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Perspective

Advancements and challenges in neuromodulation technology: interdisciplinary opportunities and collaborative endeavors

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Neurological diseases, such as intractable pain, Parkinson's disease, and depression, have imposed significant health and economic burden globally. According to the World Health Organization (WHO), approximately one billion people, one-sixth of the global population, are afflicted with neurological diseases. These disorders have become the primary contributors to disability-adjusted life-years (DALYs) and are ranked as the second leading cause of death [1]. The economic losses caused by brain diseases can exceed trillions of dollars every year in major countries. Thus, developing and applying innovative neuroscience technology for the treatment of brain diseases has been a central goal in large-scale brain research projects with a budget of billions of dollars, like the China Brain Project [2], the EU's Human Brain Project, Japan's Brain/MINDS Project, the US's BRAIN Initiative [3].

One key innovative neuroscience technology for the non-drug and non-addictive therapeutic treatment of neurological diseases is neuromodulation, "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body" (www.neuromodulation.com). To combat neurological diseases, a considerable number of neuromodulation techniques have been developed based on the concept of neuroplasticity, which refers to the ability of the nervous system to undergo reorganization or long-term modifications of its structure, function, or connections in response to intrinsic or extrinsic stimuli. Apart from treating neurological diseases, neuromodulation techniques provide a valuable approach to uncovering the causal roles of the brain in cognition and behavior by perturbing brain activity. Non-invasive modulation techniques can even reveal how specific brain areas causally support higher-order cognitive functions like language and decision-making in humans [4].

Thus far, a plethora of invasive or non-invasive neuromodulation techniques have been developed. Commonly used invasive neuromodulation techniques include deep brain stimulation (DBS), spinal cord electrical stimulation (SCS), invasive vagus nerve electrical stimulation (VNS), sacral nerve electrical stimulation (SNS), optogenetics, and chemogenetics. Typical examples of non-invasive neuromodulation techniques are transcranial magnetic stimulation (TMS), transcranial direct/alternating current stimulation (tDCS/tACS), transcranial ultrasonic stimulation (TUS), transcranial near-infrared laser stimulation (tNILS), transcutaneous vagus nerve stimulation (tVNS), and transcutaneous electrical nerve stimulation (TENS). These techniques involve the delivery of electricity, sound, light, and magnetism to individuals, which can restore or optimize brain functions by reversing maladaptive changes due to physical injuries, preventing their further progression, or enhancing ongoing adaptive changes. Many neuromodulation technologies have already demonstrated their clinical value. As an example, direct microcurrent stimulation on the spinal cord nerve corresponding to the pain site using SCS has proven to be an effective method for managing intractable pain in the trunk and limbs. This treatment, approved by the US Food and Drug Administration (FDA) and the China Food and Drug Administration (CFDA), has benefited more than 270,000 patients worldwide with chronic and refractory pain.

However, neuromodulation techniques still face various obstacles in practical application, such as dangerous virus tools, high invasiveness, poor biocompatibility, unstable therapeutic effects, and reliance on the wired power supply (Table 1). Neuromodulation techniques used in animals are generally invasive and virus dependent. For example, the widely used optogenetics utilizes the Cre-loxP gene technology to express photosensitive proteins in specific neuronal populations to achieve cell type-specific modulation, but this process frequently relies on adeno-associated virus tools and requires craniotomy for fiber implantation. Neuromodulation techniques used in humans can also be highly invasive. As an example, DBS has been approved for clinical treatment in the 1990s, but it requires simultaneous brain and body surgeries with electrodes, wires, and energy storage pulse emitters (batteries) implanted. Moreover, the wired power supply method in DBS requires patients to undergo battery replacement surgery every 3–5 years, which poses a serious risk of postoperative infection and complications. Non-invasive neuromodulation techniques are not without problems. For instance, tDCS is non-invasive and has been widely adopted in basic research and clinical applications, but the device itself is bulky and relies on complex wire connections (Fig. 1a). Furthermore, traditional neuromodulation techniques typically operate in an open-loop manner with fixed parameters, lacking the ability to adapt to changes in physiological

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Table 1
Advantages and disadvantages of existing neuromodulation technologies.

Technologies	Advantages	Disadvantages
Invasive (implantation into the body, animal use only)		
Optogenetics	Cell-type specific operation	Relying on virus and genetic tools
Chemical genetics	Customizability modulation	Limited applicability
Invasive (implantation into the body)		
Deep brain stimulation (DBS) Spinal cord electrical stimulation (SCS) Vagus nerve electrical stimulation (VNS) Sacral nerve electrical stimulation (SNS)	Highly efficient (i.e., direct intervention in the nervous system) Precise modulation (i.e., regulate specific neural circuits or brain regions) Reversibility (i.e., can be closed and removed) Widely used in basic scientific research and clinical applications	Highly invasive (i.e., craniotomy and implantation) High surgical risks (e.g., infection, injury) Side effects and complications (e.g., speech and language impairment, headache) Device issues (e.g., electrode displacement, battery depletion)
Non-invasive (transcranial or transcutaneous)		
Magnetic stimulation (TMS) Direct current stimulation (tDCS) Alternating current stimulation (tACS) Ultrasonic stimulation (TUS) Near-infrared laser stimulation (tNILS) Vagus nerve stimulation (tVNS) Electrical nerve stimulation (TENS)	Non-invasive treatment High safety (i.e., a rare occurrence of side effects or complications) Easily to operate (i.e., complex surgeries or special equipment are not required) Multiple methods can be used (e.g., magnetic/electrical/acoustic /optical stimulation) Repeatability and adjustability (i.e., can be operated multiple times, with adjustable parameters)	Limited penetration depth (i.e., unable to stimulate deep brain regions) Large individual variations in treatment effectiveness Uncertainty of efficacy persistence Bulky equipment and requires a wired power supply Limited usage scenarios (because of high equipment usage and maintenance costs)

Neuromodulation techniques have demonstrated effectiveness in treating a wide range of conditions, including chronic pain, depression, epilepsy, Parkinson's disease, and other nervous system disorders. Additionally, they have shown potential for addressing urinary system diseases, heart diseases, diabetes, obesity, and other physical ailments.

states [5]. However, the physiological system itself is dynamic, and the effectiveness of stimuli may vary depending on specific states. Thus, open-loop neuromodulation may only have suboptimal effects or potentially lead to more side effects.

Addressing these challenges in neuromodulation requires the collaborative efforts among researchers from diverse disciplines, including neuroscience, psychology, psychiatry, medicine, biophysics, biomedical engineering, computer science, materials science, and so on. Interdisciplinary work holds the potential to offer new solutions and significantly enhance the usability and effectiveness of neuromodulation techniques. In fact, multidisciplinary collaborative research has become increasingly vital for the future of neuromodulation technology. Collaboration among experts from biology, physics, chemistry, materials science, engineering, and neuroscience is making notable advancements in improving the non-invasiveness, biocompatibility, and spatial accuracy of current neuromodulation techniques, providing more energy supply strategies and more flexible application scenarios, and offering more advanced closed-loop modulation strategies. Among various avenues of exploration, three major trends are emerging in this interdisciplinary field, including the development of functional nanomaterials to reduce invasiveness and achieve multimodal modulation, the design of miniaturized devices and wireless power supply methods, and the development of closed-loop approaches for real-time modulation of neural activity (Fig. 1b). By embracing these avenues of exploration and fostering interdisciplinary collaborations, the future of neuromodulation holds tremendous potential for further advancements in the field.

Trend 1: developing functional nanomaterials to reduce invasiveness and achieve multimodal neuromodulation. Nanotechnology is fundamentally transforming the existing neuromodulation techniques, as functional nanomaterials have excellent physical and chemical properties and can minimize the side effects caused by invasive electrode insertion into the brain. Recently, upconversion nanoparticles (UCNPs) have been shown to exhibit high near-infrared light (NIR) conversion efficiency, which could absorb NIR and emit visible light of specific wavelengths to achieve minimally invasive optogenetic modulation without fiber implantation [6]. Importantly, even transcranial irradiation with NIR at a few millimeters outside the skull of mice could still be effectively transmitted to the UCNP injected into the ventral tegmental area (VTA). Combined with optogenetics, UCNPs bring about various modulation effects by emitting different light. Blue-emitting UCNP (450–470 nm) could activate the gene-labeled neurons in VTA to release dopamine, and green-emitting UCNP injected into the hippocampus (~540 nm) could inhibit hippocampal excitatory cells and seizures in mice [6].

Injectable magnetoelectric nanoparticles (MENPs) [7] and piezoelectric nanoparticles (PENPs) [8] can also serve as versatile alternatives to traditional rigid implantable electrodes. MENPs consist of magnetostrictive cobalt ferrite nanoparticles coated with a piezoelectric barium titanate coating [7] and PENPs are comprised of piezoelectric barium titanate nanoparticles coated with polydopamine [8]. They exhibit exceptional magnetoelectric and piezoelectric properties, enabling them to generate significant electrical currents when exposed to external magnetic fields and ultrasound, respectively. These nanoparticles can be aggregated into specific brain regions through microinjection, which facilitates precise neural modulation within deep brain regions while minimizing invasiveness. Notably, piezoelectric particles are able to generate nitric oxide and direct current when exposed to high-intensity focused ultrasound [8]. The release of nitric oxide allows these particles to temporarily cross the blood–brain barrier and accumulate in the brain parenchyma, providing a valuable approach to neuromodulation. Indeed, the injection of ultrasound-responsive nanoparticles through the tail vein has been shown to alleviate Parkinson's disease symptoms in a mouse model without causing significant cytotoxicity [8].

Aside from reducing invasiveness, nanoparticles implanted in proximity to specific neurons can also be harnessed to implement both single-mode and multi-mode strategies for neuromodulation. In the single-mode approach, nanoparticles can enhance the modulation efficiency of various stimuli, including light, electricity, sound, and magnetism. Furthermore, nanoparticles facilitate multi-mode neuromodulation by enabling energy conversion between different modalities and combing physical stimulation with drug release. For instance, light-to-heat and sound-to-electricity energy conversions can be simultaneously achieved, allowing for the integration of physical stimuli in different modalities and thus expanding the range of strategies available for neuromodulation.

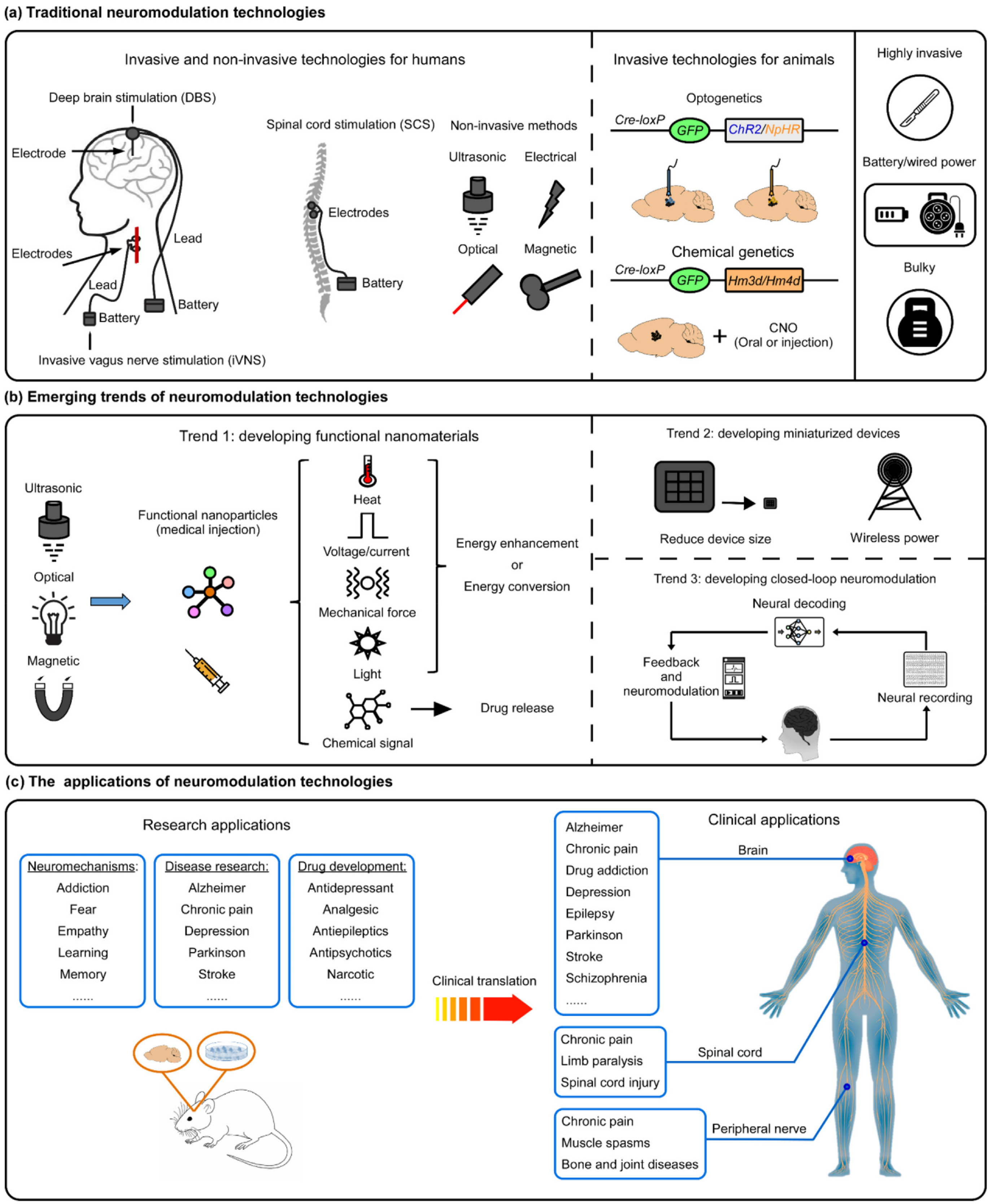

Fig. 1. Types, developments, and applications of neuromodulation technologies. (a) Conventional neuromodulation technologies, used in humans and animals, are characterized by their invasiveness, requirement of external power, and bulky design. (b) Within the interdisciplinary landscape, neuromodulation technology has exhibited three prominent trends: developing functional nanomaterials, developing miniaturized devices, developing closed-loop neuromodulation. (c) The clinical translation of neuromodulation technologies from basic research holds the potential to revolutionize the treatment of various neurological diseases in humans.

This multi-mode capability broadens the possibilities for developing innovative approaches to modulate neural circuits and functions.

Trend 2: developing miniaturized devices and achieving wireless power supply. Both invasive and non-invasive neuromodulation techniques have traditionally been limited by the large size of devices and their heavy reliance on the wired power supply. As of late, there have been continuous advancements in the development of small-sized, wire-free, and battery-free implantable neural stimulators. Notable examples include the Neuraldust or Stimdust devices, which exhibit remarkable miniaturization. For instance, the Stimdust device integrates piezoelectric ceramic transducers, energy storage capacitors, and integrated circuits, resulting in a compact volume of only 1.7 mm^3 for the whole device [9]. This device has been implanted into the muscle of a rat to effectively modulate the sciatic nerve via cuff electrodes.

Recently, a micro implantable piezoelectric ultrasonic energy acquisition device (13.5 mm × 9.6 mm × 2.1 mm in size, and 0.78 g in weight) has also been developed for DBS [10]. This device is based on a flexible structure using Sm-doped $Pb(Mg_{1/3}Nb_{2/3})O3$-PbTiO3 (SM-PMN-PT) single crystal, which exhibits impressive piezoelectric properties. The device demonstrates a high piezoelectric coefficient of up to 4000 pC/N, an electromechanical coupling coefficient of 95%, and a relative dielectric constant of 13,000 [11]. Upon implantation in the rat brain, the device is driven by 1-MHz ultrasound at a safe intensity of 212 mW/cm^2. It generates an instantaneous effective output power of 280 μW, which immediately activates the periaqueductal gray area in rats, resulting in a strong analgesic effect [10]. Altogether, these devices demonstrate the significant potential of miniaturization design in neuromodulation.

Functional materials can help solve the wired supply power problem, since some of them are capable of wirelessly interacting with diverse forms of energy, including light, magnetic fields, and ultrasound. Wireless power transmission also has obvious benefits such as extended service life and expanded application scenarios. In practice, remote power supply of microdevices can utilize abundant energy transmission carriers, including ultrasonic waves with excellent penetrability, strong directivity, and high spatial resolution, as well as photovoltaic, electromagnetic waves, and radio frequency. For instance, a wireless optoelectronic system comprising radio frequency acquisition units has been employed for wireless optogenetic modulation [12]. By incorporating flexible materials like polydimethylsiloxane or employing biocompatible coatings such as polylactic acid and polycaprolactone, these devices are suitable for neuromodulation of the brain, spinal cord, peripheral nerve regions, or muscles.

Trend 3: developing advanced closed-loop approaches for real-time neuromodulation. Closed-loop neuromodulation involves the real-time adjustment of stimulation parameters based on the underlying physiological states to optimize the modulation effects and minimize side effects. Its potential can be fully realized when the underlying physiological states change rapidly and the external stimulation has fast mechanisms of action. Implementing closed-loop neuromodulation is more challenging compared to its open-loop counterpart due to its reliance on complex closed-loop systems. However, recent advancements in machine learning, neuroimaging, neurophysiology, microelectronics, sensing technology, and wireless communication have made closed-loop neuromodulation more accessible. To decode physiological states and adjust parameters accordingly, closed-loop neuromodulation techniques extract biological signals from biosensors with a relatively high temporal resolution, such as electrocardiogram (ECG), skin conductance, electroencephalogram (EEG), and ultrasound imaging. These biological signals are amplified and digitized by the acquisition system, and then sent to a dedicated processing unit, which accurately decodes and predicts individuals' states using advanced signal processing methods. Finally, the results from the processing unit guide the output device to adaptively deliver stimulation [5].

Closed-loop neuromodulation can be invasive or non-invasive. Clinical applications of this form of neuromodulation are typically invasive, as in the treatment of Parkinson's disease, chronic pain, epilepsy, and other medical conditions. However, efforts are being made to reduce the invasiveness of these techniques. An illustrative example of the exceptional closed-loop neuromodulation capability is demonstrated through a novel brain-machine interface (BMI) [13]. Within this system, the neural spike activity in the anterior cingulate cortex can be recorded, sorted, and analyzed online using a state-space model, enabling the decoding of nociception onset. Building upon this, the system effectively combines real-time pain detection with optogenetic activation of the prefrontal cortex, showcasing its remarkable capacity for pain treatment [13]. On the other hand, non-invasive closed-loop neuromodulation is based on non-invasive techniques. For instance, using Simulink Real-Time (Mathworks Ltd. USA), the instantaneous phase of real-time EEG recording can be estimated, and the subsequent signal phase can be forward predicted to precisely trigger TMS at the desired phase [14]. Stimulation at the negative peak of sensorimotor μ-oscillation (i.e., 9–13 Hz) has been shown to facilitate long-term potentiation-like plasticity, while stimulation at the positive peak of oscillation or random phase exhibits long-term depression-like plasticity. Notably, the presence of electromagnetic artifacts can pose challenges to high-frequency closed-loop neuromodulation. While low-frequency stimuli, such as 1 Hz in [14], may be feasible, closed-loop stimuli with higher frequencies often introduce electromagnetic artifacts. To address this issue, some researchers have employed visual stimuli as a natural sensation for regulating alpha rhythms [15], rather than relying on electromagnetic stimuli.

Fueled by interdisciplinary endeavors, the field of neuromodulation is poised to make significant strides in our understanding of the nervous system and revolutionize therapeutic interventions. However, the field still faces many challenges that should be addressed before novel neuromodulation techniques can be readily applicable in various clinical settings.

Opportunities. First, nanomaterials that have undergone specific structural and functional modifications hold the potential to achieve controlled *in vivo* neuromodulation, either in the short-term through bioabsorption or metabolism, or in the long-term. This capability opens up new avenues for precise and dynamic neuromodulation. Second, nanomaterials offer a versatile platform that can be tailored to meet different demands. For instance, nanomaterials can serve as a potential drug delivery platform for targeted therapies, allowing for precise and localized treatment of neural disorders. Additionally, these materials possess the unique capability of generating physical energy and facilitating chemical reactions, thereby enabling the manipulation of nerve activity through both physical and chemical means. Third, miniaturized neuromodulation devices can benefit from commercially available magnetoelectric and piezoelectric materials, offering flexible size customization to accommodate both invasive and non-invasive neuromodulation. For instance, ultra-small devices can enable micro-invasive neuromodulation through biocompatible treatments and medical syringe injections. Fourth, the growing popularity of wearable devices presents an opportunity for closed-loop neuromodulation. These devices can integrate sophisticated functionalities like sensing and monitoring, and deliver small electrical currents, enabling personalized and intelligent closed-loop neuromodulation.

Challenges. First, advanced nanomaterials with exceptional performance are primarily synthesized in laboratory settings. They are typically expensive due to high research and development costs, and lack standardized production and application protocols, which hinders successful marketization. Consequently, the commercial availability of these materials is limited, which in turn pushes up the high costs in synthesizing such nanomaterials. Moreover, newly synthesized nanoparticles undergo insufficient safety assessment such as immune response and long-term biocompatibility, which pose challenges in effectively applying and translating them in neuromodulation. Second, miniaturized neuromodulation devices face challenges in energy supply and have limited power storage capacity. Meeting the power demands of complex systems requires the design of optimized application specific integrated circuits (ASIC) and circuit accessories or finding a balanced compromise between size and performance. However, these solutions often come with significant development expenses. Third, functional nanoparticles and miniaturized devices are largely confined to *in vitro* or animal testing. Their exact mechanisms and modulation effects are not yet fully understood, highlighting the need for more in-depth research through comprehensive parameter studies and additional animal and human experimental testing. Fourth, real-time tracking and processing of biological signals to extract targeted features (e.g., EEG phase) and the limitations of software and hardware can introduce a delay in delivering precise stimulation at the desired moment. To minimize the modulation time delay, researchers often skip some preprocessing steps. However, this approach may result in a low signal-to-noise ratio, which impedes the accurate prediction of subsequent signals. Fifth, individual differences in neuromodulation application should be recognized. Even with identical intervention targets, dosage, and diseases, the effects may still vary drastically among individuals. To account for individual differences, individual-level precise studies are in need. Only when the technique itself and the individual who is supposed to benefit from the technique are both considered, the maximum effects of neuromodulation could be achieved. Lastly, the field of neuromodulation should carefully consider the problem of reproducibility and generalizability. We have highlighted the potential opportunities that interdisciplinary collaborations can provide, but such studies are typically conducted with limited sample sizes, and their reproducibility and generalizability are not extensively examined. To improve reproducibility and generalizability, future studies need to adopt larger sample sizes, improve measurement reliability and validity, minimize research bias, and adhere to open science practices. By doing so, we can strengthen the robustness and reliability of neuromodulation research, leading to more effective and widely applicable techniques.

In conclusion, the advancement of neuromodulation technology relies on the synergy of interdisciplinary cooperation. Collaboration among neuroscientists, engineers, and clinicians is crucial to foster innovation, exchange knowledge, and tackle the complex challenges at the intersection of science, technology, and medicine. By promoting interdisciplinary cooperation, we can harness the immense potential of neuromodulation technology and pave the way for groundbreaking discoveries and transformative applications. Continued efforts in refining techniques, translating research into clinical practice, addressing ethical considerations, and fostering interdisciplinary collaboration will contribute to the further development of neuromodulation and the realization of its full potential in improving human health and well-being.

Conflict of interest

The authors declare that they have no conflict of interest.

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