Ultrasound Applications in the Treatment of Major Depressive Disorder (MDD): A Systematic Review of Techniques and Efficacy

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Abstract

Objective

Major depressive disorder (MDD) is a debilitating mental health condition characterized by persistent feelings of sadness, loss of interest, and impaired daily functioning. It affects approximately 8% of the U.S. population, posing a significant personal and economic burden. Around 30% of patients with MDD do not respond to conventional antidepressant and psychotherapeutic treatments. Current treatment options for refractory MDD include transcranial magnetic stimulation (TMS) and invasive surgical procedures such as surgical ablation, vagus nerve stimulation, and deep brain stimulation. TMS has modest efficacy, and surgical procedures are associated with surgical risk and low patient acceptance. With the unique advantage of combining non-invasiveness with selective targeting, therapeutic ultrasound emerges as a promising alternative for treating refractory MDD. Over the past 10 years, there has been a growth in focused ultrasound research, leading to an exponential increase in academic and public interest in the technology. To support the continued development of ultrasound for treating MDD, we conducted a systematic review following Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.

Methods

We included peer-reviewed prospective cohort studies, case-control studies, and randomized control trials that evaluate the efficacy of ultrasonic treatment for depression (PROSPERO registration number: CRD42024626093). We summarized ultrasonic techniques for treating depression and their efficacy. Furthermore, we identified key challenges and future directions for applying ultrasound in treating MDD.

Results

We identified 67 potentially relevant articles, of which 18 studies met all inclusion criteria. The techniques of applying ultrasound to treat depression include magnetic resonance-guided focused ultrasound (MRgFUS) for capsulotomy and low-intensity focused ultrasound (LIFUS) neuromodulation. In human trials, the response rate ($\geqslant$50% improvement from baseline on depression score) is 53.85% for MRgFUS and 80.49% for LIFUS neuromodulation. In all preclinical studies using rodent models (8 studies), LIFUS neuromodulation had a medium to large effect (|Cohen's d| > 0.6) on resolving depressive-like behavior in rodents without causing adverse effects such as tissue damage. MRgFUS faces inconsistent lesioning success and a limited response rate, while LIFUS neuromodulation lacks systematic exploration of parameter space and a clear understanding of its mechanistic effects. Future work should refine patient selection for MRgFUS and focus on individualized functional targeting.

Conclusion

LIFUS neuromodulation showed a medium to large effect in reducing depressive behaviors in both rodent models and human trials, representing a promising, noninvasive option for treating refractory MDD.

Introduction

Major depressive disorder (MDD) is a severe form of mood disorder characterized by prolonged sadness, fatigue, cognitive impairments, and, in severe cases, suicidal thoughts or behaviors. In 2021, an estimated 21.0 million adults in the United States had at least one major depressive episode, representing 8.3% of all U.S. adults[1]. The biological mechanisms underlying MDD are multifactorial, including dysregulation within monoaminergic neurotransmitter systems, hypothalamic–pituitary–adrenal axis dysfunction, elevated inflammatory cytokines, genetic predispositions, structural and functional brain changes, and social psychological events[2–5]. The serotonin theory of depression has been influential since 1990, which posits that reduced serotonin activity contributes to depressive symptoms[6]. This theory has promoted the use of antidepressants, particularly selective serotonin reuptake inhibitors, as standard treatments for MDD. However, a large-scale trial showed nearly 80% of the outpatients treated with antidepressants had chronic or recurrent major depression[7]. Furthermore, approximately 30% of patients with MDD are resistant to following treatments after failed treatment attempts[8]. For these patients, invasive neurosurgical procedures such as bilateral anterior capsulotomy, bilateral anterior cingulotomy, vagus nerve stimulation, and deep brain stimulation are sometimes pursued. These surgical approaches aiming to disrupt the aberrant brain networks implicated in MDD yield mixed clinical results and carry risks of intracranial hemorrhage, delayed edema, or brain cyst formation[9,10]. In 2008, the United States Food and Drug Administration (FDA) approved the use of transcranial magnetic stimulation (TMS) for MDD. Although TMS is non-invasive, its clinical efficacy has been modest (29.3% response rate)[11]. The standard TMS treatment protocol typically requires daily sessions over several weeks, which can hinder patient adherence. In recent years, there has been increasing interest in ultrasonic applications for treating depression largely because ultrasound can reach deeper brain targets implicated in MDD. In addition to its greater penetration, ultrasound can be precisely focused on specific brain regions, distinguishing it from other non-invasive modalities, including transcranial direct/alternating current stimulation and TMS.

Ultrasound technology can be categorized into diagnostic ultrasound and therapeutic ultrasound. Therapeutic ultrasound directs ultrasound (i.e., mechanical waves with frequencies greater than 20 kHz) to the target through focused ultrasound transducers. Effective ultrasound transmission requires a coupling medium (e.g., ultrasound gel) to be applied between the transducer and tissue because absorption and reflection occur at interfaces between materials of different acoustic impedance. Thermal and mechanical effects primarily underlie the therapeutic effects of ultrasound. In biomedical applications, high-intensity focused ultrasound (HIFUS) is used for tissue ablation. It achieves ablation either by inducing coagulative thermal necrosis due to the absorption of ultrasound energy or by causing mechanical ablation through high tensile pressure-induced cavitation[12]. In contrast, low-intensity focused ultrasound (LIFUS) has been proven to modulate neuronal activity without causing irreversible damage. While the exact mechanism of LIFUS neuromodulation remains unclear, it is thought to involve acoustic radiation force, cavitation effect, and thermal effect (for a review of the mechanism, see[13]). the cavitation effect (oscillation of gas bubbles within tissues). Preclinical studies on animal models showed promise in improving depressive-like behavior with LIFUS neuromodulation[14–20]. In the past five years, a few clinical trials have explored the use of ultrasound for thermal ablation and neuromodulation as treatment for major depressive disorders[21–23]. Despite great progress, therapeutic ultrasound has not yet seen widespread clinical adaptation for treating MDD. To fully realize its therapeutic potential in treating MDD, we conducted a systematic review of the techniques of applying ultrasound to treat depression and evaluated their efficacy. This review will discuss the challenges of developing ultrasound to treat MDD and propose directions for future research.

Methods

This systematic review was preregistered in PROSPERO (CRD42024626093) and follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines[24] (**Figure 1**). Initially, we planned to limit the review to human studies. We updated the original protocol to include both human studies and studies involving animal models due to the limited number of clinical trials evaluating ultrasound applications in treating MDD.

Eligibility Criteria

Types of Studies and Participants

We included prospective cohort studies, case-control studies, and randomized control trials that report the effects of ultrasonic treatment. Studies must include human subjects diagnosed with major depressive disorder or animal models exhibiting depression-like behaviors.

Types of Exposure

We included studies evaluating the effect of any form of ultrasonic application on depression, including but not limited to Low-intensity focused ultrasound (LIFUS), High-intensity focused ultrasound (HIFUS), or Ultrasound-guided interventions.

Types of Outcomes

We focused on clinical and functional outcomes such as Hamilton Depression Rating Scale, neuroimaging outcomes such as resting-state functional MRI, electrophysiological outcomes, and biochemical outcomes.

Types of Reports

We included reports with full texts in English.

Search Strategy

We conducted a systematic literature search using PubMed and Web of Science. The last search was conducted on December 10, 2024. We searched peer-reviewed papers that contain the keyword *Ultrasound* in the title AND the keywords *Ultrasound*, *neuromodulation*, *treatment*, and *depression* in all fields. Individual additional articles known to the authors were also added. The inclusion criteria: (1) published in English, (2) used ultrasound-based technology for treating depression.

Study Selection

One reviewer removed duplicate reports before the study selection. We assessed the eligibility of each study in 2 phases: title and abstract screening and full-text review. The first reviewer sent the assessment of eligibility to the second reviewer and discussed any disagreements in study selection. The third reviewer made the final decision if consensus was not reached. In cases of multiple studies reporting results from the same trial, we focused on the outcomes in the study with a larger sample.

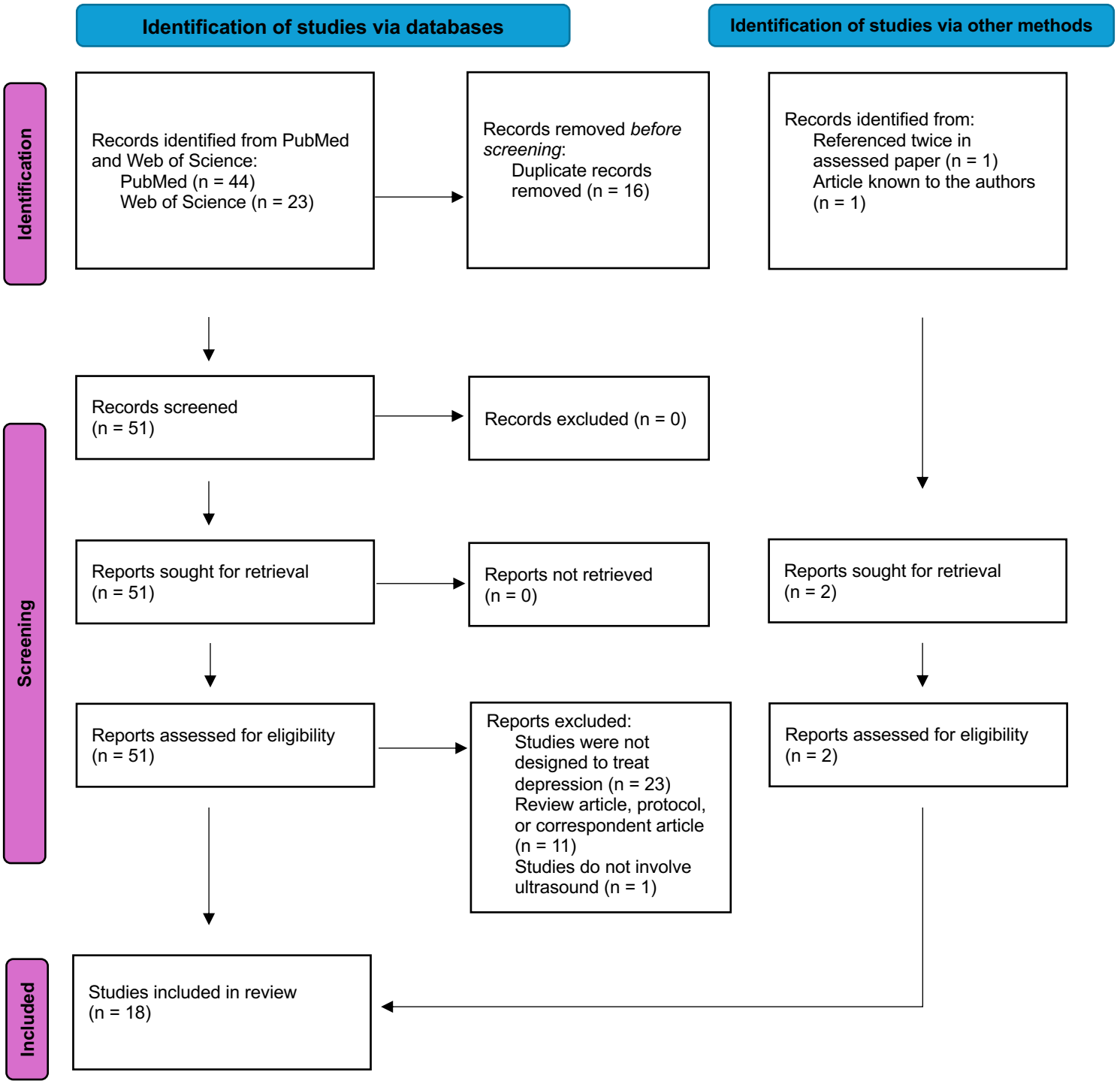

Figure 1 PRISMA flow diagram for study identification and selection.

Quality Assessment

We assessed the study quality and risk of bias based on selection, comparability, and outcome. The maximum score for a study is 1 for each category. We defined good studies as those that scored 1 in one category and at least 0.5 in the other two categories. We defined poor studies as studies that scored 0 in any one of the three categories. Moderate studies are neither of good quality nor poor quality. All reviewers discussed and resolved any disagreements on quality assessment.

Data Extraction

We extracted the mean and variance of standard depression scales, including the Hamilton Depression Rating Scale and the Montgomery-Åsberg Depression Rating Scale, at baseline and the latest follow-ups in human studies. We also extracted the number of responders in human trials. For studies using animal models, we extracted mean and variance of measures for depressive-like behavior, such as immobility time in the forced swim test and tail suspension test and sucrose preference index in the sucrose preference test. We extracted the sample size and the reported adverse effects in all included studies.

Statistical Analysis

We retrieved or inferred the effect size (e.g., Cohen's d) between the ultrasound treatment group and control group or between baseline and follow-up. When available, we used reported means, variances (e.g., standard errors or standard deviation), and sample sizes to estimate the effect size d and its variance $Var(d)$ (Eqs. 1-3). In studies where these data were not directly available, but F-statistics and degree of freedom for the treatment effect df_{effect} and residual degree of freedom df_{error} in Analysis of Variance are reported, we estimated effect sizes and variances based on Eqs. 3-6[25]. For studies where means and variances were not reported but t-statistics were available, we calculated the effect size d and its variance $Var(d)$ based on Eq. 3 and Eq. 7. We estimated the overall effect size using fixed-effect models with inverse variance as the weighting method. We estimated pooled effect size $\bar{d}$ according to Eq. 8. We estimated he 95% confidence interval (CI) as $\bar{d} \pm 1.96 \cdot SE$ (Eq. 9). We calculated I^2 as a metric measuring heterogeneity[26]. Niu et al. tested three pulse frequencies (200 Hz, 285 Hz, 500 Hz), finding a significant effect only at 200 Hz and no significant effects at 285 Hz or 500 Hz[17]. Due to the lack of exact statistics for the non-significant frequencies, we assumed their effect sizes to be zero and synthesized the results to estimate the overall effect before pooling across studies. In human studies, we adhere to the definition of responder as a 50% reduction in standard depression scale[9]. We synthesized the number of responders and total subjects across studies to calculate the overall response rate. When human randomized trials report baseline depression scale and depression scale after the treatment for both active and sham treatment groups, we estimated the effect size of ultrasonic application within the active treatment groups and the effect size of active ultrasonic application compared with sham treatment, adjusted for baseline. We considered the overall effect size large for $\bar{d} > 0.8$, medium for $0.2 \leq \bar{d} \leq 0.5$, and small for $\bar{d} < 0.2$.

$$d = \frac{mean_{ultrasound\ treatment} - mean_{control}}{Pooled\ SD} \quad \text{Eq. 1}$$

$$Pooled\ SD = \sqrt{\frac{(n_{control} - 1) \cdot SD_{control} + (n_{ultrasound\ treatment} - 1) \cdot SD_{ultrasound\ treatment}}{n_{control} + n_{ultrasound\ treatment} - 2}} \quad \text{Eq. 2}$$

$$Var(d) = \frac{n_{ultrasound\ treatment} + n_{control}}{n_{ultrasound\ treatment} \cdot n_{control}} + \frac{d^2}{2 \cdot (n_{ultrasound\ treatment} + n_{control})} \quad \text{Eq. 3}$$

$$\eta^2 = \frac{F \cdot df_{effect}}{F \cdot df_{effect} + df_{error}} \quad \text{Eq. 4}$$

$$Cohen's\ f = \sqrt{\frac{\eta^2}{1 - \eta^2}} \quad \text{Eq. 5}$$

$$d = \begin{cases} 2 \cdot Cohen's\ f & if\ number\ of\ groups = 2 \\ 2 \cdot Cohen's\ f \sqrt{\frac{number\ of\ groups}{number\ of\ groups - 1}} & if\ number\ of\ groups > 2 \end{cases} \quad \text{Eq. 6}$$

$$d = \frac{t}{\sqrt{n_{ultrasound\ treatment} + n_{control}}} \quad \text{Eq. 7}$$

$$\bar{d} = \frac{\sum \frac{1}{Var(d_i)} \cdot d_i}{\sum \frac{1}{Var(d_i)}} \quad \text{Eq. 8}$$

$$SE = \frac{1}{\sum \frac{1}{Var(d_i)}} \quad \text{Eq. 9}$$

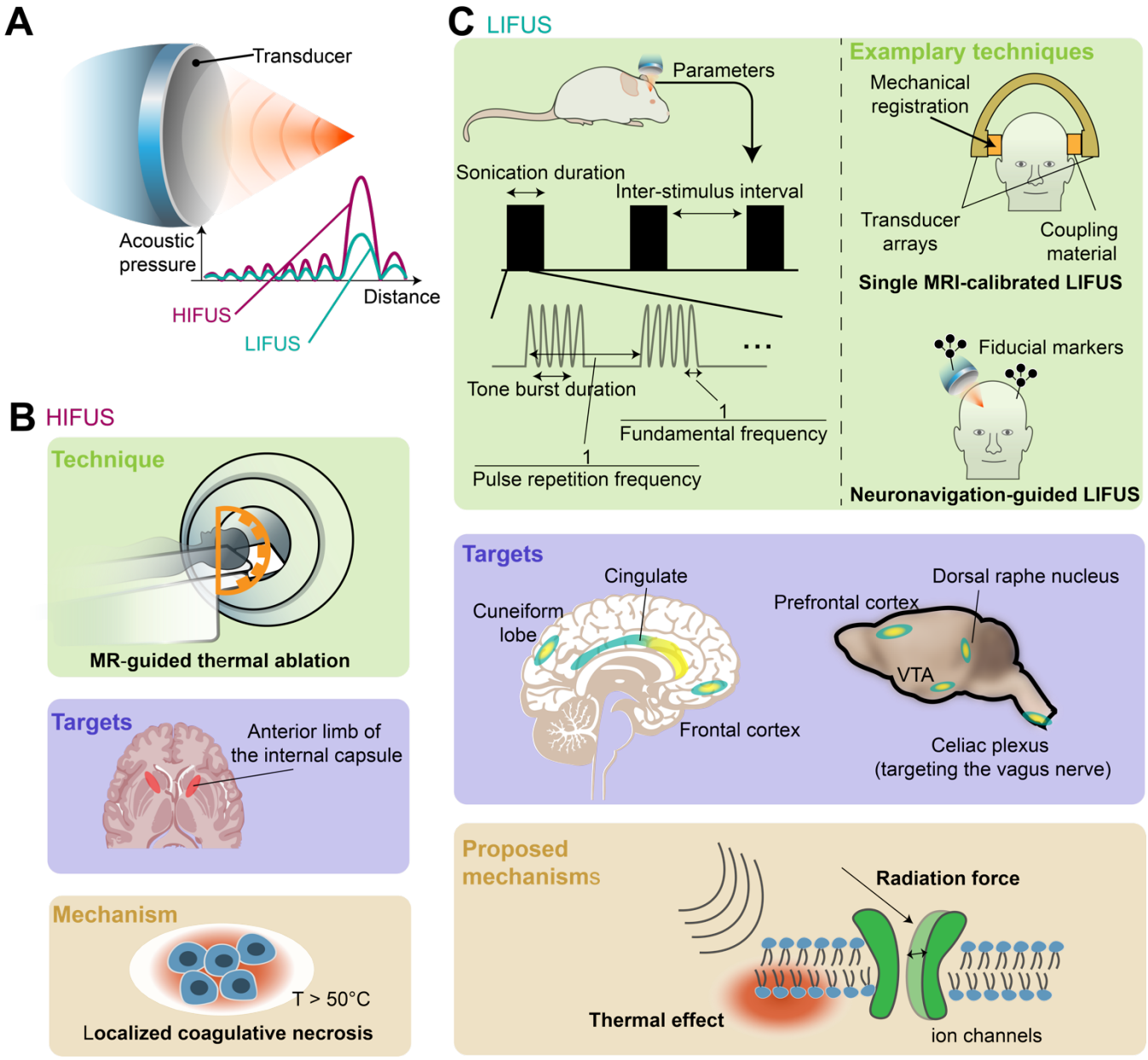

Figure 2. Summary of techniques, targets, and potential mechanisms in the application of high-intensity focused ultrasound (HIFUS) thermal ablation and low-intensity focused ultrasound (LIFUS) neuromodulation for treating depression. **A**. Ultrasonic applications can be categorized into LIFUS and HIFUS based on the intensity (e.g., acoustic pressure). Each category involves distinct techniques and mechanisms. **B**. HIFUS was primarily used for thermal ablation in humans. MR: magnetic resonance. **C**. LIFUS neuromodulation involves five independent parameters: fundamental frequency, pulse repetition frequency, tone burst duration, inter-stimulus interval, and sonication duration. The techniques of applying LIFUS include single Magnetic Resonance Imaging (MRI)-calibrated LIFUS[27,28] and Neuronavigation-guided LIFUS[22]. Single MRI-calibrated LIFUS involves mechanically registering the device to the subject's head and calibrating beamforming based on a single MR scan. Neuronavigation-guided LIFUS maps the stimulation target in the physical space using imaging data and fiducial markers. Real-time infrared tracking enables the alignment of the transducer to the target. VTA stands for the ventral tegmental area. The primary mechanisms underlying low-intensity ultrasound neuromodulation are thought to be radiation force (membrane deformation and mechanosensitive ion channel activation caused by ultrasound) and thermal effect.

Results

This review includes 18 peer-reviewed articles investigating the applications of ultrasound in the treatment of depression (**Table 1**). The 18 peer-reviewed articles comprise 10 human studies and 8 studies using animal models. The 10 human studies report results from 5 trials, including 4 registered clinical trials NCT02348411, NCT05301036, NCT04405791, NCT03421574. The 8 animal studies used mice and rats. Among the 8 animal studies, 4 studies used restraint stress models. The rodent models in the remaining studies include chronic corticosterone-induced depressive-like behaviors, chronic unpredictable stress, Lipopolysaccharide-induced depressive-like behaviors, and 6 hydroxydopamine (6-OHDA) lesion-induced anhedonic-like behaviors. Out of the included 18 studies, 11 are of good quality, 4 are of moderate quality, and 3 are of poor quality. The details of the quality assessment are shown in **Supplementary Figure 1**.

Table 1 Summary of included studies

Source	Protocol	Relevant outcomes	Efficacy	Additional findings
Preclinical studies (rodent models)				
Canwen Wu[15], 2017	Transcranial ultrasound stimulation (TUS) targeting dorsal raphe nucleus with 1.1 MHz fundamental frequency, 1000 Hz pulsed repetition frequency, 0.5 ms tone burst duration (TBD), 1 s stimulation duration (SD), 1 s inter-stimulus interval (ISI).	c-Fos immunoreactivity, sucrose preference index, immobility time in tail suspension test, time spent in elevated plus-maze test, levels of serotonin	Mice receiving TUS improves depression-like behaviors compared to the control group.	Staining showed no damage in the dorsal raphe nucleus tissue.
Xuandi Hou[16], 2024	low-frequency, low-intensity ultrasound combined with stereotactic injections of nanobubble (PEGylated gas vesicles) targeting dorsal raphe nucleus with 1 MHz frequency, 1000 Hz pulsed repetition frequency, and 0.3 ms tone burst duration.	Immobility time in forced swim test and in tail suspension test.	Mice receiving ultrasound neuromodulation showed reduced immobility time.	2.5-fold increased expression of c-Fos in 5-HT neurons in the stimulation condition compared to the control condition
Jinniu zhang[17], 2021	Low-intensity pulsed ultrasound targeting ventromedial prefrontal cortex with 800 kHz frequency, 200 Hz pulsed repetition frequency, 1 s sonication duration, 3 s inter-stimulus interval, and 0.2 ms tone burst duration.	immobility time in the forced swimming test, sucrose preference index in sucrose preference test, distance traveled in open field test, and c-Fos immunoreactivity	Four weeks of ultrasound stimulation targeting ventromedial prefrontal cortex increased sucrose preference, reduced forced swim immobility time in stressed rats, but has no significant effect of distance traveled in open field test.	The number of c-Fos-positive cells in the vmPFC was significantly increased. Histological staining revealed no gross tissue damage.
Shasha Yi[18], 2022	Low-intensity pulsed ultrasound targeting ventromedial prefrontal cortex with 500 kHz fundamental frequency, 100 Hz pulsed	c-Fos immunoreactivity in prefrontal neuron, immobility time in forced swimming test,	Ultrasound stimulation increased the expression of c-Fos and reduced immobility time.	Ultrasound stimulation did not cause any damage in prefrontal cortex based on H&E and Nissl staining.

Source	Protocol	Relevant outcomes	Efficacy	Additional findings
	repetition frequency, 60 s sonication duration, 120 s inter-stimulus interval, and 5 ms tone burst duration.	immobility time in tail suspension test.		
Yiyue Zhu[19], 2023	Transcranial low-intensity (pulsed) ultrasound stimulation targeting the dorsal raphe nucleus with 1.1 MHz frequency, 1000 Hz pulsed repetition frequency, 1 s sonication duration, 1 s inter-stimulus interval, and 0.5 ms tone burst duration.	c-Fos immunofluorescence, sucrose preference index in sucrose preference test, immobility time in tail suspension test	After three weeks of stimulation, immobility time was significantly decreased compared with the non-stimulated group. C- Fos positive cells' expression and the 5-HT level in the DRN were increased after stimulation.	H&E staining shows no tissue damage
Daqu Zhang[20], 2018	Transcranial (pulsed) ultrasound stimulation targeting the prelimbic cortex with 500 kHz fundamental frequency, 1.5 kHz pulsed repetition frequency, 0.4 s sonication duration, 3 s inter-stimulus interval, and 0.4 ms tone burst duration.	Sucrose preference index in sucrose preference test, immobility time in forced swimming test, distance travelled in open field test, Brain-Derived neurotrophic factor in left hippocampus	2 weeks of stimulation led to higher sucrose preference index, increased distance traveled, and reduced immobility time.	The H&E staining confirmed no tissue damage or hemorrhage after the sonication.
Rachael A. Herlihy[43], 2023	Peripheral (pulsed) ultrasound stimulation targeting the celiac plexus with 2.5 MHz fundamental frequency, 5 Hz pulsed repetition frequency, and 0.25 ms tone burst duration.	Immobility time in forced swim test, sucrose preference index in sucrose preference test	ultrasound stimulation increased sucrose preference in hemiparkinsonian rats	N/A
Ling Wang[14], 2024	Transcranial ultrasound stimulation targeting the ventral tegmental area with 0.5 MHz fundamental frequency, 1.5 Hz pulsed repetition frequency, and 0.3 ms tone burst duration, 0.2 s sonication duration, and 1.6 s inter-stimulus interval	immobility time in forced swimming test, immobility time in tail suspension test, and sucrose preference index in sucrose preference test, dopaminergic release in prefrontal cortex based on fiber photometry, and the number of dopaminergic neuron in ventral tegmental area.	ultrasound stimulation improved depression-like behavior and increase dopamine level in prefrontal cortex.	N/A
Human studies				
Benjamin Davidson[31], 2021	Magnetic resonance imaging-guided focused ultrasound for bilateral capsulotomy	Treatment success ratio defined by visible bilateral lesions on postoperative MRI	Clinical response was reported in [9]	The treatment success ratio is 15/22
Clement Hamani[23], 2024	Magnetic resonance-guided focused ultrasound for anterior capsulotomy	Clinical evaluation for adverse effects, Hamilton Depression Rating Scale scores	Non-significant reduction in Hamilton Depression Rating Scale scores compared to baseline in	No serious adverse effects were registered

Source	Protocol	Relevant outcomes	Efficacy	Additional findings
			major depressive disorder patients	
Benjamin Davidson[44]. 2020	Magnetic resonance-guided focused ultrasound for anterior capsulotomy	Functional connectivity based on functional MRI, cerebral glucose metabolism based on positron emission tomography,	Updated clinical efficacy and safety evaluation were reported in [23].	Magnetic resonance-guided capsulotomy did not result in cognitive decline.
Benjamin Davidson[9], 2020	Magnetic resonance-guided focused ultrasound for anterior capsulotomy	Neuropsychological tests	Improvements in clinical symptoms correlated with improvements on self-report measures of executive dysfunction and disinhibition, but not with performance-based tasks. Updated clinical efficacy and safety evaluation were reported in [23].	No serious adverse effects after the procedure. Nonserious adverse events included headaches and pin-site swelling in 7/12 patients.
Jooyoung Oh[22], 2024	Image-guided transcranial focused ultrasound stimulation targeting left dorsal lateral prefrontal cortex with 250 kHz fundamental frequency, 500 Hz pulsed repetition frequency, 1 ms tone burst duration, 0.3 s sonication duration, 5.7 s inter-stimulus interval.	Montgomery-Åsberg Depression Rating Scale and Resting-state functional magnetic resonance imaging	ultrasound stimulation led to greater reduction in Montgomery-Åsberg Depression Rating Scale, increase in connectivity between subgenual anterior cingulate cortex and prefrontal cortex.	N/A
Thomas Riis[27], 2024	Transcranial focused ultrasound stimulation targeting the subgenual cingulate cortex with 650 kHz fundamental	Depression and anxiety rating	Ultrasound stimulation improved mood states.	No adverse effect or apparent changes in structural imaging were reported. Targetting accuracy was on a scale of millimeter.
Minsoo Kim[21], 2018	Magnetic resonance-guided focused ultrasound for anterior capsulotomy	Hamilton Depression Rating Scale score and Beck Depression Inventory score	This procedure improved objective depression scale scores	N/A
Thomas Riis[28], 2023	Transcranial focused ultrasound stimulation targeting the subgenual cingulate cortex and pregenual cingulate with 650 kHz fundamental frequency for 2 minutes and 30 ms sonication duration, and 4 s inter-stimulus interval.	Hamilton Depression Rating Scale score	Ultrasound stimulation decreased Hamilton Depression Rating Scale score, which remained low 44 days following the sonication	No adverse effects were noted
Benjamin Davidson[45], 2020	Magnetic resonance imaging-guided focused ultrasound for bilateral capsulotomy	The number of sonification and acoustic energy required for each side	Clinical response was reported in [9]	More sonification and greater acoustic energy are needed for the second treated side.
Li Xu[30], 2020	A combination of transcranial magnetic stimulation and MRI-	Hamilton Depression Rating Scale score	Hamilton Depression Rating Scale score was	No statistical difference in adverse reaction between

Source	Protocol	Relevant outcomes	Efficacy	Additional findings
	guided low-intensity focused ultrasound stimulation. The ultrasound stimulation targeted lateral orbitofrontal cortex, dorsal prefrontal cortex, and cuneiform lobe with 650 kHz fundamental frequency, 100 Hz pulse repetition frequence, 30 s sonication duration, 30 s inter-stimulus interval.		lower in the treatment group compared with the control group.	the treatment and control groups.

Techniques of applying FUS to treat depression

Both LIFUS and HIFUS have been used to treat human patients with major depressive orders (**Figure 2A**). HIFUS was applied to ablate the anterior limb of the internal capsule in patients with MDD. This technique, called magnetic resonance-guided focused ultrasound (MRgFUS), directs ultrasound to generate heat at the target site, resulting in coagulative necrosis and tissue ablation (**Figure 2B**). It can create intracranial lesions without requiring a cranial window through craniotomy. The U. S. Food and Drug Administration (FDA) approved MRgFUS for the treatment of refractory essential tremor in July 2016. Building on this, MRgFUS has been investigated as a non-invasive ablation method for other neurological disorders, including MDD, Obsessive-compulsive disorder, and brain tumors[29]. In the included human studies, eligible patients for MRgFUS are those with treatment-resistant major depressive disorder. These studies utilized MRgFUS targeting the anterior limb of the internal capsule, a white matter region containing fibers from the prefrontal cortex towards the ventral striatum and the thalamus. The therapeutic mechanism underlying MRgFUS capsulotomy involves the disruption of the output from the anterior nucleus of the thalamus projecting to the paraterminal gyrus tract while preserving the dorsolateral prefrontal-thalamic tracts to avoid causing frontal lobe syndrome. During the procedure, patients remain in an intraoperative MRI scanner with a stereotactic frame. The procedure involves test sonication for target validation and adjustment and HIFUS for ablation. Before applying HIFUS, low-energy sonications are performed to induce temperatures of 40°–42°C, which serves to verify targeting accuracy. Temperature feedback from MR thermometry allows the neurosurgical team to make millimeter-scale adjustments to ensure that the focal point of heating aligns with the intended target region. Following successful verification, high-power sonications are applied iteratively, raising temperatures to between 50°C and 56°C for durations exceeding three seconds.

In contrast to HIFUS, LIFUS is used to modulate neuronal activity without creating irreversible lesions. MDD is associated with dysregulation of neurotransmitter systems and neural circuits involved in mood regulation, stress response, and reward processing. To this end, LIFUS is gaining attention as a non-invasiveness neuromodulation technique with high spatial resolution and deep penetration depth for treating patients with drug-resistant MDD. In preclinical studies with depressive rodent models, the common technique for LIFUS is transcranial low-intensity pulsed ultrasound stimulation. Compared to continuous wave ultrasound, pulsed ultrasound reduces the risk of thermal damage at the targeted brain region. In these studies, the targeted brain regions include the dorsal raphe nucleus, prefrontal cortex, and ventral tegmental area. Three out of eight included animal studies targeted the dorsal raphe nucleus to facilitate serotonin release, while another three targeted the prefrontal cortex for its role in emotion regulation. One study directed LIFUS toward the ventral tegmental area to regulate the dopamine system. Beyond central targets, one study stimulated the vagus nerve by targeting the

celiac plexus to harness the antidepressant effects of the vagus nerve stimulation. One out of eight included rodent studies uniquely combined transcranial low-intensity ultrasound with PEGylated gas vesicles. LIFUS neuromodulation protocol involves five independent parameters (**Figure 2C**): fundamental frequency, pulse repetition frequency, tone burst duration, inter-stimulus interval, and sonication duration. Fundamental frequency determines the oscillation rate of the ultrasound waves, influencing penetration depth. Pulse repetition frequency is the rate at which ultrasound pulses are emitted. Tone burst duration defines the length of each ultrasound pulse, and inter-stimulus interval is the time between consecutive pulses. Higher pulse repetition frequency combined with long sonication duration and short inter-stimulus interval may increase the risk of tissue heating. Transcranial low-intensity pulsed ultrasound in animal studies has been applied using a broad range of parameters: fundamental frequency ranging from 0.5 MHz to 2.5 MHz, pulse repetition frequency ranging from 5 Hz to 1.5 kHz, tone burst duration ranging from 0.2 ms to 5 ms, sonication duration ranging from 0.2 s to 120 s, and inter-stimulus interval ranging from 1 s to 120 s (**Table 1**).

Building on encouraging results in the preclinical studies, human trials have begun to explore the use of transcranial low-intensity pulsed ultrasound stimulation to treat patients with MDD[22,27,28,30]. To target specific brain regions implicated in depression, these trials have used neuroimaging or optical tracking-based neuronavigation as guidance. In protocols where the patient's head is immobilized with thermoplastic masks and mechanically coregistered with ultrasound transducers, MRI is utilized to map the patient's brain anatomy in relation to fiducial markers affixed to the transducers. Based on the brain anatomy, transducer locations, and acoustic pressure mapping, the ultrasound can be steered to focus on the targeted brain area. In studies where head motion is allowed, fiducial points were affixed to the patient's head and the transducers. Using real-time tracking with an infrared camera, the position of the ultrasound transducer was adjusted based on the relationship between the patient's head and the transducers. The brain regions that were targeted with low-intensity pulsed ultrasound stimulation include the sub- and pre-genual anterior cingulate cortex, dorsal prefrontal cortex, lateral orbitofrontal cortex, and cuneiform lobe. The treatment protocol varied from study to study, with fundamental frequency ranges from 250 kHz to 650 kHz and treatment protocol lasting from minutes to weeks (**Table 1**). The LIFUS protocols reported in the included human trials involved low-intensity pulsed stimulation without administering microbubbles. Based on current knowledge, these protocols are expected to have a low likelihood of inducing cavitation effects; therefore, we do not highlight cavitation effects in **Figure 2C**.

Efficacy of FUS for treating depression

Synthesized from 5 human studies reporting findings from 3 clinical trials (NCT02348411, NCT03421574, and NCT03156335), MRgFUS for anterior capsulotomy successfully created a lesion (postoperative lesion > 1mm on post-operative MRI) in 28/36 subjects[21,23]. These subjects include patients with MDD or obsessive-compulsive disorder who underwent identical MRgFUS procedures. Unsuccessful lesioning was primarily due to insufficient temperature elevation within the anterior limb of the internal capsule, under practical and safety considerations such as treatment duration and scalp heating. Davidson et al. identified skull density, skull thickness, and angle of incidence as key factors influencing the maximal temperature achieved[31]. Specifically, a lower skull density and increased skull thickness are associated with lower achieved temperature. In patients with MDD where MRgFUS successfully created lesions, 5/13 met responder criteria ($\geqslant$50% improvement from baseline on the Hamilton Depression Rating Scale) at 12 months postoperatively. At long-term (follow-up for up to 24 months), 7/13 met responder criteria. The reduction in Hamilton Depression Rating Scale is 28.13% $\pm$ 11.24% at 6 months postoperatively ($p = 0.027$, $t = 2.520$, $n = 13$, paired t-test), and 22.98% $\pm$ 12.65% at 12 months postoperatively

($p = 0.070$, $t = 1.986$, $n = 13$, paired t-test), and 39.37% ± 19.38 at the longest follow-up ($p = 0.093$, $t = 2.071$, $n = 13$, paired t-test). No serious adverse events were reported for all patients undergoing MRgFUS for capsulotomy. Nonserious adverse events included transient headaches lasting for a few hours after MRgFUS, pin-site swelling, and a sensation of fogginess.

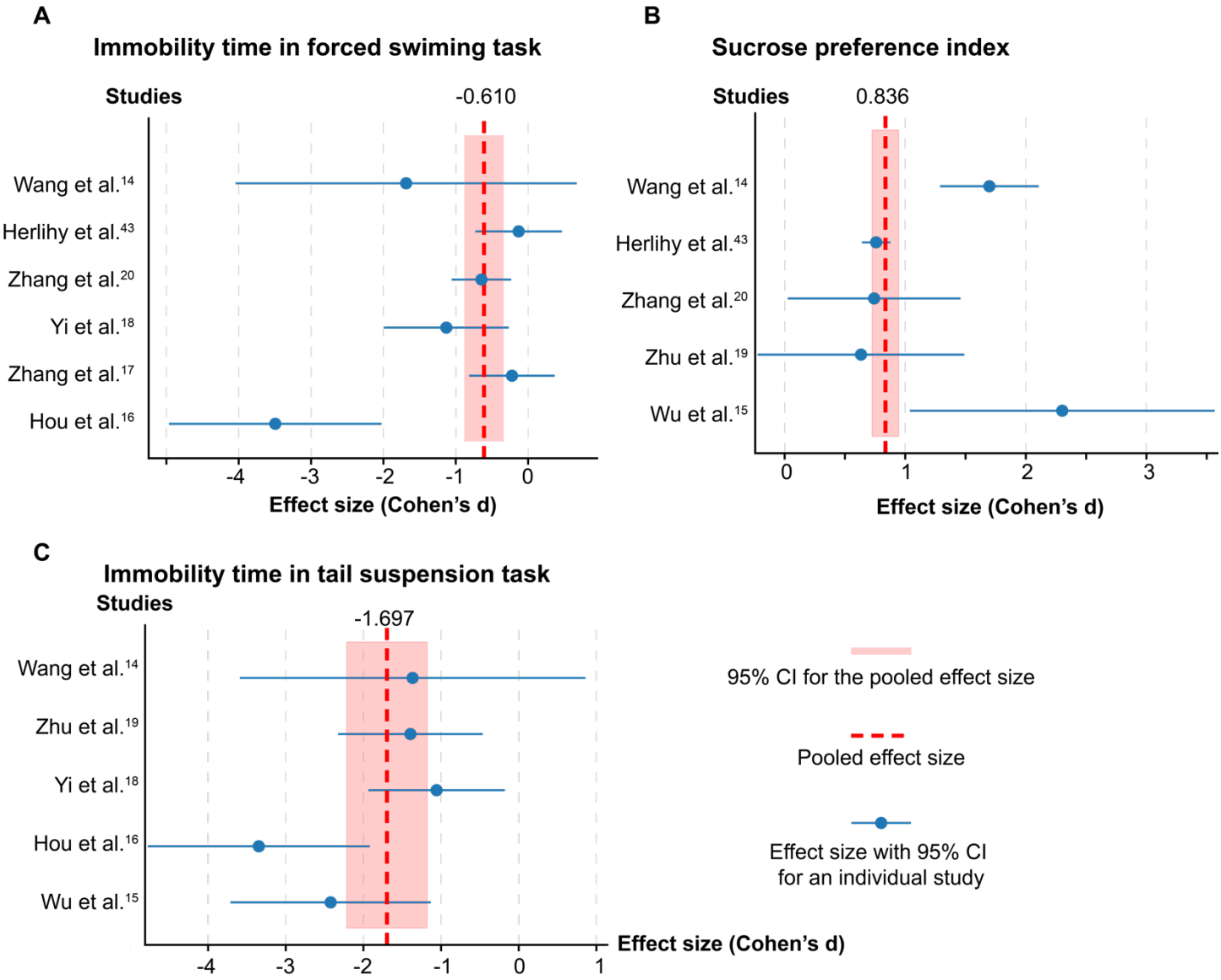

Figure 3. Efficacy of low-intensity focused ultrasound stimulation (LIFUS) in preclinical studies with rodent models. **A-C.** The effect of LIFUS on immobility time in forced swimming test (seconds), sucrose preference index (a.u.), and immobility in tail suspension test (s). The effect size was estimated using data before and after LIFUS.

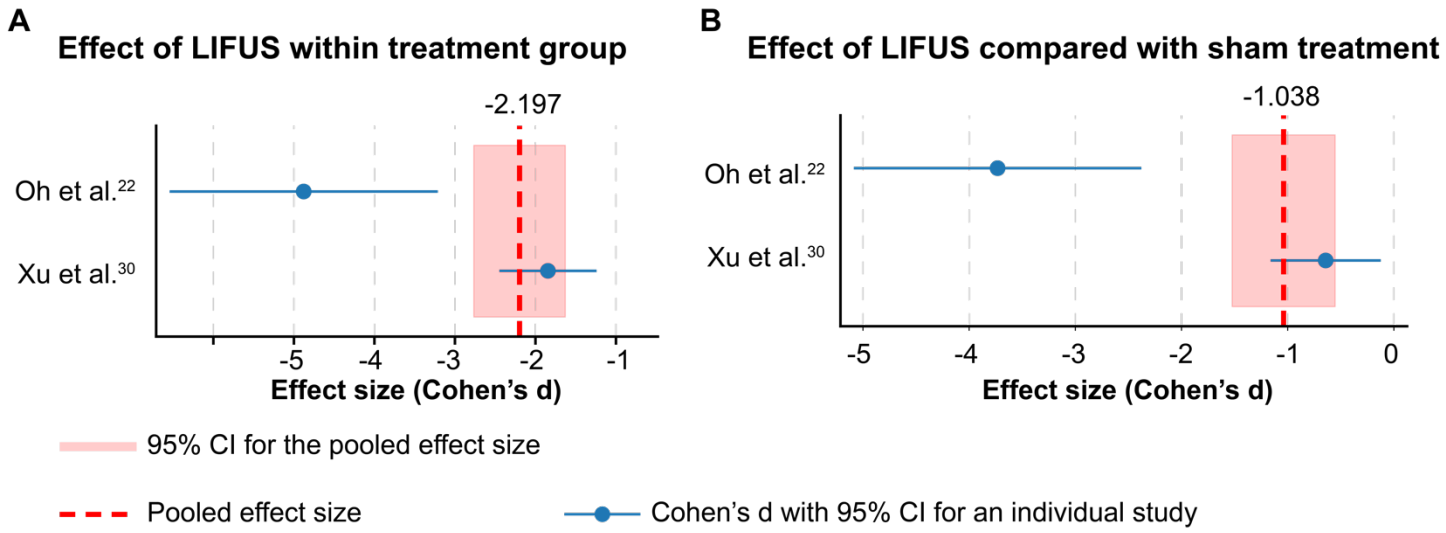

Figure 4. Efficacy of low-intensity focused ultrasound stimulation (LIFUS) in randomized clinical trials. **A.** The effect of LIFUS on depression severity within the treatment group was assessed by a depression scale before and after LIFUS treatment. B. The comparative effect of LIFUS on depression assessment scale compared to sham treatment. The effect size was calculated as the difference in changes in depression severity between the LIFUS and sham groups.

In studies using rodent models, the standard metrics assessing depressive-like behavior include immobility time in the forced swimming test (reported in 6 of the 8 included rodent studies), sucrose preference index (reported in 5 of the 8 included rodent studies), and immobility time in the tail suspension test (reported in 5 of the 8 included rodent studies). Low-intensity focused ultrasound had a medium effect (Cohen's d) on reducing immobility time in the forced swimming test ($\bar{d} = -0.610, 95\%CI = [-0.881, -0.338], I^2 = 76.369\%,$ **Figure 3A**). The pooled effect size for the sucrose preference index was large ($\bar{d} = 0.836, 95\%CI = [0.726, 0.946],$ **Figure 3B**). However, there was substantial variability in effect sizes across studies ($I^2 = 83.418\%$). In addition, low-intensity focused ultrasound reduced immobility time in the tail suspension test with a large effect ($\bar{d} = -1.697, 95\%CI = [-2.214, -1.179], I^2 = 54.759\%,$ **Figure 3C**). 5 out of the 8 included animal studies applied H&E staining and confirmed damage or hemorrhage observed in the targeted tissue.

Four out of ten included human studies investigated the use of LIFUS neuromodulation in patients with MDD. One study reported a case where LIFUS targeting the subcallosal cingulate cortex resolved depressive symptoms. The patient's Hamilton Depression Rating Scale-6 score decreased from 11 to 0, and the patient remained in remission for the 44 days of monitoring. One study documented immediate reductions in depression severity in two patients, as assessed by a psychiatrist, following ultrasonic stimulation of the subgenual cingulate cortex. The other two studies reported results of randomized clinical trials and reported standard depression assessment at baseline and follow-ups for both active stimulation and sham groups. The synthesized response rate is 80.49% (33/41) in the treatment group, compared to 47.62% (20/42) in the sham group. Low-intensity focused ultrasound had a large effect on reducing depression severity from baseline ($\bar{d} = -2.197, 95\%CI = [-2.765, -1.629],$ **Figure 4A**). In addition, after adjusting for baseline characteristics, low-intensity focused ultrasound showed a large effect on reducing depression scale compared with sham treatment ($\bar{d} = -1.038, 95\%CI = [-1.523, -0.554],$ **Figure 4B**). Low-intensity focused ultrasound neuromodulation was well tolerated in the two human randomized trials, with 3/41 patients in the active treatment group, compared with 4/42 patients in the sham group reporting dizziness, vomiting, or diarrhea.

Discussion

This review summarized techniques of applying ultrasound in treating major depressive disorder, including MRgFUS for anterior capsulotomy and low-intensity transcranial ultrasound neuromodulation. The current literature suggests the responder rate is 53.85% for MRgFUS and 80.49% for LIFUS, compared to 44.3% for TMS[32], 30-40% for vagus nerve stimulation[33], and 40–70 % for deep brain stimulation[34]. Rodent studies showed low-intensity ultrasound had a medium to large effect on resolving depressive-like behavior in rodents, suggesting its promising translation in humans. To realize the potential of ultrasound, several key challenges need to be addressed.

Challenges and future directions

To date, there are 9 completed or ongoing clinical trials registered on ClinicalTrials.gov that investigate ultrasonic interventions in treating MDD (NCT06085950, NCT05697172, NCT06285474, NCT03421574, NCT06320028, NCT06013384, NCT05301036, NCT04405791, NCT05551585). The limited number of clinical studies and small patient cohorts is a limitation of this review, highlighting the need for larger trials to establish the clinical efficacy and safety profiles of both HIFUS and LIFUS. In studies investigating HIFUS thermal ablation, a major challenge is its inconsistent success rate. Despite being non-invasive and with minimal reported serious adverse effects, Magnetic resonance-guided focused ultrasound (MRgFUS) has not consistently achieved successful ablation of the anterior limb of the internal capsule for treating MDD. Furthermore, its efficacy in MDD patients with successful lesioning is comparable to that of traditional bilateral anterior capsulotomy, which has a reported success rate of around 40%[35]. Compared with other ablative targets in ablative surgery, such as bilateral anterior cingulotomy and bilateral subcaudate tractotomy, anterior capsulotomy remains the most effective and safest option for ablative interventions in MDD[35]. Therefore, exploring alternative ablative targets with MRgFUS is unlikely to yield substantial improvements in clinical outcomes. Instead, efforts should focus on refining patient selection through neuroimaging, functional brain mapping, or neurophysiological biomarkers[36]. Individualized functional targeting, as demonstrated in other brain stimulation techniques like transcranial magnetic stimulation, may provide a model for tailoring MRgFUS treatments to the unique neurophysiological profiles of patients[37]. Key factors of successful ablation identified include skull density ratio and skull thickness. Combining these approaches holds promise for identifying MDD patients who are most likely to respond to ultrasound ablation.

The challenges that LIFUS faces include the limited exploration of its parameter space and an incomplete understanding of its underlying mechanisms. All studies included in this review were published after 2017, which may explain the lack of comprehensive investigations into the effects of specific parameters. We anticipate that future research will expand this parameter space, especially in light of the medium-to-strong effects of low-intensity ultrasound on reducing depressive behaviors observed in both animal models and human clinical studies. A further challenge is the lack of rapid and reliable biomarkers of mood. Currently, detecting therapeutic effects in MDD typically depends on outcome measures that unfold over weeks, which limits our ability to explore the parameter space systematically and comprehensively. Although structural and functional neuroimaging have been investigated as potential ways to gain shorter-term feedback, no definitive biomarker has yet been established[38].

Although various brain regions and peripheral targets have been explored, no formal guidelines currently exist to identify the optimal ultrasonic stimulation sites for treating depression. Interestingly, despite considerable

variations in stimulation protocols, low-intensity focused ultrasound has consistently produced reductions in depressive-like behaviors in rodent studies and improvements in depressive symptoms in human clinical trials. Because depression is increasingly conceptualized as arising from dysfunctional connectivity across distributed neural circuits, directing low-intensity ultrasound to key nodes within these aberrant networks may disrupt pathological activity and yield therapeutic benefits[39]. This hypothesis warrants further investigation. Nevertheless, it would be helpful to establish whether a universal stimulation target exists or if individualized approaches will ultimately prove more effective.

To date, precise mechanisms by which low-intensity ultrasound modulates neuronal activity remain insufficiently understood. Determining whether its effects are mediated by thermal, mechanical, or cavitation-based processes or a confluence of these mechanisms is crucial for optimizing stimulation protocols and aligning them with established neurobiological pathways of depression. Low-intensity ultrasound offers distinct advantages as a noninvasive neuromodulatory modality capable of penetrating deeply into brain tissue. However, temporal interference electrical neurostimulation, which uses multiple high-frequency electric fields to provide steerable, focal stimulation, has been developed as a potential rival technology[40]. How small a focal volume may be achieved via temporal interference stimulation remains an open question, but studies have shown that temporal interference stimulation can activate the mouse hippocampus without stimulating the overlying cortex[41]. In comparison, the focal volume for transcranial FUS is 23 mm^3 under a 0.5 mm mouse skull, a size comparable to the volume of the mouse hippocampus[42]. Although both approaches can stimulate subcortical structures without surgery, their differing modes of action (electrical vs mechanical) may favor specific patient populations or disease states. To remain competitive with temporal interference, future research should systematically compare the neurophysiological outcomes of ultrasonic neuromodulation and temporal interference across patient populations. Such investigations may also reveal disease categories that are better suited to mechanical or thermal mechanisms.

Conclusion

Ultrasound applications open exciting new avenues for treating MDD through noninvasive ablation and neuromodulation. HIFUS for anterior capsulotomy had a response rate of 38.46%, comparable to traditional capsulotomy with stereotactic surgery. However, it faces challenges that underscore the need for refined patient selection and technological advances to ensure consistent lesioning. The response rate of low-intensity focused ultrasound (LIFUS) in clinical studies is 80.49%. In addition, LIFUS neuromodulation showed a medium to large effect on resolving depressive-like behavior in rodents and reducing depression scale in humans. Yet, LIFUS still grapples with an incomplete understanding of its mechanisms and an insufficient exploration of stimulation parameters. As ultrasound applications continue to evolve, integrating mechanistic research and refining stimulation protocols will be crucial for developing a safer and more effective neuromodulation strategy in MDD.

Data availability

Data supporting the findings of this study are available within the article and its supplementary materials. Codes for meta-analysis are available at https://github.com/GanshengT/Meta_analysis_ultrasound/tree/main .

Declaration of interests

ECL and HC are inventors on an awarded US patent filed by Washington University in St. Louis on the sonobiopsy technique (US11667975B2), which covers the overall methods and systems for noninvasive and localized brain liquid biopsy using focused ultrasound. ECL and HC serve as advisors and shareholders of Cordance Medical, Inc., which is involved in commercializing the sonobiopsy technique. This relationship did not influence the design, execution, or interpretation of the study presented in this manuscript. The conflict of interest has been rigorously managed by Washington University in St. Louis. ECL received consulting fee from Neurolutions E15 and own stock from Neurolutions, Osteovantage, Face to Face Biometrics, Caeli Vascular, Acera, Sora Neuroscience, Inner Cosmos, Kinetrix, NeuroDev, Inflexion Vascular, Aurenar, Petal Surgical, which are not related to the present study.

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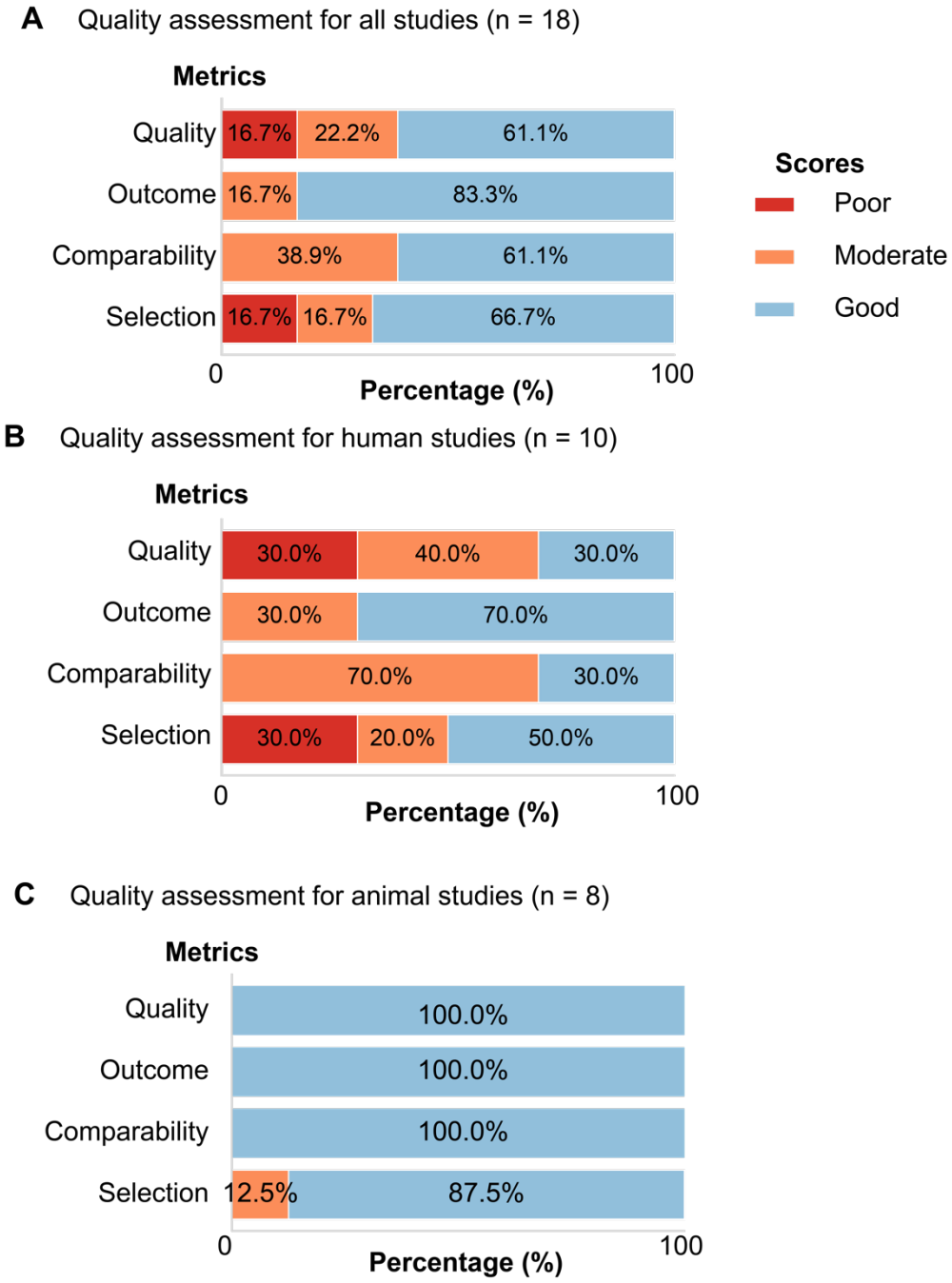
Supplementary Figure 1 Quality assessment.



Appendix 1 – Quality Assessment

Quality assessment of studies examining the technique and efficacy of therapeutic ultrasound in the treatment of major depressive disorder

The maximum score for a study is 1 for the Selection, Comparability, and Outcome categories.

Selection

1) Representativeness of the exposed cohort

1: The study includes both genders, and the sample size is> 7. If the study used an animal model, the model should be a valid depression animal model.

0.5 (somewhat representative): Sample size ≥ 5

0: case report

Comparability

1) Comparability of cohorts in study design and statistical analysis

1: The study includes both a treatment group and a control group. The outcome measures for both groups are adjusted for baseline measurement.

0.5: The study outcomes before and after ultrasonic treatment for the treatment group are available. Alternatively, the study includes outcome measures for the treatment group and the control group.

0: The outcome measures before and after treatment are not comparable, for example, due to different measures used.

Outcome

1) Outcome measure

1: standard measures or rating scales for depression that have been validated

0.5: the study includes neuroimaging outcomes, biochemical outcomes, electrophysiological outcomes, or other outcomes that are related to standard rating scales for depression

0: Subjective report

Thresholds for converting the Quality assessment to AHRQ standards (good, moderate, and poor):

Good quality: at least one score for any two of the three categories and at least 0.5 score for the other category

Moderate quality: studies that are neither of good quality nor poor quality.

Poor quality: 0 score for any one of the three categories.