as grouped by targeted brain regions, including various cortical, subcortical, and deep brain areas including the thalamus. For clinical research, a total of 22 articles were reviewed for each studied CNS disease condition, including chronic pain, disorder of consciousness, Alzheimer's disease, Parkinson's disease, depression, schizophrenia, anxiety disorders, substance use disorder, drug-resistant epilepsy, and stroke. Detailed information on subjects/cohorts, target brain regions, sonication parameters, outcome readouts, and stimulatory efficacies were tabulated for each study. In later sections, considerations for planning tFUS neuromodulation in humans were also concisely discussed. With an excellent safety profile to date, the rapid growth of human tFUS research underscores the increasing interest and recognition of its significant potential in the field of non-invasive brain stimulation (NIBS), offering theranostic potential for neurological and psychiatric disease conditions and neuroscientific tools for functional brain mapping.

Keywords Brain stimulation · Non-invasive neuromodulation · Transcranial ultrasound · Focused ultrasound · Low-intensity · Pulsing schemes · Human studies · Safety

1 Introduction

Brain stimulation techniques are indispensable tools for studying brain functions and have been substantially utilized to enhance our understanding of neural functions over the past decades [1, 2]. The development of neurotechnologies as bioelectronic medicine has provided physicians with non-pharmacological treatment options for neurological and neuropsychiatric diseases. Approaches such as deep brain stimulation (DBS) and epidural cortical stimulation (EpCS) have been effective in clinical settings [2], demonstrating excellent spatial selectivity for stimulating specific brain regions. However, the required invasive surgical procedures limit their applicability to human subjects. Transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tES) are the two mainly established and clinically available non-invasive brain stimulation

Kyuheon Lee and Tae Young Park contributed equally to this work.

✉ Wonhye Lee
wonhye.lee@gmail.com

✉ Hyungmin Kim
hk@kist.re.kr

1 Bionics Research Center, Biomedical Research Division, Korea Institute of Science and Technology, 5 Hwarangro 14-gil, Seongbuk-gu, Seoul 02792, South Korea

2 Department of Brain and Cognitive Engineering, Korea University, Seoul, South Korea

3 Division of Bio-Medical Science and Technology, KIST School, Korea University of Science and Technology, Seoul, South Korea

4 Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

(NIBS) techniques [1], but they have limited spatial specificity (on the order of centimeters) and depth penetration for targeting regional neural tissues.

The advent of focused ultrasound (FUS) techniques has provided a non-invasive means of delivering mechanical pressure waves to highly localized regions (on the order of millimeters) deep within biological tissues [3]. Further advancements in FUS techniques have enabled the transcranial delivery of acoustic energy to specific target regions in the brain [4], typically within a frequency range of 200–700 kHz. Transcranial FUS (tFUS) techniques have been employed for non-invasive functional neurosurgery in the form of high-intensity thermal ablation of localized deep brain regions [5]. When combined with the intravenous microbubble contrast agents, tFUS has also been utilized for transient and reversible localized disruption of the blood-brain barrier (BBB) for targeted central nervous system (CNS) drug delivery [6]. Alongside these therapeutic approaches, the promising potential of low-intensity acoustic waves, delivered in a train of pulses, has been discovered to reversibly modulate the excitability of sonicated regions of neural tissues and the brain in vitro [7] and in vivo [8, 9], without causing temperature elevation. With its exquisite spatial resolution and the ability to reach deep-seated brain regions, pulsated tFUS at low intensity (below the threshold for inducing thermal effects) has emerged as a novel NIBS modality. Over the last ~15 years, a remarkably increasing number of animal studies have shown the electrophysiological, behavioral, and safety evidence of bimodal (excitatory and suppressive) neuromodulatory efficacies of low-intensity FUS administered to the specific brain regions using small [8–11] and large animal models [12, 13] as well as non-human primates [13, 14].

In humans, based on the pre-clinical animal studies, a rapidly growing body of research has also been reported over the last decade, starting around 2013, to examine the neuromodulatory efficacy and safety of the low-intensity transcranial ultrasound on the brain [15]. The recent surge in relevant human studies and publications can be challenging for researchers and physicians to assimilate. Thus, the purpose of this article is to provide narrative reviews on the human research and clinical studies reported during the past decade (2013–2023) that applied low-intensity transcranial ultrasound to the brain, observing its neuromodulatory effects. Specifically, we have summarized information on subjects/cohorts, target brain regions, sonication parameters, outcome readouts, and stimulatory efficacies for each of the total of 64 human studies available as peer-reviewed articles or letters (searched through PubMed and Google Scholar). These studies are separately listed for healthy participants (42 studies) and patient groups (22 studies). Conference abstracts or preprint articles were not included for the review process. The review covers studies using unfocused transcranial ultrasound (TUS) as well as tFUS, while transcranial pulse stimulation (TPS) [16], another sonication technique using diagnostic ultrasound devices with a single ultrashort pulse (e.g., 3 μs at 111 W/cm^2 I_{SPPA}), was not included here as its mode of operation differs from that of tFUS/TUS. In the later sections of this review, we presented a brief overview of various factors that can be considered during the planning phase of human research and clinical trials using low-intensity tFUS neuromodulation.

2 tFUS sonication parameters for neuromodulation

Careful planning of sonication parameters is crucial in tFUS applications for neuromodulation. Several studies have highlighted that the selection of sonication parameters can lead to differential neuromodulatory effects, either in terms of excitation or suppression. This section provides a summary for the sonication parameters generally considered in the planning of tFUS neuromodulation research.

Ultrasound is mechanical pressure waves with frequencies higher than 20 kHz, exceeding the range of human hearing. Diagnostic ultrasound typically utilizes frequencies of ~1–25 MHz. In contrast, tFUS operates within a relatively lower frequency range of ~0.2–1.1 MHz. This lower frequency allows for transcranial transmission of acoustic energy to the targeted brain regions, reducing skull-induced attenuation and mitigating aberrations arising from differences in the acoustical properties of the ultrasound medium and the skull [4].

The fundamental frequency (FF) refers to the frequency of the sine wave used to generate ultrasound (Fig. 1; Table 1). The duration of each ultrasound stimulation trial is termed the sonication duration (SD). The interval between the end of one trial and the onset of the subsequent trial is called the inter-stimulation interval (ISI) [17]. When a pulsing scheme is used, each sonication trial with SD is pulsed with a pulse duration (PD) repeated at a pulse repetition frequency (PRF). The duty cycle (DC) is the active portion (expressed as a percentage, %) of the SD, calculated as PD multiplied by PRF.

There has been confusion in reporting ISI in previous tFUS neuromodulation articles. Some articles reported ISI as the interval between the onsets of successive sonication trials, whereas the common definition is the interval from the end of one stimulus presentation to the onset of another. In this review, we consistently tabulated ISI information based on the standard definition (Tables 2 and 3). Additionally, there has been confusion in reporting DC, with some articles calculating it as the ratio of the active sonication

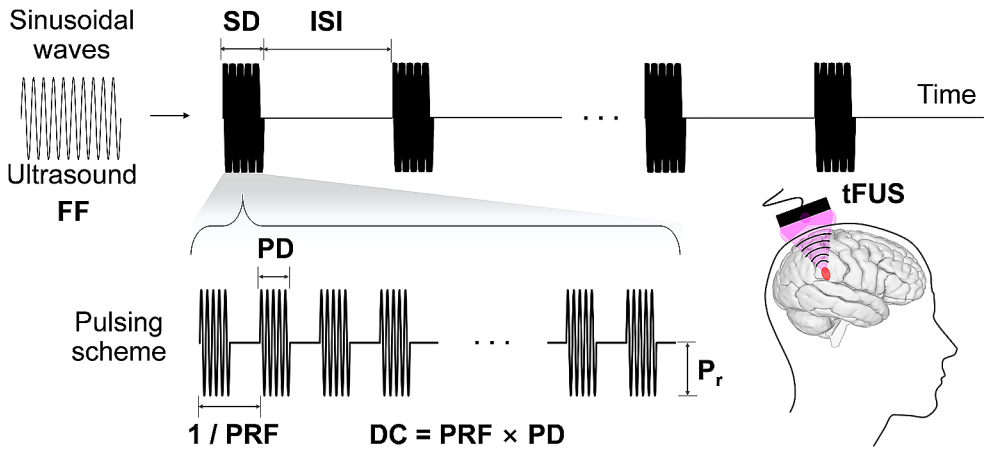

Fig. 1 Schematics of sonication parameters and pulsing schemes in ultrasonic neuromodulation. The duration of FUS stimulation trials is termed sonication duration (SD), delivered with an inter-stimulation interval (ISI) between the end of one trial and the onset of another. An experimental block in a FUS session consists of either single or multiple stimulation trials of SD. Each sonication trial (SD) is pulsed with a pulse duration (PD) repeated at a pulse repetition frequency (PRF). The duty cycle (DC) is the active portion (expressed as a percentage, %) of the SD, calculated as PD multiplied by PRF. FF represents the fundamental frequency of ultrasound and P_r is the peak rarefactional pressure of the ultrasonic mechanical pressure wave. See also Table 1

Table 1 List of sonication parameters with abbreviations, units, and synonyms. See also Fig. 1

Parameter (Abbreviation)	Unit	Synonym
Fundamental frequency (FF)	kHz, MHz	Center frequency (f_c)
Pulse duration (PD)	ms	Tone burst duration (TBD), Pulse length (PL)
Pulse repetition interval (PRI)	ms	Pulse repetition period (PRP)
Pulse repetition frequency (PRF)	Hz, kHz	-
Duty cycle (DC)	%	Duty factor (DF), as a ratio between 0 and 1
Sonication duration (SD)	ms, s	Burst duration (BD)
Inter-stimulation interval (ISI)	s, min	Burst interval (BI) - Sonication duration (SD)
Peak rarefactional pressure (P_r)	kPa, MPa	Peak negative pressure (PNP)
Spatial-peak pulse-average intensity (I_{SPPA})	W/cm^2	-
Spatial-peak temporal-average intensity (I_{SPTA})	mW/cm^2	-
Mechanical index (MI)	(unitless)	-

portion of a stimulation trial to the time span covering both SD and ISI. In Tables 2 and 3, DCs were consistently tabulated as the ratio of the active sonication portion to the time span covering only SD.

When conducting tFUS neuromodulation experiments, the acoustic intensity of ultrasound stimulation is reported as spatial-peak pulse-average intensity (I_{SPPA}) and spatial-peak temporal-average intensity (I_{SPTA}). I_{SPPA} (in W/cm^2) is calculated from the pressure of acoustic waves (i.e., *P(t)*) measured at the spatial-peak point (Eq. 1). I_{SPTA} (in W/cm^2 or mW/cm^2) is derived with I_{SPPA} multiplied by DC (Eq. 2), representing the time-averaged acoustic intensity. For evaluating mechanical safety, the mechanical index (MI, a unitless value), representing an indicator of the non-thermal mechanical bioeffects of ultrasound, is calculated as the ratio of the peak rarefactional pressure (P_r, in MPa) to the square root of FF (f_c, in MHz) (Eq. 3).

$$I_{SPPA} = max\left(\frac{1}{PD}\int_0^{PD}\frac{P(t)^2}{\rho c}dt\right) \tag{1}$$

$$I_{SPTA} = max\left(\frac{1}{1/PRF}\int_0^{1/PRF}\frac{P(t)^2}{\rho c}dt\right) = I_{SPPA}\times \mathrm{DC} \tag{2}$$

$$MI = \frac{P_r}{\sqrt{f_c}} \tag{3}$$

where ρ and c represent the medium density and speed of ultrasound in the medium, respectively. Table 1 summarizes the sonication parameters, including their corresponding units and synonyms.

According to the guidance from the United States Food and Drug Administration (FDA), $I_{SPPA.3}$ represents the value of I_{SPPA} derated by 0.3 dB·cm^{-1}·MHz^{-1} to account for the acoustic attenuation in soft tissues. Although not explicitly outlined in the FDA guidance, the notation $I_{SPPA.0}$ is also utilized for the intensity value of incident acoustic waves (i.e., before attenuation). It is important to note that, when using $I_{SPPA.3}$, the ultrasound attenuation by the skull is not considered in calculating the derated value [18]. However, some previous tFUS neuromodulation studies have used the

Table 2 Summary of a total of 42 tFUS/TUS neuromodulation studies in healthy human participants, tabulated in chronological order by the date of articles available online. The number of study subjects who received active tFUS/TUS, with female/male ratios and age information, and target regions in the brain for tFUS neuromodulation are shown. Sonication parameters used in an experimental block of tFUS session(s) are summarized. For acoustic pressure (P_r), intensity (I_{SPPA}, I_{SPTA}), and mechanical index (MI), derated in situ values at the targeted brain regions after transcranial attenuation are tabulated. When derated in situ values are not available, the corresponding information without considering a derating factor is tabulated with notations of $P_{r.0}$, $I_{SPPA.0}$, $I_{SPTA.0}$, and $MI_{.0}$. Numbers within parenthesis are either estimates or relevant values. Outcome readouts used to observe the neuromodulatory effects either online (during tFUS) or offline (after tFUS) are also listed, along with a brief statement of efficacy. Also, refer to Figs. 2 (upper panel) and 3

Author Year	Subjects, Age, Target regions	Sonication parameters	Outcome readouts	Efficacies
Legon W et al. 2014 [34]	Healthy, R-handed (EEG) $N=10$ (F:5 / M:5) 27.0 ± 9.5y (18–47) (Tasks) $N=12$ (F:7 / M:5) 30.4 ± 10.4y (23–57) 31.8 ± 11.8y (20–57) L-S1 (over EEG CP3)	FF = 500 kHz PD = 0.36 ms PRF = 1000 Hz DC = (36)% SD = 0.5 s, ISI = 6, 7 s 120, 90 trials of SD P_r = 0.41 MPa I_{SPPA} = 5.9 W/cm^2 I_{SPTA} = (2.12) W/cm^2 MI = (0.58)	Online: EEG-SEP, behavioral tasks (two-point/frequency discrimination tasks)	tFUS applied to the S1 attenuated SEP amplitudes and enhanced behavioral performance in sensory discrimina- tion tasks.
Mueller J et al. 2014 [35]	Healthy, R-handed, (EEG) $N=18$ (F:7 / M:11) 29.6 ± 10.9y (18–54) L-S1 (over EEG CP3)	FF = 500 kHz PD = 0.36 ms PRF = 1000 Hz DC = (36)% SD = 0.5 s, ISI = 6 s 120 trials of SD P_r = (0.418) MPa I_{SPPA} = 5.9 W/cm^2 I_{SPTA} = (2.12) W/cm^2 MI = (0.59)	Online: EEG-SEP	tFUS applied to the S1 modulated intrinsic and evoked EEG dynamics, an effect not observed when the transducer was moved 1 cm laterally.
Lee W et al. 2015 [36]	Healthy (Self-report) $N=12$ (F:4 / M:8) 29.4 ± 5.0y (25–41) (EEG) $N=6$ (F:1 / M:5) 28.7 ± 9.0y (21–43) L/R-S1 of the hands	FF = 250 kHz PD = 1 ms PRF = 500 Hz DC = 50% SD = 0.3 s, ISI = 2.7 s 200, 100 trials of SD P_r = (0.144) MPa I_{SPPA} = 0.7 W/cm^2 I_{SPTA} = 0.35 W/cm^2 MI = (0.29)	Online: Self-report, EEG	tFUS applied to the S1 induced sonication-specific EEG evoked poten- tials, accompanied by the elicitation of tactile sensations on the contralateral hand area, with anatomical specific- ity extending to individual fingers.
Lee W et al. 2016a [37]	Healthy $N=10$ (F:2 / M:8) 27.8 ± 4.1y (23–34) L-S1/S2 of the R-hand	FF = 210 kHz PD = 1 ms PRF = 500 Hz DC = 50% SD = 0.5 s, ISI = 6.5 s 20 trials of SD P_r = (0.51) MPa I_{SPPA} = 8.8 W/cm^2 I_{SPTA} = 4.4 W/cm^2 MI = (1.11)	Online: Self-report	tFUS applied to the unilateral S1/S2 or S2-only elicited the perception of tactile sensations in the contralateral hand.

Table 2 (continued)

Author Year	Subjects, Age, Target regions	Sonication parameters	Outcome readouts	Efficacies
Lee W et al. 2016b [41]	Healthy (fMRI) $N=19$ (F:5 / M:14) 26.1 ± 5.4y (20–45) (EEG) $N=10$ (F:1 / M:9) 26.7 ± 7.1y (20–45) V1	FF = 270 kHz PD = 1 ms PRF = 500 Hz DC = 50% SD = 0.3 s, ISI = 12.7, 2.2 s 50 trials of SD P_r = (0.298) MPa I_{SPPA} = 3.0 W/cm^2 I_{SPTA} = 1.5 W/cm^2 MI = (0.57)	Online: Self-report, fMRI, EEG	tFUS applied to the V1 elicited activation in both the sonicated brain area and the network of regions, as revealed by BOLD-fMRI. Phosphene perception was also reported. The EEG responses showed distinct peaks associated with the V1 stimulation.
Lee W et al. 2017 [38]	Healthy $N=6$ (F:1 / M:5) 28.2 ± 9.5y (23–45) L/R-S1 of the hands	FF = 210 kHz PD = 1 ms PRF = 500 Hz DC = 50% SD = 0.5 s, ISI = 6.5 s 20 trials of SD P_r = (0.51) MPa I_{SPPA} = (8.8) W/cm^2 I_{SPTA} = 4.4 W/cm^2 MI = (1.11)	Online: Self-report, finger tapping	tFUS applied to the left or right S1 selectively elicited tactile sensations from the contralateral hand.
Legon W et al. 2018a [58]	Healthy, R-handed $N=40$ (F:26 / M:14) 23.0 ± 4.4y (18–37) L-thalamic-VPL	FF = 500 kHz PD = 0.36 ms PRF = 1000 Hz DC = 36% SD = 0.5 s, ISI = 4 s 300 trials of SD P_r = 0.138 MPa I_{SPPA} = 7.03 W/cm^2 I_{SPTA} = (2.53) W/cm^2 MI = 0.56	Online: EEG-SEP, tactile discrimination task	tFUS applied to the sensory thalamus (VPL) inhibited SEP amplitudes, accompanied by alpha and beta power attenuation and time-locked gamma power inhibition. Performance in the tactile discrimination task was worse than chance.
Legon W et al. 2018b [20]	Healthy, R-handed 19–38y (MEPs) $N=12$ (F:8 / M:4) 23.4 ± 1.9y (MEPs) $N=10$ (F:7 / M:3) 22.0 ± 3.2y (Task) R(25)/L(3)-handed $N=28$ (F:19 / M:9) 22.0 ± 1.7y L/R-M1 of the hand	FF = 500 kHz PD = (0.36) ms PRF = 1000 Hz DC = 36% SD = 0.5 s ISI = 10, 3–6 s 10, 100 trials of SD P_r = (0.421) MPa I_{SPPA} = 6.0 W/cm^2 I_{SPTA} = 2.16 W/cm^2 MI = (0.6)	Online, Offline: TMS-induced MEPs, SICI and ICF, behavioral task (stimulus response reaction time)	tFUS applied to the M1 suppressed TMS-induced MEP amplitude, attenuated ICF but did not affect SICI, and reduced reaction time on a simple stimulus response task.
Ai L et al. 2018 [31]	Healthy, R(4)/L(1)-handed $N=5$ (F:2 / M:3) 22.8 ± 2.2y (20–25) L/R-M1 (thumb area of the dominant hand)	FF = 500 kHz PD = (0.36) ms PRF = 1000 Hz DC = 36% SD = 0.5 s, ISI = 5 s (5) trials of SD $P_{r.0}$ = (0.708) MPa $I_{SPPA.0}$ = 16.95 W/cm^2 $I_{SPTA.0}$ = (6.10) W/cm^2 $MI_{.0}$ = 0.97	Online: fMRI	tFUS applied to the dominant thumb representation of contralateral M1 increased BOLD activation volumes generated during a cued finger tapping task.

Table 2 (continued)

Author Year	Subjects, Age, Target regions	Sonication parameters	Outcome readouts	Efficacies
Gibson BC et al. 2018 [23]	Healthy, R-handed *N* = 19 (F:11 / M:8) 20.6 ± 1.5y (19–23) L-M1 of the hand	FF = 2.32 MHz PD = NR PRF = NR DC = (0.38)% SD = 120 s, ISI = N/A (1) trial of SD $P_{r.0}$ = 1.02 MPa $I_{SPPA.0}$ = 34.96 W/cm^2 $I_{SPTA.0}$ = 0.133 W/cm^2 $MI_{.0}$ = 0.67	Offline: TMS-induced MEPs	TUS applied to the M1 transiently increased excitability in the sonicated motor cortex.
Sanguinetti JL et al. 2020 [46]	Healthy, R-handed (VAMS) *N* = 24, out of (F:27 / M:24), 19.7y (rs-fMRI) *N* = 9 (F:4 / M:5) 19.2y R-inferior frontal gyrus (IFG)	FF = 500 kHz PD = 0.065, 0.125 ms PRF = 40 Hz DC = 0.26, 0.50% SD = 30, 120 s, ISI = N/A (1) trial of SD P_r = (0.692) MPa I_{SPPA} = 16.2 W/cm^2 I_{SPTA} = (0.04, 0.08) W/cm^2 MI = (0.98)	Offline: rs-fMRI, Self-report, VAMS (visual analog mood scales)	tFUS applied to the R-IFG enhanced self-reported mood states and decreased functional connectivity in resting-state networks.
Schimek N et al. 2020 [42]	Healthy *N* = 11 (F / M: NR) 21y (18–44) V1, over the TMS hotspot to induce phosphene perceptions	FF = 6 MHz PD = (15) s, PRF = N/A DC = (100)% SD = 15 s, ISI = 79 s 20 trials of SD $P_{r.0}$ = (1.715) MPa $I_{SPPA.0}$ = (99.32) W/cm^2 $I_{SPTA.0}$ = (99.32) W/cm^2 MI = 0.7	Offline: Self-report	Repeated diagnostic TUS applied to the V1 induced illusory visual percepts in healthy subjects.
Braun V et al. 2020 [44]	Healthy *N* = 18 (F:11 / M:7) 26.2 ± 7.3y R-V1	FF = 500 kHz PD = 0.5 ms PRF = 1000 Hz DC = 50% SD = 0.3 s, ISI = 2.7 s 50 trials of SD P_r = 0.6 MPa I_{SPPA} = (12.16) W/cm^2 I_{SPTA} = (6.081) W/cm^2 MI = (0.85)	Online: Self-report, EEG	tFUS applied to the V1 elicited audible sounds. EEG recordings indicated auditory activation associated with tFUS. An audio signal administered through earphones was able to mask the audible sounds.
Badran BW et al. 2020 [59]	Healthy *N* = 19 (F:11 / M:8) 24.5 ± 4.6y (18–38) R-anterior thalamus NCT04339972	FF = 650 kHz PD = 5 ms PRF = 10 Hz DC = 5% SD = 30 s, ISI = 30 s 10 trials of SD P_r = (0.652) MPa I_{SPPA} = (14.38) W/cm^2 I_{SPTA} = 0.719 W/cm^2 MI = (0.81)	Offline: Quantitative sensory thresholding (QST)	Thermal pain sensitivity was reduced after active tFUS applied to the right anterior thalamus.

Table 2 (continued)

Author Year	Subjects, Age, Target regions	Sonication parameters	Outcome readouts	Efficacies
Fomenko A et al. 2020 [19]	Healthy, R(17)-/L(1)-handed $N = 16$, out of (F:10 / M:8), 29–59y L-M1	FF = 500 kHz PD = (0.1–1.5) ms PRF = 200–1000 Hz DC = 10–50% SD = 0.5 s, ISI = 5 s 15 trials of SD P_r = (0.134) MPa I_{SPPA} = 2.32 W/cm^2 I_{SPTA} = 0.23–1.16 W/cm^2 MI = 0.19	Online: TMS-induced MEPs, SICI and ICF, behavioral task (visuomotor)	tFUS applied to the M1 suppressed TMS-elicited MEPs, with a longer SD and shorter DC delivered in a blocked paradigm. tFUS increased GABA-mediated SICI and decreased reaction time on a visuomotor task.
Schafer ME et al. 2021 [56]	Healthy $N = 1$ (F / M: NR) Age: NR Entorhinal cortex	FF = 650 kHz PD = (0.5) ms PRF = 100 Hz DC = 5% SD = 30 s, ISI = 30 s 10 trials of SD P_r = (0.653) MPa I_{SPPA} = (14.4) W/cm^2 I_{SPTA} = 0.72 W/cm^2 MI = (0.81)	Online: ASL-MRI	The fMRI-ASL signal increased in the entorhinal cortex due to tFUS stimulation.
Liu C et al. 2021 [39]	Healthy $N = 9$ (F:4 / M:5) 35.8 ± 14.1y L-S1 of the hand	FF = 500 kHz PD = 0.2 ms PRF = 300 Hz DC = (6)% SD = 0.5 s, ISI = 2 s 56 trials of SD P_r = 0.286 MPa I_{SPPA} = 1.1 W/cm^2 I_{SPTA} = 0.067 W/cm^2 MI = (0.4)	Online: EEG, ESI Offline: Behavioral tasks (tactile vibration frequency discrimination tasks)	Excitatory effects of tFUS applied to the S1 improved sensory discrimination capability.
Cain JA et al. 2021b [54]	Healthy $N = 16$ (F:1 / M:15) 25.3 ± 7.8y (18–44) L-globus pallidus (GP)	FF = 650 kHz PD = 0.5, 5 ms PRF = 100, 10 Hz DC = 5% SD = 30 s, ISI = 30 s 10 trials of SD P_r = (0.653) MPa I_{SPPA} = 14.39 W/cm^2 I_{SPTA} = 0.720 W/cm^2 MI = (0.81)	Online: fMRI Offline: ASL	During tFUS, decreases in the BOLD signal were observed in the targeted left globus pallidus (GP) and in large-scale cortical networks. A generalized decrease in relative perfusion throughout the cerebrum was observed following tFUS.
Guerra A et al. 2021 [57]	Healthy, R-handed $N = 16$ (F:7 / M:9) 27.1 ± 2.3y (23–33) Superior colliculus, nucleus raphe magnus, substantia nigra of the brainstem	FF = 1.75 MHz PD = NR PRF = NR DC = NR SD = 180 s, ISI = N/A 1 trial of SD P_r = 0.152 MPa I_{SPPA} = (0.78) W/cm^2 I_{SPTA} = NR MI = (0.11)	Offline: EMG of blink reflex response	Unfocused TUS applied to the brainstem increased the excitability of the brainstem circuit, as evaluated by the EMG recovery cycles of the trigeminal blink reflex.

Table 2 (continued)

Author Year	Subjects, Age, Target regions	Sonication parameters	Outcome readouts	Efficacies
Yu K et al. 2021 [32]	Healthy $N = 15$ (F:5 / M:10) 33.4 ± 14.0y L-M1 of the leg	FF = 500 kHz PD = 0.2 ms PRF = 300, 3000 Hz DC = (6, 60)% SD = 0.5 s, ISI = 2.5–4.5 s 120 trials of SD P_r = 0.288 MPa I_{SPPA} = 1.17 W/cm^2 I_{SPTA} = (0.07), 0.70 W/cm^2 MI = (0.41)	Online: EEG-MRCP (movement-related cortical potentials)	tFUS applied to the M1 was capable of increasing the M1 excitability and enhancing endogenous motor cortical processes. A higher PRF enhanced the MRCP source profile amplitude more than a lower PRF did.
Johnstone A et al. 2021 [88]	Healthy $N = 16$ (F:5 / M:11) 32y (25–46) Transducer positioned over the inion	FF = 270 kHz P_r = 0.23 MPa I_{SPPA} = 1.7 W/cm^2 MI = (0.44) Trials of SD: NR PD = (1, 2, 4) ms PRF = 500, 250, 125 Hz DC = 50% SD = 0.3 s, ISI = NR I_{SPTA} = (0.85) W/cm^2 PD = (150) ms, PRF = N/A, DC = 100% SD = 0.15 s, ISI = NR I_{SPTA} = (1.70) W/cm^2	Online: Self-report	The ramping and masking of tFUS stimulation inhibited tFUS-mediated auditory perception in participants.
Xia X et al. 2021 [21]	Healthy, L(1)-/R(21)-handed $N = 22$ (F:10 / M:12), 21–44y L-M1 of the hand	FF = 500 kHz PD = (0.3) ms PRF = 1000 Hz DC = 30% SD = 0.5 s, ISI = (5.5) s 15 trials of SD P_r = (0.262) MPa I_{SPPA} = 2.32 W/cm^2 I_{SPTA} = 0.69 W/cm^2 MI = (0.37)	Online, Offline: TMS-induced MEPs	The suppressive effects of tFUS on the ipsilateral M1 cortical excitability slightly (~20 ms) outlasted the sonication but did not result in long-lasting effects. These suppressive effects were absent in the contralateral M1.
Zhang Y et al. 2021 [24]	Healthy, R-handed $N = 24$ (F:0 / M:24) 31.9 ± 9.6y (22–53) L-M1 of the hand	FF = 500 kHz PD = 0.5 ms PRF = 100 Hz DC = 5% SD = 0.5 s, ISI = 8 s (106) trials of SD P_r = (0.29) MPa I_{SPPA} = 2.846 W/cm^2 I_{SPTA} = 0.142 W/cm^2 MI = 0.42	Offline: TMS-induced MEPs, stop-signal task	15-min repetitive tFUS applied to the left M1 increased motor cortex excitability, lasting for 30 min, and improved inhibitory control function.

Table 2 (continued)

Author Year	Subjects, Age, Target regions	Sonication parameters	Outcome readouts	Efficacies
Zeng K et al. 2022 [26]	Healthy, R-handed $N = 20$ (F:12 / M:8) 30.8 ± 7.5y (23–49) L-M1 of the hand	FF = 500 kHz $P_{r.0}$ = (0.259) MPa $I_{SPPA.0}$ = 2.26 W/cm^2 $MI._0$ = (0.37) PD = 20 ms PRF = 5 Hz, DC = (10)% SD1 = 80 s, ISI = N/A (1) trial of SD1 for tbTUS $I_{SPTA.0}$ = 0.23 W/cm^2 PD = 0.32 ms PRF = 1 kHz, DC = (32)% SD2 = 0.5 s, ISI = 1.1 s 50 trials of SD2 for rTUS $I_{SPTA.0}$ = 0.72 W/cm^2	Offline: TMS-induced MEPs, SICI and ICF, visuomotor tasks	80-s tbTUS applied to the M1 increased TMS-induced MEP amplitude for at least 30 min, decreased SICI, and increased ICF. In contrast, 80-s rTUS produced no significant change in corticospinal excitability based on TMS-induced MEPs.
Heimbuch IS et al. 2022 [30]	Healthy, R-handed (Muscle contraction) $N = 10$, 26.9y (18–42) (MEPs) $N = 8$, 26.8y (18–42) L-M1 of the hand	FF = 500 kHz PD = 0.36 ms PRF = 1000 Hz DC = 36% SD = 0.3, 0.5 s, ISI = 10 s 80 trials of SD P_r = (0.34) MPa I_{SPPA} = 3.9 W/cm^2 I_{SPTA} = 1.404 W/cm^2 MI = (0.48)	Online: EMG Offline: TMS-induced MEPs	During tFUS applied to the M1, no change in EMG of tonic muscle contraction (of the index finger) was observed. Using single-pulse TMS, no difference in the M1 excitability was found before versus after sparsely repetitive TUS to the M1.
Kim YG et al. 2022 [51]	Healthy, R-handed $N = 8$ (F:5 / M:3) 58.2 ± 5.6y (45–65) Bilateral medial PFC	FF = 250 kHz PD = 0.5 ms P_r = 0.15 MPa I_{SPPA} = (0.76) W/cm^2 MI = 0.3 PRF = (1400) Hz DC = 70% I_{SPTA} = (0.532) W/cm^2 SD1 = 0.3 s, ISI = (4.7) s (240) trials of SD1 PRF = (100) Hz, DC = 5% I_{SPTA} = (0.038) W/cm^2 SD2 = 20 min, ISI = N/A (1) trial of SD2	Online, Offline: EEG	tFUS applied to the bilateral mPFC differentially altered EEG spectral power depending on whether the stimulation was excitatory or suppressive.
Nakajima K et al. 2022 [22]	Healthy, R-handed $N = 20$ (F:11 / M:9) 22.7 ± 3.9y L-M1 of hand R-basal ganglia (subthalamic nucleus, anterior putamen) $N = 20$ (F:11 / M:9) 22.3 ± 4.1y R-anterior IFC	FF = 500 kHz PD = 30 ms PRF = 10 Hz DC = (30)% SD = 40 s, ISI = N/A (1) trial of SD P_r = (0.657–0.675) MPa I_{SPPA} = 14.6–15.4 W/cm^2 I_{SPTA} = 4.4–4.6 W/cm^2 MI = (0.93–0.95)	Offline: TMS-induced MEPs, fMRI, diffusion MRI, stop-signal task	The suppressive effects of tFUS on the M1 were confirmed by TMS-induced MEPs. tFUS applied to the basal ganglia/IFC resulted in impairments in stopping performance during the stop-signal task. Diffusion MRI revealed the anatomical linkage between the anterior putamen and IFC.

Table 2 (continued)

Author Year	Subjects, Age, Target regions	Sonication parameters	Outcome readouts	Efficacies
Butler CR et al. 2022 [43]	Healthy, normal vision *N* = 16 (F:10 / M:6) 26y (20–51) Middle temporal complex (MT+/V5) Fusiform face area (FFA, active control)	FF = 500 kHz PD = 0.5 ms PRF = 1000 Hz DC = 50% SD = 0.3 s, ISI = 2.7 s (250) trials of SD P_r = 0.44, 0.35 MPa I_{SPPA} = 6.6, 4.3 W/cm^2 I_{SPTA} = 0.37, 0.24 W/cm^2 MI = (0.62, 0.49)	Online: EEG, behavioral task (visual motion coherence detection task)	tFUS applied to the MT+/V5 improved visual motion detection and modulated the electrophysiological responses of visual motion-evoked ERPs.
Zhang M-F et al. 2022 [28]	Healthy, R-handed *N* = 20 (F:12 / M:8) 32.8 ± 13.4y (21–59) L-M1 of the hand (TMS hotspot)	FF = 800 kHz PD = 1000 ms PRF = N/A DC = (100)% SD = 1 s, ISI = 2 s (200) trials of SD $Pr._0$ = (0.188) MPa $I_{SPPA.0}$ = 1.2 W/cm^2 $I_{SPTA.0}$ = (1.2) W/cm^2 $MI._0$ = (0.21)	Offline: TMS-induced MEPs, tapping score	Unfocused TUS applied to the left M1 enhanced the M1 excitability, resulting in decreased hand reaction response time and MEP latency (shortening the transmission time of MEPs).
Park TY et al. 2022 [52]	Healthy *N* = 2 (F:0 / M:2) 42y L-dorsolateral PFC (DLPFC)	FF = 200 kHz PD = 1 ms PRF = 360 Hz DC = 36% SD = 0.5 s ISI = (8.9–32.4) s 226–325 trials of SD P_r = 0.452, 0.445 MPa I_{SPPA} = 6.91, 6.69 W/cm^2 I_{SPTA} = 2.49, 2.41 W/cm^2 MI = 1.011, 0.995	Online: behavioral assessments (anti-saccade [AS])	tFUS applied to the left DLPFC was effective reducing the error rates of anti-saccades but did not affect the latencies.
Samuel N et al. 2022 [27]	Healthy *N* = 15 (F:7 / M:8) 27.1 ± 5.1y (20–37) L-M1 of the hand	FF = 500 kHz PD = 20 ms PRF = 5 Hz DC = 10% SD = 80 s, ISI = N/A (1) trial of SD $P_{r.0}$ = (0.259) MPa $I_{SPPA.0}$ = 2.26 W/cm^2 $I_{SPTA.0}$ = 0.226 W/cm^2 $MI._0$ = (0.37)	Offline: TMS-induced MEPs, SICI, ICF, MEG during resting-state and index finger abduction/adduction task	tbTUS applied to the M1 increased MEP amplitude and decreased SICI, with no change observed in ICF. Analysis of MEG spectral power revealed tFUS-mediated desynchronization in alpha and beta spectral power. Local connectivity increased in motor areas.
Ren L et al. 2023 [25]	Healthy, R-handed *N* = 20 (F:18 / M:22) 35.6 ± 8.6y L-M1	FF = 500 kHz PD = 0.5 ms PRF = 100 Hz DC = 5% SD = 0.5 s, ISI = 8 s (106) trials of SD $P_{r.0}$ = (0.489) MPa $I_{SPPA.0}$ = 8.09 W/cm^2 $I_{SPTA.0}$ = 0.40 W/cm^2 $MI._0$ = (0.698)	Offline: C-BCT, TMS-induced MEPs	Repetitive tFUS applied to the left M1 increased ipsilateral M1 excitability for 30 min, decreased the contralateral M1 excitability for 15 min, as assessed by TMS-induced MEP amplitudes, and improved cognitive performance (C-BCT).

Table 2 (continued)

Author Year	Subjects, Age, Target regions	Sonication parameters	Outcome readouts	Efficacies
Nandi T et al. 2023 [45]	Healthy $N=14$ (F:4 / M:10) 31.0 ± 4.3y L-V1 (Transducer positioned 2 cm left to the inion)	FF = 270 kHz PD = (2) ms PRF = 250 Hz DC = 50% SD = 0.3 s, ISI = 2 s 100 trials of SD $P_{r.0}$ = 0.7 MPa $I_{SPPA.0}$ = 16.0 W/cm^2 $I_{SPTA.0}$ = (8.0) W/cm^2 $MI_{.0}$ = (1.35)	Online: EEG	Ramped tFUS (to mask the auditory confounds) applied to the V1 increased the amplitude of the VEP N75 components, but did not elicit sonication-specific evoked potentials.
Forster A et al. 2023a [48]	Healthy $N=14$, out of $N=55$ (F:44 / M:11), 26.1y R-IFG of the lateral PFC	FF = 500 kHz PD = 0.125 ms PRF = 40 Hz DC = 0.5% SD = 120 s, ISI = N/A (1) trial of SD $P_{r.0}$ = 1.09 MPa $I_{SPPA.0}$ = 40 W/cm^2 $I_{SPTA.0}$ = 0.199 W/cm^2 $MI_{.0}$ = 1.54	Offline: Self-report, EEG (midline theta oscillation), ECG, electrodermal measures	Inhibitory tFUS applied to the right IFG (of the PFC) modified midline theta EEG activities and influenced the emergence of 'learned helplessness.'
Kuhn T et al. 2023 [55]	Healthy aging adults $N=16$ (F:9 / M:7) 61.4 ± 7.8y R-amygdala L-entorhinal cortex	FF = 650 kHz PD = 5, 0.5 ms PRF = 10, 100 Hz DC = 5% SD = 30 s, ISI = 30 s (10) trials of SD P_r = (0.653) MPa I_{SPPA} = (14.4) W/cm^2 I_{SPTA} = 0.72 W/cm^2 MI = (0.81)	Online, Offline: ASL-MRI, fMRI	tFUS applied to the amygdala and entorhinal cortex selectively increased perfusion and influenced BOLD responses in both of the targeted brain region and its functional network connectivity.
Forster A et al. 2023b [47]	Healthy, R-handed $N=39$ (F:28 / M:11) 23.9 ± 8.1y R-IFG of the lateral PFC	FF = 500 kHz PD = (0.125) ms PRF = 40 Hz DC = 0.5% SD = 120 s, ISI = N/A (1) trial of SD $P_{r.0}$ = (1.09) MPa $I_{SPPA.0}$ = (39.8) W/cm^2 $I_{SPTA.0}$ = 0.199 W/cm^2 $MI_{.0}$ = 1.53	Offline: Self-report, EEG	Inhibitory tFUS applied to the right IFG (of the PFC) altered the processing of 'stimulus probability' without affecting 'control perception (CP)'. It also modulated midfrontal theta and altered its relationship with self-reported effort and worrying.
Zhang T et al. 2023 [29]	Healthy, R-handed (Single-pulse TMS) $N=10$ (F:6 / M:4) 27.0 ± 5.8y (Paired-pulse TMS) $N=9$ (F:5 / M:4) 27.5 ± 7.1y L-M1	FF = 500 kHz PD = 0.2, 0.4 ms PRF = 2000, 50 Hz DC = 40, 2% SD = 0.5 s, ISI = 1.5 s (150) trials of SD P_r = (0.27) MPa I_{SPPA} = 2.462 W/cm^2 I_{SPTA} = (0.99, 0.05) W/cm^2 MI = (0.38)	Offline: MRS, TMS-induced MEPs, SICI and ICF, GABA/Glx level	tFUS applied to the M1 with different parameters exerted either excitatory or inhibitory neuromodulation effects, as confirmed by the use of TMS-induced MEPs and MRS.

Table 2 (continued)

Author Year	Subjects, Age, Target regions	Sonication parameters	Outcome readouts	Efficacies
Kim H-C et al. 2023 [40]	Healthy $N = 8$ (F:3 / M:5) 32.1 ± 6.0y (23–42) R-S1 R-thalamic-VPL	FF = 250 kHz PD = 0.5, 1, 2 ms PRF = 1400, 700, 350 Hz DC = 70% SD = 0.2 s, ISI = 3.8 s 80 trials of SD P_r = (0.348, 0.317) MPa I_{SPPA} = 4.1, 3.4 W/cm^2 I_{SPTA} = 2.87, 2.38 W/cm^2 MI = 0.70, 0.63	Online: EEG Offline: Self-report, rs-fMRI	tFUS applied to the S1/thalamic-VPL induced evoked potentials across all participants, but not all perceived elicited tactile sensations. rs-fMRI revealed tFUS enhanced functional connectivity in sensorimotor/sensory integration areas.
Shamli Oghli Y et al. 2023 [33]	Healthy, R-handed $N = 14$ (F:4 / M:10) 30.4 ± 6.3y (23–41) L-M1 of the first dorsal interosseous muscle (FDI)	FF = 500 kHz PD = 20 ms PRF = 5 Hz DC = 10% SD = 80 s, ISI = N/A 1 trial of SD P_r = (0.294) MPa I_{SPPA} = 2.93 W/cm^2 I_{SPTA} = 0.29 W/cm^2 MI = (0.42)	Offline: TMS-induced MEPs	The effects of tbTUS on the excitability of the M1, as measured by TMS-induced MEPs, were reduced by all study drugs (carbamazepine, nimodipine, lorazepam, dextromethorphan) compared to placebo.
Ziebell P et al. 2023 [49]	Healthy, R-handed $N = 152$ (F:106 / M:46) 18–35y R-PFC	FF = 500 kHz PD = 0.125 ms PRF = 40 Hz DC = 0.5% SD = 120 s, ISI = N/A 1 trial of SD $P_{r.0}$ = 1.09 MPa $I_{SPPA.0}$ = 40 W/cm^2 $I_{SPTA.0}$ = 0.199 W/cm^2 $MI._0$ = 1.54	Offline: self-report of mood scales, EEG, virtual T-maze task	tFUS applied to the right PFC decreased EEG-MFT (mid-frontal theta), accompanied by increased 'approach behavior' and decreased 'withdrawal behavior.' Self-reported global mood was enhanced.

Table 2 (continued)

Author Year	Subjects, Age, Target regions	Sonication parameters	Outcome readouts	Efficacies
Yaakub SN et al. 2023 [53]	Healthy *N* = 24 (F:14 / M:10) 33.8 ± 9.7y (22–53) L-dorsal ACC L-PCC	FF = 500 kHz PD = 20 ms PRF = (5) Hz DC = (10)% SD = 80 s, ISI = N/A (1) trial of SD P_r = 0.66, 0.65 MPa I_{SPPA} = 15.1, 14.5 W/cm^2 I_{SPTA} = 1.51, 1.45 W/cm^2 MI = 0.95, 0.93	Offline: rs-fMRI, MRS	80-s tbTUS reduced GABA levels in the PCC but not in the dorsal ACC. Functional connectivity increased following tFUS in both regions.
Fine JM et al. 2023 [50]	Healthy, R-handed *N* = 25 (F:6 / M:19) 24.1 ± 3.2y R-IFG *N* = 23 (F:8 / M:15) 22.4 ± 3.3y R-S1 (active control)	FF = 500 kHz PD = (0.24) ms PRF = 1000 Hz DC = 24% SD = 0.5 s, ISI = 2 s 100 trials of SD P_r = (0.288) MPa I_{SPPA} = 2.8 W/cm^2 I_{SPTA} = (0.672) W/cm^2 MI = (0.41)	Online: EEG, stop-signal task	When tFUS was applied to the rIFG along with the stop signal, an improvement in inhibition performance was observed, accompanied by shorter P300 latencies.

In some studies, multiple experimental blocks were performed within a single tFUS session, or multiple tFUS sessions on different days were conducted, but these are not summarized in this table. L, left; R, right; F, female; M, male; NR, not reported; N/A, not applicable; N, number of subjects who received active tFUS; y, years old, shown as mean with standard deviation (when available); ACC, anterior cingulate cortex; AS, anti-saccade; ASL, arterial spin labeling; BOLD, blood oxygenation level-dependent; BCT, brief cognitive test; CP, control perception; DLPFC, dorsolateral prefrontal cortex; ECG, electrocardiography; EEG, electroencephalography; EMG, electromyography; ERP, event related potentials; ESI, electrophysiological source imaging; FDI, first dorsal interosseous muscle; FFA, fusiform face area; fMRI, functional magnetic resonance imaging; GABA, γ-aminobutyric acid; Glx, glutamine/glutamate; GP, globus pallidus; ICF, intracortical facilitation; IFC, inferior frontal cortex; IFG, inferior frontal gyrus; M1, primary motor cortex; MEG, magnetoencephalography; MEPs, motor evoked potentials; MFT, midfrontal theta; MRCP, movement-related cortical potentials; MRS, magnetic resonance spectroscopy; MT+/V5, middle temporal complex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; QST, quantitative sensory thresholding; rs-fMRI, resting-state fMRI; rTUS, repetitive TUS; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SEP, somatosensory evoked potentials; SICI, short-interval intracortical inhibition; tbTUS, theta burst TUS; TMS, transcranial magnetic stimulation; V1, primary visual cortex; VAMS, visual analog mood scales; VEP, visual evoked potentials; VPL, ventral posterolateral nucleus of the thalamus

term $I_{SPPA.3}$ when reporting transcranially attenuated intensity values. To avoid potential confusion, Tables 2 and 3 in this review use the notations I_{SPPA} and I_{SPTA} for derated in situ values at the targeted brain regions after transcranial attenuation. Meanwhile, $I_{SPPA.0}$ and $I_{SPTA.0}$ are employed when transcranially attenuated values were not reported and cannot be estimated. Additionally, we recommend that future tFUS neuromodulation studies report derated in situ values at the targeted brain area using methods such as numerical or analytical models or experimental measurements [18], with clear descriptions like attenuated/derated or in situ I_{SPPA}.

3 tFUS neuromodulations in healthy human participants

Over the past decade (2013–2023), a total of 42 investigations have been reported regarding the examination of tFUS neuromodulatory effects on the cortex or subcortical areas of the healthy human brain (Figs. 2 and 3; Table 2). Previous studies have suggested the possibility of selectively activating or suppressing functions in specific brain regions using non-thermal low-intensity tFUS. Some studies have also reported that tFUS-mediated changes in cortical excitability may induce neuroplasticity with effects that outlast the stimulation period itself. Recently, investigations to elucidate the metabolic and biochemical mechanisms underlying the impact of ultrasound neuromodulation have also been conducted in healthy humans.

3.1 Motor cortex

The most extensively investigated brain region in human tFUS studies to date was the primary motor cortex (M1), validating the neuromodulatory effects in the M1 and exploring changes in motor performance linked to tFUS-mediated alterations of neural activities. The excitability changes of the M1 were measured mainly using TMS-induced motor evoked potentials (MEPs) during (online effects) or after (offline effects) sonication. In some studies [19–21] examining tFUS online effects on MEPs, a TMS coil was combined

Table 3 Summary of a total of 22 tFUS/TUS neuromodulation studies in human subjects with CNS disease conditions, tabulated in chronological order by the date of articles available online. The number of subjects who received active tFUS/TUS, along with information on female/male ratios, age, and ClinicalTrials.gov registration numbers (or relevant information), is shown. The target regions in the brain for tFUS stimulation and sonication parameters used in an experimental block of tFUS session(s) are summarized. For acoustic pressure (P_r), intensity (I_{SPPA}, I_{SPTA}), and mechanical index (MI), derated in situ values at the targeted brain regions after transcranial attenuation are tabulated. When derated in situ values are not available, the corresponding information without considering a derating factor is tabulated with notations of $P_{r.0}$, $I_{SPPA.0}$, $I_{SPTA.0}$, and $MI_{.0}$. Numbers within parenthesis are either estimates or relevant values. Outcome readouts used to observe the neuromodulatory effects either online (during tFUS) or offline (after tFUS) are listed, along with a brief statement of efficacies. Also, refer to Figs. 2 (lower panel) and 4

Author Year	Subjects, Age, Target regions, ClinicalTrials.gov #	Sonication parameters	Outcome readouts	Efficacies
Hameroff S et al. 2013 [60]	Chronic pain patients $N = 31$ (F:19 / M:12) 53.8 ± 14.7y (29–83) L/R-posterior frontal cortex contralateral to most severe pain NCT#: NR	FF = 8 MHz PD = NR PRF = NR DC = (0.12)% SD = 15 s, ISI = N/A 1 trial of SD $P_{r.0}$ = (1.98) MPa $I_{SPPA.0}$ = (132.43) W/cm^2 $I_{SPTA.0}$ = 0.152 W/cm^2 $MI_{.0}$ = 0.7	Offline: Self-report of pain (NRS) and mood (VAMS/Global affect)	Unfocused TUS applied to the posterior frontal cortex improved mood and alleviated pain in patients with chronic pain.
Monti MM et al. 2016 [63]	Post-traumatic disorder of consciousness (DOC) patient $N = 1$ (F:0 / M:1) 25y R-thalamus NCT02522429	FF = 650 kHz PD = 0.5 ms PRF = 100 Hz DC = (5)% SD = 30 s, ISI = 30 s 10 trials of SD P_r = (0.653) MPa I_{SPPA} = (14.4) W/cm^2 I_{SPTA} = 0.72 W/cm^2 MI = (0.81)	Offline: CRS-R (JFK Coma Recovery Scale-Revised)	After applying tFUS to the thalamus, a DOC patient was able to reach toward objects and exhibit new behaviors. Three days after the tFUS session, the patient demonstrated full language comprehension. Five days post-tFUS, the patient attempted to walk.
Nicodemus NE et al. 2019 [66]	AD patients $N = 11$ (F:3 / M:8) 40–95y Bilateral hippocampus Parkinson's disease $N = 11$ (F:3 / M:8) 40–95y Bilateral substantia nigra NCT#: NR	FF = 2 MHz PD = NR PRF = NR DC = NR SD = 1 h, ISI = N/A 1 trial of SD $P_{r.0}$ = NR $I_{SPPA.0}$ = NR $I_{SPTA.0}$ = 0.52 W/cm^2 $MI_{.0}$ = NR	Offline: Arterial Spin Labeling (ASL) MRI, and assessments of cognitive and motor functioning (QDRS, RBANS, MoCA, T25-FW, 9-HPT)	Cognitive and motor functions improved in patients with AD or Parkinson's disease after TUS was applied to the bilateral hippocampus or substantia nigra, respectively.
Brinker ST et al. 2020 [80]	Drug-resistant epilepsy (DRE) patient $N = 1$ (F:1 / M:0) 26y L-hippocampus NCT03868293	FF = 548 kHz PD = 0.72–1.00 ms PRF = 500 Hz DC = 36–50% SD = 0.5 s, ISI = 6.5 s 20 trials of SD $P_{.0}$ = 0.14–0.32 MPa $I_{SPPA.0}$ = (1.0–6.25) W/cm^2 $I_{SPTA.0}$ = 0.5–2.25 W/cm^2 $MI_{.0}$ = (0.19–0.43)	NR	Low-intensity tFUS treatments were delivered to the left hippocampus of a patient with mTLE for the first time, with no adverse events.

Table 3 (continued)

Author Year	Subjects, Age, Target regions, ClinicalTrials.gov #	Sonication parameters	Outcome readouts	Efficacies
Reznik SJ et al. 2020 [73]	Depressed participants $N = 12$ (F:16 / M:8) 18.9 ± 1.1y R-fronto-temporal cortex NCT#: NR	FF = 500 kHz PD = 0.065 ms PRF = 40 Hz DC = 0.26% SD = 30 s, ISI = N/A 1 trial of SD P_r = (0.306) MPa I_{SPPA} = (3.153) W/cm^2 I_{SPTA} = (0.008) W/cm^2 MI = (0.432)	Offline: Self-report of VAMS, BDI-II, OASIS	Repeated tFUS applied to the right front-temporal cortex in individuals with depression decreased worry after five sessions and increased happiness over the study's duration.
Jeong H et al. 2021 [67]	AD patients $N = 4$ (F:3 / M:1) 78.8 ± 3.3y (65–85) R-hippocampus (with IV μ-bubbles) KCT0005098	FF = 250 kHz PD = 20 ms PRF = 2 Hz DC = 4% SD = 180 s, ISI = N/A 1 trial of SD P_r = 0.135 MPa I_{SPPA} = (0.620) W/cm^2 I_{SPTA} = (0.025) W/cm^2 MI = 0.27	Offline: PET (rCMRglu), and cognitive assessments (COWAT, CWST, MMSE, SVLT)	tFUS applied to the right hippocampus of AD patients improved rCMRglu at the SFG, middle cingulate gyrus, and fusiform gyrus, as well as cognitive functions of memory, executive, and global cognitive function, without BBB opening.
Cain JA et al. 2021a [64]	Chronic minimally conscious state (MCS) patients $N = 3$ (F:1 / M:2) 54.7 ± 4.2y (50–58) L-central thalamus NCT02522429	FF = 650 kHz PD = 0.5 ms PRF = 100 Hz DC = 5% SD = 30 s, ISI = 30 s 10 trials of SD P_r = (0.653) MPa I_{SPPA} = 14.39 W/cm^2 I_{SPTA} = 0.720 W/cm^2 MI = (0.81)	Offline: CRS-R (JFK Coma Recovery Scale-Revised)	After tFUS applied to the thalamus, two out of three patients with chronic MCS exhibited clinically significant increases in behavioral responsiveness.
Stern JM et al. 2021 [82]	Drug-resistant TLE patients $N = 8$ (F:5 / M:3) 35.6 ± 14.5y (18–60) L/R-anteromesial temporal lobe (to be resected) NCT#: NR	FF = 650 kHz PD = 0.5, 2.0 ms PRF = 100, 250 Hz DC = 5, 50% SD = 30, 0.5 s, ISI = NR 8 trials of SD P_r = 0.110–1.727 MPa I_{SPPA} = 0.50–115.2 W/cm^2 I_{SPTA} = 0.25–5.76 W/cm^2 MI = 0.14–2.14	Online: BOLD-fMRI (data not shown) Offline: Neuropsychological testing (verbal learning and memory [RAVLT], visuo-spatial learning and memory [ROCFT, BVMT-R, TCFT]), histology	After tFUS to the temporal lobe, neuropsychological tests did not show any significant changes, except for a slight decrease in performance on one test. The histological analysis did not reveal any detectable damages to the tissue.
Lee C-C et al. 2022 [83]	Drug-resistant epilepsy (DRE) patients $N = 6$ (F:2 / M:4) 33.0 ± 6.8y (26–42) Seizure onset zones (SOZs) in the L-temporal lobe (including the amygdala and hippocampus), L-frontal gyrus, R-frontal operculum, R-insula, and L-anterior cingulate gyrus NCT03860298	FF = NR PD = 3 ms PRF = 100 Hz DC = 30% SD = 10 min, ISI = N/A 1 trial of SD $P_{r.0}$ = (0.288) MPa $I_{SPPA.0}$ = 2.8 W/cm^2 $I_{SPTA.0}$ = (0.84) W/cm^2 $MI_{.0}$ = 0.75	Online, Offline: SEEG	tFUS applied to the SOZs of patients resulted in changes of the SEEG spectral power.

Table 3 (continued)

Author Year	Subjects, Age, Target regions, ClinicalTrials.gov #	Sonication parameters	Outcome readouts	Efficacies
Jeong H et al. 2022 [68]	AD patients *N* = 8 (F:7 / M:1) 78.1 ± 2.9y (65–85) R-hippocampus (with IV μ-bubbles) KCT0005098	FF = 250 kHz PD = 20 ms PRF = 2 Hz DC = 4% SD = 180 s, ISI = N/A 1 trial of SD P_r = (0.44) MPa I_{SPPA} = (6.54) W/cm^2 I_{SPTA} = (0.262) W/cm^2 MI = 0.88	Offline: PET (rCMRglu), cognitive assessments (COWAT, CWST, MMSE, SVLT)	tFUS applied to the hippocampus enhanced short-term regional cerebral metabolic rate of glucose (rCMRglu) and memory, even in the absence of the BBB opening.
Wang Y et al. 2022 [84]	Post-stroke patients *N* = 30 (F:7 / M:23) 57.7 ± 7.9y Five ultrasound probes were placed on the forehead NCT#: NR	FF = NR PD = NR PRF = NR DC = NR SD = 20 min, ISI = NR 1 trial of SD $P_{r.0}$ = (0.228) MPa $I_{SPPA.0}$ = 1.75 W/cm^2 $I_{SPTA.0}$ = NR $MI_{.0}$ = NR	Offline: MMSE, MoCA, MBI, P300 latency and amplitude, BDNF	Unfocused TUS applied to the forehead improved the condition of PSCI (post-stroke cognitive impairment), as indicated by all outcome readouts.
Cain JA et al. 2022 [65]	Acute disorder of consciousness (DOC) patients *N* = 11 (F:2 / M:9) 45.7 ± 20.4y (22–75) R/L-central thalamus NCT02522429	FF = 650 kHz PD = 0.5 ms, PRF = 100 Hz DC = 5% SD = 30 s, ISI = 30 s 10 trials of SD P_r = (0.653) MPa I_{SPPA} = 14.39 W/cm^2 I_{SPTA} = 0.720 W/cm^2 MI = (0.81)	Online: BOLD-fMRI Offline: Neurobehavioral assessments with CRS-R (JFK Coma Recovery Scale–Revised)	During tFUS, fMRI-BOLD signals decreased in the frontal cortex and basal ganglia. Behavioral responsiveness improved after tFUS.
Shimokawa H et al. 2022 [69]	Early stage AD patients *N* = 11 (F:6 / M:5) 70.4 ± 3.0y Whole brain through the bilateral temporal bones UMIN000033071	FF = 500 kHz PD = (0.064) ms PRF = 781 Hz DC = 5% SD = 20 min, ISI = 5 min 3 trials of SD P_r = 0.19 MPa I_{SPPA} = (1.22) W/cm^2 I_{SPTA} = (0.061) W/cm^2 MI = (0.27)	Offline: ADAS-J cog, NPIQ-J, J-ZBI, WMS-R, MMSE-J, FAQ	Diffusion-type TUS applied to the entire brain mitigated cognitive impairment in AD patients.
Zhai Z et al. 2023 [76]	Schizophrenia patients *N* = 16 (F:7 / M:9) 35.6 ± 13.0y L-DLPFC *N* = 12 (F / M: NR) Age: NR M1 NCT04620460	FF = 500 kHz PD = 0.5 ms PRF = (100) Hz DC = (5%) SD = 0.5 s, ISI = 8 s (106) trials of SD $P_{r.0}$ = (0.489) MPa $I_{SPPA.0}$ = 8.086 W/cm^2 $I_{SPTA.0}$ = 0.404 W/cm^2 $MI_{.0}$ = (0.69)	Offline: SANS, PANSS, TMS-induced MEPs	15 sessions of excitatory repetitive tFUS over the left DLPFC relieved negative symptoms in patients with schizophrenia and improved cognitive performance in continuous performance tests.
Mahoney JJ et al. 2023a [79]	Substance use disorder (SUD) patient *N* = 1 (F:0 / M:1) 43y Bilateral nucleus accumbens (NAc) NCT04197921	FF = NR PD = NR PRF = NR DC = NR SD = 10 min, ISI = NR Trials of SD: NR P_r = NR I_{SPPA} = NR I_{SPTA} = NR MI = NR	Offline: Substance craving ratings	tFUS neuromodulation applied to the bilateral NAc for SUD patients resulted in reductions in cravings for various substances.

Table 3 (continued)

Author Year	Subjects, Age, Target regions, ClinicalTrials.gov #	Sonication parameters	Outcome readouts	Efficacies
Mahoney JJ et al. 2023b [78]	Substance use disorder (SUD) patients $N=4$ (F:1 / M:3) 34.0 ± 3.7y (30–39) Bilateral nucleus accumbens (NAc) NCT04197921	FF = 220 kHz PD = 100 ms PRF = (1) Hz DC = (10)% SD = 5 s, ISI = 10 s (20) trials of SD $P_{r.0}$ = (1.276, 1.539) MPa $I_{SPPA.0}$ = 55, 80 W/cm^2 $I_{SPTA.0}$ = (5.5, 8.0) W/cm^2 $MI_{.0}$ = (2.72, 3.28)	Offline: Self-report of cue-induced substance craving, daily craving ratings (without cues), clinical evaluations	tFUS given with 80 W/cm^2 $I_{SPPA.0}$ to the bilateral NAc produced a therapeutic response in SUD patients, leading to subjective enhancements in mood and reduced cravings for substances.
Shin DH et al. 2023 [61]	Chronic neuropathic pain patients $N=11$ (F:5 / M:6) 60.6 ± 13.2y (19–75) Anterior cingulate cortex (ACC) KCT0007894	FF = 250 kHz PD = 5, 10 ms PRF = (100, 70) Hz DC = 50, 70% SD = NR, ISI = NR Trials of SD: NR $P_{r.0}$ = (0.206, 0.174) MPa $I_{SPPA.0}$ = (1.44, 1.03) W/cm^2 $I_{SPTA.0}$ = 0.720 W/cm^2 $MI_{.0}$ = (0.41, 0.35)	Offline: VAS (visual analog scale), K-BPI	Sonication for patients with chronic neuropathic pain demonstrated a notable reduction in pain, maintained over a 4-week period.
Samuel N et al. 2023 [71]	Parkinson's disease patients $N=10$ (F:2 / M:8) 63.8 ± 7.2y (54–76) L/R-M1 of the hand NCT#: NR	FF = 500 kHz PD = 20 ms PRF = 5 Hz DC = 10% SD = 80 s, ISI = N/A (1) trial of SD $P_{r.0}$ = (0.259) MPa $I_{SPPA.0}$ = 2.26 W/cm^2 $I_{SPTA.0}$ = 0.226 W/cm^2 $MI_{.0}$ = (0.37)	Offline: MDS-UPDRS-III, TMS-induced MEPs, SICI, ICF	The accelerated tbTUS (a-tbTUS) induced increased excitability in the M1 region, although it did not result in a significant improvement in clinical motor abilities.
Mahdavi KD et al. 2023 [77]	Treatment-refractory anxiety disorder patients $N=25$ (F:11 / M:14) 39.0 ± 12.6y (20–64) R-amygdala NCT04250441	FF = 650 kHz PD = 5 ms PRF = 10 Hz DC = 5% SD = 30 s, ISI = 30 s (10) trials of SD P_r = 0.61 MPa I_{SPPA} = 14.39 W/cm^2 I_{SPTA} = 0.720 W/cm^2 MI = 0.75	Offline: Self-report of HAM-A, BAI, PGI-I	10-min tFUS applied to the right amygdala weekly for 8 weeks resulted in a significant decrease in anxiety. Upon completion, 64% (16 out of 25) of subjects indicated clinically significant benefits.
Riis TS et al. 2023 [75]	Severe treatment-resistant depression patient $N=1$ (F:1 / M:0) 30y Subcallosal cingulate cortex (SCC) NCT05301036	FF = 650 kHz PD = (30) ms PRF = N/A DC = (100)% SD = 0.03 s, ISI = 4 s (15) trials of SD P_r = 1 MPa I_{SPPA} = (33.78) W/cm^2 I_{SPTA} = (33.78) W/cm^2 MI = (1.24)	Online: BOLD-fMRI Offline: HDRS-6 scores	tFUS decreased fMRI-BOLD signals at the target. Following tFUS, the patient's depressive symptoms resolved within 24 h of the stimulation, and the patient remained in remission for at least 6 weeks afterwards.

Table 3 (continued)

Author Year	Subjects, Age, Target regions, ClinicalTrials.gov #	Sonication parameters	Outcome readouts	Efficacies
Riis T et al. 2024 [74]	Treatment-resistant depression (TRD) patients *N* = 2 (F:2 / M:0) 32, 35y Subgenual cingulate cortex (SGC), ventral striatum NCT05301036	FF = 650 kHz PD = (30) ms PRF = N/A DC = (100)% SD = 0.03 s, ISI = 4 s (15–44) trials of SD P_r = 1 MPa I_{SPPA} = 31.1 W/cm^2 I_{SPTA} = (31.1) W/cm^2 MI = 1.2	Offline: Self-report of 7-point scale mood states rating, GASE (the Generic Assessment of Side Effects) questionnaire	tFUS stimulation of the SGC lowered depression scores in TRD patients, and this effect was sustained for a minimum of 6 weeks without any side effects.
Bubrick EJ et al. 2024 [81]	Drug-resistant mTLE patients *N* = 6 (F:1 / M:5) 40.3 ± 17.3y (23–73) L/R-hippocampus with mTLE lateralization NCT#: NR	FF = 548 kHz PD = (0.366) ms PRF = 500 Hz DC = 18.3% SD = NR, ISI = (7-SD) 20 trials of SD $P_{r.0}$ = 0.42 MPa $I_{SPPA.0}$ = (6.01) W/cm^2 $I_{SPTA.0}$ = 1.1 W/cm^2 $MI_{.0}$ = (0.57)	Offline: rs-fMRI, Seizure frequency	Over a 3-week period with six tFUS sessions, 5 out of 6 subjects exhibited a significant reduction in seizure frequency.

In some studies, multiple experimental blocks were performed within a single tFUS session, or multiple tFUS sessions on different days were conducted, but these are not summarized in this table. L, left; R, right; F, female; M, male; NR, not reported; N/A, not applicable; N, number of subjects who received active tFUS; y, years old, shown as mean with standard deviation, when available; 9-HPT, nine-hole peg test; ACC, anterior cingulate cortex; ADAS-cog, Alzheimer's disease assessment scale–cognitive subscale; ASL, arterial spin labeling; BAI, Beck anxiety scale; BDI-II, Beck's depression inventory; BDNF, brain-derived neurotrophic factor; BVMT-R, brief visuospatial memory test-revised; COWAT, controlled oral word association test; CRS-R, JFK coma recovery scale-revised; CWST, color word stroop test; DLPFC, dorsolateral prefrontal cortex; DOC, disorder of consciousness; DRE, drug-resistant epilepsy; FAQ, functional activities questionnaire; GAD, generalized anxiety disorder; GASE, generic assessment of side effects; HAM-A, Hamilton anxiety rating scale; HDRS-6 scores, 6-item version of Hamilton depression rating scale; IV, intravenous; BPI, brief pain inventory; MBI, modified bathel index; M1, primary motor cortex; MCS, minimally conscious state; MDS-UPDRS-III, the movement disorder society-the unified Parkinson's disease rating scale-III; MEPs, motor evoked potentials; MMSE, mini-mental state examination; MoCA, Montreal cognitive assessment; MRI, magnetic resonance imaging; mTLE, mesial temporal lobe epilepsy; NAc, nucleus accumbens; NPIQ, neuropsychiatric inventory–questionnaire; NRS, numerical rating scale (of pain); OASIS, overall anxiety severity and impairment scale; PANSS, positive and negative syndrome scale; PET, positron emission tomography; PGI-I, patient global impression of improvement; PSCI, post-stroke cognitive impairment; QDRS, quick dementia rating system; RAVLT, Rey auditory verbal learning test; RBANS, repeatable battery for the assessment of neuropsychological status; rCMRglu, regional cerebral metabolic rate for glucose; ROCFT, Rey–Osterrieth complex figure test; SANS, scale for the assessment of negative symptoms; SCC, subcallosal cingulate cortex; SEEG, stereo-EEG; SFG, superior frontal gyrus; SGC, subgenual cingulate cortex; ICF, intracortical facilitation; SICI, short-interval intracortical inhibition; SOZs, seizure onset zones; SUD, substance use disorder; SVLT, Seoul verbal learning test; T25-FW, timed twenty-five-foot walk test; TCFT, total cognitive function test; TRD, treatment-resistant depression; VAMS; visual analog mood scales; VAS, visual analog scale; WMS-R, Wechsler memory scale-revised; ZBI, Zarit burden interview; μ-bubbles, microbubble ultrasound contrast agent

with a tFUS transducer, and no interference between tFUS and TMS was reported.

Regarding the studies that utilized TMS-induced MEPs, Legon et al. (2018b) [20] demonstrated that tFUS applied to the M1 suppressed the amplitude of TMS-induced MEPs, attenuated intra-cortical facilitation (ICF) in a paired-pulse TMS protocol (with an inter-pulse latency of 10–15 ms), and reduced reaction time on a simple stimulus-response task. However, it did not affect short-interval intra-cortical inhibition (SICI) in another paired-pulse TMS protocol (with an inter-pulse latency of 1–5 ms). Fomenko and colleagues (2020) [19] reported that tFUS suppressed MEP amplitudes and decreased reaction time on a visuomotor task, similar to Legon et al. (2018b) [20], but it increased SICI and did not affect ICF. From the same group, Xia et al. (2021) [21] observed transient suppressive effects of tFUS on MEP amplitudes from the ipsilateral M1 but not from the contralateral side. Nakajima et al. (2022) [22] also reported suppressive effects of tFUS to the ipsilateral M1 excitability.

On the other hand, Gibson et al. (2018) [23] showed that unfocused TUS to the M1 transiently increased the MEP amplitudes. In the case of Zhang et al. (2021) [24], tFUS administered for 15 min increased MEP amplitudes for ~30 min and improved inhibitory control function in the tasks conducted immediately after tFUS. Using the same sonication parameters, Ren et al. (2023) [25] reported that tFUS to the left M1 increased the ipsilateral M1 excitability for ~30 min while decreased the contralateral M1 excitability for ~15 min, as assessed by TMS-induced MEP amplitudes, along with improved cognitive performance. In 2022,

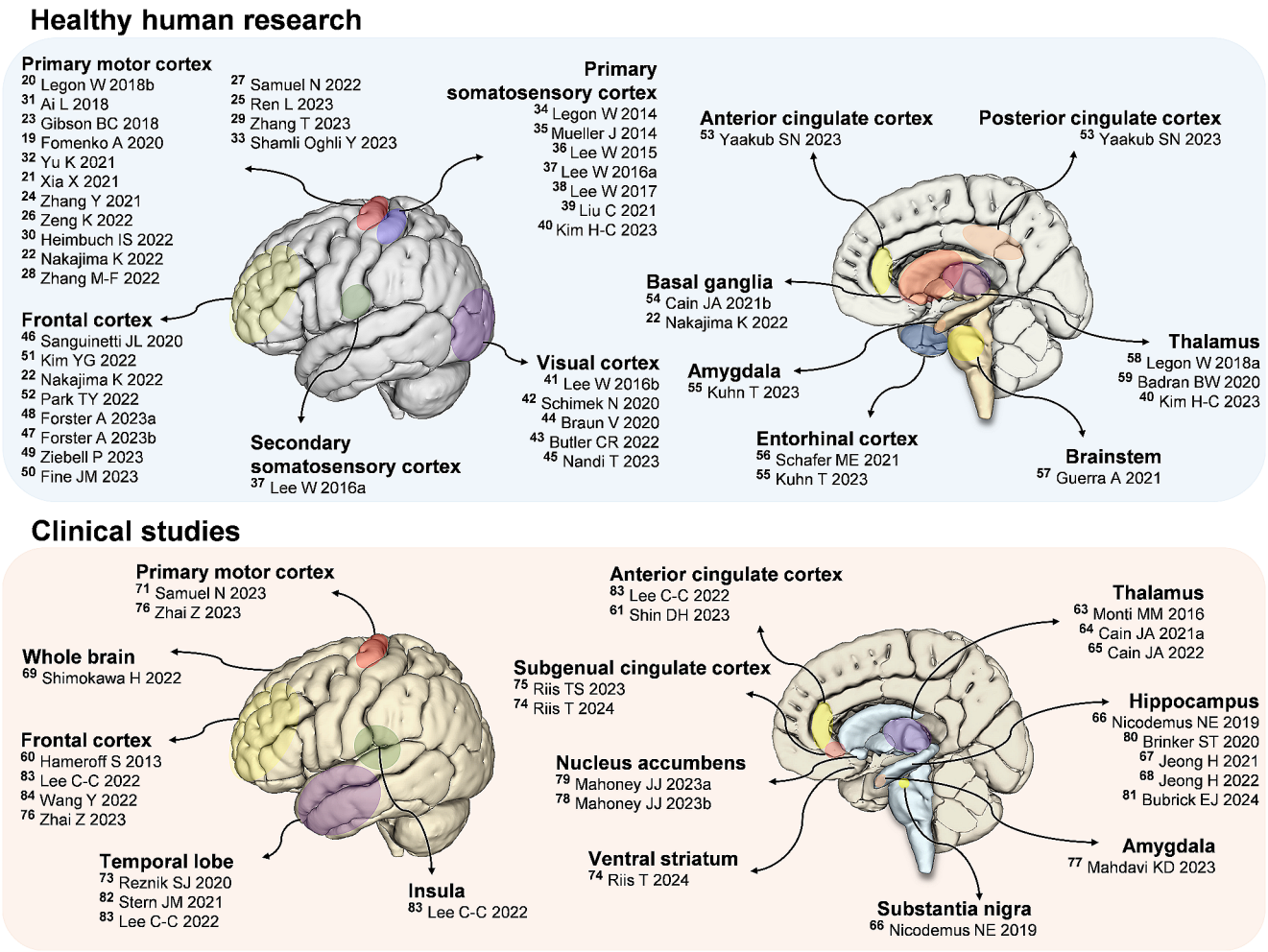

Fig. 2 Illustrations of cortical and subcortical brain regions, regardless of the left or right hemisphere, that have been stimulated by low-intensity tFUS/TUS during the past decade (2013–2023) of ultrasonic neuromodulation research in healthy human participants (upper panel, also refer to Fig. 3; Table 2) and clinical studies (lower panel, also refer to Fig. 4; Table 3) involving CNS disease conditions. The studies are listed in chronological order by the dates of articles available online within each category

Zeng et al. (2022) [26] proposed a tFUS protocol, named theta burst TUS (tbTUS), with 5-Hz PRF corresponding to the frequency of the electroencephalography (EEG) theta rhythm. The tbTUS increased the MEP amplitudes and ICF while decreasing SICI and movement time on a visuomotor task. The same tbTUS protocol was used by Samuel et al. (2022) [27], also reporting increased MEP amplitude and decreased SICI, but no change in ICF. Zhang et al. (2022) [28] administered TUS for 10 min, which enhanced the M1 excitability and decreased latency of MEPs and hand reaction response time.

Recently, Zhang et al. (2023) [29] demonstrated bimodal neuromodulatory effects of either excitation or inhibition on the TMS-induced MEPs using two different sets of sonication parameters: excitatory (500-ms SD, 40% DC, 2-kHz PRF) and inhibitory (0.5-ms SD, 2% DC, 50-Hz PRF). While all the studies reviewed above reported tFUS-/TUS-mediated changes in MEPs with TMS protocols, Heimbuch et al. (2022) [30] were unable to observe changes in either EMG of tonic muscle contraction or TMS-induced MEPs during/after tFUS.

Not only TMS-induced MEPs, but other modalities have also been employed as outcome readouts to examine the tFUS-mediated neuromodulatory effects in the M1. In a study by Ai and colleagues (2018) [31] using 7 Tesla functional magnetic resonance imaging (fMRI), tFUS applied to the corresponding M1 during subjects performing a cued finger tapping task increased blood oxygenation level-dependent (BOLD) activation volumes. Yu et al. (2021) [32] observed an elevation in movement-related cortex potentials (MRCP) through EEG when tFUS was applied during spontaneous movements. Samuel et al. (2022) [27] reported tFUS-mediated desynchronization in alpha and beta spectral power of the magnetoencephalography (MEG), along with increased local connectivities in the motor cortical areas. Zhang et al. (2023) [29] utilized proton magnetic

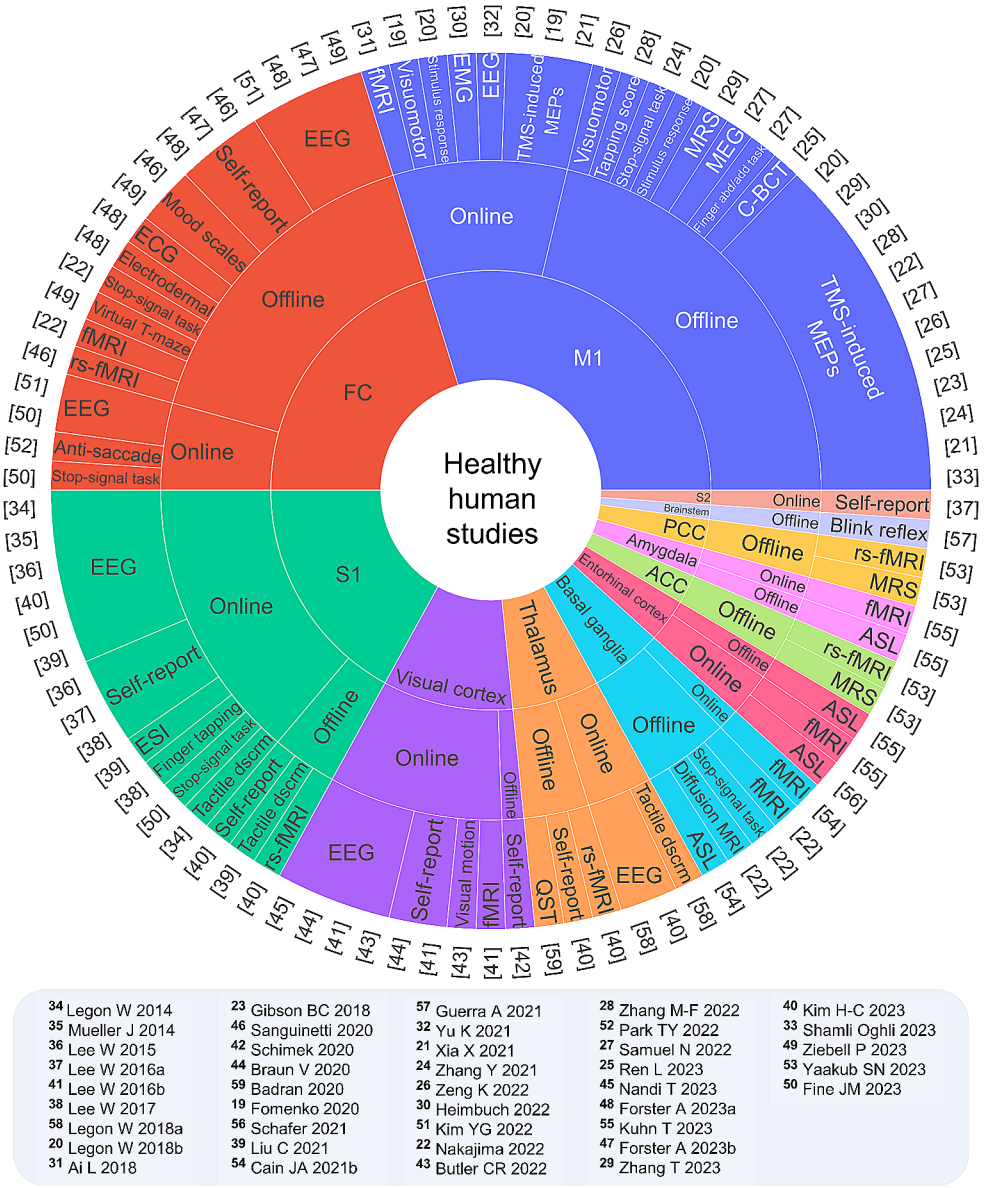

Fig. 3 Sunburst chart illustrating the outcome readouts (the outer rim) used to observe tFUS/TUS-mediated neuromodulatory efficacy in healthy human participants. The sonication target regions in the brain are noted in the inner rim. The outcome readouts were performed either online (during tFUS) or offline (after tFUS), as noted in the middle rim. See also the upper panel of Fig. 2; Table 2. Inner rim: FC, frontal cortex; M1, primary motor cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; Visual cortex, V1 or MT+/V5; ACC, anterior cingulate cortex; PCC, posterior cingulate cortex. Outer rim: EEG, electroencephalography; ESI, electrophysiological source imaging; MEG, magnetoencephalography; EMG, electromyography; MEPs, motor evoked potentials; ECG, electrocardiography; fMRI, functional magnetic resonance imaging; rs-fMRI, resting-state fMRI; MRS, magnetic resonance spectroscopy; ASL, arterial spin labeling; QST, quantitative sensory thresholding; TMS, transcranial magnetic stimulation; dscrm, discrimination task; Finger abd/add task, finger abduction/adduction task; BCT, brief cognitive test

resonance spectroscopy (MRS) as a non-invasive method to quantitatively measure the neurotransmitter levels in the brain, where excitatory tFUS increased glutamate levels and decreased γ-aminobutyric acid (GABA) levels, while inhibitory tFUS decreased the concentration of glutamate and increased that of GABA.

Recently, the first pharmacological study examining the neuromodulatory mechanisms of tFUS stimulation in the human M1 was conducted using the tbTUS protocol by Shamli Oghli and colleagues (2023) [33]. They administered medications to either block voltage-gated Na^+ (via carbamazepine) or Ca^{2+} channels (via nimodipine) or modulate GABA (via lorazepam) or N-methyl-D-aspartate (NMDA) receptors (via dextromethorphan). The study examined tFUS-mediated M1 excitabilities, as measured by amplitudes of TMS-induced MEPs, and found that tFUS-induced excitability reductions were observed with all of the study drugs. Based on the results, the study concluded that the mechanism of tFUS neuromodulation may involve activations of mechanosensitive Na^+ and Ca^{2+} channels. Furthermore, the study suggested that the tFUS applied to the M1 may induce neuroplasticity with a long-term potentiation (LTP)-like mechanism.

3.2 Somatosensory cortex

In the early stage of human tFUS studies, the neuromodulatory effects were primarily examined by stimulating the primary somatosensory cortex (S1). Legon et al. (2014) [34] reported the tFUS applied to the S1 attenuated amplitudes of somatosensory evoked potentials (SEPs) elicited by median nerve stimulation and enhanced behavioral performance in

sensory discrimination tasks. In another study by the same team, Mueller et al. (2014) [35] showed that tFUS modulated intrinsic and SEP EEG dynamics based on the phase analysis (angle and rate) of beta and gamma frequency bands. In 2015, Lee and colleagues [36] demonstrated that tFUS applied to the hand S1 induced sonication-specific EEG evoked potentials, accompanied by elicited transient tactile sensations on the contralateral hand area, with anatomical specificity extending to individual fingers. Lee et al. (2016a) [37] from the same team also reported that simultaneous tFUS stimulations of the unilateral S1 and secondary somatosensory cortex (S2), or S2-only stimulation, elicited perceptions of tactile sensations in the contralateral hand. Additionally, the ability to selectively elicit tactile sensations from the left or right hand by administering tFUS to the contralateral S1 was adapted to propose a potential non-invasive computer-to-brain interface (CBI) in humans using a wearable tFUS helmet in a study by Lee et al. (2017) [38]. In 2021, Liu and colleagues [39] presented that tFUS stimulation of the S1 improved sensory discrimination capability with excitatory effects at the targeted cortical area, as examined by EEG, while an earlier study by Legon et al. (2014) [34] showed similar behavioral task results with attenuated SEP amplitudes. Recently, Kim and colleagues (2023) [40] demonstrated that tFUS given to the S1 generated EEG evoked potentials with elicited tactile sensations and enhanced functional connectivity in sensorimotor and sensory integration networks, as revealed by resting-state fMRI (rs-fMRI). These effects persisted for more than an hour, suggesting the potential for inducing neuroplasticity.

3.3 Visual cortex

The ability of tFUS to stimulate the primary visual cortex (V1) has also been investigated. Lee et al. (2016b) [41] demonstrated that tFUS delivered to the V1 induced activations in the sonicated target brain region and the network of regions involved in visual and higher-order cognitive processing, as revealed by BOLD-fMRI acquired during sonication. The elicited phosphene perception and the EEG response associated with the V1 stimulation were also reported. The capability of TUS to stimulate the V1 was further examined by Schimek et al. (2020) [42], where repeated unfocused TUS induced illusory visual percepts in healthy subjects. Butler et al. (2022) [43] investigated the efficacy of tFUS applied to the middle temporal visual area (MT+/V5), highly selective for visual motion processing. tFUS to the MT+/V5 modulated the event related potentials (ERPs) evoked by the visual motion, reduced reaction times, and improved accuracy in visual motion detection tasks. In an earlier study by the same team in 2020, Braun et al. [44] reported that tFUS to the V1 elicited phosphenes in only one participant out of a total of 18 healthy subjects. They discussed that the rarity of phosphene detection was likely due to the differences in experimental protocols compared to that of Lee et al. (2016b) [41]. Recently, Nandi et al. (2023) [45] used ramped tFUS (to mask auditory confounds; see Sect. 5.4) to stimulate the V1, which did not elicit phosphenes or sonication-specific evoked potentials but modulated the amplitude (N75 component) of visual evoked potentials (VEPs) elicited using a checkerboard stimulus.

3.4 Frontal cortex

The neuromodulatory effects of tFUS on the frontal cortices have been explored in studies involving healthy humans. Sanguinetti et al. (2020) [46] reported that tFUS applied to the right inferior frontal gyrus (IFG) enhanced mood states and reduced functional connectivity in resting-state networks, as revealed by using rs-fMRI. In psychological investigations by Forster and colleagues (2023a,b) [47, 48], tFUS administration to the right IFG modulated the emergence of 'learned helplessness' and midline theta EEG activities [48], and altered the processing of 'stimulus probability' and midfrontal theta EEG, without affecting 'control perception' [47]. Another study by the same group, conducted by Ziebell et al. (2023) [49], demonstrated that tFUS to the right prefrontal cortex (PFC) decreased midfrontal theta EEG activity, accompanied by increased 'approach behavior' while 'withdrawal behavior' decreased, during a virtual T-maze task. Fine et al. (2023) [50] reported that when tFUS was applied to the right IFG during a 'stop' signal in a stop-signal task, behavioral inhibition was improved, accompanied by shorter P300 onset latencies. Nakajima et al. (2022) [22] found that suppressive tFUS delivered to the right anterior inferior frontal cortex (IFC) resulted in impairments in stopping performance during a stop-signal task. In a study by Kim and colleagues (2022) [51], tFUS applied to the medial PFC differentially changed EEG spectral power depending on the chosen acoustic parameters, which induced either excitatory or suppressive effects. Park et al. (2022) [52] demonstrated that tFUS targeting the left dorsolateral PFC (DLPFC) effectively reduced error rates in anti-saccade tasks, but not latencies.

3.5 Other cortical, subcortical and deep brain regions

Alongside human tFUS studies targeting the sensorimotor areas (S1/S2, M1), visual regions (V1, MT+/V5) and frontal cortical areas (IFC, PFC), tFUS neuromodulatory efficacy has also been investigated in various other regions, including subcortical and deep brain areas. Yaakub et al. (2023)

[53] demonstrated that excitatory tbTUS reduced GABA levels in the posterior cingulate cortex (PCC) but not in the dorsal anterior cingulate cortex (ACC). Simultaneously, functional connectivity increased in both PCC and dorsal ACC, as assessed by MRS and rs-fMRI. The neuroplastic changes induced by tFUS persisted for at least 50 min.

Among subcortical regions, Cain et al. (2021b) [54] reported that tFUS applied to the left globus pallidus (GP) decreased fMRI-BOLD signals in the targeted GP and large-scale cortical networks during the sonication. It also decreased perfusion throughout the cerebrum for at least several minutes following tFUS, as observed by using arterial spin labeling (ASL). In another study employing ASL and BOLD-fMRI, Kuhn et al. (2023) [55] found that tFUS directed at the right amygdala and left entorhinal cortex selectively increased perfusion and BOLD responses in the targeted brain region and its functional connectivity to other regions. The seemingly inconsistent tFUS effects between Cain et al. (2021b) [54] and Kuhn et al. (2023) [55] were discussed as likely due to the differences in the vasculature and connectivity of the thalamus. In a single-participant study by Schafer et al. (2021) [56], tFUS applied to the unilateral entorhinal cortex increased the cerebral blood perfusion in the targeted area, consistent with the findings of Kuhn et al. (2023) [55]. In a study by Nakajima et al. (2022) [22], suppressive tFUS to the subthalamic nucleus (STN) and the anterior putamen of the right basal ganglia were also investigated, respectively, both of which resulted in impairments in stopping performance during a stop-signal task. Additionally, Guerra et al. (2021) [57] demonstrated that unfocused TUS applied to the substantia nigra, superior colliculus, and nucleus raphe magnus of the brainstem increased the excitability of the brainstem circuits, as assessed by electromyography (EMG) recovery cycles of the trigeminal blink reflex (in response to electrical stimulation applied to the right supraorbital nerve).

Thalamic tFUS neuromodulation in healthy participants has also been investigated. In Legon et al. (2018a) [58], tFUS applied to the left ventral posterolateral nucleus (VPL) of the thalamus inhibited the amplitude (P14 component) of EEG SEP, attenuated EEG power in alpha, beta, and time-locked gamma frequencies, and reduced performance of tactile discrimination tasks. On the other hand, in a recent study by Kim and colleagues (2023) [40], tFUS stimulation of the right thalamic VPL generated sonication-specific EEG evoked potentials across all participants. Some participants reported elicited tactile sensations, and functional connectivity in sensorimotor and sensory integration areas was enhanced, as revealed by rs-fMRI. In another study, Badran et al. (2020) [59] applied tFUS to the right anterior nuclei of the thalamus, which attenuated thermal pain sensitivity.

4 tFUS neuromodulations in clinical studies with CNS disease conditions

Alongside studies involving healthy human participants (Sect. 3), a total of 22 clinical investigations have been reported in subjects with various CNS disease conditions (Table 3), with the majority published in the last 5 years (2019–2023). These studies delve into the therapeutic potentials of tFUS-mediated brain neuromodulation. The CNS disease conditions investigated using tFUS/TUS to date include chronic pain, disorder of consciousness (DOC), Alzheimer's disease (AD), Parkinson's disease, depression, schizophrenia, anxiety disorder, substance use disorder (SUD), epilepsy, and stroke (Fig. 4). For patients with these conditions, neuromodulatory tFUS was administered to various regions of the brain (Fig. 2, lower panel), including the frontal cortex, temporal lobe, motor cortex, ACC, subgenual cingulate cortex (SCC), nucleus accumbens (NAc), ventral striatum, amygdala, hippocampus, thalamus, and the whole brain.

4.1 Chronic pain

As one of the earlier clinical studies, Hameroff et al. (2013) [60] applied unfocused TUS to chronic pain patients, targeting the left or right posterior frontal cortex contralateral to the most severe pain or the non-dominant hemisphere in the case of non-lateralized pain. This intervention resulted in improved mood and pain, observed at least 40 min after TUS. Recently, about a decade later, Shin et al. (2023) [61] demonstrated that the tFUS to the dorsal ACC in chronic neuropathic pain patients reduced pain, and this effect was maintained over a period of 4 weeks. Although clinical trials on the acute/chronic pains are still scarce, there are a few preprint articles targeting the insula or dorsal ACC in the field (not included in this review). Pre-clinical studies using animal models have been actively conducted, and these can be found in previous review articles about ultrasound neuromodulation for the chronic or neuropathic pains [62].

4.2 Disorder of consciousness (DOC)

In 2016, Monti and a UCLA research team [63] reported a case study of tFUS stimulation applied to the right thalamus in a patient suffering from post-traumatic DOC 19 days post-injury. Remarkably, the patient exhibited recovery of motor function on day 1, reliable communication on day 3, and attempted walking on day 5 after the tFUS intervention. Cain et al. (2021a) [64], working with the same team, demonstrated that, within a week after tFUS to the left central thalamus, two out of three chronic patients with minimally conscious state (MCS), 15 and 32 months post-injury,

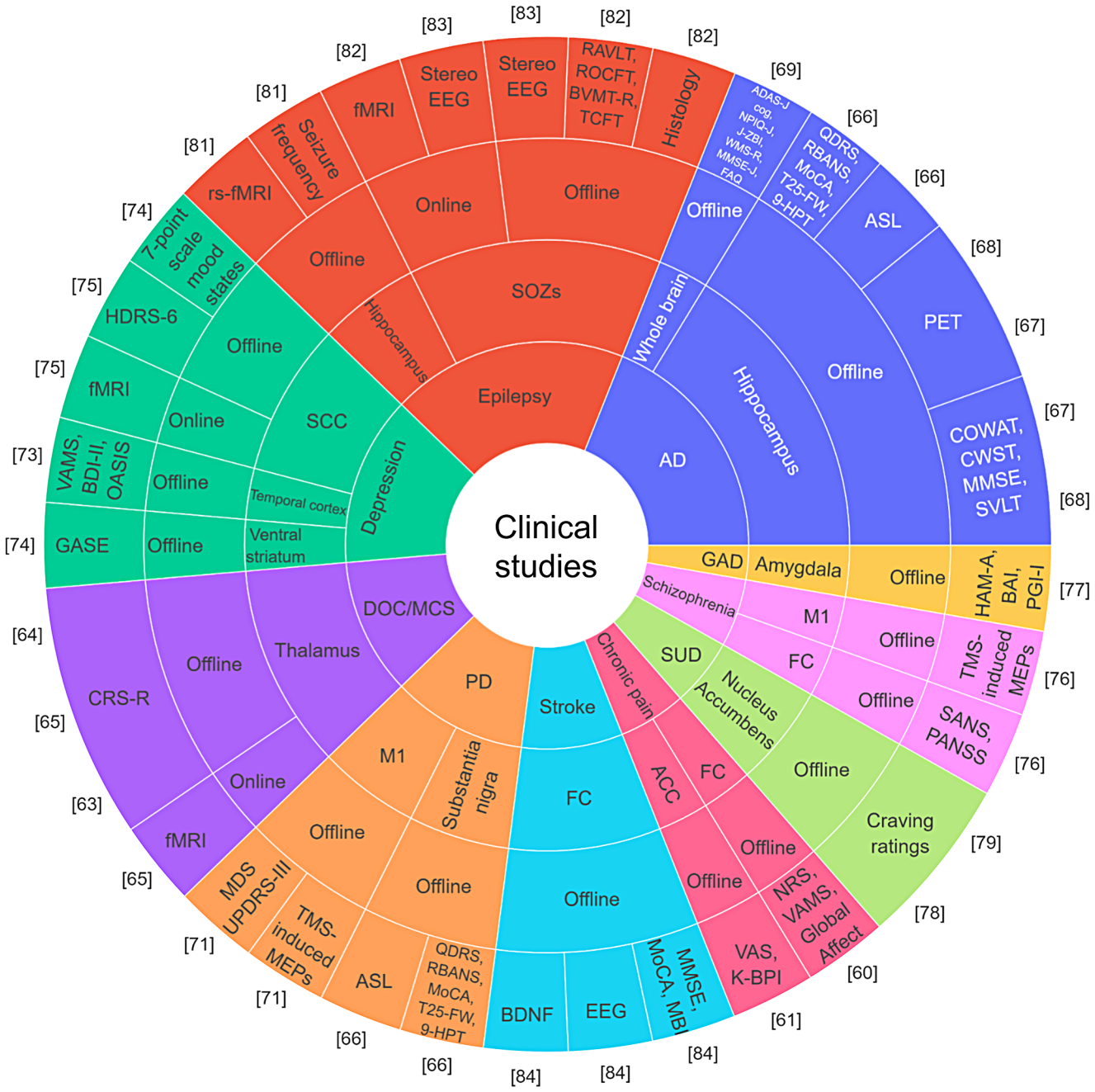

Fig. 4 Sunburst chart illustrating the outcome readouts (the outer rim) and sonication targets (the 2nd rim) in tFUS/TUS-mediated neuromodulation studies for CNS disease conditions (the inner rim). The outcome readouts were performed either online (during tFUS) or offline (after tFUS), as noted in the 3rd rim. See also the lower panel of Fig. 2; Table 3. Inner rim: AD, Alzheimer's disease; PD, Parkinson's disease; DRE, drug-resistant epilepsy; DOC, disorder of consciousness; MCS, minimally conscious state; GAD, generalized anxiety disorder; SUD, substance use disorder. 2nd rim: FC, frontal cortex; M1, primary motor cortex; ACC, anterior cingulate cortex; SCC, subcallosal cingulate cortex; SOZs, seizure onset zones. Outer rim: EEG, electroencephalography; TMS, transcranial magnetic stimulation; MEPs, motor evoked potentials; fMRI, functional magnetic resonance imaging; ASL, arterial spin labeling; rs-fMRI, resting-state fMRI; PET, positron emission tomography; BDNF, brain-derived neurotrophic factor. For the full names of abbreviations of cognitive tests/assessments, refer to the footnote of Table 3

exhibited clinically significant increases in behavioral responsiveness, while the third patient (66 months post-injury) did not show any benefits of tFUS. In another study (Cain et al. 2022) [65], tFUS applied to the left or right central thalamus in acute DOC patients (5 days–4 months post-injury) resulted in the recovery of behavioral responsiveness within a week for nine out of 11 subjects. The researchers observed a decrease in fMRI-BOLD signals in the frontal cortex and basal ganglia during the tFUS session. Additionally, a post-FUS correlation was found between the degree of recovery and altered connectivity of the sonicated thalamus.

4.3 Alzheimer's disease (AD) and Parkinson's disease

The efficacy of TUS/tFUS in neurodegenerative diseases such as AD and Parkinson's disease has been investigated. In a study by Nicodemus et al. (2019) [66], 1-h TUS was applied to the bilateral hippocampus in AD patients while sleep was induced using standard clinical techniques or pharmacologically (dexmedetomidine), weekly for 8 sessions. This intervention led to improvements in cognitive and motor functions, along with enhanced perfusion in the targeted region as revealed by ASL-MRI. Jeong and colleagues (2021, 2022) [67, 68] demonstrated that tFUS administration to the right hippocampus in AD patients enhanced cognitive functions and increased the regional cerebral metabolic rate of glucose (rCMRglu) in the right hippocampus, superior frontal gyrus, middle cingulate gyrus, and left fusiform gyrus, based on ^{18}F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET). In these studies, microbubble ultrasound contrast agents were intravenously injected, but the observed results occurred without the BBB opening. Shimokawa et al. (2022) [69] used a custom-built diffusion-type TUS device to deliver 1-h ultrasound, three times per week for six weeks, repeated every three months for 1.5 years, through the bilateral temporal bones for whole brain stimulation in early-stage AD patients. Based on clinical assessments at week 0, 24, 48, and 72 during the study period, the progression of cognitive impairments remained unchanged for at least 72 weeks, while those of the placebo group worsened progressively, although statistical differences were not observed due to small sample size. For more detailed reviews on the tFUS studies for AD, including animal research, other review articles are available [70].

Regarding Parkinson's disease, a study by Nicodemus et al. (2019) [66] applied 1-h TUS to the substantia nigra, using a similar protocol as described above for AD patients. This approach enhanced both motor and cognitive functions, along with increased perfusion at the substantia nigra. In another study, Samuel et al. (2023) [71] delivered 80-s tbTUS three times at 30-minute intervals, a technique named 'accelerated tbTUS' to provide multiple sessions in a single day, akin to 'accelerated rTMS.' This was applied to the bilateral M1 of Parkinson's disease patients, resulting in increased TMS-induced MEP amplitudes. However, this did not lead to an improvement of clinical motor outcomes. For more detailed reviews for Parkinson's disease, including pre-clinical studies on potential tFUS treatments, other review articles are available [72].

4.4 Psychiatric disorders

tFUS has been investigated as a potential adjunctive tool for the treatment of mental and psychiatric disorders, as demonstrated in recent neuromodulatory tFUS articles focusing on depression, schizophrenia, anxiety disorders, and substance use disorder (SUD). In a study involving depressed participants, Reznik et al. (2020) [73] applied tFUS to the right front-temporal cortex in five sessions within seven days, resulting in increased happiness during the course of the study and decreased worry after repeated tFUS sessions. Riis and colleagues (2023, 2024) [74, 75] demonstrated that suppressive tFUS applied to the subgenual cingulate cortex (SCC) in three patients with severe treatment-resistant depression (TRD) lowered depression and anxiety metrics in all cases, with the relief of symptoms maintained for at least 6 weeks. The tFUS stimulation resulted in decreased fMRI-BOLD signals at the target, supporting the suppressive effects on the SCC.

In a schizophrenia study by Zhai et al. (2023) [76], 15 sessions of excitatory tFUS administered to the left dorsolateral PFC (DLPFC) over three weeks alleviated negative symptoms, leading to improved cognitive performance in continuous performance tests. Investigating anxiety disorder, Mahdavi et al. (2023) [77] applied 10-min tFUS sessions weekly for eight weeks to the right amygdala in patients with treatment-refractory generalized anxiety disorder (GAD). This resulted in a significant decrease in anxiety, with subjective reporting indicating clinically significant benefits for 16 out of 25 subjects (64%) upon completion. Also, the potential use of neuromodulatory tFUS as a treatment for SUD patients was explored by Mahoney and colleagues (2023a,b) [78, 79]. tFUS delivered to the bilateral nucleus accumbens (NAc) led to mood enhancements in these patients and decreased cue-induced substance cravings for various substances immediately after tFUS, persisting for at least 90 days.

4.5 Drug-resistant epilepsy (DRE)

Concerning low-intensity tFUS neuromodulation for epilepsy treatments in humans, Brinker and colleagues (2020)

[80] delivered tFUS to the left hippocampus of a DRE patient for the first time, confirming its safety in humans. Recently, Bubrick (2024) [81] and the same research team reported a study in patients with drug-resistant mesial temporal lobe epilepsy (mTLE), where six neuromodulatory tFUS sessions over three weeks to the left or right hippocampus, with mTLE lateralization, exhibited a significant reduction in seizure frequency from five out of six participants. In another study by Stern et al. (2021) [82], tFUS was delivered with varying intensities to the left or right human anteromesial temporal lobe before resection for epilepsy treatments. Post-FUS neuropsychological tests did not show any changes, except a slightly decrease in performance on one of the tests. Histological analysis of the resected tissues following tFUS did not reveal any detectable tissue damages, corroborating the safety profile. Lee et al. (2022) [83] applied tFUS to the seizure onset zones (SOZs) localized with stereo-EEG (SEEG) implanted in DRE patients. SOZs were located in various regions, including the anterior/mesial/posterior temporal lobe (including amygdala and hippocampus), superior frontal gyrus, frontal operculum/anterior sulcus of the insula, and anterior cingulate gyrus. The SEEG revealed changes in the EEG spectral power at the sonicated SOZs during tFUS, without brain tissue damage as examined in post-FUS MRI. Seizure frequency decreased in two patients but increased in one patient, warranting further studies with a larger cohort and optimizations of sonication parameters.

4.6 Stroke

To date, only one publication has been found on TUS neuromodulation for stroke in humans. Wang et al. (2022) [84] applied 20-min unfocused TUS daily, five days weekly for six weeks to the forehead of stroke patients using five ultrasound probes, while the subjects received conventional cognitive rehabilitation training. Post-stroke cognitive impairments improved in the patient group that received TUS compared to the control group without TUS interventions, as assessed with higher scores in executive function, nomination, attention, language, and delayed recall. Additionally, there was an upregulated post-TUS level of brain-derived neurotrophic factor (BDNF), a biomarker associated with cognitive and memory recovery in post-stroke patients. Although clinical tFUS/TUS studies are still scarce, preclinical tFUS studies using animal models and perspective of tFUS studies for stroke rehabilitation in humans can be found in a recent review article by Yüksel et al. (2023) [85]. Furthermore, the interhemispheric inhibition (IHI) hypothesis is a concept of neurophysiological mechanism in which one hemisphere, when excited, inhibits the activity of the other, playing a role in the regulation of motor functions. The IHI hypothesis has been employed as an effective strategy in stroke treatments, utilizing NIBS such as repetitive TMS (rTMS) and transcranial direct current stimulation (tDCS) to normalize interhemispheric imbalances in stroke patients. In the case of tFUS, although not a study involving stroke patients, Ren et al. (2023) [25] (listed in Table 2) observed that the excitatory effects of tFUS stimulation on the unilateral M1 in humans were accompanied by decreased excitability in the contralateral M1, suggesting the potential of tFUS in clinical interventions such as a rebalancing modality of the interhemispheric imbalances in stroke.

5 Considerations for tFUS neuromodulations in humans

5.1 tFUS transducers with acoustic coupling

As tabulated in Table 4, several types of tFUS/TUS systems have been utilized in human studies to date, including single-element FUS transducers, multi-element/phased-array FUS transducers, or (modified/unfocused) diagnostic ultrasound devices. It is notable that the fundamental frequencies (FF) of the utilized FUS transducers were in the range of 200–800 kHz, while those of the diagnostic ultrasound devices were in the range of 1.75–8.0 MHz. As acoustic attenuation through the skull increases with higher ultrasound frequency, the level of transcranially transmitted acoustic energy can be much decreased when using diagnostic ultrasound devices. Additionally, the exquisite spatial resolution (in mm-scale) of stimulation may not be achieved with diagnostic TUS transducers. Therefore, the use of FUS transducers with lower FF (e.g., 200–650 kHz) should be considered for region-specific neuromodulation in the brain.

The acoustic coupling methods between the tFUS transducer and the scalp/skull play a crucial role in delivering ultrasound to the targeted regions in the brain. In conventional diagnostic/therapeutic ultrasound, generic ultrasound gel is applied to facilitate the transmission of sound waves. In the case of tFUS transducers, a liquid, such as degassed water or mineral oil in a separate container, or a compressible hydrogel, is often used as an acoustic coupling media in the gap between the transducer and the scalp/skull. Regarding hair as a potential barrier for ultrasound, in high-intensity FUS procedures, such as thermal ablation, shaving the patient's head on the treatment day is a current practice. However, negligible or minimal additional loss of acoustic energy at the focus was observed when FF below ~700 kHz was delivered through human hair/skull compared to the skull-only, likely due to the relatively large wavelength compared to the hair thickness. Therefore, shaving may not be necessary in low-intensity tFUS procedures with FF below ~700 kHz.

Table 4 List of tFUS/TUS transducers grouped by manufacturer, transducer type, and fundamental frequency (FF) used in the reviewed human studies, along with the targeting methods utilized

Manufacturer	Transducer type	FF	Human study	Targeting method
Custom-built	Single-element, focused	250 kHz	Lee W et al. 2015 [36]	Neuronavigation
		270 kHz	Lee W et al. 2016b [41]	MR-guided
		500 kHz	Legon W et al. 2018b [20]	TMS hotspot
			Ai L et al. 2018 [31]	MR-guided
			Zhang T et al. 2023 [29]	Neuronavigation
		548 kHz	Brinker ST et al. 2020 [80]	Neuronavigation
			Bubrick EJ et al. 2024 [81]	Neuronavigation
	Diffusion-type	500 kHz	Shimokawa H et al. 2022 [69]	A custom-built headset
	Multi-element, phased-array, focused	650 kHz	Riis TS et al. 2023 [75]	A MR-compatible custom-built system
			Riis T et al. 2024 [74]	
Blatek Industries Inc.	Single-element, focused	500 kHz	Legon W et al. 2014 [34]	EEG site CP3
			Mueller J et al. 2014 [35]	EEG site CP3
			Yu K et al. 2021 [32]	Neuronavigation
			Liu C et al. 2021 [39]	Neuronavigation
			Heimbuch IS et al. 2022 [30]	Neuronavigation
			Fine JM et al. 2023 [50]	Neuronavigation
BrainSonix Corp.	Single-element, focused (BXPulsar 1001 or 1002)	650 kHz	Monti MM et al. 2016 [63]	MR-guided
			Badran BW et al. 2020 [59]	MR-guided
			Schafer ME et al. 2021 [56]	MR-guided
			Cain JA et al. 2021a [64]	MR-guided
			Cain JA et al. 2021b [54]	MR-guided
			Stern JM et al. 2021 [82]	MR-guided
			Cain JA et al. 2022 [65]	MR-guided
			Kuhn T et al. 2023 [55]	MR-guided
			Mahdavi KD et al. 2023 [77]	Neuronavigation
Neurosona Co Ltd.	Single-element, focused (NS-US100)	250 kHz	Jeong H et al. 2021 [67]	Neuronavigation
			Jeong H et al. 2022 [68]	Neuronavigation
			Kim YG et al. 2022 [51]	Neuronavigation
			Shin DH et al. 2023 [61]	Neuronavigation
Olympus NDT Inc.	Single-element, focused (V391-SU)	500 kHz	Zhang Y et al. 2021 [24]	Not reported
			Zhai Z et al. 2023 [76]	Not reported
			Ren L et al. 2023 [25]	A localizer cap
Sonic Concepts Inc.	Single-element, focused (H-107)	500 kHz	Braun V et al. 2020 [44]	Neuronavigation
			Butler CR et al. 2022 [43]	Neuronavigation
	Two-element, annular array, focused (H115-2AA)	270 kHz	Johnstone A et al. 2021 [88]	Over the inion
			Nandi T et al. 2023 [45]	2 cm left from the inion
	Two-element, annular array, focused (H-246)	500 kHz	Fomenko A et al. 2020 [19]	Neuronavigation
			Xia X et al. 2021 [21]	TMS hotspot
			Zeng K et al. 2022 [26]	TMS hotspot
			Samuel N et al. 2022 [27]	TMS hotspot
			Samuel N et al. 2023 [71]	TMS hotspot
			Shamli Oghli Y et al. 2023 [33]	TMS hotspot
Thync Inc.	Single-element, focused (Neurotrek U+)	500 kHz	Sanguinetti JL et al. 2020 [46]	EEG site F8
			Reznik SJ et al. 2020 [73]	EEG site F8
			Forster A et al. 2023a [48]	EEG site F8
			Forster A et al. 2023b [47]	EEG site F8
			Ziebell P et al. 2023 [49]	EEG site F8
Ultran Group Inc.	Single-element, focused	200 kHz	Park TY et al. 2022 [52]	3D-printed helmet
		210 kHz	Lee W et al. 2016a [37]	Neuronavigation
			Lee W et al. 2017 [38]	Neuronavigation
		250 kHz	Kim H-C et al. 2023 [40]	Neuronavigation with acoustic simulation
		500 kHz	Legon W et al. 2018a [58]	Neuronavigation

Table 4 (continued)

Manufacturer	Transducer type	FF	Human study	Targeting method
Brainbox Ltd.	Four-element, annular array, focused (NeuroFUS CTX-500)	500 kHz	Yaakub SN et al. 2023 [53]	Neuronavigation
			Nakajima K et al. 2022 [22]	Neuronavigation
NaviFUS Corp.	Multi-element, phased array, focused (NaviFUS)	Not reported	Lee C-C et al. 2022 [83]	Neuronavigation
Insightec Ltd.	Multi-element, phased array, focused (ExAblate Neuro Type 2)	220 kHz	Mahoney JJ et al. 2023a [79]	MR-guided
			Mahoney JJ et al. 2023b [78]	MR-guided
Beijing Ruao Medical Technology Co Ltd.	An ultrasound transducer, unfocused (UE860A)	800 kHz	Zhang M-F et al. 2022 [28]	TMS hotspot around C3
Compumedics Germany GmbH	Transcranial Doppler device, unfocused (DWL Doppler-BoxX)	2.0 MHz	Nicodemus NE et al. 2019 [66]	MR-guided
Fujifilm Sonosite	L25×13 transducer, unfocused (with Sonosite M-Turbo system)	6.0 MHz	Schimek N et al. 2020 [42]	Neuronavigation and TMS hotspot
GE Healthcare	12 L-RS probe, unfocused (with LOGIQe ultrasound machine)	8.0 MHz	Hameroff S et al. 2013 [60]	At the scalp over the posterior frontal cortex
Philips	S5-1 broadband plane sector transducer array, unfocused (with CX50 diagnostic imaging system)	2.32 MHz	Gibson BC et al. 2018 [23]	Neuronavigation and TMS hotspot
Shengxiang Technology	An ultrasound transducer, unfocused (838B-M-C-II)	Not reported	Wang Y et al. 2022 [84]	Over the forehead
Siemens Healthcare	Acuson 4P1 phased array probe, unfocused (with S2000 system)	1.75 MHz	Guerra A et al. 2021 [57]	B-mode imaging

5.2 tFUS targeting methods

As summarized in Table 4, various methods have been used for tFUS/TUS targeting in human studies, including image-guided neuronavigation, MR-guided navigation, the use of custom-built headsets/helmets, or the transducer positioning based on TMS hotspots (for M1/V1), EEG sites, or regions of the scalp. Inaccurate tFUS targeting may stimulate brain regions away from the desired target areas, leading to confounding results or unintended neuromodulatory outcomes. Therefore, image-guided neuronavigation systems are recognized as one of the most preferred methods for precise tFUS targeting with real-time monitoring outside an MR suite [36, 37]. The neuronavigation system visualizes the geometric location of acoustic focus over the neuroimage of each individual subject in real-time, based on the relative position and orientation of a tFUS transducer to a subject's head location, tracked by an infrared camera and optical trackers. Along with neuronavigation, numerical acoustic simulations can be performed based on the computerized tomography (CT) scan data of each individual subject's head to predict or retrospectively analyze the in situ location, geometry, and pressure field of the acoustic focus in the brain after transcranial attenuations, refractions, or reflections. Recent technological advances even allow for semi-real/real-time acoustic simulation, previously challenging due to high computational load. Combining this with image-guided neuronavigation [40, 86] would further enhance the accuracy of tFUS targeting as well as stimulation safety in future studies. Additionally, when MR-guided navigation is employed for tFUS targeting, the location of in situ acoustic focus can be imaged using MR thermometry or MR acoustic radiation force imaging (ARFI) when the sonicated tissue temperature can be increased. For the MR localization of the non-thermal low-intensity tFUS acoustic focus in the human brain, further developments, such as advanced MR-ARFI without thermal change, would be needed.

5.3 tFUS sonication parameters and potential mechanisms

As arranged in Tables 2 and 3, various sets of sonication parameters have been used to examine the tFUS neuromodulatory efficacies in humans, many of which were based on earlier pre-clinical animal studies. Detailed reviews on the tFUS parameters are beyond the scope of this article and can be found in other review articles [15, 17]. Briefly,

depending on the choice of sonication parameters and pulsing schemes, the anticipated tFUS neuromodulatory outcomes can be either excitatory or suppressive, and the effects can be either transient (online effects) or long-lasting (offline effects) after the stimulation period (such as minutes or hours, possibly even days, after tFUS stimulation). As long-lasting effects of tFUS neuromodulation have been reported, potential accumulative effects, long-term plasticity, or the duration of a washout period should be considered in the study design, especially when multiple tFUS experimental blocks or sessions are planned.

Related to sonication parameters, although the underlying mechanisms of tFUS neuromodulation are yet to be fully elucidated, detailed information about potential mechanisms can be found in other review articles [15, 17]. To briefly outline, for tFUS neuromodulation studies using low-intensity pulsed ultrasound with negligible temperature increase, the thermal mechanism may be ruled out. Regarding non-thermal mechanical bioeffects of tFUS to trigger neuronal action potentials, a few potential mechanisms have been suggested, including (1) the induction of transmembrane capacitive currents via membrane displacements (flexoelectricity) either by conformational changes or by intramembrane cavitation, (2) the activation of mechanosensitive ion channels (piezoelectricity) in neurons and/or glial cells, (3) the creation of physical pores (sonoporation) in the lipid bilayer or the membrane permeability changes, and (4) the mechanical stimulation of elastic interface waves along the axonal/neuronal membrane, leading to the generation of coupled electrical potentials in neurons. It is important to consider that these mechanisms may operate in parallel and function differentially depending on the selection of tFUS parameters as well as on each subtype of neural/glial cells.

5.4 Auditory confounding effects

Since 2018, the potential of auditory confounding effects, which may be intertwined with direct/online tFUS neuromodulatory effects, have been reported in a few prior studies involving animal models [87] and humans [44, 88]. Future tFUS neuromodulation studies should incorporate appropriate control conditions to disentangle the tFUS-mediated indirect stimulation of the peripheral auditory pathway. To address these concerns in human studies, methods such as ramping of tFUS actuation signals [45, 88], auditory masking (e.g., using noise signals) [19, 43, 44] or the use of earplugs [20, 32] have been used, in addition to the inclusion of sham-/placebo-control groups.

5.5 Safety guidelines and adverse events

Regarding the safety of tFUS brain stimulation in humans, most studies have adhered to the guidelines set forth by the FDA and/or the International Electrotechnical Commission (IEC) 60601 part 2 standard, where $I_{SPPA} \leq 190$ W/cm^2, $I_{SPTA} \leq 720$ mW/cm^2 and MI ≤ 1.9 for diagnostic ultrasound (by the FDA) or $I_{SPTA} \leq 3$ W/cm^2 for therapeutic equipment (by IEC 60601 part 2) are recommended. In a few studies in Tables 2 and 3, however, I_{SPTA} or MI values exceeded the guidelines, but adverse effects from tFUS were either not reported or reported as absent. Potential temperature increases in the sonicated brain tissues at low intensities used in most of the reviewed studies (Tables 2 and 3) were far below 1 °C, as anticipated by using acoustic thermal simulation or numerical estimations. It is important to note that no safety guidelines are yet specifically established for the application of tFUS neuromodulation in humans, beyond those for diagnostic or therapeutic ultrasound. Currently, a collaborative team named the International Consortium for Transcranial Ultrasonic Stimulation Safety and Standards (ITRUSST, https://itrusst.com/) is working to establish expert consensus on the safety of tFUS neuromodulation techniques [18].

Regardless of the levels of $I_{SPPA,}$ I_{SPTA} or MI used, no 'serious adverse events (SAE)' were reported across all the reviewed studies. The occurrence of mild side effects such as headache, fatigue, or sleepiness in some tFUS studies, was transient and resolved shortly (e.g., within 24 h) after tFUS. Whether or not the mild/moderate adverse events were causally related to tFUS was not clear [15]. However, it is noteworthy that in a recent study on drug-resistant epilepsy (DRE) by Lee et al. (2022) [83], it was reported that "one patient developed transient naming and memory impairment that resolved within 3 weeks after FUS." No lesion or brain edema was found in post-FUS MRI, and the causes for the adverse event were not clear. Therefore, caution is still needed, especially when neuromodulatory tFUS is used in clinical studies including patients.

6 Conclusions

In this narrative review, we have summarized low-intensity tFUS/TUS brain stimulation studies reported during the past decade in healthy humans and subjects with CNS disease conditions. The field of tFUS neuromodulation is rapidly evolving as a new mode of NIBS methods, with exciting potential to become a practicable theranostic solution for neurological and neuropsychiatric diseases, as well as a tool for functional brain mapping with exquisite spatial resolution and deep tissue penetration. Its excellent safety

profile to date, coupled with reversible neuromodulation, would further expedite technological advancements of tFUS stimulation. However, more work is still warranted to fully examine the sonication parameter space for robust bimodal (i.e., excitatory or suppressive) stimulation, with careful monitoring of safety and long-lasting effects that may affect neuroplasticity. When examining the online effects of tFUS neuromodulation, appropriate methods should be considered to mitigate the potential auditory confounding effects during sonication. Further development of methods is also needed for precise tFUS targeting to the intended brain regions, with a feedback system (e.g., based on certain imaging/monitoring) to assess the targeting accuracy in real-time. As no official guideline is set yet for the safe application of ultrasonic neuromodulation in humans, the establishment of good standard practices for tFUS neuromodulation, such as the ITRUSST consortium (https://itrusst.com/) [18], is needed, as has been done for TMS and tES. It is also recommended in future tFUS studies that reporting of sonication parameters should include, at a minimum, FF, P_r, I_{SPPA}, SD, ISI, PD and PRF, along with information on relevant timescales (e.g., length of tFUS/resting blocks or the number of tFUS blocks/session). Although the exact mechanisms behind the tFUS neuromodulation are yet to be ascertained, tFUS is becoming a promising tool for clinical studies and neuroscientific investigations, even with the current knowledge and understanding.

Acknowledgements This work was supported by Brain Pool program funded by the Ministry of Science and ICT through the National Research Foundation of Korea (RS-2023-00221187).

Declarations

Competing interests The authors have declared that no competing interest exists.

References

1. George MS, Aston-Jones G. Noninvasive techniques for probing neurocircuitry and treating illness: Vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Neuropsychopharmacology. 2010;35(1):301–16. https://doi.org/10.1038/npp.2009.87.
2. Hoy KE, Fitzgerald PB. Brain stimulation in psychiatry and its effects on cognition. Nat Rev Neurol. 2010;6(5):267–75. https://doi.org/10.1038/nrneurol.2010.30.
3. Jolesz FA, Hynynen K, McDannold N, Tempany C. MR imaging-controlled focused ultrasound ablation: a noninvasive image-guided surgery. Magn Reson Imaging Clin N Am. 2005;13(3):545–60. https://doi.org/10.1016/j.mric.2005.04.008.
4. White PJ, Clement GT, Hynynen K. Longitudinal and shear mode ultrasound propagation in human skull bone. Ultrasound Med Biol. 2006;32(7):1085–96. https://doi.org/10.1016/j.ultrasmedbio.2006.03.015.
5. Elias WJ, Huss D, Voss T, Loomba J, Khaled M, Zadicario E, Frysinger RC, Sperling SA, Wylie S, Monteith SJ, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. N Engl J Med. 2013;369(7):640–8. https://doi.org/10.1056/NEJMoa1300962.
6. Cammalleri A, Croce P, Lee W, Yoon K, Yoo S-S. Therapeutic potentials of localized blood-brain barrier disruption by non-invasive transcranial focused ultrasound: a technical review. J Clin Neurophysiol. 2020;37(2):104–17. https://doi.org/10.1097/WNP.0000000000000488.
7. Tyler WJ, Tufail Y, Finsterwald M, Tauchmann ML, Olson EJ, Majestic C. Remote excitation of neuronal circuits using low-intensity, low-frequency ultrasound. PLoS ONE. 2008;3(10):e3511. https://doi.org/10.1371/journal.pone.0003511.
8. Kim H, Chiu A, Lee SD, Fischer K, Yoo S-S. Focused ultrasound-mediated non-invasive brain stimulation: examination of sonication parameters. Brain Stimul. 2014;7(5):748–56. https://doi.org/10.1016/j.brs.2014.06.011.
9. Lee W, Croce P, Margolin RW, Cammalleri A, Yoon K, Yoo S-S. Transcranial focused ultrasound stimulation of motor cortical areas in freely-moving awake rats. BMC Neurosci. 2018;19:57. https://doi.org/10.1186/s12868-018-0459-3.
10. Jo Y, Lee S-M, Jung T, Park G, Lee C, Im GH, Lee S, Park JS, Oh C, Kook G, et al. General-purpose ultrasound neuromodulation system for chronic, closed-loop preclinical studies in freely behaving rodents. Adv Sci (Weinh). 2022;9(34):e2202345. https://doi.org/10.1002/advs.202202345.
11. Kim H, Kim S, Sim NS, Pasquinelli C, Thielscher A, Lee JH, Lee HJ. Miniature ultrasound ring array transducers for transcranial ultrasound neuromodulation of freely-moving small animals. Brain Stimul. 2019;12(2):251–5. https://doi.org/10.1016/j.brs.2018.11.007.
12. Lee W, Lee SD, Park MY, Foley L, Purcell-Estabrook E, Kim H, Fischer K, Maeng L-S, Yoo S-S. Image-guided focused ultrasound-mediated regional brain stimulation in sheep. Ultrasound Med Biol. 2016c;42(2):459–70. https://doi.org/10.1016/j.ultrasmedbio.2015.10.001.
13. Gaur P, Casey KM, Kubanek J, Li N, Mohammadjavadi M, Saenz Y, Glover GH, Bouley DM, Pauly KB. Histologic safety of transcranial focused ultrasound neuromodulation and magnetic resonance acoustic radiation force imaging in rhesus macaques and sheep. Brain Stimul. 2020;13(3):804–14. https://doi.org/10.1016/j.brs.2020.02.017.
14. Kubanek J, Brown J, Ye P, Pauly KB, Moore T, Newsome W. Remote, brain region-specific control of choice behavior with ultrasonic waves. Sci Adv. 2020;6(21):eaaz4193. https://doi.org/10.1126/sciadv.aaz4193.
15. Darmani G, Bergmann TO, Butts Pauly K, Caskey CF, de Lecea L, Fomenko A, Fouragnan E, Legon W, Murphy KR, Nandi T, et al. Non-invasive transcranial ultrasound stimulation for neuromodulation. Clin Neurophysiol. 2022;135:51–73. https://doi.org/10.1016/j.clinph.2021.12.010.
16. Beisteiner R, Matt E, Fan C, Baldysiak H, Schönfeld M, Philippi Novak T, Amini A, Aslan T, Reinecke R, Lehrner J, et al. Transcranial pulse stimulation with ultrasound in Alzheimer's disease—A new navigated focal brain therapy. Adv Sci (Weinh). 2020;7(3):1902583. https://doi.org/10.1002/advs.201902583.
17. Blackmore J, Shrivastava S, Sallet J, Butler CR, Cleveland RO. Ultrasound neuromodulation: a review of results, mechanisms and safety. Ultrasound Med Biol. 2019;45(7):1509–36. https://doi.org/10.1016/j.ultrasmedbio.2018.12.015.
18. Aubry J-F, Attali D, Schafer M, Fouragnan E, Caskey C, Chen R, et al. ITRUSST consensus on biophysical safety for transcranial ultrasonic stimulation. arXiv. 2023;arXiv:2311.05359v1 [physics.bio-ph]. https://doi.org/10.48550/arXiv.2311.05359.

19. Fomenko A, Chen K-HS, Nankoo J-F, Saravanamuttu J, Wang Y, El-Baba M, Xia X, Seerala SS, Hynynen K, Lozano AM, Chen R. Systematic examination of low-intensity ultrasound parameters on human motor cortex excitability and behavior. eLife. 2020;9:e54497. https://doi.org/10.7554/eLife.54497.
20. Legon W, Bansal P, Tyshynsky R, Ai L, Mueller JK. Transcranial focused ultrasound neuromodulation of the human primary motor cortex. Sci Rep. 2018b;8(1):10007. https://doi.org/10.1038/s41598-018-28320-1.
21. Xia X, Fomenko A, Nankoo J-F, Zeng K, Wang Y, Zhang J, Lozano AM, Chen R. Time course of the effects of low-intensity transcranial ultrasound on the excitability of ipsilateral and contralateral human primary motor cortex. NeuroImage. 2021;243:118557. https://doi.org/10.1016/j.neuroimage.2021.118557.
22. Nakajima K, Osada T, Ogawa A, Tanaka M, Oka S, Kamagata K, Aoki S, Oshima Y, Tanaka S, Konishi S. A causal role of anterior prefrontal-putamen circuit for response inhibition revealed by transcranial ultrasound stimulation in humans. Cell Rep. 2022;40(7):111197. https://doi.org/10.1016/j.celrep.2022.111197.
23. Gibson BC, Sanguinetti JL, Badran BW, Yu AB, Klein EP, Abbott CC, Hansberger JT, Clark VP. Increased excitability induced in the primary motor cortex by transcranial ultrasound stimulation. Front Neurol. 2018;9:1007. https://doi.org/10.3389/fneur.2018.01007.
24. Zhang Y, Ren L, Liu K, Tong S, Yuan T-F, Sun J. Transcranial ultrasound stimulation of the human motor cortex. iScience. 2021;24(12):103429. https://doi.org/10.1016/j.isci.2021.103429.
25. Ren L, Zhai Z, Xiang Q, Zhuo K, Zhang S, Zhang Y, Jiao X, Tong S, Liu D, Sun J. Transcranial ultrasound stimulation modulates the interhemispheric balance of excitability in human motor cortex. J Neural Eng. 2023;20(1):016043. https://doi.org/10.1088/1741-2552/acb50d.
26. Zeng K, Darmani G, Fomenko A, Xia X, Tran S, Nankoo J-F, Shamli Oghli Y, Wang Y, Lozano AM, Chen R. Induction of human motor cortex plasticity by theta burst transcranial ultrasound stimulation. Ann Neurol. 2022;91(2):238–52. https://doi.org/10.1002/ana.26294.
27. Samuel N, Zeng K, Harmsen IE, Ding MYR, Darmani G, Sarica C, Santyr B, Vetkas A, Pancholi A, Fomenko A, et al. Multi-modal investigation of transcranial ultrasound-induced neuroplasticity of the human motor cortex. Brain Stimul. 2022;15(6):1337–47. https://doi.org/10.1016/j.brs.2022.10.001.
28. Zhang M-F, Chen W-Z, Huang F-B, Peng Z-Y, Quan Y-C, Tang Z-M. Low-intensity transcranial ultrasound stimulation facilitates hand motor function and cortical excitability: a crossover, randomized, double blind study. Front Neurol. 2022;13:926027. https://doi.org/10.3389/fneur.2022.926027.
29. Zhang T, Guo B, Zuo Z, Long X, Hu S, Li S, Su X, Wang Y, Liu C. Excitatory-inhibitory modulation of transcranial focus ultrasound stimulation on human motor cortex. CNS Neurosci Ther. 2023;29(12):3829–41. https://doi.org/10.1111/cns.14303.
30. Heimbuch IS, Fan TK, Wu AD, Faas GC, Charles AC, Iacoboni M. Ultrasound stimulation of the motor cortex during tonic muscle contraction. PLoS ONE. 2022;17(4):e0267268. https://doi.org/10.1371/journal.pone.0267268.
31. Ai L, Bansal P, Mueller JK, Legon W. Effects of transcranial focused ultrasound on human primary motor cortex using 7T fMRI: a pilot study. BMC Neurosci. 2018;19(1):56. https://doi.org/10.1186/s12868-018-0456-6.
32. Yu K, Liu C, Niu X, He B. Transcranial focused ultrasound neuromodulation of voluntary movement-related cortical activity in humans. IEEE Trans Biomed Eng. 2021;68(6):1923–31. https://doi.org/10.1109/TBME.2020.3030892.
33. Shamli Oghli Y, Grippe T, Arora T, Hoque T, Darmani G, Chen R. Mechanisms of theta burst transcranial ultrasound induced plasticity in the human motor cortex. Brain Stimul. 2023;16(4):1135–43. https://doi.org/10.1016/j.brs.2023.07.056.
34. Legon W, Sato TF, Opitz A, Mueller J, Barbour A, Williams A, Tyler WJ. Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. Nat Neurosci. 2014;17(2):322–9. https://doi.org/10.1038/nn.3620.
35. Mueller J, Legon W, Opitz A, Sato TF, Tyler WJ. Transcranial focused ultrasound modulates intrinsic and evoked EEG dynamics. Brain Stimul. 2014;7(6):900–8. https://doi.org/10.1016/j.brs.2014.08.008.
36. Lee W, Kim H, Jung Y, Song I-U, Chung YA, Yoo S-S. Image-guided transcranial focused ultrasound stimulates human primary somatosensory cortex. Sci Rep. 2015;5:8743. https://doi.org/10.1038/srep08743.
37. Lee W, Chung YA, Jung Y, Song I-U, Yoo S-S. Simultaneous acoustic stimulation of human primary and secondary somatosensory cortices using transcranial focused ultrasound. BMC Neurosci. 2016a;17:68. https://doi.org/10.1186/s12868-016-0303-6.
38. Lee W, Kim S, Kim B, Lee C, Chung YA, Kim L, Yoo S-S. Non-invasive transmission of sensorimotor information in humans using an EEG/focused ultrasound brain-to-brain interface. PLoS ONE. 2017;12(6):e0178476. https://doi.org/10.1371/journal.pone.0178476.
39. Liu C, Yu K, Niu X, He B. Transcranial focused ultrasound enhances sensory discrimination capability through somatosensory cortical excitation. Ultrasound Med Biol. 2021;47(5):1356–66. https://doi.org/10.1016/j.ultrasmedbio.2021.01.025.
40. Kim H-C, Lee W, Weisholtz DS, Yoo S-S. Transcranial focused ultrasound stimulation of cortical and thalamic somatosensory areas in human. PLoS ONE. 2023;18(7):e0288654. https://doi.org/10.1371/journal.pone.0288654.
41. Lee W, Kim H-C, Jung Y, Chung YA, Song I-U, Lee J-H, Yoo S-S. Transcranial focused ultrasound stimulation of human primary visual cortex. Sci Rep. 2016b;6:34026. https://doi.org/10.1038/srep34026.
42. Schimek N, Burke-Conte Z, Abernethy J, Schimek M, Burke-Conte C, Bobola M, Stocco A, Mourad PD. Repeated application of transcranial diagnostic ultrasound towards the visual cortex induced illusory visual percepts in healthy participants. Front Hum Neurosci. 2020;14:66. https://doi.org/10.3389/fnhum.2020.00066.
43. Butler CR, Rhodes E, Blackmore J, Cheng X, Peach RL, Veldsman M, Sheerin F, Cleveland RO. Transcranial ultrasound stimulation to human middle temporal complex improves visual motion detection and modulates electrophysiological responses. Brain Stimul. 2022;15(5):1236–45. https://doi.org/10.1016/j.brs.2022.08.022.
44. Braun V, Blackmore J, Cleveland RO, Butler CR. Transcranial ultrasound stimulation in humans is associated with an auditory confound that can be effectively masked. Brain Stimul. 2020;13(6):1527–34. https://doi.org/10.1016/j.brs.2020.08.014.
45. Nandi T, Johnstone A, Martin E, Zich C, Cooper R, Bestmann S, Bergmann TO, Treeby B, Stagg CJ. Ramped V1 transcranial ultrasonic stimulation modulates but does not evoke visual evoked potentials. Brain Stimul. 2023;16(2):553–5. https://doi.org/10.1016/j.brs.2023.02.004.
46. Sanguinetti JL, Hameroff S, Smith EE, Sato T, Daft CMW, Tyler WJ, Allen JJB. Transcranial focused ultrasound to the right prefrontal cortex improves mood and alters functional connectivity in humans. Front Hum Neurosci. 2020;14:52. https://doi.org/10.3389/fnhum.2020.00052.
47. Forster A, Rodrigues J, Ziebell P, Sanguinetti JL, Allen JJ, Hewig J. Investigating the role of the right inferior frontal gyrus in control perception: a double-blind cross-over study using ultrasonic neuromodulation. Neuropsychologia. 2023b;187:108589. https://doi.org/10.1016/j.neuropsychologia.2023.108589.

48. Forster A, Rodrigues J, Ziebell P, Sanguinetti JL, Allen JJB, Hewig J. Transcranial focused ultrasound modulates the emergence of learned helplessness via midline theta modification. J Affect Disord. 2023a;329:273–84. https://doi.org/10.1016/j.jad.2023.02.032.
49. Ziebell P, Rodrigues J, Forster A, Sanguinetti JL, Allen JJ, Hewig J. Inhibition of midfrontal theta with transcranial ultrasound explains greater approach versus withdrawal behavior in humans. Brain Stimul. 2023;16(5):1278–88. https://doi.org/10.1016/j.brs.2023.08.011.
50. Fine JM, Mysore AS, Fini ME, Tyler WJ, Santello M. Transcranial focused ultrasound to human rIFG improves response inhibition through modulation of the P300 onset latency. eLife. 2023;12:e86190. https://doi.org/10.7554/eLife.86190.
51. Kim YG, Kim SE, Lee J, Hwang S, Yoo S-S, Lee HW. Neuromodulation using transcranial focused ultrasound on the bilateral medial prefrontal cortex. J Clin Med. 2022;11(13):3809. https://doi.org/10.3390/jcm11133809.
52. Park TY, Jeong JH, Chung YA, Yeo SH, Kim H. Application of subject-specific helmets for the study of human visuomotor behavior using transcranial focused ultrasound: a pilot study. Comput Methods Programs Biomed. 2022;226:107127. https://doi.org/10.1016/j.cmpb.2022.107127.
53. Yaakub SN, White TA, Roberts J, Martin E, Verhagen L, Stagg CJ, Hall S, Fouragnan EF. Transcranial focused ultrasound-mediated neurochemical and functional connectivity changes in deep cortical regions in humans. Nat Commun. 2023;14(1):5318. https://doi.org/10.1038/s41467-023-40998-0.
54. Cain JA, Visagan S, Johnson MA, Crone J, Blades R, Spivak NM, Shattuck DW, Monti MM. Real time and delayed effects of subcortical low intensity focused ultrasound. Sci Rep. 2021b;11(1):6100. https://doi.org/10.1038/s41598-021-85504-y.
55. Kuhn T, Spivak NM, Dang BH, Becerra S, Halavi SE, Rotstein N, Rosenberg BM, Hiller S, Swenson A, Cvijanovic L, et al. Transcranial focused ultrasound selectively increases perfusion and modulates functional connectivity of deep brain regions in humans. Front Neural Circuits. 2023;17:1120410. https://doi.org/10.3389/fncir.2023.1120410.
56. Schafer ME, Spivak NM, Korb AS, Bystritsky A. Design, development, and operation of a low-intensity focused ultrasound pulsation (LIFUP) system for clinical use. IEEE Trans Ultrason Ferroelectr Freq Control. 2021;68(1):54–64. https://doi.org/10.1109/TUFFC.2020.3006781.
57. Guerra A, Vicenzini E, Cioffi E, Colella D, Cannavacciuolo A, Pozzi S, Caccia B, Paparella G, Di Stefano G, Berardelli A, Bologna M. Effects of transcranial ultrasound stimulation on trigeminal blink reflex excitability. Brain Sci. 2021;11(5):645. https://doi.org/10.3390/brainsci11050645.
58. Legon W, Ai L, Bansal P, Mueller JK. Neuromodulation with single-element transcranial focused ultrasound in human thalamus. Hum Brain Mapp. 2018a;39(5):1995–2006. https://doi.org/10.1002/hbm.23981.
59. Badran BW, Caulfield KA, Stomberg-Firestein S, Summers PM, Dowdle LT, Savoca M, Li X, Austelle CW, Short EB, Borckardt JJ, et al. Sonication of the anterior thalamus with MRI-guided transcranial focused ultrasound (tFUS) alters pain thresholds in healthy adults: a double-blind, sham-controlled study. Brain Stimul. 2020;13(6):1805–12. https://doi.org/10.1016/j.brs.2020.10.007.
60. Hameroff S, Trakas M, Duffield C, Annabi E, Gerace MB, Boyle P, Lucas A, Amos Q, Buadu A, Badal JJ. Transcranial ultrasound (TUS) effects on mental states: a pilot study. Brain Stimul. 2013;6(3):409–15. https://doi.org/10.1016/j.brs.2012.05.002.
61. Shin DH, Son S, Kim EY. Low-energy transcranial navigation-guided focused ultrasound for neuropathic pain: an exploratory study. Brain Sci. 2023;13(10):1433. https://doi.org/10.3390/brainsci13101433.
62. Yu K, Niu X, He B. Neuromodulation management of chronic neuropathic pain in the central nervous system. Adv Funct Mater. 2020;30(37):1908999. https://doi.org/10.1002/adfm.201908999.
63. Monti MM, Schnakers C, Korb AS, Bystritsky A, Vespa PM. Non-invasive ultrasonic thalamic stimulation in disorders of consciousness after severe brain injury: a first-in-man report. Brain Stimul. 2016;9(6):940–1. https://doi.org/10.1016/j.brs.2016.07.008.
64. Cain JA, Spivak NM, Coetzee JP, Crone JS, Johnson MA, Lutkenhoff ES, Real C, Buitrago-Blanco M, Vespa PM, Schnakers C, Monti MM. Ultrasonic thalamic stimulation in chronic disorders of consciousness. Brain Stimul. 2021a;14(2):301–3. https://doi.org/10.1016/j.brs.2021.01.008.
65. Cain JA, Spivak NM, Coetzee JP, Crone JS, Johnson MA, Lutkenhoff ES, Real C, Buitrago-Blanco M, Vespa PM, Schnakers C, Monti MM. Ultrasonic deep brain neuromodulation in acute disorders of consciousness: a proof-of-concept. Brain Sci. 2022;12(4):428. https://doi.org/10.3390/brainsci12040428.
66. Nicodemus NE, Becerra S, Kuhn TP, Packham HR, Duncan J, Mahdavi K, Iovine J, Kesari S, Pereles S, Whitney M, et al. Focused transcranial ultrasound for treatment of neurodegenerative dementia. Alzheimers Dement (N Y). 2019;5:374–81. https://doi.org/10.1016/j.trci.2019.06.007.
67. Jeong H, Im JJ, Park J-S, Na S-H, Lee W, Yoo S-S, Song I-U, Chung Y-A. A pilot clinical study of low-intensity transcranial focused ultrasound in Alzheimer's disease. Ultrasonography. 2021;40(4):512–9. https://doi.org/10.14366/usg.20138.
68. Jeong H, Song I-U, Chung Y-A, Park J-S, Na S-H, Im JJ, Bikson M, Lee W, Yoo S-S. Short-term efficacy of transcranial focused ultrasound to the hippocampus in Alzheimer's disease: a preliminary study. J Pers Med. 2022;12(2):250. https://doi.org/10.3390/jpm12020250.
69. Shimokawa H, Shindo T, Ishiki A, Tomita N, Ichijyo S, Watanabe T, Nakata T, Eguchi K, Kikuchi Y, Shiroto T, et al. A pilot study of whole-brain low-intensity pulsed ultrasound therapy for early stage of Alzheimer's disease (LIPUS-AD): a randomized, double-blind, placebo-controlled trial. Tohoku J Exp Med. 2022;258(3):167–75. https://doi.org/10.1620/tjem.2022.J078.
70. Kovalenko EA, Makhnovich EV, Osinovskaya NA, Bogolepova AN. The therapeutic potential of focused ultrasound in patients with Alzheimer's disease. Neurosci Behav Physi. 2023;53(5):793–800. https://doi.org/10.1007/s11055-023-01471-z.
71. Samuel N, Ding MYR, Sarica C, Darmani G, Harmsen IE, Grippe T, Chen X, Yang A, Nasrkhani N, Zeng K, et al. Accelerated transcranial ultrasound neuromodulation in Parkinson's disease: a pilot study. Mov Disord. 2023;38(12):2209–16. https://doi.org/10.1002/mds.29622.
72. Zhong Y-X, Liao J-C, Liu X, Tian H, Deng L-R, Long L. Low intensity focused ultrasound: a new prospect for the treatment of Parkinson's disease. Ann Med. 2023;55(2):2251145. https://doi.org/10.1080/07853890.2023.2251145.
73. Reznik SJ, Sanguinetti JL, Tyler WJ, Daft C, Allen JJB. A double-blind pilot study of transcranial ultrasound (TUS) as a five-day intervention: TUS mitigates worry among depressed participants. Neurol Psychiatry Brain Res. 2020;37:60–6. https://doi.org/10.1016/j.npbr.2020.06.004.
74. Riis T, Feldman D, Losser A, Mickey B, Kubanek J. Device for multifocal delivery of ultrasound into deep brain regions in humans. IEEE Trans Biomed Eng. 2024;71(2):660–8. https://doi.org/10.1109/TBME.2023.3313987.
75. Riis TS, Feldman DA, Vonesh LC, Brown JR, Solzbacher D, Kubanek J, Mickey BJ. Durable effects of deep brain ultrasonic neuromodulation on major depression: a case report.

J Med Case Rep. 2023;17(1):449. https://doi.org/10.1186/s13256-023-04194-4.
76. Zhai Z, Ren L, Song Z, Xiang Q, Zhuo K, Zhang S, Li X, Zhang Y, Jiao X, Tong S, et al. The efficacy of low-intensity transcranial ultrasound stimulation on negative symptoms in schizophrenia: a double-blind, randomized sham-controlled study. Brain Stimul. 2023;16(3):790–2. https://doi.org/10.1016/j.brs.2023.04.021.
77. Mahdavi KD, Jordan SE, Jordan KG, Rindner ES, Haroon JM, Habelhah B, Becerra SA, Surya JR, Venkatraman V, Zielinski MA, et al. A pilot study of low-intensity focused ultrasound for treatment-resistant generalized anxiety disorder. J Psychiatr Res. 2023;168:125–32. https://doi.org/10.1016/j.jpsychires.2023.10.039.
78. Mahoney JJ, Haut MW, Carpenter J, Ranjan M, Thompson-Lake DGY, Marton JL, Zheng W, Berry JH, Tirumalai P, Mears A, et al. Low-intensity focused ultrasound targeting the nucleus accumbens as a potential treatment for substance use disorder: safety and feasibility clinical trial. Front Psychiatry. 2023b;14:1211566. https://doi.org/10.3389/fpsyt.2023.1211566.
79. Mahoney JJ, Thompson-Lake DGY, Ranjan M, Marton JL, Carpenter JS, Zheng W, Berry JH, Farmer DL, D'Haese P, Finomore VS, et al. Low-intensity focused ultrasound targeting the bilateral nucleus accumbens as a potential treatment for substance use disorder: a first-in-human report. Biol Psychiatry. 2023a;94(11):E41–3. https://doi.org/10.1016/j.biopsych.2023.06.031.
80. Brinker ST, Preiswerk F, White PJ, Mariano TY, McDannold NJ, Bubrick EJ. Focused ultrasound platform for investigating therapeutic neuromodulation across the human hippocampus. Ultrasound Med Biol. 2020;46(5):1270–4. https://doi.org/10.1016/j.ultrasmedbio.2020.01.007.
81. Bubrick EJ, McDannold NJ, Orozco J, Mariano TY, Rigolo L, Golby AJ, Tie Y, White PJ. Transcranial ultrasound neuromodulation for epilepsy: a pilot safety trial. Brain Stimul. 2024;17(1):7–9. https://doi.org/10.1016/j.brs.2023.11.013.
82. Stern JM, Spivak NM, Becerra SA, Kuhn TP, Korb AS, Kronemyer D, Khanlou N, Reyes SD, Monti MM, Schnakers C, et al. Safety of focused ultrasound neuromodulation in humans with temporal lobe epilepsy. Brain Stimul. 2021;14(4):1022–31. https://doi.org/10.1016/j.brs.2021.06.003.
83. Lee C-C, Chou C-C, Hsiao F-J, Chen Y-H, Lin C-F, Chen C-J, Peng S-J, Liu H-L, Yu H-Y. Pilot study of focused ultrasound for drug-resistant epilepsy. Epilepsia. 2022;63(1):162–75. https://doi.org/10.1111/epi.17105.
84. Wang Y, Li F, He M-J, Chen S-J. The effects and mechanisms of transcranial ultrasound stimulation combined with cognitive rehabilitation on post-stroke cognitive impairment. Neurol Sci. 2022;43(7):4315–21. https://doi.org/10.1007/s10072-022-05906-2.
85. Yüksel MM, Sun S, Latchoumane C, Boch J, Courtine G, Raffin EE, Hummel FC. Low-intensity focused ultrasound neuromodulation for stroke recovery: a novel deep brain stimulation approach for neurorehabilitation? IEEE Open J Eng Med Biol. 2023;4:300–18. https://doi.org/10.1109/OJEMB.2023.3263690.
86. Park TY, Koh H, Lee W, Park SH, Chang WS, Kim H. Real-time acoustic simulation framework for tFUS: a feasibility study using navigation system. NeuroImage. 2023;282:120411. https://doi.org/10.1016/j.neuroimage.2023.120411.
87. Sato T, Shapiro MG, Tsao DY. Ultrasonic neuromodulation causes widespread cortical activation via an indirect auditory mechanism. Neuron. 2018;98(5):1031–1041. https://doi.org/10.1016/j.neuron.2018.05.009.
88. Johnstone A, Nandi T, Martin E, Bestmann S, Stagg C, Treeby B. A range of pulses commonly used for human transcranial ultrasound stimulation are clearly audible. Brain Stimul. 2021;14(5):1353–5. https://doi.org/10.1016/j.brs.2021.08.015.