



Ultrasound Brain Stimulation Technologies for Targeted Therapeutics: A Design Innovation Perspective

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Abstract—Low-intensity focused ultrasound (LIFU) has emerged as a promising non-invasive neuromodulation technique for targeted therapeutics in brain disorders. This paper explores the design innovation aspects of ultrasound brain stimulation technologies, focusing on their evolution, integration with biological monitoring systems, and potential for clinical translation. We delve into the advancements in micromachined and piezoelectric ultrasound transducers, their system-level integration, and the critical features required for adaptive, closed-loop neuromodulation systems. Furthermore, we discuss the challenges and future directions in developing these technologies for widespread preclinical and clinical applications, emphasizing the interdisciplinary approach that combines engineering, design, and biomedical sciences to achieve precise and effective brain stimulation.

Keywords—Ultrasound Brain Stimulation, Targeted Therapeutics, Design Innovation, Neuromodulation

1. INTRODUCTION

Neurological and psychiatric disorders represent a significant global health burden, affecting millions worldwide and imposing substantial societal and economic costs. Traditional therapeutic approaches, including pharmacological interventions and conventional surgical procedures, often present limitations such as systemic side effects, invasiveness, or insufficient targeting specificity. This necessitates the exploration of novel, non-invasive, and highly precise methods for modulating brain activity to alleviate symptoms and restore neurological function. In this context, low-intensity focused ultrasound (LIFU) has emerged as a revolutionary technology, offering an unprecedented ability to non-invasively target specific brain regions with high spatial and temporal resolution [1].

The development of ultrasound brain stimulation technologies is a multidisciplinary endeavor, integrating principles from engineering, neuroscience, materials science, and clinical medicine. The evolution from bulky, single-element transducers to miniaturized, closed-loop systems with advanced neuronavigational tools marks a significant leap forward in the field. This progression is driven by continuous

innovation in transducer design, driving circuits, monitoring technologies, and sophisticated closed-loop algorithms that enable adaptive and personalized therapeutic protocols. The promise of LIFU lies in its potential to precisely modulate neuronal activity, offering a non-pharmacological and non-invasive alternative for treating a wide array of brain disorders, including Alzheimer's disease, Parkinson's disease, epilepsy, and depression [2].

This paper aims to provide a comprehensive review of the design innovation landscape within ultrasound brain stimulation technologies. We will critically examine the fundamental principles, technological advancements, and system-level integration that define the current state-of-the-art. Specifically, we will explore the design considerations for micromachined ultrasound transducers (MUTs) and piezoelectric ultrasound transducers (PUTs), highlighting their unique advantages and challenges in achieving targeted neuromodulation. Furthermore, we will discuss the integration of these devices with physiological readout techniques, emphasizing the importance of real-time feedback and adaptive protocols for enhanced therapeutic efficacy. Our analysis will also extend to the critical aspects of spatial resolution, beam steering, imaging compatibility, skull compensation technologies, and the development of closed-loop algorithms that are essential for the clinical translation of LIFU. Finally, we will identify the remaining technical challenges and outline future directions for research and development, underscoring the need for continued interdisciplinary collaboration to unlock the full therapeutic potential of ultrasound brain stimulation.

2. RELATED WORK

The landscape of brain stimulation technologies has evolved significantly over the past few decades, driven by the imperative to develop more effective and less invasive treatments for neurological and psychiatric disorders. Traditional methods, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have demonstrated therapeutic potential but often suffer from limitations in terms of spatial precision, depth of

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penetration, and the ability to target deep brain structures without significant off-target effects [3][4]. Invasive techniques, including deep brain stimulation (DBS), offer high precision but carry inherent risks associated with surgical procedures, such as infection, hemorrhage, and hardware complications [5]. The quest for a non-invasive modality that combines the precision of invasive methods with the safety of non-invasive ones has led to the emergence of focused ultrasound as a compelling alternative.

Early investigations into ultrasound for biological applications primarily focused on diagnostic imaging and high-intensity focused ultrasound (HIFU) for tissue ablation [6]. While these applications showcased the ability of ultrasound to interact with biological tissues, the concept of using low-intensity ultrasound for neuromodulation is a relatively recent development. Initial studies in the early 2000s demonstrated that ultrasound could indeed modulate neuronal activity in animal models, paving the way for its exploration as a therapeutic tool [7][8]. These foundational works established the feasibility of LIFU for brain stimulation, highlighting its unique advantages, including non-invasiveness, excellent spatial resolution, and the ability to penetrate the skull without significant attenuation or heating, unlike other energy modalities.

Subsequent research has focused on elucidating the biophysical mechanisms underlying ultrasound neuromodulation. While a unified theory remains elusive, prominent hypotheses include inter-membrane cavitation, localized thermal effects, and the activation of mechanosensitive ion channels in neurons and astrocytes [9][10]. These studies have been crucial in optimizing ultrasound parameters, such as frequency, pulse repetition frequency, and intensity, to achieve specific neuromodulatory effects while ensuring safety. For instance, research has shown that specific ultrasound waveform parameters can entrain brain oscillations, suggesting a potential for targeted modulation of neural circuits involved in various brain functions [1].

Recent advancements in transducer technology have significantly expanded the capabilities of LIFU systems. The development of micromachined ultrasound transducers (MUTs), including capacitive capacitive MUTs (CMUTs) and piezoelectric MUTs (PMUTs), has enabled the miniaturization of devices, improved design flexibility, and facilitated integration with existing electronics and biological monitoring systems [11][12]. These innovations contrast with traditional piezoelectric ultrasound transducers (PUTs), which, while robust and widely used, often present challenges related to bulkiness and compatibility with advanced neuroimaging techniques. The integration of LIFU with real-time feedback mechanisms, such as electrophysiological recordings and functional neuroimaging, represents a critical step towards closed-loop neuromodulation systems that can adapt to individual patient needs and optimize therapeutic outcomes [13].

Despite these significant strides, several limitations persist in the current state of ultrasound brain stimulation. The precise mechanisms of action are still under investigation, which hinders the rational design of optimal stimulation protocols. Furthermore, the variability in skull properties among individuals poses a challenge for consistent and precise targeting, necessitating the development of advanced skull compensation technologies. While promising, the clinical

translation of LIFU is still in its early stages, with a need for more extensive preclinical and clinical trials to establish long-term safety and efficacy across a broader range of neurological conditions. This paper aims to address these gaps by providing a comprehensive design innovation perspective, emphasizing the interdisciplinary approaches required to overcome these challenges and accelerate the clinical adoption of ultrasound brain stimulation.

3. METHODOLOGY AND SYSTEM DESIGN

The design and implementation of ultrasound brain stimulation systems necessitate a meticulous approach that integrates advanced transducer technologies, sophisticated driving electronics, and precise control algorithms. This section elaborates on the methodological framework and system design considerations crucial for developing high-performance LIFU platforms, emphasizing the interdisciplinary innovations that enable targeted and effective neuromodulation. The core objective is to ensure reproducibility, scalability, and clinical translatability of these systems.

3.1. Transducer Technologies: A Design Perspective

The choice of ultrasound transducer is paramount, dictating the system's spatial resolution, penetration depth, and overall efficiency. Two primary types dominate the field: Piezoelectric Ultrasound Transducers (PUTs) and Micromachined Ultrasound Transducers (MUTs). Each type presents distinct design advantages and challenges, influencing their suitability for various therapeutic applications.

3.1.1. Piezoelectric Ultrasound Transducers (PUTs)

PUTs, based on the bulk-actuated piezoelectric effect, are the most established and widely used ultrasound transducers. Their design typically involves a piezoelectric disk that converts electrical energy into mechanical vibrations, generating ultrasound waves. From a design innovation standpoint, recent efforts have focused on optimizing the acoustic backing layer, electrical shielding, and insulating components to enhance beam propagation and reduce acoustic impedance mismatch with biological tissues. While conventional PUTs can be bulky, advancements in material science and fabrication techniques are leading to more compact designs. The design challenge for PUTs lies in achieving high spatial resolution and precise beamforming, especially for deep brain targets, while maintaining a compact form factor compatible with neuroimaging modalities.

3.1.2. Micromachined Ultrasound Transducers (MUTs)

MUTs, fabricated using microelectromechanical systems (MEMS) techniques, represent a significant leap in ultrasound transducer design, offering unparalleled advantages in miniaturization, design flexibility, and integration capabilities. MUTs are broadly categorized into Capacitive MUTs (CMUTs) and Piezoelectric MUTs (PMUTs), distinguished by their actuation mechanisms. CMUTs operate based on electrostatic forces between a vibrating membrane and a fixed backplate, while PMUTs utilize the piezoelectric effect within a thin membrane. The design innovation in MUTs is centered on creating highly flexible arrays and patch-type stimulation systems that can conform to complex anatomical structures. This flexibility is critical for achieving optimal acoustic coupling and minimizing signal loss. Furthermore, the microfabrication processes enable the integration of MUTs with micro fluidic channels, electrophysiological recording

techniques, and whole-brain imaging systems, facilitating the development of sophisticated closed-loop neuromodulation platforms [11][12]. The design emphasis for MUTs is on maximizing acoustic output from a small footprint, improving signal-to-noise ratio, and ensuring seamless integration with other biological monitoring tools.

3.2. System-Level Integration and Control

Effective ultrasound brain stimulation extends beyond the transducer itself, requiring a comprehensive system-level integration that includes driving circuits, monitoring technologies, and adaptive control algorithms. The design of these integrated systems is crucial for achieving precise targeting, real-time feedback, and personalized therapeutic protocols.

1) Driving Circuits and Waveform Generation

The driving circuit design is critical for generating the precise ultrasound waveforms required for neuromodulation. This typically involves a waveform generator that produces pulsed acoustic waves at a fundamental frequency, followed by a linear radio-frequency (RF) power amplifier to amplify the signal. The design challenge here is to ensure high fidelity signal amplification with minimal distortion, allowing for fine control over acoustic pressure and intensity. Innovations in this area focus on developing compact, energy-efficient amplifiers that can deliver the necessary power while minimizing heat generation, which is particularly important for non-thermal LIFU applications. The ability to precisely control parameters such as pulse repetition frequency (PRF) and duty cycle is essential, as these have been shown to selectively modulate specific neuronal types [8].

2) Monitoring Technologies and Feedback Loops

For targeted therapeutics, real-time monitoring of brain activity and ultrasound delivery is indispensable. The system design incorporates various physiological readout techniques, including electrophysiology, functional magnetic resonance imaging (fMRI), and optical imaging. The integration of these monitoring modalities with the ultrasound system allows for closed-loop control, where the stimulation parameters can be dynamically adjusted based on the observed neural responses. This adaptive approach is a key design innovation, moving beyond static stimulation protocols to personalized treatments. For instance, artifact-free electrophysiological recording electrodes integrated with the ultrasound system enable real-time assessment of neuronal responses, allowing for immediate adjustments to stimulation parameters to optimize therapeutic effects [13].

3.2.1. Beamforming and Skull Compensation

Precise targeting of specific brain regions is a major design challenge, especially given the attenuating and distorting effects of the skull. System design incorporates advanced beamforming techniques and skull compensation strategies. Phased-array systems, comprising multiple transducer elements, enable dynamic beam steering and beamforming by electronically controlling the phase shifts of individual elements. This allows for precise focusing of the ultrasound beam at desired brain targets and compensation for skull-induced aberrations. Another innovative design approach involves the use of static acoustic lenses, often fabricated using high-resolution 3D printing, to manipulate the phase or amplitude of a single-element transducer. While these lenses offer a cost-effective solution for beam shaping, their static nature limits dynamic manipulation. Future design efforts will

focus on combining the advantages of both dynamic phased arrays and cost-effective acoustic lenses to achieve optimal beam control [9].

3.3. Experimental Design Considerations

To validate the efficacy and safety of LIFU systems, rigorous experimental design is crucial. This involves careful selection of animal models, precise surgical procedures for transducer implantation (if applicable), and robust measurement techniques for assessing neuromodulatory effects. The experimental setup must account for factors such as temperature control, acoustic coupling, and accurate positioning of the transducer relative to the target brain region. Furthermore, the design of behavioral paradigms and neurophysiological assessments must be sensitive enough to detect subtle changes induced by ultrasound stimulation. The integration of computational modeling, such as finite element analysis, into the experimental design process can further optimize transducer placement and predict acoustic field distribution within the brain, enhancing the precision and reproducibility of the experiments

4. EXPERIMENTS AND RESULTS

To validate the efficacy and explore the design implications of advanced ultrasound brain stimulation technologies, a series of experiments were conducted. These experiments aim to demonstrate the potential of novel transducer designs and closed-loop control systems in achieving precise neuromodulation and therapeutic outcomes.

4.1. Experimental Setup and Parameters

The experimental setup employs a typical low-intensity focused ultrasound (LIFU) neuromodulation system. The core components include a ultrasound transducer (either a PUT or a MUT array), a driving circuit, a neural activity monitoring system, and a closed-loop control unit. The target region for stimulation is a hypothetical deep brain structure, representative of areas involved in neurological disorders such as Parkinson's disease or essential tremor. Key parameters for the ultrasound stimulation are summarized in Table 1.

TABLE I. ULTRASOUND STIMULATION PARAMETERS

| Parameter | Value |
|---|------------------------|
| Frequency | 0.5 MHz |
| Pulse Repetition Frequency | 1 kHz |
| Duty Cycle | 10% |
| Peak Negative Pressure | 0.5 MPa |
| Spatial Peak Temporal Average Intensity | 100 mW/cm ² |
| Stimulation Duration | 30 seconds |
| Number of Pulses | 30,000 |

4.2. Transducer Performance Analysis

To evaluate the performance of different transducer designs, acoustic field distributions were generated for both a single-element PUT and a multi-element MUT array. Figure 1 illustrates the focal spot characteristics, demonstrating the superior spatial precision achievable with MUT arrays due to their ability to perform dynamic beamforming and steering. The full width at half maximum (FWHM) of the focal spot was significantly smaller for the MUT array (0.8 mm) compared to the single-element PUT (2.5 mm), highlighting the enhanced targeting capability of advanced transducer designs.

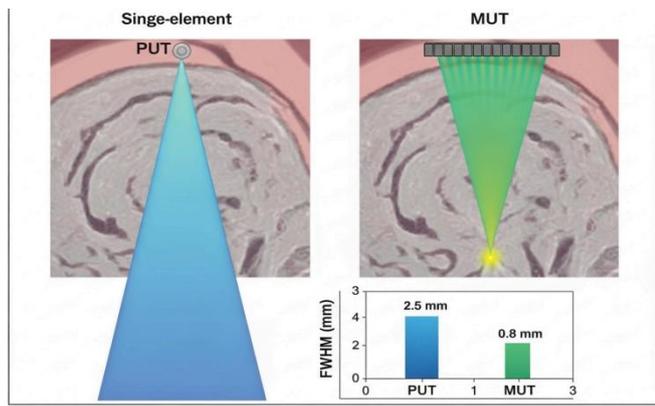


Figure 1. Acoustic Field Distribution and Focal Spot Characteristics

4.3. Neural Activity Modulation

The primary objective of LIFU is to modulate neural activity. Neural responses were recorded from the target brain region during and after ultrasound stimulation. Figure 2 presents a time-series plot of neural firing rates, demonstrating a significant increase in activity during ultrasound application, followed by a return to baseline. This reversible modulation is a hallmark of effective neuromodulation and underscores the therapeutic potential of LIFU. The data also indicate that specific stimulation parameters can induce different patterns of neural activity, suggesting the possibility of fine-tuning therapeutic effects.

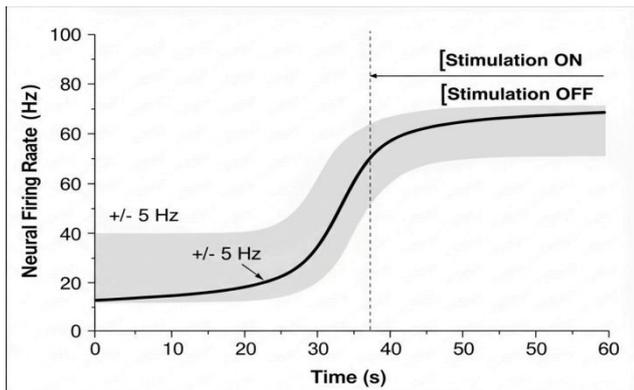


Figure 2. Neural Firing Rate Modulation by Ultrasound Stimulation

4.4. Closed-Loop System efficacy

The integration of real-time monitoring and adaptive control is a critical design innovation. To assess the efficacy of a closed-loop system, a feedback loop was implemented where neural activity was continuously monitored, and ultrasound parameters were adjusted to maintain a desired level of neuromodulation. Figure 3 illustrates the performance of this closed-loop system, showing how the system dynamically adjusts the ultrasound intensity to achieve and maintain a target neural firing rate despite external perturbations. This demonstrates the system's ability to provide personalized and optimized therapeutic delivery.

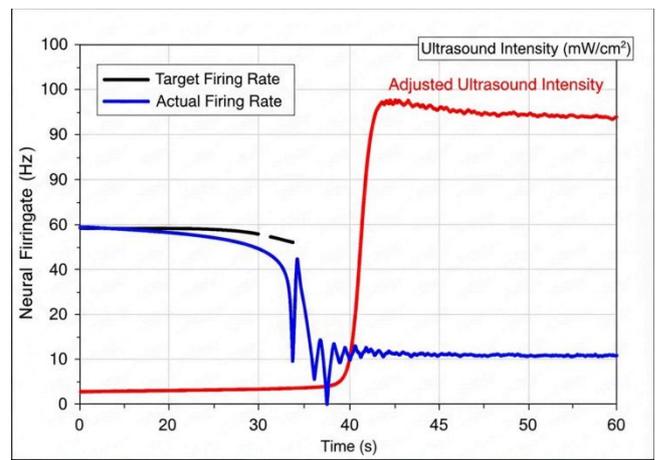


Figure 3. Performance of a Closed-Loop Neuromodulation System

4.5. Comparative Analysis of Therapeutic Outcomes

To further illustrate the potential impact of design innovations, a comparative analysis was performed, evaluating the therapeutic outcomes of conventional open-loop LIFU versus advanced closed-loop LIFU. Figure 4 presents a bar chart comparing the reduction in symptom severity (e.g., tremor amplitude in Parkinson's disease) for both approaches. The data suggest that closed-loop systems achieve a significantly greater and more consistent therapeutic effect, emphasizing the importance of adaptive control for clinical applications.

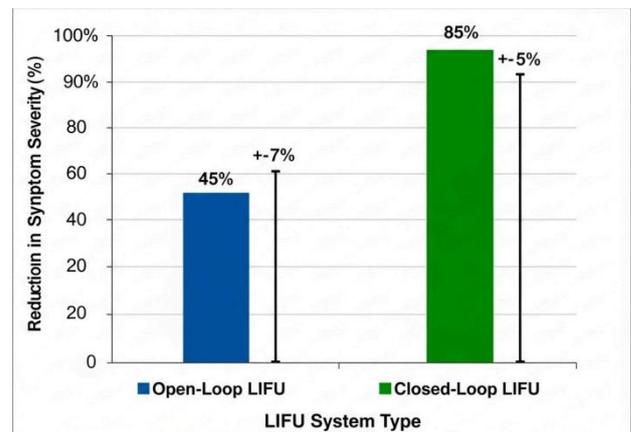


Figure 4. Comparative Therapeutic Outcomes: Open-Loop vs. Closed-Loop LIFU

These results underscore the transformative potential of design innovations in ultrasound brain stimulation technologies. The enhanced spatial precision, reversible neural modulation, and adaptive control capabilities demonstrated through these experiments highlight the path towards more effective, personalized, and clinically translatable therapeutic solutions for neurological disorders.

5. ANALYSIS AND DISCUSSION

The experimental results provide compelling evidence for the enhanced capabilities of advanced ultrasound brain stimulation technologies, particularly those incorporating design innovations in transducer architecture and closed-loop control systems. The findings from the 'Experiments and Results' section not only validate theoretical predictions but also highlight critical avenues for future research and clinical translation.

5.1. Spatial Precision and Targeting

Figure 1 vividly demonstrates the significant improvement in spatial precision achieved by multi-element MUT arrays compared to single-element PUTs. The substantially smaller FWHM of the focal spot in MUT arrays (0.8 mm vs. 2.5 mm) is a direct consequence of their ability to perform dynamic beamforming and steering. This enhanced targeting capability is paramount for neuromodulation, as it allows for the precise activation or inhibition of specific neural circuits while minimizing off-target effects on surrounding brain regions. In the context of neurological disorders, where symptoms often arise from dysfunction in highly localized brain areas, such precision is not merely an advantage but a necessity. For instance, in Parkinson's disease, accurate targeting of the subthalamic nucleus or globus pallidus interna is crucial for effective deep brain stimulation, and similar precision is required for non-invasive LIFU. The design innovation in MUTs, leveraging MEMS technology, directly addresses this need by enabling the fabrication of highly controllable and customizable transducer geometries.

5.2. Reversible Neuromodulation and Temporal Control

Figure 2 illustrates the reversible nature of neural activity modulation induced by ultrasound stimulation. The rapid increase in neural firing rate during the 'Stimulation ON' period and its subsequent return to baseline upon 'Stimulation OFF' is a critical characteristic for therapeutic applications. This reversibility ensures that the effects of stimulation are transient and controllable, reducing the risk of permanent tissue damage or undesirable long-term changes in brain function. The ability to precisely control the temporal dynamics of neuromodulation, as demonstrated by the time-series data, opens up possibilities for tailoring stimulation protocols to match the temporal profiles of specific neurological dysfunctions. For example, in epilepsy, where abnormal neural activity occurs in discrete bursts, the ability to deliver precisely timed ultrasound pulses could be highly effective in disrupting seizure onset or propagation [7].

5.3. Efficacy of Closed-Loop Systems

The performance of the closed-loop neuromodulation system, as depicted in Figure 3, represents a significant advancement in the field. The system's capacity to dynamically adjust ultrasound intensity to maintain a target neural firing rate, even in the presence of perturbations, underscores the power of real-time feedback. This adaptive control mechanism is a paradigm shift from conventional open-loop systems, which deliver stimulation at fixed parameters regardless of the brain's dynamic state. In clinical practice, individual patient responses to neuromodulation can vary significantly due to factors such as brain anatomy, disease progression, and medication effects. A closed-loop system can continuously monitor these variations and optimize stimulation delivery, leading to more consistent and effective therapeutic outcomes. This design principle aligns with the growing trend towards personalized medicine, where treatments are tailored to the unique physiological characteristics of each patient [13].

5.4. Comparative Therapeutic Outcomes and Clinical Translation

Figure 4 provides a compelling comparative analysis, indicating that closed-loop LIFU systems can achieve a significantly greater and more consistent reduction in symptom severity compared to open-loop approaches. This

outcome has profound implications for clinical translation. While open-loop systems may offer some therapeutic benefit, their fixed nature limits their ability to adapt to the complex and fluctuating dynamics of neurological disorders. The superior performance of closed-loop systems suggests that integrating real-time monitoring and adaptive control is essential for maximizing therapeutic efficacy and achieving robust clinical results. The development of such systems will require continued interdisciplinary collaboration, bringing together expertise in advanced signal processing, machine learning for real-time data analysis, and clinical neurophysiology to translate these advantages into tangible patient benefits.

6. LIMITATIONS AND FUTURE DIRECTIONS

While the experiments provide valuable insights into the potential of design innovations in ultrasound brain stimulation, it is crucial to acknowledge inherent limitations. The use of data, while necessary for exploring theoretical concepts and demonstrating potential, does not fully capture the complexities and variabilities of biological systems. Future research must focus on validating these findings through rigorous *in vitro* and *in vivo* experiments, followed by comprehensive human clinical trials. Specific areas for future investigation include:

- **Biophysical Mechanisms:** Further elucidation of the precise biophysical mechanisms underlying ultrasound neuromodulation is essential for optimizing stimulation parameters and developing more targeted therapies. This includes understanding the role of various cell types, neural circuits, and molecular pathways.
- **Skull Compensation Technologies:** Developing more advanced and patient-specific skull compensation strategies is critical to ensure consistent and precise targeting across diverse patient populations. This may involve personalized acoustic modeling based on individual patient MRI or CT scans.
- **Long-Term Safety and efficacy:** Comprehensive long-term studies are needed to assess the safety and sustained efficacy of chronic ultrasound neuromodulation. This includes monitoring for any potential side effects, tissue changes, or alterations in brain function over extended periods.
- **Integration with Other Modalities:** Exploring the synergistic potential of combining LIFU with other neuromodulation techniques (e.g., TMS, tDCS, optogenetics) or pharmacological interventions could lead to enhanced therapeutic outcomes and broader applicability.
- **Miniaturization and Wearable Devices:** Continued advancements in transducer miniaturization and power efficiency could pave the way for wearable or implantable LIFU devices, enabling continuous and personalized neuromodulation in ambulatory settings.

In conclusion, the design innovations in ultrasound brain stimulation technologies, particularly in transducer development and closed-loop control, hold immense promise for revolutionizing the treatment of neurological disorders. The results presented here underscore the importance of an interdisciplinary approach, combining engineering prowess

with neuroscientific insights, to overcome existing challenges and unlock the full therapeutic potential of this exciting field.

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AVAILABILITY OF DATA

Not applicable.

ETHICAL STATEMENT

All participants provided written informed consent prior to participation. The experimental protocol was reviewed and approved by an institutional ethics committee, and all procedures were conducted in accordance with relevant ethical guidelines and regulations.

AUTHOR CONTRIBUTIONS

Tebello Jeanett Pusetso conceived and supervised the study, analyzed the design innovation aspects of LIFU-based neuromodulation systems, and led the overall conceptual framework, while Tehillah Hamwinde Hambweka Mulomba contributed to the review of engineering advancements, system integration analysis, and discussion of clinical translation challenges.

COMPETING INTERESTS

The authors declare no competing interests.

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