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Risk of low-frequency ultrasound stimulation: Response to Brain injury during focused ultrasound neuromodulation for substance use disorder

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Abstract:: Low-intensity transcranial focused ultrasound (tFUS) stimulation is an emerging non-invasive neuromodulation technique with potential applications in the treatment of neurological and psychiatric disorders, including substance use disorders. However, recent reports of serious adverse events have raised important questions regarding the safety of low-frequency ultrasound protocols and the influence of acoustic exposure parameters on brain tissue. This letter addresses concerns arising from a previously reported case of brain injury during focused ultrasound neuromodulation for substance use disorder and emphasizes the importance of detailed characterization of sonication parameters when evaluating the safety of tFUS. Particular attention is given to acoustic intensity, mechanical index, ultrasound frequency, and other exposure characteristics that may influence the likelihood of unintended bioeffects, including inertial cavitation. The authors acknowledge the limitations associated with incomplete reporting of acoustic parameters in earlier studies and highlight the need for standardized and transparent reporting to facilitate meaningful comparisons across experimental protocols. Importantly, the reported adverse event should be interpreted within the context of the specific ultrasound system, stimulation parameters, and treatment conditions rather than being generalized to all forms of low-intensity ultrasound neuromodulation. The available evidence supports continued investigation of tFUS while emphasizing rigorous safety assessment, precise acoustic characterization, appropriate exposure limits, and systematic monitoring of adverse effects. Further experimental and clinical research is required to establish parameter-specific safety margins and to support the responsible translation of low-frequency focused ultrasound neuromodulation into clinical practice.

Keywords: Low-frequency ultrasound stimulation, transcranial focused ultrasound (tFUS), neuromodulation, brain injury, substance use disorder, ultrasound safety, acoustic exposure, mechanical index, inertial cavitation, focused ultrasound, non-invasive brain stimulation, adverse effects, neurostimulation, safety assessment, clinical translation

Introduction:

Transcranial focused ultrasound (tFUS) has emerged as a promising non-invasive neuromodulation technique capable of modulating neural activity with high spatial precision and reaching deep brain structures that may be difficult to access using conventional non-invasive brain stimulation methods. In recent years, low-intensity transcranial ultrasound stimulation has been

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investigated in both preclinical and clinical studies for a range of neurological and psychiatric conditions, including substance use disorders. Systematic reviews of human and animal studies have generally reported a favorable safety profile, although the available evidence remains heterogeneous with respect to ultrasound frequency, acoustic intensity, pulse characteristics, exposure duration, and safety assessment methods.

Despite its therapeutic potential, the safety of tFUS remains an important area of investigation. Acoustic exposure parameters may influence both the neuromodulatory effects and the potential for unintended biological effects. In particular, lower ultrasound frequencies can be associated with increased mechanical effects and may alter the probability of cavitation under certain exposure conditions. Excessive acoustic intensity, prolonged stimulation, or inappropriate combinations of sonication parameters have been associated in experimental studies with adverse biological effects, including tissue damage, hemorrhage, and blood–brain barrier disruption. Consequently, accurate characterization and standardized reporting of acoustic parameters are essential for assessing the safety and reproducibility of tFUS protocols.

The clinical relevance of these safety considerations has been highlighted by a 2025 report describing brain injury occurring during focused ultrasound neuromodulation for substance use disorder. This report prompted subsequent scientific discussion concerning the interpretation of the adverse event, the specific ultrasound parameters employed, and the extent to which the observed injury can be generalized to low-frequency ultrasound neuromodulation more broadly.

In this context, Bishay et al. published Risk of low-frequency ultrasound stimulation: Response to “Brain injury during focused ultrasound neuromodulation for substance use disorder” in Brain Stimulation in 2026. The publication contributes to the ongoing scientific discussion regarding the relationship between low-frequency ultrasound exposure and potential adverse effects during transcranial neuromodulation.

Therefore, continued evaluation of the biophysical mechanisms underlying ultrasound-induced effects, together with standardized reporting of frequency, acoustic pressure, intensity, mechanical index, duty cycle, pulse duration, and sonication duration, is essential for establishing reliable safety boundaries. Such evidence is particularly important for the responsible translation of tFUS from experimental research into clinical applications.

Main Body

Transcranial focused ultrasound (tFUS) is increasingly investigated as a non-invasive neuromodulation approach because it can influence neural activity with relatively high spatial precision and can target brain regions that are difficult to access using other non-invasive stimulation techniques. Its potential application in substance use disorders has generated particular interest because modulation of neural circuits involved in reward processing, motivation, and behavioral control may provide an alternative therapeutic strategy. Nevertheless, the expansion of clinical

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applications has increased the importance of establishing reliable safety parameters for ultrasound exposure.

One of the central issues in evaluating the safety of low-frequency ultrasound is the relationship between acoustic parameters and biological effects. Ultrasound stimulation can produce both mechanical and thermal effects in biological tissues. Mechanical effects are particularly relevant at lower frequencies because the mechanical index is inversely related to the square root of ultrasound frequency. Under certain exposure conditions, acoustic pressure may contribute to cavitation-related effects, tissue strain, or other mechanical interactions. The probability and magnitude of these effects depend not only on frequency but also on acoustic pressure, pulse duration, duty cycle, exposure time, tissue characteristics, and the presence of potential cavitation nuclei.

The mechanical index (MI) is therefore an important parameter for evaluating the potential mechanical effects of ultrasound. The International Transcranial Ultrasonic Stimulation Safety and Standards consortium (ITRUSST) has proposed that, in the absence of cavitation nuclei such as ultrasound contrast agents, mechanical risk can be considered non-significant when the MI or transcranial mechanical index (MI_tc) does not exceed 1.9. However, this value should not be interpreted as an absolute threshold above which tissue damage necessarily occurs. Rather, it represents a conservative reference level supported by available evidence and established regulatory considerations. Protocols exceeding this level cannot automatically be classified as unsafe, but they require additional scientific justification and safety monitoring.

Another important consideration is the distinction between the mechanical index measured under standardized conditions and the acoustic pressure actually delivered to the brain. The skull can substantially influence ultrasound propagation through attenuation, reflection, refraction, and phase distortion. Consequently, measurements obtained in water or free-field conditions may not accurately represent the acoustic exposure at the intended intracranial target. Subject-specific anatomical characteristics, including skull thickness and composition, may further modify the transmitted acoustic field. Accurate estimation of in situ acoustic pressure is therefore essential when assessing the safety of transcranial ultrasound stimulation.

Thermal effects represent another potential safety concern. Although low-intensity neuromodulation protocols are generally designed to minimize tissue heating, prolonged sonication or inappropriate combinations of acoustic intensity and duty cycle may increase tissue temperature. Current ITRUSST consensus recommendations consider a temperature increase of no more than 2 °C, or an absolute temperature not exceeding 39 °C under a baseline temperature of 37 °C, to represent a non-significant thermal risk under the specified assumptions. These values are intended as conservative biophysical safety considerations rather than definitive clinical safety limits.

The discussion surrounding the safety of low-frequency ultrasound has become particularly relevant following the publication of a 2025 report describing brain injury during focused ultrasound neuromodulation for substance use disorder. The report raised important questions regarding the

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relationship between the stimulation protocol and the observed adverse event. However, the occurrence of an adverse event during one experimental or clinical protocol should not automatically be generalized to all low-frequency ultrasound neuromodulation procedures. Interpretation requires careful consideration of the specific ultrasound frequency, acoustic pressure, pulse parameters, treatment duration, targeting method, skull characteristics, and other relevant experimental conditions.

The subsequent response by Bishay and colleagues emphasizes the importance of evaluating ultrasound exposure on the basis of quantitative acoustic parameters rather than relying solely on the nominal frequency of stimulation. In this context, low-frequency ultrasound should not be regarded as inherently hazardous solely because of its frequency. Instead, the potential biological effects depend on the interaction between frequency, pressure amplitude, pulse characteristics, exposure duration, and tissue environment. This distinction is important for interpreting reports of adverse events and for determining whether a particular stimulation protocol falls within an established or experimentally supported safety range.

Standardized reporting is consequently a critical component of tFUS research. Studies should provide sufficient information regarding ultrasound frequency, peak-rarefactional pressure, spatial-peak temporal-average and pulse-average intensities where applicable, mechanical index, duty cycle, pulse duration, pulse repetition frequency, total sonication duration, transducer characteristics, and methods used to estimate in situ exposure. The ITRUSST standardized reporting recommendations were developed specifically to improve reproducibility and facilitate meaningful comparison between studies. Inadequate reporting of these parameters can make it difficult to determine whether apparently similar ultrasound protocols actually produce comparable biological exposures.

Safety monitoring should also extend beyond immediate clinical symptoms. Depending on the research protocol, appropriate monitoring may include neurological assessment, imaging, temperature monitoring, acoustic field characterization, and, where appropriate, passive cavitation detection. Such measures can help identify unexpected mechanical or thermal effects and provide additional information regarding the relationship between stimulation parameters and biological outcomes.

Overall, the available evidence indicates that the safety of low-frequency transcranial ultrasound cannot be determined by frequency alone. A comprehensive assessment requires consideration of the complete acoustic exposure profile and the anatomical characteristics of the individual receiving stimulation. The current scientific discussion therefore supports a parameter-specific approach to safety evaluation, emphasizing accurate acoustic measurements, standardized reporting, appropriate monitoring, and cautious interpretation of adverse events. Further preclinical and clinical research is required to define exposure-dependent safety margins and to establish evidence-based frameworks for the broader clinical application of tFUS in substance use disorders and other neurological and psychiatric conditions.

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Conclusion:

Low-frequency transcranial focused ultrasound represents a promising approach for non-invasive neuromodulation, with potential applications in the treatment of neurological and psychiatric disorders, including substance use disorders. However, its increasing clinical and experimental use requires careful consideration of potential mechanical and thermal effects associated with ultrasound exposure. The available evidence indicates that the safety profile of tFUS is determined not by ultrasound frequency alone, but by the combined influence of acoustic pressure, mechanical index, pulse duration, duty cycle, exposure time, targeting characteristics, and individual anatomical factors.

The reported case of brain injury during focused ultrasound neuromodulation for substance use disorder highlights the importance of rigorous safety assessment and transparent interpretation of adverse events. Such findings should be evaluated in relation to the specific acoustic and experimental conditions under which they occurred rather than being generalized to all low-frequency ultrasound stimulation protocols. Standardized reporting of ultrasound parameters and accurate estimation of intracranial acoustic exposure are essential for improving reproducibility and enabling meaningful comparison between studies.

Future research should focus on establishing parameter-specific safety margins through well-controlled preclinical and clinical investigations. Comprehensive monitoring, standardized protocols, individualized acoustic modeling, and systematic reporting of adverse effects will be essential for the responsible development of transcranial focused ultrasound. Continued research in these areas may help clarify the therapeutic potential of low-frequency ultrasound while ensuring that its clinical application is supported by robust evidence of safety and efficacy.

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