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Ultrasound Neuromodulation: Mechanisms and the Potential of Multimodal Stimulation for Neuronal Function Assessment

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Focused ultrasound (FUS) neuromodulation has shown that mechanical waves can interact with cell membranes and mechanosensitive ion channels, causing changes in neuronal activity. However, the thorough understanding of the mechanisms involved in these interactions are hindered by different experimental conditions for a variety of animal scales and models. While the lack of complete understanding of FUS neuromodulation mechanisms does not impede benefiting from the current known advantages and potential of this technique, a precise characterization of its mechanisms of action and their dependence on experimental setup (e.g., tuning acoustic parameters and characterizing safety ranges) has the potential to exponentially improve its efficacy as well as spatial and functional selectivity. This could potentially reach the cell type specificity typical of other, more invasive techniques, e.g., opto- and chemogenetics or at least orientation-specific selectivity afforded by transcranial magnetic stimulation. Here, the mechanisms and their potential overlap are reviewed along with discussions on the potential insights into mechanisms that magnetic resonance imaging sequences along with a multimodal stimulation approach involving electrical, magnetic, chemical, light, and mechanical stimuli can provide.

Keywords: central nervous system, focused ultrasound, magnetic resonance imaging, peripheral nervous system, therapeutic ultrasound, ultrasound neuromodulation

INTRODUCTION

The ability to probe spatially specific brain regions enable understanding brain functioning and connectivity. In turn, this can unlock a wealth of potential investigative and therapeutic applications. Focused ultrasound (FUS) has been proven capable of eliciting excitatory and inhibitory effects non-invasively and locally in the central nervous system (CNS) and peripheral nervous system (PNS), depending on the adopted pulsing regime [1]. Several studies have demonstrated the elicitation of motor responses in rodents obtained from the FUS stimulation of cortical brain regions [2–6]. Furthermore, the capability of FUS to reach deeper brain structures (which is one of the major challenges of other current- or voltage-controlled neuromodulation techniques) can provide access to subcortical areas of the brain. For example, the stimulation of deep-seated structures such as locus coeruleus and superior colliculus caused pupil dilation and

eyeball movements in mice [6]. Also, FUS stimulation of the putamen induced improvements in speed and accuracy of visual–motor tasks in non-human primates (NHPs) [7]. In humans, targeting the head of the caudate resulted in hemodynamic responses visible through functional magnetic resonance imaging (fMRI) [8] and stimulating the thalamus induced changes in somatosensory evoked responses [9].

The mechanisms proposed to explain the FUS neuromodulation effects are based on multiple hypotheses on how ultrasound interferes with depolarization through mechanical deformation of the cell membrane. In addition, experimental evidences have shown that ultrasound can activate mechanosensitive ion channels in neurons [10–13] and other brain cell types like astrocytes [14], providing additional avenues for FUS to interfere with the membrane potential. Despite the advances provided by *in vitro*, *ex vivo*, and *in vivo* experiments, the high variability in experimental conditions and setups, as well as partially conflicting results, has led to somewhat contradictory interpretations and a variety of possible hypotheses about underlying physiological mechanisms, which may be acting concurrently in a dynamic interplay every time FUS is applied. Moreover, most current animal experiments are performed under anesthesia. The interaction of pharmacological sedation with FUS neuromodulation is not entirely understood and may partially obfuscate the interpretation of a number of FUS neuromodulation experiments [15].

The use of MRI can provide insights into brain structure and activity and hence support FUS-based neuromodulation through targeting, safety evaluation, and the evaluation of brain function and mechanisms. In this context, multimodal stimulation coupled with neuroelectric or MRI may present a better opportunity to understanding of the multiple factors that play a role in neuron functioning as well as how FUS interferes with it.

In this review, the proposed mechanisms for ultrasound neuromodulation and interactions of FUS with tissue are revisited, and current contradictory findings are discussed in light of varying experimental conditions and anesthesia effects. Finally, the potential of multimodal stimulation and the use of MRI is discussed as a promising future avenue for spatiotemporally selective, non-invasive neuromodulation.

MECHANISMS OF ULTRASOUND NEUROMODULATION

Ultrasound propagation in biological tissue is characterized by vibrational waves traveling with frequencies above the hearing range (>20 kHz). In the compressional phase, ultrasound displaces tissue particles and fluid molecules, generating an elastic restoring force. As the tissue and fluids return to their normal configurations, molecules experience a rarefaction phase. During this process, waves propagate through the tissue, giving rise to an acoustic radiation force (ARF) where part of the energy is stored in the tissue in the form of elastic deformation, and part is dissipated as heat due to viscous frictional forces. When acoustic wave flow experiences

opposition due to acoustic impedance discontinuities, parts of the wave are transmitted, reflected, and refracted. Both scattering and heating dissipation are frequency-dependent, where energy deposition in the medium occurs through absorption. The scattered waves can be subsequently partially absorbed and partially re-scattered multiple times. Other effects during the rarefaction phase can occur, such as cavitation (nucleation) [16], which has a higher probability of occurring at higher pressures and lower frequencies. Potential mechanisms for ultrasound neuromodulation are associated with changes in membrane potential due to ultrasound-induced neuronal membrane deformation and the activation of mechanosensitive channels (**Table 1**) (see Jerusalem et al. [15] for a review). In this context, both theoretical and experimental studies have proposed that mechanical deformations induced by strain gradients produce a membrane polarization, giving rise to a flexoelectric effect [21, 28]. A study using a model lipid bilayer membrane demonstrated that the displacement of the membrane caused by the ARF results in changes in the membrane area and its capacitance, which in turn creates capacitive currents measured with voltage-clamp techniques [17]. Another recent study evoked neuronal calcium responses obtained from local mechanical indentation delivered by a piston in cultured rat cortical and hippocampal neurons [18], giving experimental evidences that neurons are sensitive to mechanical stress. Also, Muratore et al. [19] have shown that ARF can deform the cell membrane. Intriguingly, other theoretical studies have proposed that the rarefactional phase of ultrasound waves can pull apart the two membrane lipid leaflets, leading the formation of bubbles in the intramembrane space, which in turn induces currents by modulating membrane capacitance in an oscillatory manner [23, 29]. However, an *ex vivo* study has shown that micron-scale tissue displacements consistent with ARF generation triggered spiking activity that remained unchanged to a broad acoustic frequency range (0.5–43 MHz), hence excluding a potential cavitation-related effect at least in an *ex vivo* setting [30]. Moreover, a new theory known as the soliton model proposes that the action potential (AP) involves an adiabatic process, where a mechanical pulse propagates in phase with an electrical pulse along the axon [22]. The reversed pathway could mean that deformations of the neuronal membrane induced by the ARF could potentially both annihilate or enhance axonal electrophysiology [20]. Also, for specific regimes (high pulse repetition frequency, high duty cycle, high pressure), ultrasound may increase temperature and alter the electrical capacitance of the plasma membrane [25], as demonstrated through light-induced temperature increase [26]. Interestingly, a behavioral study using mutants *C. elegans* model demonstrated that knocking out mechanosensitive ion channels abolishes neuronal responses to mechanical stimulation, while knocking out thermosensitive ion channels kept responses unaffected [31]. In this context, Thompson et al. [27] have demonstrated a temperature dependence of neuronal membrane conductance and synaptic potentials, while recent studies have shown that ultrasound can directly drive a number of mechanosensitive ion channels (K^+ channel family TREK-1, TREK-2, and TRAAK [11], voltage-gated Na^+ and Ca^+ [10], and piezo-type mechanosensitive channel Piezo1 [12, 13] and

TABLE 1 | Summary of potential mechanisms associated with ultrasound neuromodulation.

Mechanisms	Description
Membrane deformation causing capacitance changes	Capacitance changes have been observed during artificial membrane deflection [17] and deformation of *in vitro* membranes [18, 19] and modeled in simulations [20]. Capacitance can be altered by membrane volume changes or be associated with a flexoelectric effect (a property of the membrane that causes a spontaneous electric polarization when submitted to a mechanical strain gradient [21]).
Soliton model	Changes in membrane conformation could arise from interfering with a thermodynamic process involved in electromechanical pulse traveling during AP [22].
Intramembrane cavitation model	Ultrasound-induced intramembrane cavitation within the bilayer membrane induces a current through membrane capacitance changes [23].
Mechanosensitive ion channel modulation	A number of mechanosensitive ion channels were seen *in vitro* to be sensitive to ultrasound waves (TREK-1, TREK-2, TRAAK [11]; voltage-gated Na^+ and Ca^+ [10]; Piezo1 [12, 13]; and Piezo2 [24]).
Modulation of TRPA1 channels in astrocytes	Ultrasound opens TRPA1 channels in astrocytes, inducing glutamate-releasing Best1 as a mediator of glia–neuron interaction [14].
Thermal modulation	Heating reversibly alters the membrane capacitance, resulting in depolarization [25, 26]. FUS can increase temperature at specific regimes. Neuronal membrane conductance and synaptic potentials are altered by temperature changes [27].

AP, action potential; FUS, focused ultrasound; TRPA, transient receptor potential ankyrin.

Piezo2 [24]) as well as indirectly control neuronal responses *via* modulation of transient receptor potential ankyrin 1 (TRPA1) channels in astrocytes with glutamate-releasing bestrophin-1 (Best1) as a mediator of glia–neuron interaction [14]. Therefore, it is highly likely that, depending on the pulse regime, different combinations of partially overlapping mechanisms would concur to the final result of the interaction between ultrasound and the cell membrane.

EX VIVO/IN VITRO VS. IN VIVO

Despite the advances provided by *ex vivo* and *in vitro* studies, contradictory results regarding the absence [30] or presence [32, 33] of cavitation and its role [23] in ultrasound neuromodulation have been reported. These conflicts may potentially be due to differences in experimental conditions. For instance, the oxygenation process inherent to culturing cells may introduce bubbles in *in vitro* preparations [32]. Furthermore, *in vivo* translation of *in vitro* and *ex vivo* results is hampered by differences in a number of parameters and effects such as cavitation threshold, the rapid cooling effects associated with brain perfusion [34], the contribution of different cells to the neuromodulatory effect [14] and skull-related effects such as attenuation due to absorption and scattering, and shear wave from mode conversion [35]. Indirect confounding effects may also include activation through auditory pathways [36, 37]. Nevertheless, all ultrasound neuromodulation studies have demonstrated that the paradigm of framing neural activity within and electromagnetic perspective is too simplistic, confirming that ultrasound neuromodulation studies can be of great aid in all applications requiring fast and painless interference of brain function, both in investigative and in therapeutic contexts.

IN VIVO STUDIES-ANESTHESIA EFFECTS

Anesthesia effects have long represented a major confounding factor in neuromodulation studies. It has been shown that motor-evoked potentials induced by electrical stimulation are suppressed by isoflurane in a dose-dependent manner [38]. Similarly, ketamine blocks cortical neuron activity, which suppresses ultrasound-elicited motor responses [39]. In this context, in FUS neuromodulation studies, the isoflurane dose was reduced down to 0.1%, which corresponds to operating on a semi-awake animal [4]. However, some experiments have reported auditory artifacts and audible buzzing sounds generated by the ultrasound transducer, which may affect experiments in animals [36, 37], as well as in humans [40–42]. Therefore, the use of low-level anesthesia to maintain animal semi alert requires careful considerations in the setup and techniques such as signal smoothing [43] to avoid confounds. From deep brain stimulation (DBS) studies, it is known that anesthesia affects the spontaneous background firing and the neuronal spike activity patterns, as well as potentiates the inhibitory actions of gamma-aminobutyric acid (GABA) and causes a global depression in neuronal discharge, among other effects [44, 45]. In a repetitive transcranial magnetic stimulation (rTMS) study in rats, isoflurane, dexmedetomidine, and propofol caused significant different effects on functional connectivity, particularly between the sensorimotor cortex and thalamus [46]. In general, as reviewed by Jerusalem et al. [15], anesthetics lead to unconsciousness, immobility, amnesia, and analgesia without a complete understanding of the mechanisms underlying loss of consciousness and depth of anesthesia, which is mirrored by even more partial insights into the implication of sedation and deep anesthesia in humans [47] to the extent that anesthesia itself can be considered an instrument to explore the neural substrates of cognitive processes [48]. Importantly, several hypotheses about how anesthetic drugs modulate membrane excitability overlap with potential mechanisms of FUS neuromodulation. These include membrane deformation, changes in the thermodynamic properties of the membrane, and bubble formation. Therefore, awake studies are needed for a more precise characterization of the neural underpinning of FUS neuromodulation.

MRI

MRI can help advance neuromodulation technologies in a number of ways [49]. Importantly, MRI and ultrasound neuromodulation share similar spatial resolutions, which lies in the order of millimeters or submillimeters. MRI resolution depends on several factors, including magnetic field strength [50–52], coil performance, and subsequent imaging gradients [53, 54]. High magnetic field strengths from 3 to 7 T for humans [55] and above 7 T for preclinical studies [56], dedicated multi-transmit head coils [57, 58], and strong imaging gradients up to 100 mT/m for human scanners and 1,000 mT/m for preclinical systems [59–61] can provide spatial resolutions ranging from 1 to 2 mm^3 to submillimeter (depending on imaging modality) for human and animals studies, respectively [60, 62].

On the other side, the lateral resolution (L) of ultrasound neuromodulation for a concave transducer can be characterized as $L = 1.4\lambda F/A$, where λ is the wavelength (equal the ratio of the speed of sound in the medium and the ultrasound frequency), F is the focal length, and A is the aperture size (F/A is also known as the f-number). However, the frequency dependence of the ultrasound attenuation factor, mainly influenced by the skull, imposes a trade-off in the frequency choice. The attenuation factor is given by $\alpha_0 f^n$, where α_0 is a temperature-dependent attenuation factor at 1 MHz, f is the ultrasound frequency, and n lies in the range of 0.9–2.1 for the human skull bone and 1.05–1.1 for brain [63]. Typically, ultrasound neuromodulation delivers submillimetric to millimetric resolution that employs frequencies in the kHz range for humans (i.e., f = 250 kHz, L = 7 mm [64]) and NHPs (i.e., f = 320 kHz, L = 5 mm [64]) and kHz to MHz range for rodents (i.e., f = 1.9 MHz, L = 1 mm [6]; f = 5 MHz, L = 0.29 mm [65]).

Motion-sensitizing gradients can detect phase shifts in MR data that encode brain tissue displacements caused by FUS application [66, 67]. This specific MRI technique, called magnetic resonance-acoustic radiation force imaging (MR-ARFI), has been shown to be safe despite the need for high-intensity FUS pulses to displace tissue [68]. Currently, just like in transcranial magnetic stimulation (TMS, which employs pulsed magnetic fields to induce eddy currents in the brain) or transcranial direct current stimulation (tDCS), neuromodulation studies rely on numerical simulations to perform targeting. However, a confirmation of tissue engagement through MR-ARFI would be highly desirable, especially for small brain structures. In this context, targeting accuracy can be improved by using low-frequency ranges and normal incidence angles [69] both minimizing FUS beam distortions and by adopting neuronavigation systems based on MR images [70].

MR phase-difference images can also be used for temperature monitoring during FUS [71, 72] in order to avoid artifacts that would arise from local temperature measurements based on thermocouples [73, 74]. While no significant temperature elevation has been detected in low-intensity neuromodulation protocols [75], higher intensity protocols [6] may cause physiologically relevant temperature elevations [74, 76], and monitoring temperature may provide insights into FUS neuromodulation mechanisms. Other MRI modalities, such as T2-weighted and T2*-weighted imaging, can provide safety evaluation such as the detection of potential hemorrhages and edema formation [77]. Also, T2-weighted fluid-attenuated inversion recovery (FLAIR) can provide safety assessment with better differentiation between cerebrospinal fluid (CSF) and abnormal tissue [78]. In addition, diffusion-weighted imaging (DWI) is highly sensitive to both reversible and irreversible changes in brain microstructure [79]. Moreover, in order to reveal intentional [7] or unintentional breakdown in the blood–brain barrier in the context of neuromodulation, T2- or T1-weighted MR images can be used to evaluate T2 or T1 contrast agent deposition in brain tissue after ultrasound application [80–82]. Finally, fMRI has been used in NHP to identify brain areas to be modulated [64] or to reveal the extent and connectivity of spatial changes in hemodynamic responses caused by FUS [8, 83–87].

OTHER NEUROMODULATION TECHNIQUES: MULTIMODAL STIMULATION

In general, among the numerous techniques available for neuromodulation, keeping more and more of the neurophysiology under experimental control goes hand in hand with an increase in invasiveness and biotechnological constraints. For example, neuronal activity of specific neuronal populations could be reversibly silenced by genetic approaches [88] while FUS would probe specific brain structures. This could potentially reveal the spatial and temporal scales of the different mechanisms of action, the contribution of FUS neuromodulation in different brain cells, and the contribution of defined projection pathways to neuronal network dynamics and animal behavior. On the non-invasive side, which is more immediately translatable to humans, combining magnetic and ultrasound stimuli is capable of enhancing the effect of FUS [89]. It has been proposed that ions in motion under a static magnetic field could be subjected to a Lorentz force, giving rise to electric currents that would contribute to the neuromodulatory effect of FUS [89, 90]. For example, in humans, concurrent FUS and TMS applied to the primary motor cortex (M1) attenuated motor evoked potential amplitude, reduced intracortical facilitation, and slightly shortened (10 μs) the response time in visual tasks [42]. Notably, FUS parameters can span a range of values that has been shown capable of inducing mechanical [91] or thermal effects to obtain excitatory or inhibitory effects on mice sciatic nerve [92]. In general, the ability of FUS to probe spatially specific brain regions enables understanding of, e.g., brain functioning and connectivity in non-invasive and spatially selective manner, with little or no cell type specificity. In this respect, FUS is somewhat similar to TMS, although it may offer better focusing of deeper structures (at least with a single coil) [93, 94]. Interestingly, TMS and FUS still share the large potential for non-invasive brain enhancing and silencing, as well as the lack of a thorough understanding of the mechanisms of action underlying the diversity of effects observed throughout the literature, which may include involuntary cell type specificity,

axonal stimulation [95], uncontrolled/uncontrollable activation at different loci of the neuron, distributed stimulation peaks [96], and complex interplay of modulating inhibitory and excitatory synaptic potentials [97]. In this context, current-controlled "priming" techniques such as tDCS can be used in conjunction with time-localized TMS [98] (or possibly FUS) to modify the underlying neuronal activity substrate and possibly enhance specificity.

Conversely, techniques such as optogenetics [99] and chemogenetics/pharmacogenetics [100] can provide cell type-specific, selectively inhibitory, excitatory or combined control of neuronal activity by expressing light-sensitive ion channels called opsins, which can be either excitatory (e.g., channelrhodopsin) or inhibitory (e.g., halorhodopsin). The specificity [100] may be selectively activated [101] with light at different frequencies allowing a virtually infinite combination of stimuli, which can open/close ion channels with extremely high frequencies (up to 30 Hz). The drawbacks of such techniques lie both in practical challenges, e.g., the implantation of fiber optics for stimulation (which may interfere with behavioral experiments and limit human translational potential) and the high spatial selectivity (200 μm) of light delivery (which, interestingly, may not suffice to inhibit the function of a particular brain region and hence examine its function) and in neurobiological effects such the need to genetically modify the organisms to achieve cell type specificity, non-physiological hyperpolarization (which in turn can generate rebound phenomena), and in the potential generation of antidromic potentials (which may blur the physiological significance of the stimulation). While the first set of constraints may be partially solved by pharmacogenetic approaches (which employ chemical stimuli to activate the opsins and hence eliminate the surgical requirements and the need for constant stimulation when envisaging future treatment strategies in humans), the second may not. This calls for a new generation of combined biotechnological and physical neuromodulation techniques in order to achieve successful translation to the human context, especially in the therapeutic and clinical trial arena.

Interestingly, novel paradigms have been proposed involving the combination of genetic approaches with either magnetic or ultrasound stimulation. In magnetogenetics, thermosensitive, and mechano-sensitive ion channels (typically transient receptor potential vanilloid class receptors TRPV, which are selective calcium Ca^{2+} transporters) are genetically engineered to be tightly coupled to the iron storage protein ferritin (or another paramagnetic protein), so that they can be activated by external magnetic fields [102]. In sonogenetics, through a similar approach, it has been demonstrated that neuron-specific misexpression of TRP-4 (a pore-forming subunit of a mechanotransduction channel) can sensitize neurons to ultrasound stimuli with detectable behavioral outputs [103]. It appears, therefore, evident that combined multimodal strategies are the principal future avenues for tailoring neuromodulation intervention to an application-specific and possibly patient-specific context within a precision medicine paradigm.

DISCUSSION

In this review, we have summarized potential mechanisms underlying the neural substrates of FUS neuromodulation and outlined conflicting hypotheses of the current literature. Similar to what has been shown for TMS, it is our opinion that apparent contradictions observed in some experimental and modeling studies could be resulted mainly due to variability from different experimental conditions *in vitro*, *ex vivo*, and *in vivo* applications and that they could be reconciled by detailed standardization and translation studies. In turn, this would allow drawing more informed conclusions on the FUS neuromodulation mechanisms. Additionally, the lack of a complete understanding of anesthesia effects on neurons encourages further awake FUS neuromodulation studies, which with the aid of MRI in assessing brain activity, targeting, and safety, will provide a clearer picture of both the neurophysiological underpinnings and of the potential translational applications of FUS, whether alone or in a multimodal context.

A number of experimental evidences show that the AP involves an electromechanical process and that the deformation of tissues induced by the ARF plays a crucial role in neuromodulation through potential capacitance change modulation or a flexoelectric effect triggering. Another possibility is that FUS could cause a neuronal membrane deformation capable of interfering with membrane electrical depolarization by mechanical coupling with the endogenous mechanical waves (soliton) associated with APs. In addition, ultrasound propagation can deform tissues elastically while the pulse energy is lost through heating due to viscous frictional forces. Whether the thermal effect is detectable or important in the context of neuromodulation will depend on the temperature level that is reached, neuronal sensitivity to temperature transients, tissue diffusion, and perfusion capability. In the soliton model, the membrane temperature is a crucial factor, and it should be noted that the membrane melting point is slightly below physiological temperature. Therefore, small temperature elevations caused by viscous frictional forces during ultrasound propagation may cause an interference with electromechanical membrane physiology. Most studies have consistently strived to avoid thermal effects from FUS effects, which is important to separate ablative from non-ablative effects. However, the mechanical and low-temperature increase generated by FUS could also potentially improve the neuromodulatory effects [104]. In this context, animal experiments based on sedation or anesthesia need to take thermal effects into account as mild hypothermia is common during deep sedation [105].

While the lack of a complete understanding of the FUS neuromodulation mechanisms does not currently impede reaping potential benefits in a more application-driven context, it is reasonable to expect that a better mechanistic understanding will immediately reverberate onto the applicability and efficacy of FUS-based neuromodulation. Importantly, as the technology continues to gain ground and acceptance, safety must remain a prime concern. Therefore, overcoming current limitations in both target confirmation and safety monitoring through the human skull is imperative. Techniques

such as mapping of cavitation, temperature, and displacement will ensure a successful clinical translation of ultrasound neuromodulation, at the same time providing more control over the acoustic parameters. This will allow employing precisely determined mechanism combinations for achieving targeted neuronal excitation and inhibition. While more and more studies are being planned, several investigations have already demonstrated the existence of a wide range of safe parameters [106–108].

While fMRI is undoubtedly the gold standard for functional brain imaging, other techniques can provide complementary information on brain function. Recent studies have combined fMRI and optical imaging to show that ultrasound neuromodulation induces cerebral hemodynamic changes in different animals at variable peak latencies: mice ~2.5 s [109, 110], rabbits ~3.2 s [111], and NHPs ~6.5 s [86]. Furthermore, a technique termed functional ultrasound (fUS) is capable of detecting transient changes in blood volume [112], and it has been demonstrated capable of providing deep brain functional images with high spatial resolution (from 50 to 200 μm) [113] and temporal resolution of <1 s [114]. In addition, fUS features high sensitivity and portability, which enable awake experiments with freely moving subjects. The development of 2D transducer arrays [115], capable of generating images and steerable, highly focused beams, potentially with multifrequency capability [116], may facilitate human fUS during the ultrasound neuromodulation.

Crucially, while *in vitro* and *ex vivo* studies are necessary for understanding mechanisms, *in vivo* brain activity studies are essential to gather mesoscale and macroscale information about the effect of FUS on brain functioning. In small animals, experiments in ultra-high-field (UHF) MRI (7–21 T) can provide higher signal-to-noise and contrast-to-noise ratios as well as in the case of fMRI increased susceptibility [60, 117]. In turn, this will unlock more in-depth insights into how the intact brain works and into the available windows in interfering with its activity in a non-invasive or minimally

invasive manner, accelerating the translation toward human applications and especially the empowerment of clinical trials. This may include applications to neurological diseases like epilepsy and chronic pains, psychiatry [Obsessive-compulsive disorder (OCD), pharmacoresistant depression, agoraphobia], as well as fostering neuronal plasticity in, e.g., rehabilitation or slowing the progression of degenerative brain diseases. Especially in this latter context, multimodal stimulation (as electrical, magnetic, chemical, light, mechanical), possibly coupled with a state-of-the-art monitoring tool like UHF MRI for non-invasive techniques and calcium imaging [118], may enable simultaneous, multi-scale, brain structure- or cell type-specific silencing or excitation, allowing the exploration of both brain-wide pathways and specific cognitive, emotional, and pathological mechanisms. This can provide a significant step change in keeping more and more neurophysiological aspects under experimental control and hence ultimately approaching the neurobiological goal of neuromodulation in a more precise, targeted, painless, and direct manner.

AUTHOR CONTRIBUTIONS

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