Brain Stimulation 19 (2026) 103091

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.journals.elsevier.com/brain-stimulation

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

Dear Editor,

We are writing to offer our perspective on the correspondence by Rezai et al. [1], disclosing a serious adverse event (SAE) incurred by low-intensity transcranial focused ultrasound stimulation (tFUS). Like others, we recognize the limitation in only providing the 90 W free-field power output in the initial report and commend the tFUS community for successfully pushing for the release of more detailed sonication parameterization, including mechanical index (MI) and intensity, to compare to the published record of safety of low-intensity tFUS [2]. Recently published work by the International Transcranial Ultrasonic Stimulation Safety and Standards (ITRUSST) consortium synthesizes these observations into practical biophysical limits: in the absence of contrast agents, MI (or MItc) ≤ 1.9 and conservative thermal constraints ($\Delta T < 2$ °C, low thermal dose) define a nonsignificant-risk for neuromodulation [3]. New reports have shown that Rezai et al. exceeded these guidelines, with MI estimates ranging from 2.7 to 5.1 [4]. However, beyond index exceedance alone, this case highlights another safety consideration for the field: when neuromodulation is conducted using low carrier frequencies in combination with high-output, repurposed ultrasound systems, mechanical and spatial safety margins may be intrinsically narrowed.

At mid-frequency (~500–700 kHz), low-intensity pulsed tFUS neuromodulation has an excellent record of safety. Systematic reviews of human tFUS report no serious adverse effects across dozens of studies (many clustered around ~500–650 kHz), with only mild, transient symptoms (e.g., scalp sensations or headache) and no lasting neurological or radiological abnormalities when parameters remain conservative [2]. In a recent study, 650 kHz tFUS was safe when applied to the right amygdala with stimulation parameters up to MI = 2.803 and $I_{SPTA.3} = 10.08$ W/cm^2 [5], both well beyond the ITRUSST recommendations. While these values could be lower than those used during the SAE, they shouldn't be interpreted as a direct comparator. Rather, they illustrate that neuromodulation may be performed safely beyond conservative guideline limits when operating in parameter regimes with wider mechanical tolerance, under carefully controlled conditions, and with full transparency of acoustic exposure.

Subsequently, an important factor to consider in the Rezai et al. case is the narrowed cavitation safety margin of tFUS at low fundamental frequencies using a repurposed device such as that used in the report of Rezai et al. (i.e., 220 kHz). Since cavitation thresholds increase with frequency, protocols at ~600–700 kHz have a wider mechanical safety margin at a given pressure than those at ~200–340 kHz, all else equal—a key reason many neuromodulation programs have converged on the mid-frequency range [3]. Low-frequency operation (~200–340 kHz), such as the 220 kHz employed by the device used by Rezai et al. narrows safety margins via lower cavitation thresholds and broader focal volumes, increasing susceptibility to off-target energy deposition and baro-mechanical bioeffects. It is an established fact that lowered frequency increases the risk of standing waves in the brain given the longer wavelengths, leading to increased risk of cavitation and hemorrhaging [6].

Modeling and experimental work has further quantified this narrowing of cavitation safety margins at low frequencies. For example, McDannold et al. estimated that, for low-frequency transcranial ultrasound, cavitation levels whose mechanical energy dissipation would produce non-negligible secondary heating correspond to MItc values in the range of approximately 3.8–4.4 [7]. These estimates are substantially higher than typical low-intensity tFUS exposures and provide an upper bound for cavitation-related bioeffects in the absence of contrast agents.

This is not just a theoretical concern; historical clinical experience highlights how low-frequency transcranial ultrasound exposures can narrow safety margins under certain biological conditions, even when nominal acoustic indices appear acceptable. One example of this was the prematurely suspended TRUMBI Phase II clinical trial for acute ischemic stroke which applied transcranial ultrasound at 300 kHz to patients with severe cerebral small vessel disease. Patients were assigned to receive either tPA or tPA plus ultrasound, and in that context, characterized by pre-existing vascular pathology, impaired cerebral hemodynamics, and pharmacologic thrombolysis, the ultrasound arm exhibited a significantly increased rate of intracranial hemorrhage, prompting early termination [8]. These clinically significant bioeffects were observed at MI and TI values within the envelope described by the ITRUSST guidelines, employing a conventional pulsation scheme (e.g., 100 Hz pulse repetition frequency, 5% duty cycle) and energy levels (i.e., $I_{SPTA} = 700$ mW/cm^2, MI < 0.2, Tis<0.5, TIC≈4) consistent with the FDA's guidelines for diagnostic ultrasound. Subsequent analyses and commentaries around TRUMBI have repeatedly highlighted the bleeding signal observed with ~300–340 kHz sonication through the skull. While TRUMBI was not a neuromodulation study and involved patients with severe vascular pathology, it clearly demonstrates that low-frequency exposures can potentiate harm transcranially, especially when other risk factors (e.g., thrombolysis, microbubbles) are present [9].

Notably, the Insightec ExAblate Neuro system operating at 220 kHz was originally engineered and FDA-approved for transient blood–brain barrier (BBB) disruption, not for neuromodulation [10]. Its use for neuromodulation in this context, therefore, represents a substantial repurposing of the device. While the focal spot reported by Rezai et al. is on the order of a few millimeters (~5 × 5 × 7 mm), the ExAblate Neuro platform is capable of generating substantially broader effective treatment volumes through electronic steering, sonication sequencing, and high-power operation at low fundamental frequencies [11]. As a result,

https://doi.org/10.1016/j.brs.2026.103091
Received 18 November 2025; Received in revised form 5 January 2026; Accepted 27 March 2026
Available online 29 March 2026

its physical and acoustic architecture, including large aperture geometry and high output headroom, may place greater reliance on careful parameter selection and monitoring than devices developed specifically for neuromodulation with inherent output limits. When researchers use systems not built for this purpose, full transparency around sonication parameters is essential to enable proper safety evaluation and to protect patients.

As it stands, the field has a contemporary neuromodulation SAE to consider. The WVU/RNI report provides a concrete reminder that modern protocols can still breach safety measures if margins are inadequate. Notably, this same WVU/RNI group previously described nucleus accumbens tFUS as "safe and a potential adjunctive treatment," underscoring that the sonication target was not the point of safety concern [12]. These collectively point to the safety risk associated with decreased safety margins at low fundamental frequencies. Additionally, since frequency interacts strongly with device design, especially focal geometry and cavitation thresholds, the choice of hardware is inseparable from the resulting safety margins.

The WVU/RNI case underscores predictable constraints on mechanical and spatial safety margins of tFUS: when using systems with a low fundamental frequency not designed specifically for neuromodulation, the margins for mechanical effects narrow, and adverse events may become more likely. Carefully parameterized ~650 kHz stimulation using devices developed for neuromodulation, at low intensities and duty cycles, has consistently shown an excellent safety profile, even at MI values above 2.5 and $I_{SPTA.3}$ exceeding 10 W/cm^2. Notably, MI incorporates frequency (the lower the frequency the higher the MI), so by using higher frequency ultrasound devices, a greater pressure and intensity of sonication could be delivered at the same MI than what would've been achieved with a lower frequency. Accordingly, while some will call for stricter guidelines on tFUS parameterization, reminding the field of the narrowed safety margins during low-frequency operation, and aligning future protocols and device selection accordingly, is the most immediate, evidence-aligned path to reduce the likelihood of similar events.

CRediT authorship contribution statement

Andrew A.E.D. Bishay: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Formal analysis, Data curation, Conceptualization. **Samantha Schafer:** Writing – review & editing, Writing – original draft, Visualization, Validation. **Alexander Bystritsky:** Writing – review & editing, Writing – original draft, Visualization, Validation, Conceptualization. **William J. Tyler:** Writing – review & editing, Writing – original draft, Visualization, Validation, Funding acquisition. **Martin M. Monti:** Writing – review & editing, Writing – original draft, Visualization, Funding acquisition. **Jan Kubanek:** Writing – review & editing, Writing – original draft, Visualization, Funding acquisition. **Joseph L. Sanguinetti:** Writing – review & editing, Writing – original draft, Visualization, Funding acquisition. **Norman M. Spivak:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Disclosures

Mr. Bishay and Dr. Spivak are consultants to BrainSonix Inc. Ms. Schafer is an inventor on neuromodulation patents. Dr. Bystritsky is the CEO and shareholder of BrainSonix and inventor on neuromodulation and treatment patents. Dr. Tyler is a co-founder and shareholder of IST, LLC and Diamond Therapeutics, Inc and inventor on neuromodulation and pharmaceutical patents. Dr. Kubanek is a co-founder of SPIRE Therapeutics Inc. Dr. Sanguinetti is co-founder, CEO, and shareholder of Sanmai Technologies, PBC. Other authors report no conflicts of interest.

Funding

Funding Sources: NIH T32GM008042(to NMS), NIH F30MH136802 (to NMS), DOD CDMRP HT9425-24-1-1081 (to MMM), NIH R21EB034428 (to MMM). NIH grants RF1NS128569(JK) and MH134943(JK), NSF NCS-FO 2220677(WJT), NSF CBET 2325125(JK), and Wellcome Leap (JK).

Declaration of competing interest

Mr. Bishay and Dr. Spivak are consultants to BrainSonix Inc. Ms. Schafer is an inventor on neuromodulation patents. Dr. Bystritsky is the CEO and shareholder of BrainSonix and inventor on neuromodulation and treatment patents. Dr. Tyler is a co-founder and shareholder of IST, LLC and Diamond Therapeutics, Inc and inventor on neuromodulation and pharmaceutical patents. Dr. Kubanek is a co-founder of SPIRE Therapeutics Inc. Dr. Sanguinetti is co-founder, CEO, and shareholder of Sanmai Technologies, PBC. Other authors report no conflicts of interest.

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Andrew A.E.D. Bishay[a,*], Samantha Schafer[b], Alexander Bystritsky[a], William J. Tyler[c], Martin M. Monti[a,d,e], Jan Kubanek[f], Joseph L. Sanguinetti[g], Norman M. Spivak[a,e,h,1]

[a] *Department of Psychiatry & Biobehavioral Sciences, UCLA, 760 Westwood Plaza, Los Angeles, CA, 90095, United States*

[b] *School of Biomedical Engineering, Science and Health Systems, Drexel University, Philadelphia, PA, United States*

[c] *Department of Biomedical Engineering, University of Alabama at Birmingham and Heersink UAB School of Medicine, Birmingham, AL, 35233, United States*

[d] *Department of Psychology, UCLA, 760 Westwood Plaza, Suite C8-519, Los Angeles, CA, 90095, United States*

[e] Department of Neurosurgery, UCLA, 760 Westwood Plaza, Suite C8-519, Los Angeles, CA, 90095, United States
[f] Departments of Psychiatry, Radiology, Neurology, and Biomedical Engineering, Washington University, St. Louis, MO, 63130, United States
[g] Department of Psychology, University of Arizona, Tucson, AZ, 85711, United States
[h] UCLA-Caltech Medical Scientist Training Program, United States

[*] Corresponding author.
E-mail addresses: andrewbishay@ucla.edu (A.A.E.D. Bishay), Nspivak@mednet.ucla.edu (N.M. Spivak).

[1] Senior Author.