

The New Era of Neural Modulation Led by Smart Nanomaterials

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Abstract: Understanding the physiology and pathology of neural circuits is crucial in neuroscience research. A variety of techniques have been utilized in medical research, with several established methods applied in clinical therapy to enhance patient's neurological functions. Traditional methods include generating electric fields near neural tissue using electrodes, or non-contact modulation using light, chemicals, magnetic fields, and ultrasound. The advent of nanotechnology represents a new advancement in neural modulation techniques, offering high precision and the ability to target specific cell types. Smart nanomaterials enable the conversion of remote signals (such as light, magnetic, or ultrasound) into local stimuli (eg, electric fields or heat) for neurons. Surface treatment technologies of nanomaterials have enhanced biocompatibility, making targeted delivery to specific cell types possible and paving the way for precise neural modulation. This perspective will explore neural modulation techniques supported by nanomedical materials, focusing on photoelectric, photothermal, magnetoelectric, magnetothermal, and acoustoelectric conversion mechanisms, and looking forward to their medical applications.

Keywords: neurodegenerative diseases, neural modulation, nanomaterials

Introduction

Neural modulation technology has experienced significant advancements, especially in the treatment of neurological disorders and the correction of nervous system dysfunctions.¹ These technologies are widely used to restore hearing and vision, and treat diseases such as Parkinson's,² essential tremor,³ epilepsy,⁴ and obsessive-compulsive disorder.⁵ According to the World Health Organization, Parkinson's disease affects approximately 8.5 million people globally, with the prevalence having doubled over the past 25 years. Essential tremor impacts around 7 million individuals in the United States alone.^{6,7} Additionally, epilepsy remains one of the most common neurological conditions, impacting around 50 million people worldwide. Obsessive-compulsive disorder has a global prevalence rate of 1% to 2%.⁸ Moreover, the peripheral nervous system's regular function, which is essential for the operation of various organs, underscores the vast clinical potential of neural modulation technologies targeting peripheral nerves. However, traditional methods, such as vagus nerve stimulation, often necessitate surgical electrode implantation, raising concerns about biosafety, surgical trauma, and the limitations posed by electrical field attenuation.^{9,10}

In recent years, to tackle these challenges, researchers have devised optical, thermal, and chemogenetic tools, allowing for more minimally invasive and cell-specific neural modulation.^{2,11–13} These methods allow researchers to control the activation or inhibition of neurons through external stimuli, such as light or heat. While these technologies have demonstrated potential in animal experiments, the reliance on genetic engineering and translating from animal models to clinical use presents challenges. Furthermore, the timeliness and conversion efficacy of these methods still need further enhancement.

The utilization of smart nanomaterials has opened new opportunities in nervous system research (Figure 1). Unlike traditional methods, smart nanomaterials not only serve as drug delivery vehicles but also act as energy converters in

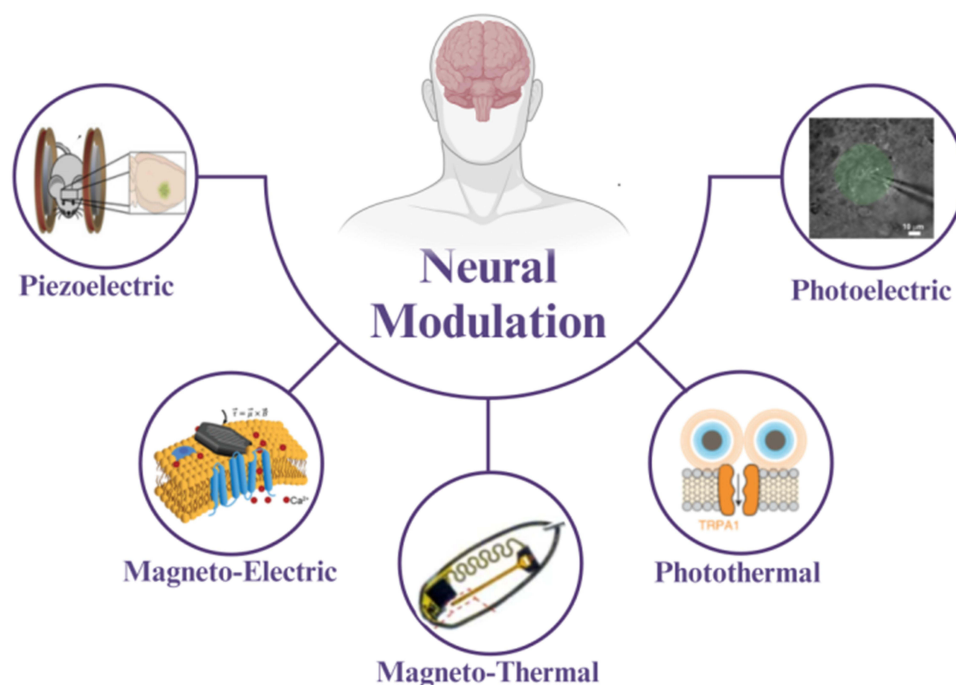


Figure 1 Application of Smart Nanomaterials in Neural Modulation.

neural stimulation.¹⁴ These materials, such as metallic or inorganic compound nanomaterials, respond to external stimuli—including light, heat, or electromagnetic fields—facilitating neural activation.^{15,16} Spatial selectivity optimization is key, achievable through precise placement of stimulation signals or nanomaterials. In many experiments, smart nanomaterials have played a key role in neural activation through mechanical, thermal, and electromagnetic effects, which are crucial for understanding how smart nanomaterials function in the nervous system.

Distinct from existing reviews, this perspective uniquely synthesizes the latest advancements in smart nanomaterials for neural modulation, offering a comprehensive overview of their multifunctional roles beyond conventional applications. We aim to provide a critical analysis of how these materials transcend traditional paradigms, particularly focusing on their potential to address the limitations of current neural modulation techniques. This perspective is timely, considering the rapid evolution of nanotechnology in neuroscience, and serves as an essential resource for researchers aiming to explore the frontier of neural modulation with smart nanomaterials.

Key Mechanisms of Nanotechnology in Neural Modulation

Application of the Photoelectric Effect

Quantum dots (QD), as semiconductor nanoparticles ranging from 2 to 6 nanometers in diameter, exhibit photoconductive properties, demonstrating potential as optically-controlled neural stimulation mediators.¹⁷ Under light stimulation, QDs generate dipole moments and electric fields, potentially sufficient to activate neurons' voltage-gated ion channels. Currently, research mainly employs two methods to direct QDs to the surface of neurons:^{18–20} the first is by modifying QDs with antibodies or peptides to bind them to the neuron membrane; the second is fixing QDs on a specific material substrate, then attaching them to the neuron surface.

However, several limitations arise when QDs are directly bound to neuron cell membranes. One major issue is the potential internalization of QDs by neuronal cells, which compromises the stability and efficacy of the photoelectric interface. Additionally, the binding specificity of antibodies can be insufficient, making it difficult to achieve consistent and stable neural regulation. To address these challenges, alternative techniques have been developed. One such method involves coupling QDs to carriers to form thin films, reducing the likelihood of internalization. While this approach improves stability, it often only achieves short-term efficacy. For instance, research has demonstrated that multilayered

Hg-Te-QD films can generate photocurrents capable of triggering action potentials in neuroblastoma NG108 cells, thereby activating neuronal responses.^{21–23}

Further advancements have been made using materials like Cd-Te-QD and Cd-Se-QD films, which have been utilized to create photoelectric interfaces with different cell types, including LnCap prostate cancer cells and cortical neurons. When illuminated, these cells exhibit various responses, from depolarization to hyperpolarization, and in some cases, action potentials are induced in cortical neurons. Nevertheless, QD-mediated photoelectric stimulation remains limited, with studies showing that only around 11% of neurons are effectively activated.²³ Additionally, cellular responses can vary significantly, with some neurons depolarizing and others hyperpolarizing under identical stimuli.

To improve performance and biocompatibility, researchers have engineered composite materials by chemically coupling Cd-Se/Cd-S core-shell nanorods with carbon nanotubes. These composites have demonstrated the ability to activate under pulsed light at a wavelength of 405 nm,¹⁸ successfully stimulating chick retinas lacking developed photoreceptors. However, their clinical application is still limited to superficial neural stimulation due to the poor tissue penetration of visible light. Notably, Maya-Vetencourt et al²⁴ demonstrated that subretinally injected semiconducting polymer nanoparticles can rescue vision in a rat model of retinal dystrophy by mediating light-evoked stimulation of retinal neurons, highlighting the potential of semiconducting polymer nanoparticles in vision restoration.

The Role of Photothermal Effects in Neural Stimulation

The temperature sensitivity of neuronal activity makes it possible to utilize photothermal effects for neural stimulation. Gold nanomaterials, due to their localized surface plasmon resonance properties, have become ideal photoabsorbers. Under illumination at resonant frequencies, gold nanomaterials generate electronic oscillations and collisions, inducing a photothermal effect and successfully activating neurons. However, the internalization of gold nanorods and the inconsistency in neuronal responses remain key issues to be addressed. Research indicates that spatial local temperature gradients on neuronal tissues are the cause of increased membrane capacitance and action potentials.^{25,26} Conversely, due to the regulatory role of ion channels, slow and prolonged heating can inhibit neuronal activity. Additionally, the specific temperature sensitivity of transient receptor potential vanilloid (TRPV)²⁷ is another widely studied trigger for neuronal modulation. To generate localized heat for stimulating neurons, nanoparticles are used as photoabsorbers to convert light into heat.²⁸ Due to localized surface plasmon resonance, gold nanomaterials are particularly suitable as photoabsorbers for neural stimulation.^{29,30} Under illumination from light sources at resonance frequencies, electrons in gold nanomaterials oscillate and collide, producing photothermal effects.

Gold nanorods coated with silica have been observed to successfully activate rat auditory neurons *in vitro*.^{31,32} Under pulsed laser illumination at a resonant wavelength of 780 nm, these gold nanorods activate nearby neurons, with a linear relationship to the duration of the laser pulses. Researchers also found that internalized gold nanorods, under continuous and pulsed irradiation of near-infrared at a resonant wavelength of 780 nm, promoted synaptic outgrowth in NG108-15 cells and induced Ca^{2+} influx.^{33,34} Under pulsed laser irradiation at the near-infrared resonance wavelength of 980 nm, the response of the sciatic nerve injected with gold nanorods to compound action potentials increased by nearly 6 times, and the action potential threshold decreased by 3 times. Therefore, this method can significantly reduce the power and duration of laser stimulation, thereby significantly reducing the risk of tissue damage. In an *in vivo* animal study, researchers injected polyethylene glycol-modified PEG-Au NRs into the left stellate ganglion of dogs and irradiated them with 810 nm near-infrared light. They found that the photothermal effect reversibly suppressed the function and activity of the stellate ganglion, significantly reducing ventricular arrhythmias after myocardial ischemia. Furthermore, a decrease in c-fos protein expression was observed in the stellate ganglion, providing a solution for future non-invasive optical control of the autonomic nervous system.³⁵

However, the internalization of gold nanorods remains a significant issue for these photothermal neuronal stimulations, often leading to variable outcomes, inconsistent phenomena, and tissue damage.^{32,33} Studies indicate that the internalization of gold nanorods may lead to a decrease in Ca^{2+} influx when pulsed laser irradiance is enhanced.³³ Studies have also observed that gold nanorods, electrostatically attached to neuronal membranes, exert inhibitory effects on hippocampal, cortical, and olfactory bulb neurons.³⁶ These phenomena are hypothesized to be caused by the temperature-sensitive inhibitory TREK-1 channels. Consequently, another challenge is to precisely determine the different pathways

of photothermal regulation by nanomaterials, enabling accurate control of neuronal responses. A recent study by Hescham et al³⁷ presents a wireless magnetothermal approach to deep brain stimulation (DBS) that alleviates parkinsonian-like symptoms in mice using synthetic magnetic nanoparticles and alternating magnetic fields to activate heat-sensitive TRPV1-expressing neurons, enhancing the discussion on wireless magnetothermal neuromodulation for Parkinson's disease treatment (Figure 2).

Application of Magneto-Electric Effect in Neural Stimulation

Researchers have proposed a new method of controlling neural stimulation using magnetic fields, based on the magneto-electric effect of magneto-electric nanoparticles.³⁸ These nanoparticles are capable of converting magnetic fields into electric fields, thereby activating neurons. Building on this effect, researchers have validated the use of core-shell structured magneto-electric nanoparticles (10 μ g CoFe₂O₄-BaTiO₃ 30 nm) in mice, demonstrating these materials' capability to modulate deep brain circuits under low-intensity magnetic fields.³⁹ However, more research is needed in this area to assess the stability of their physicochemical properties and the feasibility of long-term biocompatibility and safety in the body. Gregurec et al⁴⁰ explored the use of magnetic vortex nanodiscs for remote magnetomechanical neural stimulation. The transition from vortex to in-plane magnetization in iron oxide nanodiscs allows for the modulation of mechanosensory cells, triggering Ca²⁺ influx in low magnetic fields. Additionally, Kozielski et al⁴¹ introduced injectable, magnetoelectric nanoelectrodes that wirelessly transmit electrical signals to the brain in response to an external magnetic field, enabling less invasive deep brain stimulation in freely moving mice. Lee et al⁴² introduced m-Torquer, a magnetic toolkit that delivers piconewton-scale forces to cells, enabling non-contact long-range magnetic stimulation of mechanosensitive ion channels in freely moving animals. The application of biological magnetic nanomaterials, such as magnetotactic bacteria and synthetic magnetic nanoparticles, holds promise for developing biocompatible, neuron-targeted magneto-electric stimulation strategies.⁴³

Neural Stimulation Strategies Using the Magneto-Thermal Effect

Superparamagnetic nanoparticles achieve magneto-thermal neural stimulation by converting alternating magnetic fields into localized heat through magneto-thermal conversion.⁴⁴ Studies have utilized streptavidin-modified superparamagnetic Mn Fe₂O₄ nanoparticles, and with genetic engineering, induced neurons to express temperature-gated TRPV1 ion channels and anchored biotinylated peptides, allowing nanoparticles to specifically bind to target neuronal membranes.

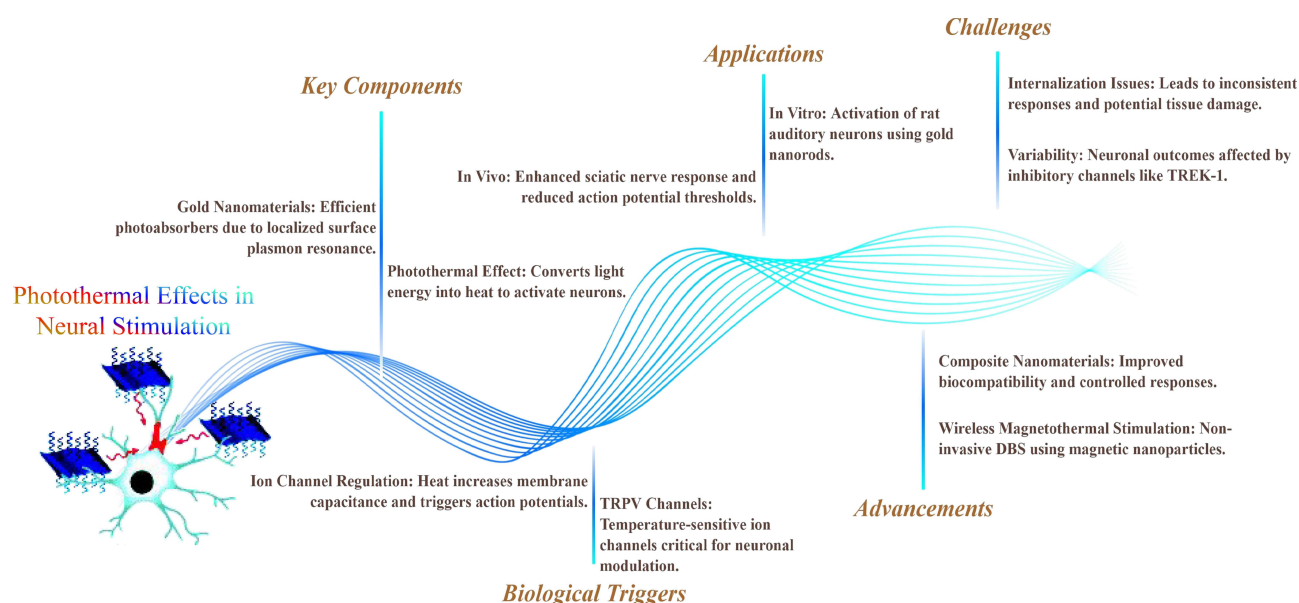


Figure 2 Photothermal Effects in Neural Stimulation – Mechanisms, Applications, Challenges, and Advancements.

Upon application of a radio frequency magnetic field, the localized thermal effect of magneto-thermal conduction induces Ca^{2+} influx through the TRPV1 ion channels, causing neuronal depolarization and the generation of action potentials.⁴⁵

Given that TRPV1 ion channels can be uniformly expressed in target cells across a tissue through genetic engineering, the magneto-thermal neural stimulation enabled by superparamagnetic nanoparticles can uniformly stimulate targeted cell populations.^{45–47} Although both photothermal and magneto-thermal stimulation use thermal effects as local stimulation signals, the latter involves genetic modification of target neurons for specific cellular and tissue targeting.^{46,47} However, due to the use of genetic engineering and the high permeability of TRPV1 ion channels to Ca^{2+} , other temperature-gated ion channels are gradually being explored for application.⁴⁸ Thermally induced nanomaterials, such as those covered in recent studies, offer innovative ways to achieve spatial and temporal control over neuronal activity, which can be especially useful in developing minimally invasive neuromodulation techniques.⁴⁹

The study “Subsecond multichannel magnetic control of select neural circuits in freely moving flies”⁵⁰ achieves subsecond, multichannel stimulation of different groups of neurons in *Drosophila melanogaster* using magnetic nanoparticles, enabling precise temporal modulation of neural activity. This reference can be integrated to discuss advancements in multichannel magnetic control for neural circuits.

Application of the Piezoelectric Effect in Neural Regulation

Piezoelectric materials can convert mechanical stimuli into electrical signals, generating a localized electromagnetic field (EMF). There is evidence that EMF can affect various voltage-gated ion channels on the cell surface, influencing the influx and efflux of electrolytic ions inside and outside the cell, thus regulating cell function and activity, impacting ion channels on the cell surface.^{51,52} Piezoelectric nanomaterials have been successfully used in experiments to activate specific neuronal cells, demonstrating their potential in non-invasive neural regulation.⁵³

After treating SH-SY5Y neuron-like cells with piezoelectric nanomaterial barium titanate nanoparticles (BTNPs) and applying ultrasonic treatment, particle dynamic fluorescence imaging indicated significant cellular responses in terms of calcium and sodium flux. The process was validated using appropriate blockers to be caused by the activation of voltage-gated membrane channels. When cells were treated with cubic non-piezoelectric barium titanate nanoparticles, this phenomenon disappeared, confirming the hypothesis of piezoelectric stimulation in neuron-like cells.⁵⁴ Following this, research by Rojas et al⁵⁵ demonstrated that adsorbing piezoelectric barium titanate nanoparticles onto neuronal membranes enabled the activation of specific neuronal cells with piezoelectric material using ultrasound. This activation ceased with the discontinuation of ultrasound, indicating high specificity and selectivity in neural regulation by piezoelectric materials, as neurons without piezoelectric nanoparticles or with non-piezoelectric nanoparticles were not activated by ultrasound. Zhao et al⁵⁶ study applied this technology to regulate specific neurological disease models. Carbon-coated piezoelectric Ba Ti O₃ nanoparticles entering TH neurons in a Parkinson's disease model zebrafish could affect voltage-sensitive L-type calcium channels under ultrasound induction, influencing intracellular calcium ion flow in neurons, modulating the plasticity of impaired substantia nigra neurons, and improving symptoms in the experimental animals. In a later animal study, researchers injected chitosan-coated Ba Ti O₃ nanoparticles into the right inferior cardiac ganglia of beagles. Using ultrasound-mediated activation, they stimulated ganglion activity, effectively lowering the ventricular rate in a canine model of atrial fibrillation.⁵⁷ This series of experiments fully foreshadows the prospects of piezoelectric nanomaterials in neural modulation. In the near future, piezoelectric materials are expected to serve as an effective means of autonomic nervous regulation of organs, used in more clinical disease diagnostics, research, and translation (Table 1).

Prospects and Challenges of Smart Nanomaterials in Neural Modulation

This perspective provides an overview of the mechanisms by which smart nanomaterials function in neural stimulation and their potential clinical uses. Most nanomaterials achieve neural regulation by directly acting on ion channels in neuronal cell membranes, while a minority influence by modulating intracellular pH and reactive oxygen species.⁵⁸ Despite being at an early stage, the field is growing with the advancement of nanomaterials and neurobiology, leading to a rise in research on stimulus-responsive nanoparticles that specifically target ion channels. These novel nanomaterials not only propel research in non-genetic neural regulation across multidisciplinary fields but also open new possibilities for effective treatment of nervous system diseases and understanding the deep mechanisms of the human nervous system.

Table 1 Key Mechanisms of Nanotechnology in Neural Modulation

Mechanism	Description	Methods	Findings	Challenges	References
Photoelectric Effect	Quantum dots (QDs) exhibit photoconductive properties, acting as optically-controlled neural stimulation mediators.	1. Modifying QDs with antibodies/peptides to bind to neuron membranes. 2. Fixing QDs on specific material substrates and attaching them to neuron surfaces.	1. Activation of voltage-gated ion channels. 2. Thin film construction for more stable interfaces 3. Depolarization/hyperpolarization of responsive cells. 4. Action potentials observed in neuroblastoma NG108 cells. 5. Only a small portion (11%) of cells stimulated.	1. Potential internalization of QDs. 2. Lack of specificity in antibody binding. 3. Short-term regulatory stability. 4. Limited light penetration.	[14–24]
Photothermal Effect	Gold nanomaterials generate heat to activate neurons through localized surface plasmon resonance.	1. Coating gold nanorods with silica. 2. Using near-infrared light sources. 3. Applying pulsed and continuous laser irradiation.	1. Successful activation of auditory neurons. 2. Enhanced synaptic outgrowth. 3. Ca ²⁺ influx in NG108-15 cells. 4. Reduction of ventricular arrhythmias. 5. Reduced power and duration of laser stimulation 6. Decrease in c-fos protein expression.	1. Internalization of gold nanorods. 2. Variable neuronal responses. 3. Potential tissue damage. 4. Inhibitory effects on certain neurons.	[25–37]
Magneto-Electric Effect	Magnetic fields converted to electric fields to activate neurons using magneto-electric nanoparticles.	1. Utilizing core-shell structured magneto-electric nanoparticles.	1. Modulation of deep brain circuits in mice 2. Triggers Ca ²⁺ influx in mechanosensory cells. 3. Enables wireless deep brain stimulation.	1. Stability of physicochemical properties. 2. Long-term biocompatibility and safety. 3. Variable neuronal responses.	[38–43]
Magneto-Thermal Effect	Alternating magnetic fields converted to localized heat for neural stimulation.	1. Utilizing streptavidin-modified superparamagnetic MnFe ₂ O ₄ nanoparticles. 2. Genetic engineering to express TRPV1 ion channels. 3. Anchoring biotinylated peptides for specific binding.	1. Uniform stimulation of target cells. 2. Ca ²⁺ influx causing neuronal depolarization and action potentials. 3. In vivo application showing effectiveness in animal models.	1. Genetic modification complexities 2. High permeability of TRPV1 channels. 3. Gradual exploration of other temperature-gated ion channels.	[44–50]
Piezoelectric Effect	Mechanical stimuli converted to electrical signals by piezoelectric materials.	1. Applying barium titanate nanoparticles. 2. Using barium titanate nanoparticles (BTNPs) with ultrasonic treatment 3. Coating with carbon or chitosan for targeted delivery.	1. Activation of specific neuronal cells. 2. Regulation of neurological disease models. 3. Improved symptoms in Parkinson's disease model. 4. Lowering ventricular rates in atrial fibrillation models.	1. Precise control of stimulation signals. 2. Ensuring biocompatibility and specificity. 3. Variability in neuronal responses.	[51–57]

Current research in nanomaterial design and signal selection broadly categorizes nanoparticles into two types: those with single signal conversion, like photothermally regulated gold nanorods, and those with multiple signal conversion capabilities, such as core-shell structured piezoelectric nanoparticles capable of ultrasound/electrical conversion. These designs are often influenced by the researchers’ expertise, typically favoring the development of multifunctional rather than specialized nanoparticles for specific clinical challenges. Future research should prioritize designing multifunctional nanoparticles tailored to address particular clinical needs, such as creating targeted delivery systems for neurodegenerative disorders. Additionally, the trend in nanomaterial development is shifting from inorganic nanoparticles to hybrid organic-inorganic materials and even purely organic systems. While inorganic nanomaterials excel in signal conversion and transmission, their limitations in biocompatibility and specificity hinder widespread clinical adoption. Thus, developing organic-inorganic hybrid nanoparticles that incorporate organic groups, antibodies, or other organic nanostructures is critical for enhancing clinical relevance.

However, it is worth noting the emergence of additional neuromodulation nanotechnologies, such as the magneto-mechanical effect and NIR-based optogenetics.^{59,60} The magnetomechanical effect leverages magnetic nanomaterials to

induce mechanical forces capable of modulating neuronal activity, offering an innovative alternative to conventional electrical stimulation methods. In contrast, NIR-based optogenetics utilizes near-infrared light to activate optogenetic constructs, providing advantages such as deeper tissue penetration and minimized thermal damage. This non-invasive technique holds significant promise for achieving precise and controlled neural modulation. Collectively, these advanced approaches complement traditional methods and broaden the repertoire of neuromodulation strategies, paving the way for more effective and versatile applications in neuroscience and clinical practice.

Key challenges in translating smart nanomaterials to clinical applications include precise targeting, minimally invasive delivery, and the accurate control of stimulation signals to modulate neuronal excitation or inhibition. Currently, there are few effective methods or materials to overcome these challenges. Some studies have leveraged gene editing to express specific molecules on target cells, enabling the attachment of complementary antibodies to nanoparticles for precise binding. With advancements in gene editing technology, future strategies are expected to become safer and more reliable, offering refined approaches for targeted and efficient neuromodulation. Furthermore, addressing these application issues requires interdisciplinary collaboration between materials science, genetics, and clinical research.

Potential future action lines include developing highly specific, non-invasive delivery techniques, improving the biocompatibility and targeting efficiency of nanomaterials, and exploring alternative non-genetic strategies for neural modulation. In addition, research should aim to integrate real-time monitoring and feedback mechanisms into smart nanomaterials to achieve dynamic and adaptive control of neuronal activity. In the future, non-genetic neural regulation based on smart nanomaterials is anticipated to emerge as a groundbreaking interdisciplinary field with tremendous potential in treating neurological diseases, including currently untreatable conditions like Parkinson's and Alzheimer's. Beyond therapy, these materials could become indispensable tools in neuroscience research, facilitating exploration into the mechanisms of the human nervous system and the regulation of autonomic functions in organs and systems, such as those involved in cardiovascular and neuroendocrine diseases.

While smart nanomaterials are still in the early stages of clinical translation, there is a pressing need for continued innovation. Developing specific intervention methods, optimizing existing strategies, and enhancing the application and translational potential of these advanced materials will be crucial as technology continues to advance.

Data Sharing Statement

This manuscript is a review article and does not involve content related to raw data.

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Disclosure

All authors of this research group have no conflicts of interest related to the publication of this article to declare.

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