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The promise of transcranial focused ultrasound in disorders of consciousness: a narrative review

Dongdong Yang[1†], Shengqi Fu[1†], Meng Zhao[1] and Yu Shi[2*]

Abstract

Transcranial focused ultrasound (tFUS) has emerged as a promising non-invasive neuromodulation technique for disorders of consciousness (DOC). This work critically evaluates tFUS's potential, highlighting its unique ability to precisely modulate deep brain structures, particularly the thalamus, while maintaining non-invasiveness. The mechanisms of action span multiple levels, from membrane-level ion channel modulation to network-wide changes in neural connectivity. Preclinical and early clinical studies have demonstrated tFUS's potential to improve DOC outcomes. Preliminary clinical trials in both acute and chronic DOC patients have shown encouraging results, including diagnostic category shifts, improvements in behavioral responsiveness, and alterations in thalamo-cortical connectivity. However, significant challenges remain. These include optimizing stimulation parameters, addressing variability in patient responses, and ensuring long-term safety. The current evidence base is limited, necessitating larger, more rigorous investigations. Future research should focus on multicenter randomized controlled trials to comprehensively evaluate tFUS across different DOC etiologies and chronicity. Key priorities include identifying predictive biomarkers, exploring combination therapies, and addressing ethical considerations. While tFUS shows significant promise in DOC management, further investigation is crucial to refine its application and establish its definitive clinical role.

Keywords Disorders of consciousness (DOC), Transcranial focused ultrasound (tFUS), Neuromodulation, Brain stimulation, Thalamus

Introduction

Disorders of consciousness (DOC), including coma, vegetative state, and minimally conscious state, present a significant challenge in clinical neurology [1]. Despite advances in diagnosis and supportive care, effective treatments for DOC remain limited [2]. In recent years, transcranial focused ultrasound (tFUS) has emerged as a promising non-invasive neuromodulation technique that can modulate deep brain structures in DOC patients, potentially improving consciousness and functional connectivity [3–6]. While tFUS has shown promise in several other neurological conditions such as Parkinson's disease [7], chronic pain [8], essential tremor [9], epilepsy [10], and stroke [11], clinical evidence in these disorders remains limited compared to DOC, highlighting the need for further investigation to establish tFUS's therapeutic role across neurological diseases. In this narrative review, we examine current evidence, challenges, and future directions to establish a foundation for the clinical translation of tFUS in DOC management.

†Dongdong Yang and Shengqi Fu are co-first authors who contributed equally to this work.

*Correspondence:
Yu Shi
windrv@126.com
[1] Department of Neurology, The Fifth Clinical Medical College of Henan University of Chinese Medicine (Zhengzhou People's Hospital), Zhengzhou 450000, China
[2] Department of Rehabilitation, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, China

Unique advantages of tFUS in DOC treatment

tFUS utilizes low-intensity ultrasound waves (0.25–0.5 MHz) delivered through a single-element transducer or multi-element array to focally modulate specific brain regions (Fig. 1). Its unique ability to target small areas (few millimeters in diameter) deep within the brain while maintaining non-invasiveness makes it particularly promising for DOC treatment [5, 12–14].

The unique properties of tFUS offer significant advantages over other neuromodulation techniques. Unlike deep brain stimulation (DBS), which has shown promise in DOC but requires invasive surgery, tFUS is associated with lower risks and broader applicability [15]. While transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are also non-invasive, they primarily affect superficial cortical regions and lack the spatial specificity and deep brain targeting capability of tFUS [16, 17]. This limitation restricts their ability to directly modulate subcortical structures crucial for consciousness, such as the thalamus.

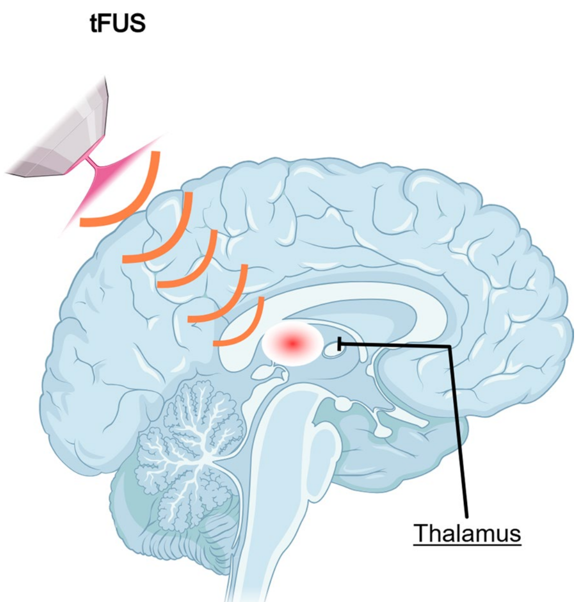

Fig. 1 Schematic illustration of tFUS targeting the thalamus. Abbreviation: tFUS: Transcranial focused ultrasound

Thus, tFUS uniquely combines non-invasiveness with precise targeting of deep brain structures, positioning it as a potentially transformative approach in DOC treatment. Its ability to focus on specific deep brain regions without affecting intervening tissues offers a level of precision and safety that is unmatched by other current neuromodulation techniques.

Mechanisms of action

The precise mechanisms by which tFUS modulates neural activity are still under investigation. However, several hypotheses have been proposed. One prevailing hypothesis suggests that ultrasound waves cause mechanical deformation of neuronal membranes. This deformation results in changes in membrane capacitance and the opening of voltage-gated ion channels [18, 19] (Fig. 2). This can result in altered neural excitability and firing patterns. Another hypothesis proposes that ultrasound induces cavitation in the lipid bilayer of cell membranes, potentially affecting membrane properties and cellular signaling [20].

Recent studies have provided insights into the neurophysiological effects of tFUS, particularly in the context

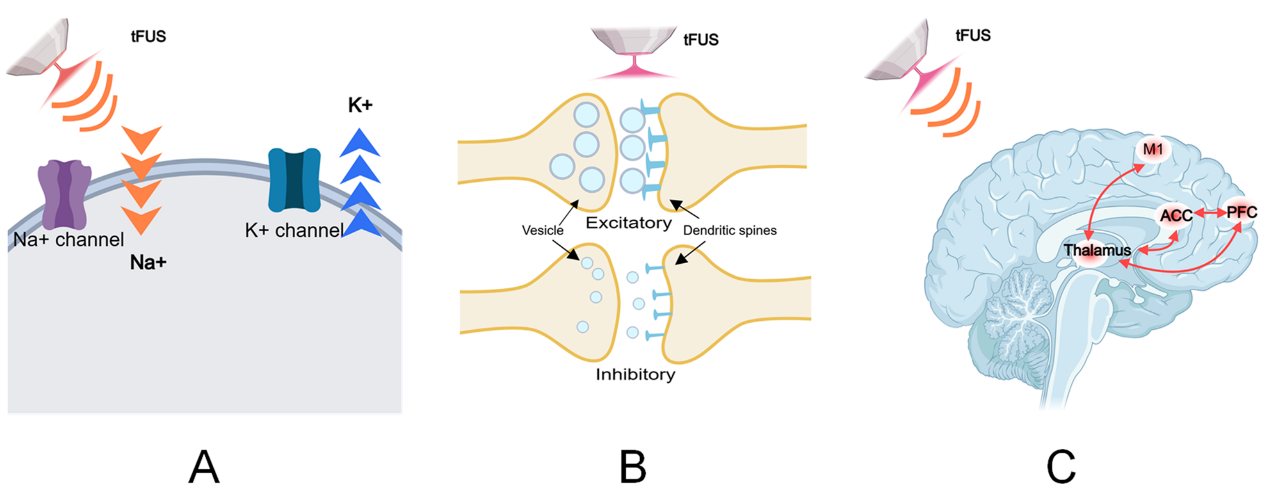

Fig. 2 Multi-level mechanisms of tFUS neuromodulation. **A** Membrane-level effects showing ultrasound-induced modulation of ion channels; **B** Synaptic-level changes demonstrating enhanced excitatory and reduced inhibitory transmission; **C** Network-level modulation of thalamo-cortical connectivity. *ACC* Anterior cingulate cortex, *PFC* Prefrontal cortex, *M1* Primary motor cortex, *tFUS* Transcranial focused ultrasound

of DOC. Thalamo-cortical connectivity, which is crucial for the regulation of consciousness, appears to be a primary target of tFUS modulation. Legon et al. demonstrated that tFUS targeting the thalamus in healthy humans could modulate thalamo-cortical functional connectivity, as measured by electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) [21]. This finding is particularly relevant for DOC, as disrupted thalamo-cortical connectivity is a hallmark of these conditions [22, 23].

Furthermore, emerging evidence suggests that tFUS may influence multiple pathways relevant to consciousness and recovery. Studies have shown that tFUS can enhance dopamine release in the striatum [24], suggesting its potential to modulate neurotransmitter systems involved in arousal and consciousness. Additionally, preclinical studies have demonstrated that tFUS can improve neurological outcomes through various mechanisms, including enhanced cerebral blood flow, reduced neuroinflammation, and improved brain edema clearance [25, 26]. These findings suggest that tFUS may be particularly beneficial in DOC resulting from various etiologies, including ischemic injuries and traumatic brain injury.

Interestingly, the effects of tFUS appear to be highly dependent on stimulation parameters such as frequency, intensity, and duty cycle. Plaksin et al. demonstrated that different tFUS parameters could induce either excitatory or inhibitory effects on neural activity in mice [27]. This parameter-dependent effect offers the potential for precise tuning of neural modulation, which could be crucial for optimizing tFUS protocols in DOC treatment.

Clinical evidence in DOC

The clinical translation of tFUS in DOC began with a groundbreaking case report by Monti et al. in 2016. They applied tFUS to the thalamus of a 25-year-old male patient with acute DOC, 19 days post-injury, using a frequency of 650 kHz and a pulse repetition frequency of 100 Hz. The patient showed remarkable improvement, with Coma recovery scale–revised (CRS-R) scores increasing from 14–15 to 13–17 post-tFUS. More significantly, the patient demonstrated full language comprehension and reliable communication three days post-tFUS, and attempted to walk five days post-tFUS [28]. This initial success demonstrated both the feasibility and potential efficacy of tFUS in DOC patients.

Building on this promising result, Cain and colleagues conducted a series of systematic investigations that progressively expanded both the scope and scale of tFUS application in DOC. Their research trajectory began with a pilot study of three chronic DOC patients [4], evolved to include 11 acute DOC patients [29], and culminated in a larger cohort study of 10 chronic DOC patients [30]. These studies shared a common protocol of targeting the left central thalamus, but varied in patient characteristics and follow-up duration.

The results across these studies showed a consistent pattern of improvement in a subset of patients. In the 11 acute DOC patients, a single tFUS session led to significant increases in CRS-R scores ($p=0.014$), with 4 patients (approximately 36%) showing diagnostic category improvements (coma to VS, VS to MCS) [29]. In the 10 chronic DOC patients, two sessions administered one week apart resulted in similar positive outcomes, with 4 patients (40%) demonstrating diagnostic improvements (VS/MCS- to MCS+/eMCS) and significant linear increases in CRS-R scores ($p=0.019$ for total score) [30]. Importantly, fMRI analyses revealed that behavioral improvements correlated with specific changes in thalamic functional connectivity—decreased connectivity between the targeted thalamus and frontal regions (including prefrontal cortex and striatum) coupled with increased connectivity with the contralateral motor cortex, parietal and occipital lobes in both acute and chronic patients [29, 30]. These bidirectional connectivity changes provide mechanistic support for the observed clinical benefits.

Challenges and limitations

While initial tFUS studies in DOC patients show promise, the current evidence base remains limited. To date, only four clinical studies have been published [4, 28–30], including one case report and three small cohort studies with a total of 24 patients (1 patient in the initial case report, 3 patients in the first pilot study, 11 patients in the acute DOC study, and 10 patients in the chronic DOC study). This small sample size and limited number of studies represent a significant limitation. Additionally, several other challenges need to be addressed to fully harness tFUS's potential as a therapeutic intervention. The efficacy of tFUS varies across different patient subgroups, with patients suffering from traumatic brain injury, acute DOC, or in a minimally conscious state potentially showing better responses. Younger patients and those with preserved thalamo-cortical connections might also benefit more from this treatment. However, the factors influencing treatment outcomes are not fully understood, as evidenced by the study of Cain et al., where one out of three chronic DOC patients exhibited no significant improvement after tFUS sessions [4]. This variability in patient responses highlights the need for a better understanding of the characteristics predicting treatment efficacy, which could help refine patient selection criteria and personalize tFUS protocols (Fig. 3).

A significant challenge in tFUS application is the determination of optimal stimulation parameters. Current

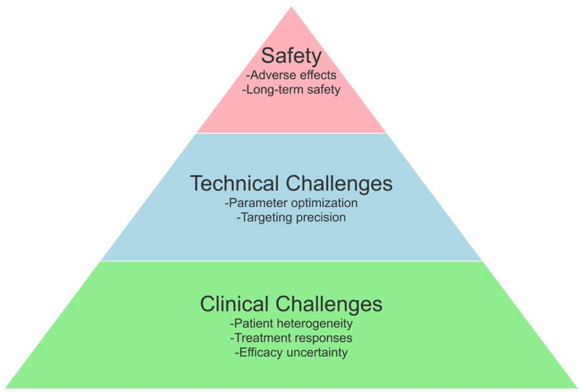

Fig. 3 Hierarchical challenges of tFUS application in DOC treatment. *DOC* Disorders of consciousness, *tFUS* Transcranial focused ultrasound

studies have employed a range of frequencies, intensities, and durations, necessitating a systematic comparison of their efficacy and safety [31]. Additionally, individual variability in skull thickness and density can affect ultrasound wave propagation, potentially leading to inconsistent tFUS effects across patients [32]. These technical challenges underscore the importance of developing advanced neuronavigation techniques and personalized computational models. Such advancements could ensure more precise targeting of deep brain structures, potentially improving response rates and minimizing adverse effects [21, 33].

While tFUS is generally considered safe, current safety assessments in DOC patients have been limited to basic vital parameter monitoring and adverse event documentation, with no serious adverse effects reported across 24 patients in 4 DOC studies [4, 28–30]. However, small studies in other neurological conditions have reported mild and transient adverse effects, including headache, neck pain, somnolence, scalp tingling, and drowsiness, typically resolving within 24 h without worsening upon repeated stimulation [34–36]. Establishing safety thresholds specific to therapeutic neuromodulation in DOC patients, accounting for factors such as skull density, repeated exposures, and patient conditions, remains crucial. Future DOC studies should implement rigorous safety protocols, including advanced neuroimaging to assess tissue effects, extended follow-up periods (6–12 months), and standardized adverse event monitoring [34, 37, 38].

Future directions

Advancing the clinical translation of tFUS for DOC requires a comprehensive research strategy centered on large-scale, multicenter randomized controlled trials. These trials should incorporate rigorous methodological standards, including appropriate sample size calculations, predefined outcome measures, and proper randomization and blinding techniques [39]. Particular attention should be paid to controlling potential confounders such as spontaneous recovery and concurrent treatments, while implementing standardized assessment protocols to ensure reliable and comparable results across different centers (Fig. 4).

The optimization of tFUS protocols represents another crucial research direction. This includes developing personalized approaches based on individual patient characteristics such as etiology, duration of DOC, and neuroanatomical features [40]. The identification of reliable biomarkers or clinical characteristics that predict treatment response could significantly enhance patient selection and treatment outcomes [1].

Exploring combination therapies offers a promising avenue for enhancing tFUS efficacy. Future studies should investigate potential synergistic effects between tFUS and other therapeutic modalities, including pharmacological agents (e.g., amantadine, zolpidem) and rehabilitation programs [41]. Such combination approaches could potentially provide more comprehensive and effective treatment strategies for DOC patients.

As tFUS research advances, addressing ethical, legal, and social implications becomes increasingly important

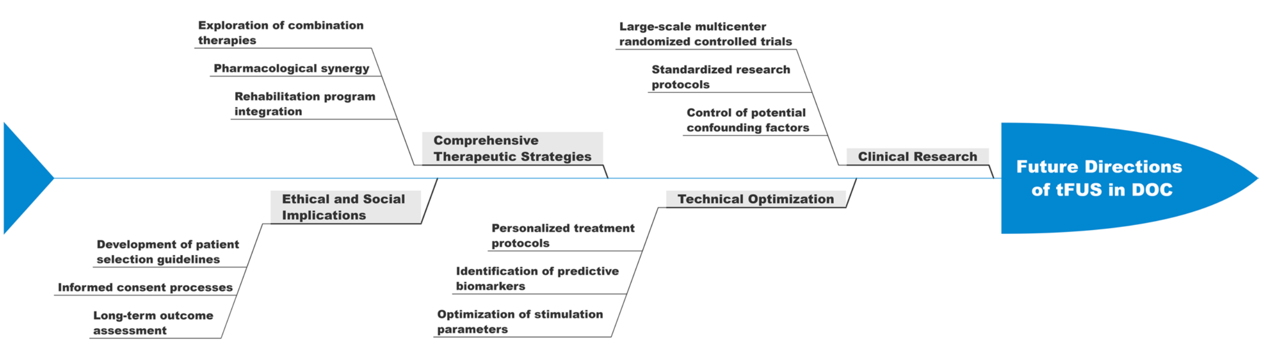

Fig. 4 Key future directions for tFUS in DOC. *DOC* Disorders of consciousness, *tFUS* Transcranial focused ultrasound

[42]. This includes developing guidelines for patient selection and informed consent, as well as assessing the impact on patients' quality of life and long-term outcomes [22]. Engaging diverse stakeholders—including healthcare professionals, patient advocates, and policymakers—will be crucial for responsible implementation of tFUS-based interventions.

Finally, while DOC remains the primary focus, the unique capabilities of tFUS suggest potential applications in other neurological conditions [43, 44]. Expanding research into these areas could broaden the therapeutic impact of this technology while providing valuable insights for its optimization in DOC treatment [13].

Conclusion

tFUS represents a promising frontier in DOC treatment, offering unique advantages through its ability to non-invasively modulate deep brain structures. Early clinical evidence has demonstrated encouraging results in both acute and chronic DOC patients, with improvements in consciousness levels and functional connectivity. While these findings are promising, several key challenges remain to be addressed, including optimization of stimulation parameters and understanding patient response variability. The path forward requires rigorous clinical trials, development of personalized protocols, and careful consideration of safety and ethical implications. As research progresses, tFUS has the potential to not only transform DOC treatment but also extend its benefits to other neurological conditions [45–48], bringing new hope to patients and families affected by these devastating disorders.

Abbreviations

ACC	Anterior cingulate cortex
CRS-R	Coma recovery scale–revised
DBS	Deep brain stimulation
DOC	Disorders of consciousness
EEG	Electroencephalography
fMRI	Functional magnetic resonance imaging
PFC	Prefrontal cortex
M1	Primary motor cortex
TBI	Traumatic brain injury
tDCS	Transcranial direct current stimulation
tFUS	Transcranial focused ultrasound
TMS	Transcranial magnetic stimulation

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Author contributions
DY, SF, MZ and YS drafted the original manuscript. All authors read and approved the final manuscript. DY and SF contributed to the work equally and should be regarded as co-first authors.

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Declarations

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The authors declare that they have no competing interests.

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