Symposium

Focused Ultrasound Neuromodulation: Biophysical Mechanisms, Neural Effects, and Clinical Translation

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Low-intensity transcranial ultrasound stimulation (TUS) has emerged as a promising noninvasive neuromodulation technology capable of targeting both cortical and deep brain structures with millimeter-scale spatial precision. Recent advances in ultrasound hardware, acoustic modeling, neuronavigation, and multimodal imaging have accelerated the field from proof-of-concept demonstrations toward mechanistic investigation and early clinical translation. In parallel, growing evidence from animal and human studies has begun to clarify how ultrasound influences neural activity across cellular, circuit, and systems levels. In this review, we synthesize recent progress in understanding the biophysical mechanisms, neurophysiological effects, and network-level consequences of TUS. We discuss insights from optical imaging, electrophysiology, EEG source imaging, and functional MRI, highlighting how these complementary approaches reveal cell-type-specific responses, bidirectional modulation of neural circuits, and distributed changes in functional connectivity beyond the sonicated target. We further examine evidence that functional imaging is evolving from a simple measure of regional activation to a multidimensional biomarker of target engagement, circuit modulation, and treatment response. Despite these advances, important challenges remain. We conclude that TUS is approaching a translational inflection point in which rigorous mechanistic studies, standardized methodologies, and imaging-based biomarkers can establish ultrasound as both a powerful causal neuroscience tool and a clinically viable neuromodulation therapy for disorders involving dysfunctional brain circuits.

Significance Statement

Transcranial ultrasound stimulation offers a noninvasive way of modulating the brain with high spatial precision. TUS is reaching a translational inflection point: improved targeting, modeling, and safety monitoring now enable precise, noninvasive stimulation of both cortical and deep targets, while early human studies and growing preclinical evidence are clarifying mechanisms and dose parameters. This is the moment to align mechanistic insight with human study design and standards. In this review, we discuss evidence from optical tagging, hemodynamic changes, and electrophysiology of focused ultrasound's effects on both regional and network-wide brain circuitry.

Introduction

Low-intensity transcranial ultrasound stimulation (TUS; also termed tFUS for transcranial focused ultrasound and LIFU for low-intensity focused ultrasound) has gained traction as a noninvasive neuromodulation tool, enabling high-precision modulation of neuronal activity in both excitatory and inhibitory directions, as well as assessment of cortical and deep brain regions. This topic of TUS as a circuit integration tool appeals broadly across systems and clinical neuroscience fields because it enables causal tests of brain function across domains and compatibility with common readouts [behavior, electroencephalogram (EEG), functional magnetic resonance imaging (fMRI)]. It also addresses shared questions about mechanisms, safety, and standards, while offering a path toward new therapies for high-burden brain disorders. Accumulating evidence, particularly from human fMRI and EEG studies, has shed novel insights into the dysfunction of brain networks in various neurological and psychiatric disorders. In this context, TUS has strong clinical relevance as a noninvasive, potentially network-based brain therapy for disorders with circuit dysfunction. By enabling precise engagement of networks implicated in depression,

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obsessive-compulsive disorder, addiction, chronic pain, epilepsy, and movement disorders, it may expand treatment options beyond medication and invasive procedures. Ongoing work on dosing, biomarkers, and safety is accelerating responsible translation to clinical trials.

This review will highlight recent advances in the direct cellular and network mechanisms underlying TUS neuromodulation, as well as progress toward clinical translation. Focused ultrasound neuromodulation is timely because it is reaching a translational inflection point: improved targeting, modeling, and safety monitoring now enable precise, noninvasive stimulation of both cortical and deep targets, while early human studies and growing preclinical evidence are clarifying mechanisms, dose parameters, and behavioral consequences. This is the moment to align mechanistic insight with clinical study design and standards. Comprehensive reviews are available elsewhere (Naor et al., 2016; Darmani et al., 2022; Lee et al., 2024; Pellow et al., 2024; Ho et al., 2025; Arulpragasam et al., 2026; Davidson et al., 2026; Kubanek, 2026).

Biophysical and Neurophysiological Mechanisms Underlying Transcranial Ultrasound Stimulation

To bridge the gap between macroscopic ultrasonic waves and microscopic neural circuit engagement, researchers are increasingly leveraging the advanced optical imaging toolkit as well as electrophysiology techniques to reverse engineer the neural, vascular, and hemodynamic consequences of TUS in vivo.

Reverse engineering TUS effects using in vivo functional fluorescence imaging

Understanding how TUS interacts with discrete neural populations requires imaging modalities capable of directly resolving cellular dynamics in the intact brain, highlighting the tremendous potential offered by the recently emerging toolbox of molecular indicators and modalities for functional fluorescence imaging. However, early attempts to implement in vivo fluorescence imaging faced severe physiological hurdles. In performing the first in vivo widefield calcium imaging during TUS, a landmark study by Sato et al. (2018) demonstrated that focused ultrasound inadvertently activates auditory pathways, causing widespread, indirect brain activation that obscures localized neuromodulation [see also Guo et al. (2023)]. Subsequent studies (Mohammadjavadi et al., 2019) further investigated this auditory activation, revealing that direct neuromodulatory responses can still be elicited independently of these peripheral confounds, while others have shown that tuning the ultrasound pulse repetition frequency can preferentially activate different neuronal populations to help bypass these confounds (Choi et al., 2023; Sherman et al., 2024; see EEG source imaging of neuromodulatory effects of focused ultrasound stimulation in humans for further discussion).

Another way to increase stimulation specificity and partially mitigate the auditory confound is to tightly focus the excitation spot by increasing the carrier frequency and the numerical aperture. However, this focused acoustic delivery could under certain conditions also introduce significant physical confounds. Estrada et al. (2021b) demonstrated that the intense, localized heat deposited by tightly focused ultrasound causes rapid, temperature-dependent fluorescence quenching (Estrada et al., 2021b). To isolate functional neural activity from these temperature artifacts, Davoudi et al. introduced model-based correction techniques that computationally subtract thermal transients from widefield fluorescence data (Davoudi et al., 2024). Thermal effects become especially apparent when pushing acoustic parameters further away from the typical TUS regime; for instance, using very high carrier frequencies (e.g., 30 MHz) results in purely suppressive calcium responses, likely because thermal effects completely dominate at these frequencies (Cheng et al., 2022), in contrast to their relatively minor putative role in "typical" TUS.

With confounds increasingly under control, researchers are recently extracting unprecedented mechanistic detail across multiple spatial scales. Leading these efforts, Estrada et al. (2026b) demonstrated for the first time a strictly localized in vivo calcium response to TUS using widefield calcium imaging in the cortex of GCaMP6f-expressing transgenic mice, establishing a characteristic dose–response relationship for tight submillimeter foci at 3 MHz (Estrada et al., 2026a). Building upon this foundational validation of spatial precision, they implemented holographic transcranial ultrasound neuromodulation (hTUS) to selectively target spatially distributed cortical networks. The synthesis of multifocal acoustic wavefronts with concurrent widefield fluorescence imaging confirms that hTUS can cooperatively recruit distributed circuits, greatly enhancing overall stimulation efficacy while monitoring brain-wide network dynamics in real time (Estrada et al., 2026b).

Zooming in to the microcircuit level, two-photon calcium imaging in several GCaMP6s transgenic lines reveals that TUS-evoked responses are driven by both direct mechanical perturbation and subsequent local network interactions (Lemaire et al., 2024). Crucially, by mapping the single-cell dose–response in awake animals, this study identified the spatial-peak temporal-average intensity (I_{spta}) as the universal predictor of neuromodulatory efficacy across diverse sonication protocols, establishing a unifying biophysical metric for parameter tuning. Interestingly, this work also shows that in the absence of anesthesia, TUS-evoked cellular responses emerge at intensities far below those associated with thermal effects. The field is also expanding its toolkit to capture much faster subthreshold dynamics by using voltage imaging with the indicator SomArchon, which revealed that TUS evokes rapid (sub-10 millisecond) membrane depolarizations that directly entrain synaptic inputs across broad timescales (Bortz et al., 2025).

In a parallel line of work aiming to bypass the depth limitations of cortical fluorescence microscopy, researchers developed a photometry coupled to ultrasound (PhoCUS) system. Utilizing fiber photometry, this approach enabled the real-time recording of aggregated, cell-type specific calcium dynamics in deep subcortical regions. This approach demonstrated how focused ultrasound can drive distinct behavioral responses and suppress epileptiform activity (Murphy et al., 2022, 2024). By systematically mapping these deep brain responses, this work showed that TUS efficacy is highly dependent on specific sonication parameters, identifying optimal duty cycles and pulse repetition frequencies that maximize targeted neural activation while mitigating thermal accumulation. However, caution is also called for here as optical fibers could potentially introduce vibration-related confounds by coupling vibration from the ultrasound transducer.

Decoding hemodynamic responses with optical imaging

While fluorescence imaging provides critical high-resolution data on neural spiking, the clinical translation of TUS heavily relies on noninvasive hemodynamic readouts such as fMRI. Early investigations into TUS-induced hemodynamic changes to understand the basis of these readouts utilized techniques

such as in vivo optical intrinsic signal imaging, which directly captured concurrent functional responses to ultrasound (Kim et al., 2017). Advancing these optical approaches, in vivo laser speckle contrast imaging subsequently demonstrated that ultrasound induces dose-dependent increases in cortical blood flow that are linearly coupled to neural activity (Yuan et al., 2020).

To look deeper into the brain and map these precise acoustic-hemodynamic interactions, foundational hardware was established through the development of dedicated spherical array systems designed for high-precision TUS and simultaneous optoacoustic imaging (POTUS) in rodents (Estrada et al., 2021a). Building on these POTUS systems, optoacoustic tomography utilizes the photoacoustic effect to generate high-contrast images based on the differential optical absorption spectra of molecules, allowing for label-free spectroscopic differentiation of hemoglobin states. To resolve even more complex neurovascular interactions, researchers have recently advanced these approaches by developing hybridized systems for concurrent optoacoustic and magnetic resonance imaging during TUS (OMRITUS; Chen et al., 2025).

This multimodal imaging capability has been crucial for resolving a major neuroimaging paradox: interpreting the blood oxygenation level-dependent (BOLD) signals induced by TUS, where unexpected negative BOLD signals are frequently observed in target areas. Recent optoacoustic studies have revealed that these paradoxical negative BOLD responses in TUS-activated cortical regions are actually coupled with an increase in total hemoglobin (Chen et al., 2025; Estrada et al., 2026a). Multispectral optoacoustic readings demonstrate a disproportionately larger increase in deoxygenated hemoglobin compared with oxygenated hemoglobin during TUS. This suggests a rapid, localized increase in metabolic oxygen consumption that outpaces the compensatory influx of oxygenated blood (Chen et al., 2025), highlighting the profound neurovascular coupling elicited by precise ultrasound neuromodulation in these settings.

E-phys dissection of mechanisms underlying focused ultrasound stimulation

Neuromodulatory effects of focused ultrasound stimulation have been explored and quantified using electrophysiological recordings. Invasive electrodes, providing spatially precise information, were used to demonstrate the first evidence of ultrasound neuromodulation capabilities (Fry et al., 1958). In that study, ultrasound was shown to have a transient inhibitory effect on visual evoked potentials. Later, it was demonstrated that ultrasound could elicit its own neural activations in rodents (Tufail et al., 2010). Using an intracranial multielectrode array, Bin He and his collaborators discovered that the response to TUS in the primary somatosensory cortex (S1) of rodent models varied by cell type (Yu et al., 2021a). Regular-spiking units (RSUs), presumably excitatory neurons, exhibited time-locked responses, while fast-spiking units (FSUs), presumably inhibitory interneurons, showed delayed responses (Gao et al., 2025; Ramachandran et al., 2025). Focused ultrasound neuromodulation has a high-dimensional parameter space, and animal models have demonstrated that the cell-type selective response is also parameter dependent (Yu et al., 2021a; Niu et al., 2022; Murphy et al., 2024; Gao et al., 2025; Ramachandran et al., 2025). It was reported that increasing pulse repetition frequency (PRF) corresponded with increased firing rates for RSUs but not FSUs (Yu et al., 2021a). Using opto-tagged rodent models, CamKII-positive neurons and PV-positive neurons exhibited distinctive characteristics in their responses to PRFs (Yu et al., 2021a). The cell-type selectivity of TUS may be explained by several mechanistic frameworks, including the intramembrane cavitation theory (Plaksin et al., 2016). Using multisite intracranial electrophysiological recordings in both S1 and posterior medial thalamic nucleus (POm) in rats, it was reported that TUS can modulate the feedback and feedforward cortico-thalamo-cortical (CTC) pathways by selectively activating cortical RSUs and adjusting the TUS parameters, particularly the PRF, to maximize cortical RSU activity which could enhance the modulation of the CTC pathway (Gao et al., 2025). Local perturbation of S1 modifies thalamic relay and corticothalamic feedback that are not reducible to local firing rate alone. A recent study further demonstrated that TUS exerts bidirectional, parameter-dependent modulation of the CTC pathway and highlights the critical role of CaMKII-positive neurons in mediating these effects (Gao et al., 2026). To mitigate electrode vibration under high ultrasound pressures, flexible intracranial electrodes have been shown to enable direct electrophysiological recordings in rats at the high ultrasound pressure levels used in human studies (Ramachandran et al., 2026). TUS not only can induce instantaneous neural responses but also can lead to long-term depression as reported in rodent models (Niu et al., 2022), underscoring the potential neurophysiological mechanism of plasticity of TUS neuromodulation.

Concurrent TUS and single-unit recording in anesthetized and awake, behaving nonhuman primates has provided further evidence that TUS targeting one cortical node can rapidly modulate neuronal discharge in a connected, nonsonicated region during active behavior (Wattiez et al., 2017). During an antisaccade task, TUS was delivered to the frontal eye field (FEF) while action potentials were recorded from neurons in the reciprocally connected supplementary eye field (SEF). Relative to control sonication of the visual cortex, FEF TUS significantly altered the firing of ~40% of recorded SEF neurons shortly after sonication onset. The responses were heterogeneous, with subsets of neurons exhibiting transient increases or decreases in firing. Under anesthesia, direct electrophysiological recordings in macaques have further clarified the spatial and temporal relationships among TUS-induced spiking, LFP, and BOLD responses (Zheng et al., 2026). Using the somatosensory thalamic ventral posterolateral (VPL) nucleus and insular cortex as an interconnected circuit, low-intensity TUS elicited localized BOLD signal increases and preferentially modulated low-frequency delta-, theta-, and alpha-band LFP activity and single-unit firing in the VPL. VPL activity was altered not only by direct VPL sonication but also by remote sonication of the insular cortex, providing electrophysiological evidence that TUS effects can propagate between interconnected brain regions. Together, these studies demonstrate the feasibility of using concurrent TUS and electrophysiology in awake and anesthetized primates to quantify circuit-level effects and optimize sonication parameters.

TUS Modulates Both Local and Large-Scale Network Activity: fMRI and Intracranial Electrophysiology Evidence

Brain function arises from coordinated activity across distributed neural networks rather than isolated brain regions. Consequently, fMRI has become one of the primary imaging modalities for evaluating TUS neuromodulation because it enables whole-brain assessment of regional activation, large-scale functional network changes, treatment targeting, and safety

monitoring. Its widespread availability in both preclinical and clinical settings has further accelerated its adoption. Converging evidence from animal and human studies demonstrates that TUS can noninvasively modulate regional neural activity, alter functional connectivity, influence behavior, and do so with a favorable safety profile (Blackmore et al., 2019; Gaur et al., 2020; Munoz et al., 2022; Phipps et al., 2026).

Animal models, particularly nonhuman primates (NHPs), provide the strongest evidence that TUS directly modulates neural activity, functional networks, and behavior (Deffieux et al., 2013; Wattiez et al., 2017; Yang et al., 2018; Fouragnan et al., 2019; Kubanek et al., 2020; Munoz et al., 2022). Across multiple studies, TUS targeting cortical areas, including the primary somatosensory cortex and motor cortices, as well as subcortical structures such as the thalamus, hippocampus, and basal ganglia, produces measurable BOLD signals and electrophysiological activity (Mohammadjavadi et al., 2022; Webb et al., 2023; Lybbert et al., 2024; Zheng et al., 2026). Depending on the sonication parameters, target location, and underlying brain state, these responses may be enhancive or suppressive, indicating that TUS can achieve bidirectional neuromodulation (Yang et al., 2018; Mishra et al., 2023, 2025). One recent electrophysiological recording study demonstrates that these BOLD responses closely correspond to changes in neuronal spiking activity or local field potentials, supporting the neural origin of the observed TUS-evoked fMRI BOLD signals (Zheng et al., 2026). While the behavioral relevance of these bidirectional neuromodulations by TUS remains to be determined, these observations underscore the complexity of interactions between TUS waves and brain tissues, which will likely differ across brain regions, given the distinct compositions of neuronal types and their interactions with inhibitory neurons and supporting glial cells.

Whereas fMRI and intracranial recordings reveal how TUS influences local and distributed neural activity, behavioral perturbation studies demonstrate that the functional consequences of TUS depend not only on the targeted region but also on the dynamic computational role of that region within a distributed network. This principle was demonstrated in macaques. TUS studies of reversal learning further demonstrate that the relationship between network activity and behavior is dynamic and node dependent. Dorsomedial frontal and thalamic regions represented latent-state transitions and choice-related variables, whereas the hippocampus continuously tracked reversal probability. Ultrasound disruption of each node impaired behavior in a distinct manner, demonstrating that TUS can causally dissociate temporally and computationally specialized contributions within a distributed network (Marche et al., 2026). Patterns of interaction among these regions further revealed a distributed circuit supporting task performance. Transient ultrasonic disruption of each node impaired reversal learning, but in distinct ways, consistent with their different computational roles. These findings illustrate that similar behavioral impairments can arise from disruption of different components of a network and that the relationship between TUS-induced neural modulation and behavior depends on both network location and task phase. While this study demonstrates that TUS acts as a causal perturbation tool for identifying how distinct, interacting network nodes contribute to behavior, it also cautions against interpreting a behavioral change as evidence for a single regional function: the same task-level impairment may result from disruption of different computations at different network nodes.

One of the most reproducible findings is that TUS affects not only the targeted brain region locally but also connected networks (Lee et al., 2024). Both task-based (online) and resting-state (offline) fMRI demonstrate that ultrasound-induced activity propagates through large-scale brain circuits. For example, stimulation of thalamic nuclei alters activity throughout corticothalamic networks (Legon et al., 2018; Kim et al., 2022; Mishra et al., 2023, 2025; Atkinson-Clement et al., 2024; Jang et al., 2025). In contrast, motor cortex stimulation modifies activity in premotor cortex, basal ganglia, cerebellum, and contralateral motor cortex (Ai et al., 2018; Pellow et al., 2026). Likewise, sonication of the somatosensory cortex produces changes throughout bilateral sensory networks (Ho et al., 2025). Interestingly, many immediate off-target effects extend beyond the canonical functional networks associated with the stimulated region (Mishra et al., 2023, 2025). Some activated brain areas lack known direct anatomical connections to the sonicated target. For example, TUS targeting of the VPL thalamic nucleus, a key relay for nociceptive heat processing, altered its functional connectivity with the visual cortex (Mishra et al., 2025). Figure 1 illustrates the changes in the effective functional connectivity network. These observations demonstrate that fMRI is particularly valuable because it captures distributed circuit responses rather than only local effects. These observations raise important mechanistic questions regarding the underlying mechanism for TUS-induced network modulation. For example, through what pathways and mechanisms does TUS-induced neuron activity propagate through direct monosynaptic or anatomical connections? How do broader network dynamics affect these interregional interactions? This information will not only serve as biomarkers of TUS engagement and network effects but also enable refinement of the TUS stimulation paradigm and dosing, defined by the outcome of the interaction between TUS and brain tissue. Addressing these questions will require multimodal approaches that integrate high-spatial-resolution fMRI, high-temporal-resolution electrophysiological recordings (such as spiking and local field potentials), and anatomical tracing. NHPs will be invaluable models for addressing these questions.

Translation to Human Subjects: How TUS Modulates Human Brain Functions?

Functional MRI reveals focal target engagement and network-specific effects of human TUS

TUS and fMRI are highly complementary technologies for investigating causal brain function in humans. Among currently available noninvasive neuromodulation approaches, TUS uniquely combines millimeter-scale control over the location of acoustic energy deposition with the ability to reach both superficial cortex and deep brain structures. fMRI, in turn, provides whole-brain measurements with sufficient spatial resolution to assess responses at the sonicated target and changes elsewhere in the circuit. It is important, however, to distinguish these two spatial scales. Focality refers primarily to the acoustic exposure and the neural population directly perturbed by it; it does not imply that the physiological consequences must remain confined to that population. Because brain regions operate as components of distributed circuits, a focal perturbation can produce downstream changes in anatomically and functionally connected regions. Thus, local target engagement and distributed network effects are not contradictory. The central question is whether the network response is structured and target-dependent, rather than whether every consequence is restricted to the acoustic focus.

This distinction follows a fundamental principle of functional neuroanatomy: each brain area is characterized by a distinctive

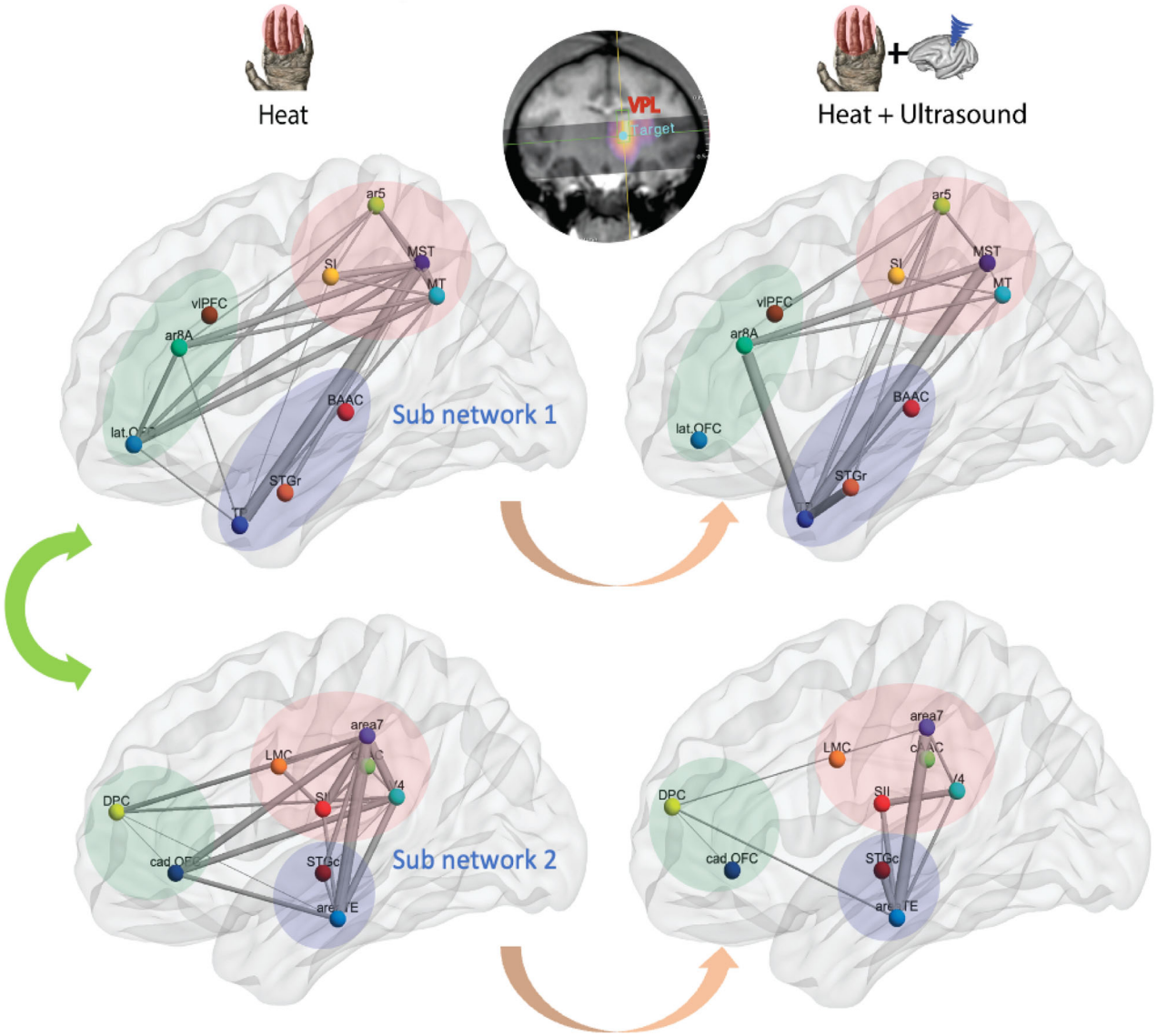


Figure 1. Sonication of the thalamic VPL nucleus reorganizes nociceptive heat processing networks. The figure is adapted from Mishra et al. (2025), which is licensed under CC BY-NC-ND 4.0.

"connectional fingerprint," even when it shares some connections with neighboring or interacting regions (Passingham et al., 2002). Consequently, perturbing two interconnected areas need not produce identical whole-brain effects. Each target should preferentially alter the subset of interactions and computations in which it participates. Network-level fMRI effects should therefore be interpreted as evidence of circuit engagement only when they are anatomically plausible, differ with the stimulated target, and, ideally, correspond to a predicted change in behavior or task-related computation. Conversely, spatially widespread or unexpected BOLD changes cannot automatically be attributed to neural propagation from the focus; vascular effects, arousal, auditory or somatosensory confounds, motion, and analysis choices must also be considered.

The first human TUS-fMRI studies focused primarily on technical feasibility. Ai and colleagues demonstrated that focused ultrasound could be safely delivered within both 3 and 7 T MRI systems without introducing substantial imaging artifacts while targeting cortical and subcortical structures. High-field (7 T) fMRI was subsequently used to examine stimulation of an individually localized thumb representation within the primary motor cortex. TUS increased the spatial extent of task-evoked activation without changing percent BOLD signal and, importantly, without affecting neighboring finger representations or connected motor regions. These findings established that concurrent TUS-fMRI was feasible and could reveal spatially selective modulation (Ai et al., 2016, 2018; Lee et al., 2016). They also anticipated a recurring observation: a physiologically meaningful TUS effect need not appear as a large, stimulus-locked increase or decrease in raw BOLD amplitude.

Nonhuman primate studies of the somatosensory system provide an especially direct demonstration that focal stimulation and network-level consequences can coexist. Yang and colleagues first used tactile fMRI to localize the hand representation within areas 3a/3b and to map its established somatosensory circuit. MRI-guided TUS was then delivered to this functionally defined cortical target during 7 T fMRI. Sonication evoked a robust local BOLD response together with responses in areas 1/2, secondary somatosensory cortex, insula, cingulate cortex, and ventral posterior lateral thalamus—regions also recruited by natural tactile

stimulation (Yang et al., 2018). The remote effects were therefore not spatially arbitrary: they substantially recapitulated a circuit defined independently by sensory input. At the same time, TUS and tactile stimulation did not produce identical regional response profiles. Relative to the response in areas 3a/3b, their effects differed in insular, cingulate, and thalamic regions, consistent with the fact that direct cortical perturbation enters the circuit at a different node and bypasses the normal ascending route through the thalamus. This combination of a spatially restricted acoustic target and an organized, circuit-constrained response illustrates why distributed fMRI effects should not be equated with a broad or poorly localized acoustic exposure.

Subsequent work from the same group strengthened this interpretation by manipulating acoustic pressure and the functional state of the circuit (Yang et al., 2022). The position of the focus in areas 3a/3b was verified using MR-acoustic radiation force imaging, and BOLD responses were quantified at the target, at known somatosensory regions, and in mediodorsal thalamus and auditory cortex as out-of-network controls. During rest, graded reductions in acoustic pressure produced graded decreases in the target and several interconnected cortical regions. During tactile activation, however, the response was not a uniform scaled version of this pattern: higher pressure TUS enhanced the response in areas 1/2, whereas medium- and low-pressure TUS suppressed tactile responses in areas 3a/3b and downstream cortical regions, with little corresponding modulation in ventral posterior lateral or mediodorsal thalamus. The dose–response relationship therefore depended on both brain state and the region's position within the circuit. In particular, downstream cortical regions with strong feedforward input from areas 3a/3b differed from the upstream thalamic relay, where interactions with the cortical target are predominantly feedback. These dissociations would be difficult to explain as indiscriminate spread of stimulation; they instead indicate that a focal perturbation is transformed by the direction, strength, and current state of the connections linking the targeted node to the rest of the network.

Other primate studies provide convergent evidence for this principle without requiring that every remote response follow a single canonical circuit. Offline TUS of amygdala and anterior cingulate cortex produced distinct target-centered changes in whole-brain functional coupling, despite connections between the two targets (Folloni et al., 2019). Likewise, supplementary motor area and frontal polar cortex stimulation generated dissociable connectivity profiles (Verhagen et al., 2019), and perturbation of prefrontal area 47/12o selectively altered credit-assignment-related activity and behavior while sparing a distinct reward-state signal in adjacent anterior insula (Folloni et al., 2021). Together with the somatosensory findings, these results support a common interpretation: the acoustic perturbation can be focal while its physiological consequences are expressed through the target's particular connectivity and computational role.

Task-based human fMRI increasingly supports the same logic. Motor cortex stimulation produced effects restricted to the sonicated finger representation (Ai et al., 2018), whereas amygdala stimulation fear- and emotion-related activity and connectivity within a target-relevant circuit (Chou et al., 2024; Barksdale et al., 2025; Algermissen et al., 2026). TUS of the nucleus accumbens and dorsal anterior cingulate has likewise modified reward-related and pain-related processing together with behavior (Yaakub et al., 2025; Clarke et al., 2026). Across these studies, the strongest evidence for specificity is not the absence of remote effects, but the conjunction of accurate targeting, a target-dependent pattern of brain changes, and a selective behavioral or computational consequence.

Resting-state fMRI has been used to characterize how these consequences persist after sonication. Studies targeting inferior frontal cortex, posterior cingulate cortex, dorsal anterior cingulate, medial prefrontal cortex, amygdala, thalamus, anterior temporal lobe, and white matter within the anterior limb of the internal capsule report changes in functional coupling that can last 30–60 min or longer. In some cases, these changes parallel behavioral effects or alterations in neurochemistry measured with magnetic resonance spectroscopy, consistent with prolonged modulation of the targeted circuit. The spatial pattern is nevertheless expected to depend on the connectional fingerprint of the target, the sonication parameters, the brain state during and after stimulation, and the interval at which imaging is acquired. For example, Atkinson and colleagues further showed that connectivity effects evolve over time and vary with delivered acoustic pressure (Atkinson-Clement et al., 2024, 2025). Resting-state connectivity may therefore provide a sensitive marker of TUS-induced neuromodulation, but it should not be treated as a generic signature of efficacy or as evidence that the acoustic field itself extended throughout the observed network (Sanguinetti et al., 2020; Yaakub et al., 2023; Park et al., 2025; Tsuchiyagaito et al., 2026).

The choice of fMRI outcome is also consequential. The BOLD signal drifts over time and reflects hemodynamic responses rather than a direct measure of neuronal firing. Many TUS-fMRI studies therefore do not test whether sonication produces a sustained change in raw signal. Task-based experiments typically estimate whether TUS changes the regression coefficient linking BOLD activity to a task event or computational variable. Resting-state studies instead assess whether TUS changes the statistical relationship between BOLD time series in different regions. These outcomes can reveal target engagement even when mean regional BOLD amplitude changes little. The connectivity analyses used by Folloni and colleagues and Verhagen and colleagues, for example, identified the most pronounced changes at the stimulated region by comparing its coupling with the rest of the brain, whereas the task-based study of area 47/12o tested how TUS altered specific value-related signals. Accordingly, an absent or small raw BOLD-amplitude response should not by itself be interpreted as evidence that TUS failed to modulate neural function; the inference depends on whether the relevant outcome is stimulus-evoked amplitude, task modulation, functional or effective connectivity, perfusion, or another imaging measure.

fMRI is therefore most informative when used as a multidimensional biomarker of target and circuit engagement rather than as a simple detector of local activation. A persuasive demonstration of TUS specificity should ideally establish (1) that the acoustic focus was accurately placed and modeled; (2) that the local and remote fMRI effects form a target-dependent, anatomically plausible pattern; (3) that stimulation of a nearby or connected control target produces a dissociable pattern; and (4) that the imaging changes correspond to a predicted behavioral, computational, electrophysiological, or neurochemical effect. This framework preserves the principal advantage of TUS—focal, noninvasive access to deep or superficial neural targets—while recognizing that the functional consequence of perturbing any target is inherently network level.

Recent technological advances make these tests increasingly tractable. Large phased arrays (Riis et al., 2024, 2025; Martin

et al., 2025), individualized acoustic modeling, stereotactic neuronavigation, and MRI-based targeting and validation improve control over the location reproducibility of acoustic exposure. Martin and colleagues, for example, demonstrated reproducible modulation of the lateral geniculate nucleus with concurrent fMRI using a 256-element transducer array (Martin et al., 2025). When such hardware is combined with appropriate control targets, task models, connectivity analyses, and multimodal validation, TUS-fMRI can distinguish focal energy delivery from network-specific physiological consequences and thereby provide a rigorous platform for causal systems neuroscience and precision therapeutics.

EEG source imaging of neuromodulatory effects of focused ultrasound stimulation in humans

Due to practical limitations, intracranial electrophysiological recordings are not an option for healthy populations and even for many clinical populations. While fMRI has high spatial resolution, its temporal resolution is limited due to hemodynamic responses. Electroencephalography (EEG), as the scalp manifestation of the underlying neural activation, has been used to explore neurophysiological responses of the brain to TUS stimulation with high temporal resolution (Legon et al., 2014; Lee et al., 2016). Due to signal attenuation from the skull and volume conduction, EEG measurements have lower spatial precision compared with intracranial electrophysiological recordings. EEG source imaging (ESI) has been developed as a technology that "undoes" the volume conduction problem and backprojects the scalp-based signals onto the cortex (He et al., 2018). A number of studies have demonstrated the significantly improved spatial resolution of ESI in localizing and imaging the underlying brain activation (Sun et al., 2022). ESI has been applied to map brain responses to TUS stimulation in motor, somatosensory, and visual systems (Liu et al., 2021; Yu et al., 2021b; Kosnoff et al., 2024, 2026). Figure 2 illustrates representative EEG source imaging for TUS neuromodulatory effects.

By segmenting the brain into specific regions, ESI can provide insight into cortical network-level analysis. In terms of targeted circuit modulation, when V5-targeted ultrasound was combined with a visual motion-based task, increased power in alpha and theta bands was observed throughout the dorsal visual processing pathway, while the ventral visual processing pathway was unaffected compared with non-modulated and audio sham conditions (Kosnoff et al., 2024). When TUS was applied to the primary motor cortex (M1) in resting-state humans, substantial off-target activation, particularly in deep brain regions, was observed (Kosnoff et al., 2026). Time series were isolated for the ultrasound targeted M1, primary auditory cortex (A1), and the deep brain regions. Granger causality analysis revealed that the observed deep brain activations were driven not by the ultrasound's targeted region, but instead by auditory cortices. These findings join the TUS studies reporting auditory-driven activations (Guo et al., 2018; Sato et al., 2018; Braun et al., 2020; Kop et al., 2024).

Though holistically a part of TUS application, these auditory-driven activations are typically considered undesirable confounds since they activate the brain independently of the highly focused pressure beam. Differences in perceivable hearing ranges may lead to species-specific susceptibility to these effects, though the presence of indirect auditory activations has been demonstrated in multiple species including mice (Sato et al., 2018), guinea pigs (Guo et al., 2018), and humans (Braun et al., 2020; Kop et al., 2024). Macaque monkeys' hearing range substantially overlaps with humans (Heffner, 2004; Burton et al., 2019) but extends to higher frequencies. Their regions of greatest sensitivity—approximately 1–16 kHz in macaques and 2–5 kHz in humans—are lower than those of rodents (10–25 kHz in mice and 8–38 kHz in rats). Thus, rodents are especially sensitive to higher harmonics, whereas macaques and humans are highly sensitive to the low-frequency TUS PRFs. Consequently, using the same TUS waveform across species does not produce equivalent auditory effects. The sham or masking stimulus should be designed according to each species' audiogram and the measured spectrum of the actual skull-transmitted signal. Offline TUS protocols, in which ultrasound is applied for relatively long sonication durations prior to a task, and the effects of induced plasticity are measured, have been speculated to circumvent these auditory effects (Verhagen et al., 2019).

An important aspect of neuromodulation is understanding whether the stimulation is suprathreshold, in which it will directly elicit neural activations on its own, or if it is subthreshold, in which case it will modulate the neuronal response to other inputs. Answering this question requires online TUS protocols, in which the concurrent neural response to ultrasound is measured, as offline plasticity changes can arise either from direct suprathreshold neural activation or compounded effects from subthreshold stimulation over time (Soldado-Magraner et al., 2020). In animal models, region-specific suprathreshold activations have been observed with invasive electrodes (Tufail et al., 2010; Yu et al., 2021a; Gao et al., 2025; Ramachandran et al., 2025), behavioral muscle responses (Tufail et al., 2010), and through ESI (Yu et al., 2016; Yu and He, 2025). In humans, however, the extent of TUS modulation was less well characterized. Most often, human studies investigate how ultrasound alters neural responses to other stimuli [e.g., tactile discrimination (Legon et al., 2014; Liu et al., 2021), motor-evoked potentials (Fomenko et al., 2020; Yu et al., 2021b), and visual motion perception (Butler et al., 2022; Kosnoff et al., 2024)]. Studies that investigated suprathreshold behavioral responses pointed toward inconsistent percept elicitation (Lee et al., 2015, 2016). A recent ESI study investigated TUS human modulation extent by applying ultrasound to the cortex of resting-state humans and recording the concurrent response (Kosnoff et al., 2026). The study did not observe any region-specific suprathreshold activity. Instead, EEG evoked potentials localized to auditory and deep brain regions. However, region-specific subthreshold effects were elucidated when TUS was paired with subthreshold electrical

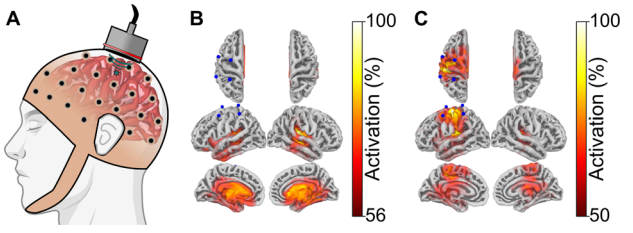


Figure 2. EEG source imaging for TUS neuromodulatory effects. ***A***, Electrophysiological brain signals can be measured using EEG electrodes. Scalp EEG is negatively affected by volume conduction, resulting in smeared spatial distributions of electric potential over the scalp. ***B***, ***C***, EEG source imaging deconvolves the volume conduction and spatially unmixes the recordings. The resultant backprojected cortical mapping can be used to elucidate the underlying mechanisms of TUS by localizing and imaging (***B***) nonspecific auditory confounds and (***C***) targeted region-specific engagement. Panels ***B*** and ***C*** are for M1-targeted 3 kHz PRF TUS without (***B***) and with (***C***) concurrent electrical stimulation, which are reproduced from Kosnoff et al. (2026), licensed under CC BY-NC-ND 4.0.

stimulation. Given subthreshold effects of TUS were demonstrated, it is likely that TUS can produce suprathreshold direct cortical activations in humans at some intensity, for example, at higher acoustic pressure. However, practically and safely achieving the needed pressure through the human skull and in the brain remains a challenge.

At first glance, this result appears to be at odds with another human study that utilized invasive electrodes and reported heightened power spectra following offline TUS stimulation (Darmani et al., 2025). However, since the heightened power spectra recordings came in an offline protocol, as opposed to during stimulation, it is uncertain whether they are a result of sustained supra- or subthreshold modulation. There are also studies that report deep brain neurons have higher concentrations of mechano-sensitive ion channels (Zhu et al., 2023) and lower activation thresholds (Stephani and Koubeissi, 2015) than cortical neurons, so it is also possible that physiological differences across targeted areas may impact the extent of TUS's effect. As a result, the two studies (Darmani et al., 2025; Kosnoff et al., 2026) are not inherently in disagreement with each other. Of course, they are not inherently supportive of each other, either. Future studies should further directly investigate TUS sub- or suprathreshold activations in humans.

Remaining Challenges and Future Directions

Despite encouraging progress, several important challenges remain. First, there is currently no consensus regarding the optimal acoustic pressure, pulse repetition frequency, duty cycle, or sonication duration for different brain targets and therapeutic applications. While there have been extensive parameter optimization efforts within animal models, the translation of these findings to human models is largely unestablished. Because different brain regions have distinct compositions of excitatory and inhibitory neurons, it has been proposed that the net TUS modulatory outcome likely varies across regions. Existing evidence suggests that the neuromodulatory effects of TUS depend on both stimulation parameters and regional neuronal and circuit architecture, emphasizing that acoustic dosing will likely require optimization for individual brain targets rather than a universal protocol. Second, substantial variability in ultrasound hardware, targeting approaches, MRI acquisition, and image analysis limits direct comparison across studies and highlights the need for standardized protocols. Third, quantitative measures of the delivered neuromodulation dose remain poorly defined, motivating the development of imaging-based dosimetry approaches such as quantitative MR-acoustic radiation force imaging (MR-ARFI). Finally, while most studies demonstrate acute or short-term neuromodulatory effects, the durability of repeated stimulation and its long-term impact on brain networks remain largely unknown. Future work integrating multimodal imaging with electrophysiological recordings, anatomical connectivity mapping, and quantitative dosimetry should improve mechanistic understanding, establish dose–response relationships at both the cellular and circuit levels, and facilitate the translation of TUS into reliable neuroscience and clinical applications.

Overall Conclusion

Accumulating evidence from both animal and human studies supports the conclusion that low-intensity focused ultrasound can noninvasively modulate regional brain activity and large-scale functional networks. Electrophysiology, providing direct quantifications of neural activity, has been used to demonstrate TUS' cell-type selectivity and real-time effects on the brain. Animal studies, particularly in nonhuman primates, provide compelling evidence linking fMRI responses with underlying neuronal activity, whereas human studies demonstrate that these imaging changes are associated with measurable behavioral effects and are achieved within a favorable safety profile. As the field matures, advances in quantitative targeting, imaging-based dosimetry, standardized stimulation protocols, and multimodal validation will be critical for establishing TUS as a reproducible tool for basic neuroscience research and a clinically effective neuromodulation therapy.

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