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Transducer Materials Mediated Deep Brain Stimulation in Neurological Disorders

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Deep brain stimulation (DBS) is an established therapeutic approach for treating various neurological disorders, including Parkinson's disease, epilepsy, etc. Traditional DBS systems rely on implanted batteries, which pose challenges such as limited lifespan and the need for replacement surgeries. Transducer materials have provided new opportunities for developing DBS technology in recent years. These materials can convert remotely delivered energy forms, such as light, ultrasound, or magnetic fields, into electrical, thermal, light, or mechanical energy that can interface with neural signals. By injecting these materials into effective DBS targets of neurological disease and applying remote stimulation, they can generate signals such as electric, heat, or light that can interface with neurons, thus effectively regulating neural signal disturbances in the disease and treating disorders related to motor or emotional. This review offers insights into developing a class of materials to advance DBS technology for related neurological disorders. It provides a promising approach to replacing conventional electrodes and inducing neural stimulation in a noninvasive way. Future research should focus on optimizing material performance, ensuring biocompatibility, accurately modulating neural signals, and conducting clinical trials to advance this innovative field.

1. Introduction

Neurological disorders are characterized by nervous system abnormalities, particularly affecting neurons' structure and function. These disorders encompass a range of conditions, such as Parkinson's disease (PD) and Alzheimer's disease (AD), which result from the dysfunction due to the loss of neurons or their myelin sheaths. Other neurological disorders, such as epilepsy and mood disorders, are also common diseases in modern society. Such diseases significantly affect the life quality of patients and burden the healthcare system.[1]

Neurons are the basic components of the nervous system, and the coordinated firing activities of neurons form the functional circuits of the brain.[2] Neurological information exchange comes mainly from the transmission of chemical and electrical signals. When the exchange of neural signals is blocked or interrupted, it usually leads to a progressive loss of neuronal structure and function, ultimately to death.[3] The issues of regulating the process of neuronal information exchange, saving damaged neurons from death, and regenerating or repairing damaged neurons are crucial for treating these diseases. Deep brain stimulation (DBS) has revolutionized the treatment of neurological disorders by modulating abnormal neural activity through the surgical implantation of electrodes in specific brain regions. For PD patients, DBS can effectively improve motor symptoms such as tremors and bradykinesia in patients in the middle and late stages by implanting electrodes at specific targets in the brain, such as the subthalamic nucleus, to regulate neural activity. It also has a certain relieving effect on accompanying symptoms such as anxiety and depression. In recent years, DBS has been expanded to other neurological disorders, such as epilepsy, anxiety, and depression.[4] However, traditional DBS systems rely on implantable pulse generators powered by batteries, which are limited by finite lifespan, the need for periodic replacement surgeries, and risks associated with invasive procedures.[5] These challenges have spurred the exploration of alternative approaches to neural modulation, particularly those leveraging transducer materials to enable noninvasive or minimally invasive DBS.

Transducer materials are designed to transform one form of energy into another, enabling remote and targeted stimulation of neural tissue. These materials can respond to external stimuli such as light, ultrasound, and magnetic fields and convert them into electrical, thermal, light, or mechanical signals that interact with nerve cells, allowing precise neural control.[6,7] When

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injected or implanted into the brain, they act as transducers, converting external energy into localized electrical, thermal, or mechanical signals that modulate neural activity.[8,9] By integrating these materials into DBS systems, researchers aim to overcome the limitations of traditional battery-powered devices, offering a more precise and patient-friendly approach to treating neurological disorders. Specifically, optogenetics allows precise activation and regulation of neurons, but it requires genetic modification.[10] Upconversion nanoparticles can extend the reach of optogenetics by converting near-infrared light into visible light, enabling noninvasive stimulation of deeper brain structures. Photothermal materials convert light into thermal signals to efficiently stimulate nerve cells.[11] Ultrasound-activated materials, such as piezoelectric materials or microbubbles, can convert mechanical energy from ultrasound waves into electrical signals or localized pressure changes that modulate neural activity.[12] Magnetic nanoparticles, such as iron oxide, can be engineered to generate heat or mechanical forces in response to alternating magnetic fields, triggering neural activity.[13] This approach is particularly promising for precise and reversible stimulation of neural tissue.

The mechanisms of external signals modulating cell fate and neuronal activity have been researched. Li et al. have emphasized the latest advancements in neuromodulation supported by nanosensors, summarizing their design, operating principles, and the current challenges in developing the next generation of neuromodulation technologies.[14] Cafarelli et al. have focused on piezoelectric materials, summarizing the fundamental mechanisms and primary applications of piezoelectric nanoparticles and ultrasound in biomedical applications.[15] This review explores transducer materials for noninvasive neural modulation, focusing on their ability to convert external energy (e.g., light, ultrasound, magnetic fields) into precise neural signals. We systematically evaluate their applications in neurological disorders, emphasizing targeted DBS with minimal tissue damage.

This review aims to provide a comprehensive overview of transducer materials for DBS, highlighting their advantages, challenges, and future directions for optimizing performance, biocompatibility, and clinical translation. We begin with the current status of DBS for neurological disorders, detailing the brain regions, therapeutic parameters, and effects involved. Subsequently, we examine the use of remote energy-mediated nanomaterials, including those responsive to light, ultrasound, and magnetic fields, for precise neural modulation. By designing transducer materials for regulating neurons in specific brain regions, we provide a universal approach for regulating deep tissues and understanding how external energy affects cellular signaling and relieves symptoms. Finally, we discuss the challenges, development prospects, and clinical significance of this field, focusing on safety, toxicity, and enhancing the efficacy of neural stimulation. This paper aims to inspire further research, ultimately improving therapeutic outcomes for neurological disorders.

2. DBS Targets in Neurological Disorders

Electrical stimulation is widely regarded as the benchmark in neuromodulation research. The use of implanted electrodes for DBS has been authorized for treating clinical conditions in PD, depression, and epilepsy.[16,17] DBS is an innovative neurosurgical technique that treats neurological diseases by sending electrical signals to specific brain regions to regulate abnormal neural activity. For PD, DBS mainly targets the subthalamic nucleus (STN) and the globus pallidus internalis (Gpi) to improve motor symptoms.[18] In addition, DBS also shows potential in diseases such as obsessive-compulsive disorder, depression, and epilepsy, relieving symptoms by targeting different brain regions.[19] This section highlights how DBS addresses complex symptoms of neurological disorders, especially highlighting key regulatory regions for different diseases, thereby providing spatial positioning references for the design of stimulation materials. DBS targeting various brain regions offers therapeutic benefits for diseases like PD, epilepsy, depression, and anxiety (**Table 1**).

PD is the second most prevalent neurodegenerative disorder, characterized pathologically by the selective loss of dopaminergic neurons in the substantia nigra pars compacta,[20] the aggregation of α-synuclein,[21] neuroinflammation,[22] and iron deposition.[23] Our team has extensive research experience in the pathogenesis and prevention and treatment strategies of PD. It has summarized the latest advancements in motor impairments and modulation in PD from the perspectives of brain regions and neural circuits. Additionally, we have also discussed various therapeutic strategies, including DBS, that can ameliorate motor impairments in PD patients.[18] DBS is a leading treatment for advanced PD, particularly targeting STN, an FDA-approved DBS target site,[24] which can significantly reduce or even eliminate the need for dopamine drugs.[25] Another common DBS target for PD is Gpi.[26] The zona incerta, a primarily inhibitory region located in the subthalamus, plays a role in the broad modulation of behavior.[27] DBS can modify neuron firing, trigger calcium waves, and influence neurotransmitter release, therefore enhancing motor and emotional functions. Clinically, DBS improves both motor and non-motor symptoms like mood, memory, and sleep.[28,29] While DBS is a safe treatment for advanced PD, it carries surgical and neuropsychiatric risks, highlighting the growing need for noninvasive alternatives.

Epilepsy is another neurological disorder marked by recurrent, unprovoked seizures due to abnormal electrical brain activity, leading to symptoms like convulsions and sensory disturbances. Epilepsy affects a substantial population of 65 million individuals worldwide, with a significant proportion, ranging from ≈30% to 40%, demonstrating resistance to pharmacological interventions. Consequently, DBS emerges as a promising therapeutic strategy for these refractory cases.[30] The anterior nucleus of the thalamus (ANT) is a common DBS target, shown to reduce seizure frequency by regulating neuronal network excitability and minimizing neuronal cell loss.[31] Other potential targets for electrical stimulation in epilepsy treatment include the hypothalamus[32,33] and bilateral central thalamic nucleus.[34]

Anxiety and depression are significant mental health challenges globally.[35] DBS offers promising treatment avenues for these emotional disorders. For anxiety, DBS has shown effectiveness in conditions like obsessive-compulsive disorder and post-traumatic stress disorder.[36] In animal studies, DBS targeting the ventromedial prefrontal cortex (vmPFC) has been shown to reduce activity in the basolateral amygdala (Amy), a key region associated with anxiety.[37] Furthermore, DBS directly targeting the basolateral amygdala can significantly ameliorate anxiety-like behaviors in the post-traumatic stress Disorder (PTSD) model

Table 1. DBS of different brain regions and treatment of neurological disorders.

DBS Diseases	Brain region	Working conditions	Effects
PD	STN	Adjustable voltage	Improving motor symptoms and nonmotor symptoms[51]
	Gpi	Right Gpi: 2.0–4.5 V Left Gpi: 1.8–4.5 V	Improving tremors, motor fluctuations, and disorders[52]
Epilepsy	ANT	5 V	Reducing seizure frequency by regulating neuronal network excitability and minimizing neuronal cell loss[31]
	Subiculum	3 V	Reducing focal to bilateral tonic–clonic seizures[32]
Anxiety	vmPFC	200 μA	Inducing anti-anxiety-like behavior[37]
	Amy	100 mA	Alleviating anxiety symptoms of PTSD mouse[38]
Depression	SCC	5–9 mA	3/4 participants met the treatment-response criterion for more than half of the duration[41]
	LHb	300 μA	Depressive symptoms are relieved[53]

mice.[38] Additionally, DBS of the hypothalamus rapidly silences anxiety-related neurons, providing immediate relief.[39]

In depression, DBS targeting areas such as the subcallosal cingulate (SCC),[40,41] nucleus accumbens (NAc),[42] and lateral habenula (LHb)[40,43] shows potential. Clinical studies indicate that specific DBS parameters in the SCC can yield antidepressant effects in treatment-resistant cases. Earlier studies demonstrated a 49% reduction in depressive symptoms following habenular nucleus stimulation and significant symptom alleviation with NAc-DBS in animal models.[44,45] These findings highlight DBS as a novel and promising approach to treating emotional disorders.

Currently, preclinical research primarily concentrates on investigating the specific brain areas and underlying mechanisms of DBS therapy in the context of diverse disorders. For clinical treatment, FDA-approved uses include STN-DBS and GPi-DBS for PD[46] and ANT-DBS for epilepsy.[47] While DBS for depression and anxiety has not yet been FDA-approved, symptom improvements have been noted in obsessive-compulsive disorder treatments, which are approved by the FDA. Although traditional DBS offers a reliable option for patients, its reliance on intracranial electrode implantation inherently leads to core deficiencies such as the risk of invasive injury, postoperative infections, and difficulties in dynamically adjusting stimulation parameters. Based on an in-depth analysis of the mechanisms underlying DBS target engagement, the key proposition in the development of next-generation neuromodulation technologies lies in how to inherit the precise targeting advantages of existing therapies while overcoming the physical invasiveness defects. It is this challenge that has driven the innovative intervention in transducer materials.

Transducer material offers a breakthrough in redefining the therapeutic logic of conventional DBS by converting external noninvasive energy sources into localized secondary stimuli at the neuronal interface. Current research on neural modulation based on transducer materials has not only identified key brain regions implicated in disease regulation but also partially elucidated the mechanisms underlying neural modulation.[48–50]

The identified therapeutic targets assist in clarifying critical regulatory zones for various pathologies, thereby providing spatial localization references for the design of transducer materials. DBS modulates neural circuits by delivering electrical impulses to specific brain areas, ameliorating disease symptoms. Previous studies have illuminated the mechanisms of neural modulation, such as regulating neuronal excitability and enhancing neurotransmitter release, which also offer functional insights for the development of transducer materials. For instance, these materials can be engineered to mimic the regulatory effects of electrical stimulation or amplify local energy metabolism. This knowledge further serves as a theoretical foundation for material design. The development of transducer materials must integrate both the pathological characteristics of diseases and modulation requirements. The therapeutic mechanisms of traditional DBS have provided valuable insights, enabling more precise material design. How to identify the specific brain regions that require intervention, understanding how materials interact with neural tissues, and optimizing energy transfer or conversion processes are important for applying transducer materials for neurological diseases.

3. Transducer Material-Mediated DBS Therapy

Transducer material-mediated DBS is emerging as an exciting alternative to influence neuronal activity via external stimuli. The advantage of transducer materials resides in their minute size, which confers reduced invasiveness and diminishes the potential for eliciting immune responses in biological systems, in contrast to the electrodes necessitated by conventional DBS technologies. Transducer materials can wirelessly transduce external electric fields, photonic radiation, magnetic fields, or ultrasonic waves into optical, thermal, mechanical, electrical, or chemical energy signals within the designated target zone, thereby inducing localized neuromodulatory effects.

Depending on chemical composition, transducer materials can be segregated into organic, inorganic, and composite. Illustratively, within the realm of piezoelectric nanomaterials, polyvinylidene fluoride exemplifies an organic material widely used for its flexibility and biocompatibility. Boron nitride Nanotubes and barium titanate ($BaTiO_3$) Nanoparticles are categorized under inorganic materials known for their high piezoelectric efficiency and stability.[54] Based on their structural dimensionality, they can be further subclassified into 0D materials, 1D materials, 2D materials, 3D materials, and hybrid materials.

Transducer nanoparticles act as local force actuators, leveraging their unique ability to respond to external energy and deliver

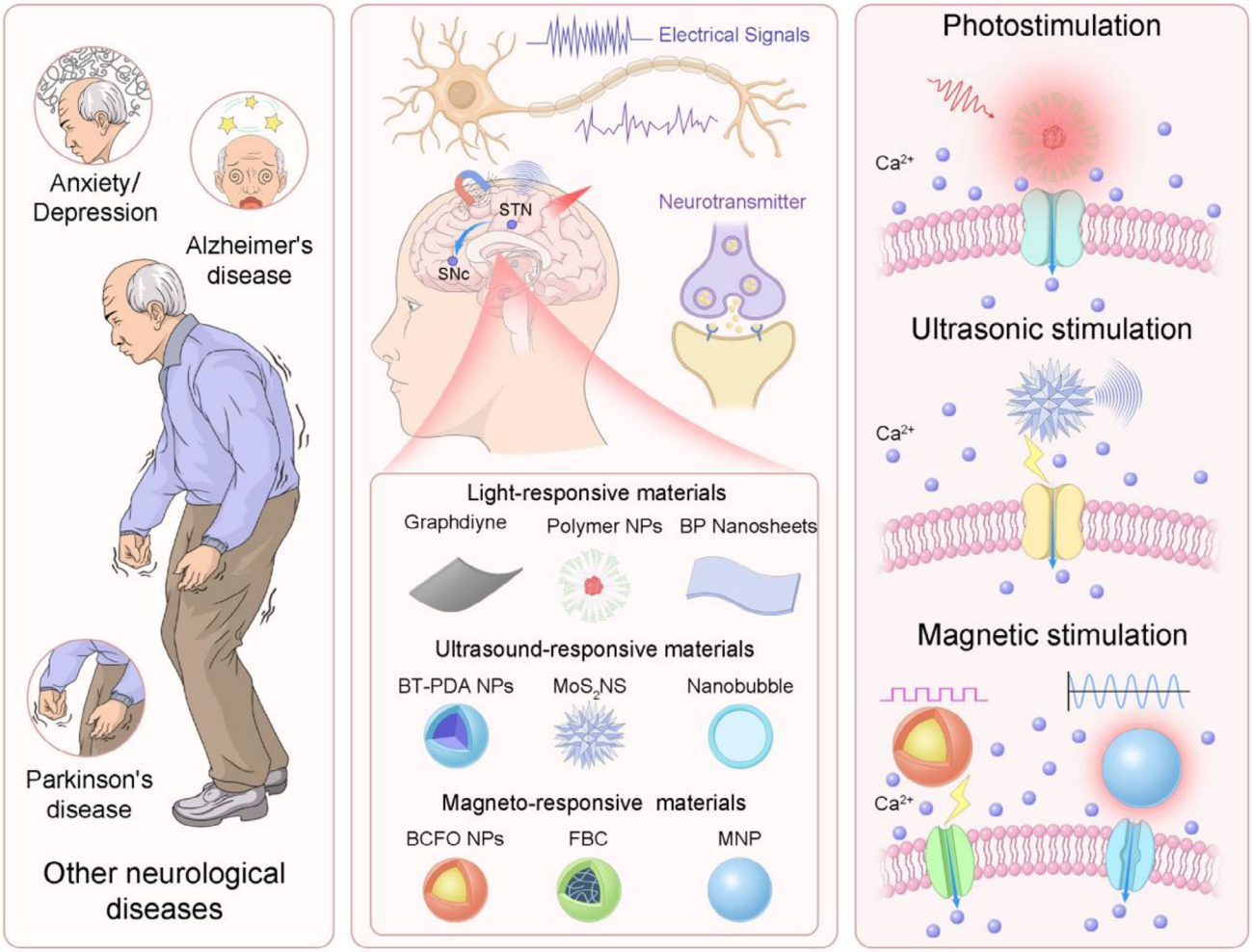

Figure 1. Scheme of transducer material-mediated wireless deep brain therapy platform.

targeted treatments. Unlike traditional DBS requiring surgical implantation, nanoparticles can be delivered to the brain through less invasive methods like intranasal delivery or injection. They can also be engineered to target specific neural populations or circuits, potentially minimizing side effects. This section illustrates the fundamental mechanisms of transducer materials in treating neurological disorders such as PD, epilepsy, anxiety, and depression. **Figure 1** shows that the use of transducer materials in DBS offers a novel strategy for treating neurological disorders. **Table 2** summarizes the working conditions and mechanisms of light, ultrasound, and magnetic field-activated materials used for neural modulation. Representative works based on these classes of materials will be reviewed in the following sections.

3.1. Light-Responsive Materials-Mediated Neurostimulation

Light-responsive materials-mediated neurostimulation offers an innovative approach by utilizing light conversion to precisely stimulate targeted brain regions.[71] Light offers precise control over space and time, making it easy to be tuned and operated. Near-infrared (NIR) light, especially NIR-II, penetrates deeper into tissues and causes less damage to target cells, showing great promise in neural modulation.[72–76] To modify the luminescent properties of phosphor materials beyond traditional chemical techniques. This may include the use of physical methods such as altering the crystal structure through mechanical means, applying external fields (like electric or magnetic fields), or utilizing advanced fabrication techniques like nanostructuring.[77,78] Optogenetics allows precise control of specific neuron types in living animals. However, traditional optogenetic methods face challenges, such as limited penetration of visible light due to brain tissue absorption and scattering, and the potential for implanted fibers to cause brain damage and immune responses.[52] Photothermal nanomaterials, including organic semiconducting polymer nanoparticles, graphene oxide, and black phosphorus (BP) nanosheets, can generate local heat under light, affecting neuronal membranes.[40] These nanomaterials convert light into heat, influencing nearby neurons to activate or inhibit based on temperature changes and thermal sensitivity. This technique offers a minimally invasive alternative to traditional electrical DBS, with the potential for precise spatial and

Table 2. The working conditions and mechanisms governing transducer materials for DBS and neurological disorders.

Transducer types	Materials	Excitation source	Objects	Biological effects	Refs.
Photoconversion modulation	PT-UCNP-B/G	808 nm 0.8 W cm^{-2}	C57BL/6 mice Lateral hypothalamus	Food consumed↑	[55]
		980 nm 0.8 W cm^{-2}		Food consumed↓	
	UCNPs	808 and 1532 nm	C57BL/6 mice Primary visual cortex	The running distance of mice↑	[25]
		980 nm		The running distance of mice↓	
Photo-thermal modulation	GDY	808 nm 10 mW mm^{-2}	C57BL/6 mice Hippocampus	Neuron firing rate↑	[56]
	ICG	793 nm 12.5 mW mm^{-2}	Caenorhabditis elegans D-Class motor neurons	The swimming behaviors↓	[57]
	MINDS	1064 nm 10 mW mm^{-2}	C57BL/6 mice Hippocampus	Neuron firing rate↑	[50]
	BP-PEG-NSs	808 nm 20 mW mm^{-2}	C57BL/6 mice Secondary motor cortex	Average velocity↑ Total distance traveled↓ Immobility↓	[58]
	BP flakes	980 nm 194 mW mm^{-2}	C57BL/6 mice Hippocampus	Epileptic signals↓	[59]
	PDA nanoparticles	808 nm 4–14 mW mm^{-2}	iPS-derived cardiac tissue	Beating rate↑	[60]
		808 nm 14–25 mW mm^{-2}		Beating rate↓	
	ZST	532 nm	C57BL/6 mice STN	PD mouse motor symptoms↓	[13]
Ultrasound-mechanical modulation	GVs	0.4/0.47/0.54 MPa	C57BL/6 mice Motor cortex	Myoelectric response ↑ c-Fos quantity ↑	[61]
Ultrasound-electric modulation	C@BT NPs	0.64 W cm^{-2}	Zebrafish Midbrain	The motor ability ↑ TH expression level↑	[62]
	PEP@BT NCs	5 W cm^{-2}	C57BL/6 mice Striatum	TH fiber count in the striatum↑ α-synuclein↓	[48]
	BTNP–pDA–BNN6	462.4 W cm^{-2}	BALB/c mice STN	SNc TH+ neurons↑ c-Fos in the STN region↑	[63]
	PEMPs	100 mW cm^{-2}	Primary hippocampal neurons	Hippocampal neurons are depolarized	[48]
Ultrasound-optical modulation	MLNTs	365 nm 1.5 MHz	Thy1-ChR2-YFP mice Motor cortex	Activation of motor cortex neurons	[64]
	HOF	470 nm 1.5 MHz 1.55/2.45 MPa	Thy1-ChR2-YFP mice Motor cortex SD rats PV-GPe	c-Fos in motor cortex region↑ c-Fos in PV-GPe region↑	[65]
Magneto–thermal modulation	MNPs	160 kHz 30 kA m^{-1}	C57BL/6 mice STN	The running distance of PD mice↑	[66]
Magneto–mechanical modulation	MNDs	10 Hz 50 mT	C57BL/6 mice STN	c-Fos in STN region↑	[49]
	m-Torquer	0.5 Hz 25 mT	C57BL/6 mice STN	PD mouse motor symptoms↓	[67]
Magneto–electric modulation	FBC	100 Hz 15 mT	SD rats ANT	The latency of seizures↑ The duration of seizures↓ Seizure stage of seizures↓ The survival rate↑	[30]
	BCFO	1 kHz 13.6 mT	Brain tissues of AD mouse model	Aβ plaques are dissociated	[68]
	MENPs	220 mT 6 mT and 140 Hz	C57BL/6 mice STN	Altering mouse behavior	[69]
	c-MSST	5 Hz	C57BL/6 mice Visual cortex	Depressive-like behavior in mice↓	[70]

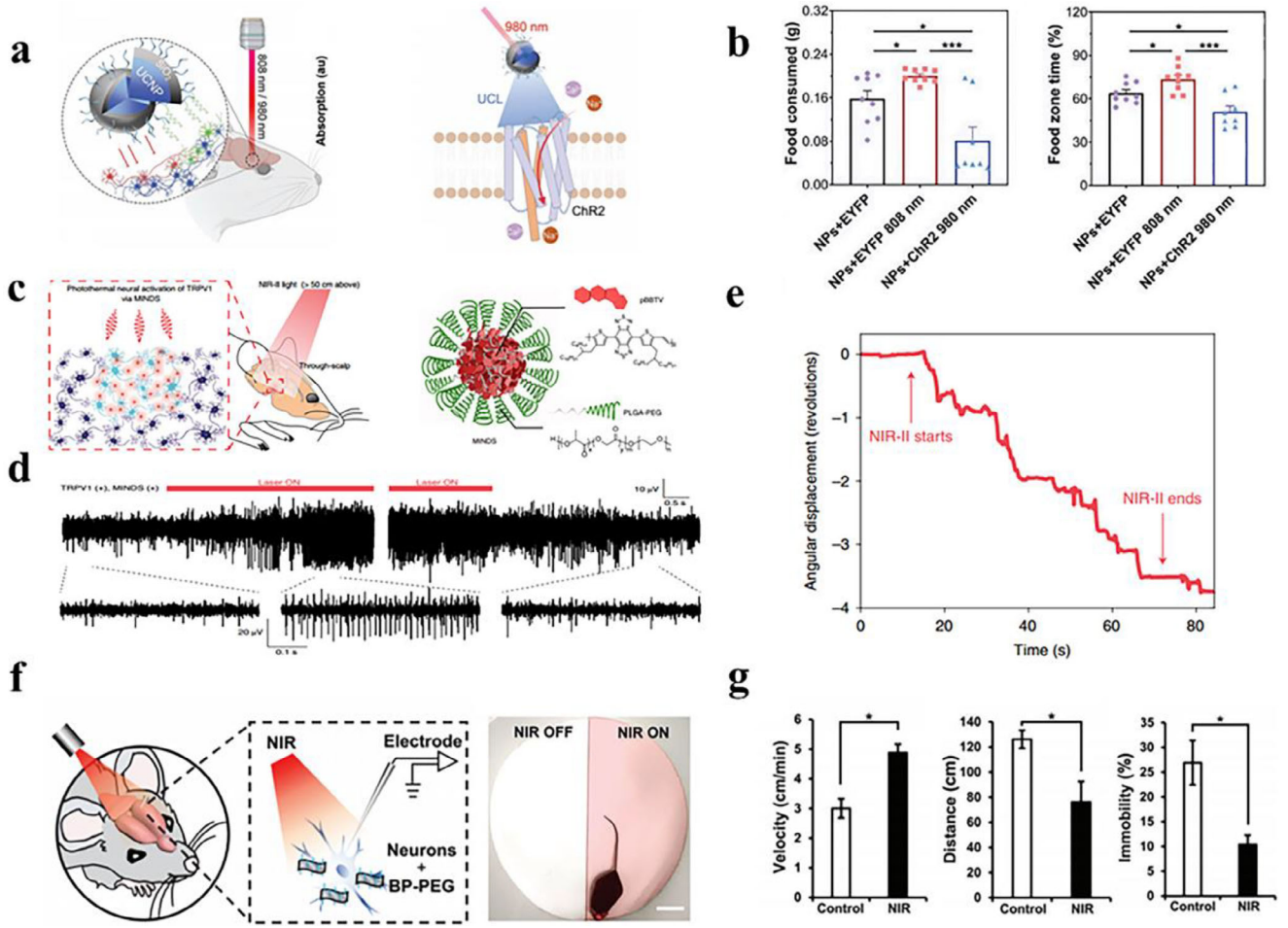

Figure 2. The representatives of photothermal DBS. a) Diagram showing the operational mechanism and utilization of PT-UCNPB/G in the context of the brain and the operational framework of PT-UCNP-B when subjected to 980 nm photostimulation. b) The food consumed and time spent in the food zone during exposure to laser stimulation at wavelengths of 808 or 980 nm. Reproduced with permission.[55] Copyright 2023, John Wiley and Sons. c) The illustration on the left depicts NIR-II light regulating nerves via the scale positioned at a height exceeding 50 units above the mouse's head, and activating the temperature-sensitive transient receptor potential vanilloid 1 (TRPV1) via MINDS-induced sensitivity. Conversely, the image on the right exhibits the constituent parts of MINDS, comprising a core of pBBTV-conjugated copolymer encapsulated within a shell of PLGA-PEG polymer. d) Upon application of 1064 nm light, an enhancement in the spiking frequency of hippocampal neurons was noted in mice (left). Following the termination of 1064 nm light exposure, the neuronal spiking frequency reverted to its original baseline (right). e) The angular displacement, both before, during, and after NIR-II illumination, is indicated, with positive values signifying a counterclockwise rotational direction and negative values indicating a clockwise direction. Reproduced with permission.[50] Copyright 2022, Springer Nature. f) A schematic diagram depicting BP-PEG nanosheets serving as wireless thermal transducers for neural stimulation in the brain of anesthetized mice is presented on the left. On the right, an open field featuring two distinct compartments (NIR-activated and NIR-inactive zones) is shown for conditioning with NIR irradiation. g) Quantitative analysis of mouse movement behavior in the aforementioned open field. Reproduced with permission.[58] Copyright 2021, John Wiley and Sons.

temporal control. In this part, we describe the mechanisms of this method, focusing on its ability to modulate neuronal activity through localized heating effects and the efficacy of materials in animal models.

3.1.1. Photoconversion-Responsive Neuromodulation

Optogenetics has advanced neurobiological research by using photosensitive proteins to control neuronal activity. However, it faces challenges like the need for visible light, limited light penetration in brain tissue, and potential brain damage from implants. To address these issues, researchers have developed up-conversion nanoparticles (UCNPs), which convert NIR light into visible light, enabling DBS with different wavelengths.

UCNPs have been proven to be suitable for biomedical applications such as biological analysis, biomedical imaging, and therapeutic diagnostics.[79–82] Sun et al. reported two UCNP-based materials, PT-UCNP-B (blue) and PT-UCNP-G (green), composed of NaYF4:Yb/Tm and NaYF4:Yb/Er, coated with photothermal agents (**Figure 2**a). They attached a photothermal agent based on benzothiadiazole (BBT) and 4,4′-dimethoxytriphenylamine (TPAO) on the surface of nanoparticles, where TPAO exhibited molecular motion and dark twisted intramolecular charge transfer (TICT) states, promoting efficient photothermal conversion. They can regulate the activity of neurons by thermal stimulation

under the irradiation of 808 nm NIR laser and by light stimulation under the irradiation of 980 nm NIR laser to achieve bidirectional regulation. Remarkably, PT-UCNP-B significantly augmented extracellular sodium currents in neuro2a cells expressing the light-sensitive ion channel, channelrhodopsin-2 (ChR2), under 980 nm irradiation, while it suppressed potassium currents in vitro in human embryonic kidney 293 cells harboring voltage-gated potassium channels (KCNQ1) under 808 nm irradiation. Furthermore, bidirectional modulation of feeding behavior in mice was successfully accomplished under untethered illumination at either 980 or 808 nm (0.8 W cm^{-2}) following stereotactic injection of PT-UCNP-B into the lateral hypothalamus expressing ChR2 (Figure 2b).[55]

Liu et al. designed similar UCNPs that emit blue, green, and red light to activate different neuronal populations selectively.[25] However, UCNPs have some limitations, such as the need for gene transfection for ChR2 and KCNQ1 applications. Researchers have used UCNPs to stimulate the endogenous transient receptor potential ankyrin-repeat 1 (TRPA1), controlling scratching behavior in mice without gene transfection.[83] PT-UCNP-B/G cannot target specific neurons, complicating precise thermal stimulation within subgroups.[52] The study has shown that commonly used photogenetic regulation of light intensity can cause a temperature rise of 0.2 to 2 °C in local brain tissue, which can inhibit neuronal discharge.[84] Therefore, when explaining the experimental results, it is necessary to consider the influence of photothermal effects on neuronal discharge. In addition, the low efficiency of the upconversion process calls for more effective systems.

3.1.2. Photothermal-Responsive Neuromodulation

A variety of photothermal materials have been meticulously designed to address and mitigate the onset of diverse diseases, encompassing epilepsy,[59] sudden cardiac death,[85] and depression.[86] The structure and dimensionality of nanomaterials exert a direct influence on their properties, and the multidimensional nature of these materials allows for the design of biological interfaces across diverse scales. 0D materials, such as gold nanoparticles,[87] inorganic nanoparticles, and polymeric nanoparticles, have been employed in biomedical applications encompassing drug delivery, medical imaging, and neuromodulation. 1D materials, predominantly nanorods and nanowires (e.g., Si nanowires), find applications in electrophysiological recording and manipulation at biological interfaces.[11] Meanwhile, 2D materials such as BP and MXene have shown great potential in neural regulation due to their unique photothermal conversion efficiency and good biocompatibility.[88,89] 3D and hybrid nanomaterials represent a burgeoning class of nanomaterials suitable for biomedical applications, attributed to their exceedingly high and exposed surface areas, electrochemical properties, and capacity to establish intimate interfaces with cells.[11]

Photothermal neuromodulation regulates neuronal activity by transducing light into heat, primarily targeting the temperature-sensitive TRPV1 in specific brain regions. Notably, photothermal nanomaterials have been extensively utilized to conduct NIR light into deep tissues, facilitating noninvasive and remote stimulation of deep brain structures.[56] Shao et al. reported that graphdiyne (GDY) has strong TRPV1 targeting ability in the NIR region, leading to the release of neurotransmitters in cells and regulating neural discharges in living mice.[56] Zhuang et al. developed a photothermal technique to regulate cell excitability and animal behavior of Caenorhabditis elegans in vivo through the TRPV1 channel and FDA-approved photothermal agent indocyanine green (ICG).[57] Chen et al. developed the ATB NPs combining a gold nanoshell, TRPV1 antibody, and β-synuclein peptides. Delivered via stereotactic injection, ATB NPs target dopamine neurons in the substantia nigra. NIR irradiation triggers heat generation, activating TRPV1 to restore neuronal activity, while released β-synuclein promotes α-synuclein clearance via autophagy. This dual-action approach improves motor function, offering a minimally invasive therapy for PD.[90]

The short-wavelength light stimulation within the traditional NIR window (700–900 nm) is susceptible to nonspecific absorption by the scalp and brain surface, resulting in reduced energy delivery to deeper brain regions. However, NIR-II light (1000–1700 nm) offers enhanced tissue penetration by minimizing scattering and brain tissue absorption. Specifically, 1064 nm NIR-II light can penetrate through the scalp and skull into the brain by at least 5 mm.[50] Wu et al. designed a macroscopic infrared transducer (MINDS) that can absorb light in the NIR-II window and convert light into heat for DBS (Figure 2c). MINDS uses π-conjugated semiconductor polymer pBBTV (poly(benzobisthiadiazole-alt-vinylene)) as its core, which can efficiently absorb light at the wavelength of m. The transducer stimulates neurons expressing TRPV1 channel, enabling DBS in freely behaving mice when irradiated with NIR-II light. Studies have indicated that, at a laser power density of 1.0×10^6 mW mm^{-2}, TRPV1 activation reaches its fastest time constant of 5 ms.[91] The authors validated in HEK293T cells transfected with TRPV1 that NIR-II light with a power density of 400 mW mm^{-2} (1040 nm) can effectively activate TRPV1 channels in the presence of MINDS. 1064 nm infrared light is selected and illuminated at a low power density (10 mW mm^{-2}) above the mouse (>50 cm). MINDS absorbs infrared light and generates heat, activating the neural cell signals expressing TRPV1 and regulating brain nerve activity. Additionally, NIR-II neural stimulation (1064 nm, 8 mW mm^{-2}) in the mouse hippocampus showed a statistically significant increase in neuron firing rate (Figure 2d), and the same stimulation in the motor cortex effectively induced unilateral circling behavior (Figure 2e).[50] However, TRPV1 transfection still requires invasive intracranial injections and may result in a similar level of acute invasiveness as other neural modulation techniques,[50] which limits its application.

Neurons can achieve precise stimulation by photo/thermal sensitive protein expression, but this technique requires gene transfection and is invasive. Tang et al. designed BP-PEG nanosheets attached to cell membranes to serve as miniature NIR light transducers, generating localized heating to stimulate neural activity.[58] BP-PEG-NSs-treated cells showed a rapid increase in membrane capacitance of 0.5–1% after turning on near-infrared irradiation. This indicates that BP-based wireless neural stimulation is related to the intrinsic relationship between cell photosensitivity and membrane heating without involving any temperature/photosensitivity of membrane proteins. They performed whole-cell patch clamping in BP-PEG-NSs-treated

cultured primary neurons and found that the pulsed NIR (4 Hz, 50 ms, and 18 mW mm^{-2}) could additionally stimulate neurons to generate an action potential. Subsequently, they microinjected BP-PEG-NSs into the secondary motor cortex of the mice and introduced an open field with defined two-compartment conditioning NIR irradiation to compare the locomotion behaviors in the NIR on the side with the NIR offside (Figure 2f). The average velocity, total distance traveled, and immobility were significantly adjusted during NIR illumination (808 nm, 10 Hz, 15 ms pulse width, and 20 mW mm^{-2}), indicating that BP nanosheets with NIR illumination can consistently modulate the cells in deep brain regions in freely moving animals (Figure 2g). Compared to the mentioned PT-UCNP-B/G and MINDS, BP-PEG-NS-mediated neuromodulation not only obviates the need for invasive transfection but also requires a lower laser power density, indicating a higher photothermal conversion efficiency. However, further research is needed to optimize their size and concentration, as well as to investigate real-time monitoring of nanosheet diffusion in the brain. Similarly, Yang et al. found that crystal peeling photothermal BP flakes can enhance neural activity by modulating the membrane capacitance current of hippocampal neurons through near-infrared photothermal neural regulation and can suppress epileptic signals in epilepsy model mice through this neural regulation.[59] This proves that the near-infrared neural modulation supported by BP nanomaterials may open up opportunities for non-implantable optical therapy of epilepsy and other diseases.

Previous studies suggest two mechanisms for the photothermal regulation of neurons, namely, altering cell membrane capacitance or resistance and changing ion channel activity.[11] For instance, BP-PEG-NSs change neuronal membrane resistance with a photothermal effect under NIR light.[58] The activation of different ion channels or changes in membrane resistance of different neurons can lead to different changes in neuronal electrical activity, resulting in activation or inhibition of neuronal activity. Sun et al. found that ChR2 currents are harder to activate with 808 nm light but easier with 980 nm, affecting neuronal excitability.[52] Furthermore, for the same ion channel, the excitation possessing different power densities can also produce different effects. Derami et al. found that the response of iPS-derived cardiac tissue to local nanoheating can shift from excitability at lower laser power densities to inhibition at laser power densities higher than 14 mW mm^{-2} in the presence of polydopamine nanoparticles irradiated with NIR laser.[60] Research has shown that photothermal conversion materials can modulate neural signals in the olfactory system of simple invertebrates, suggesting wider therapeutic applications.

Photothermal stimulation offers precise spatial control without direct contact with brain tissue. However, extensive research is needed to ensure its safety and efficacy before clinical use. It is essential to carefully manage heat generation to prevent brain damage. Although NIR light penetrates deeper than visible light, its reach within the brain is still limited. Ensuring that nanoparticles are accurately delivered and remain in place is crucial. Furthermore, the clearance pathways of these materials in vivo have not been fully evaluated, and the challenges of further enhancing their biocompatibility and photothermal conversion efficiency remain unresolved. Additionally, photoelectric conversion materials are emerging in neural regulation research alongside photothermal materials. Recently, it has been reported that ZnTPyP self-assembled nanorods coated with TiO_2 (ZST) can generate action potential under 532 nm laser irradiation. This also provides a new exploration for the application of light conversion nanomaterials in neural regulation and the new generation of photothermal conversion.[13]

3.2. Ultrasound-Mediated Deep Brain Stimulation

Ultrasound (US) therapy is a noninvasive treatment approach widely used across numerous medical fields. Its distinct properties, including the ability to penetrate deeply, maintain strong directionality, and focus energy, make it particularly valuable in addressing neurological disorders. By accurately targeting specific brain areas, ultrasound can induce thermal or cavitation effects, offering effective treatment options for various neurological conditions. Ultrasound-mediated DBS is an emerging noninvasive technique offering precise neuromodulation for neurological disorders. Ultrasound has been widely used in medical diagnosis and neural modulation due to its characteristics of deep tissue penetration and minimal damage. Ultrasound can target and influence deep brain areas by passing through the intact human skull. Research shows the US can enhance the release of dopamine levels and restore the behaviors in the PD mouse model.[92,93] This effect is likely due to neuronal regeneration and enhanced membrane permeability caused by ultrasonic mechanical forces. Low-intensity ultrasound can activate biomechanically sensitive ion channels like Piezo1, leading to calcium influx and increased c-Fos expression in neurons.[94] Additionally, ultrasound can trigger other mechanically sensitive ion channels, such as TREK-1/2,[95] MscL,[96] MsclG22S,[94] and TRPA1.[97] Therefore, ultrasound holds significant potential for regulating the nervous system. These channels respond to mechanical stimuli like pressure or stretch. Ultrasonic waves traveling through tissue can open these channels, allowing ions to enter and generate electrical signals in neurons.

3.2.1. Ultrasound-Mechanical Responsive Neuromodulation

Ultrasound-mediated neuromodulation faces challenges due to its limited spatial resolution, which can inadvertently activate multiple neuron types or brain areas. After penetrating the skull, ultrasound frequencies are lower, resulting in spatial resolutions ranging from millimeters to centimeters.[61] Additionally, the varying acoustic properties of skulls can distort ultrasound focus, and some brain areas may have lower mechanical sensitivity, reducing stimulation effectiveness. To improve precision and specificity, researchers have turned to acoustic-genetics research using mechanosensitive ion channels to improve ultrasound sensitivity.[94,98] For example, Fan et al. introduced the engineered auditory protein mPrestin into dopaminergic neurons in PD mice, finding that ultrasound stimulation improved neuron degeneration and alleviated symptoms.[99] Similarly, expressing the mechanosensitive channel MscL-G22S allows for more precise brain region targeting under ultrasound stimulation.[97] Xian et al. reported an MSCL-G22-mediated sound genetic approach to activate specific neurons in intact mouse brains,

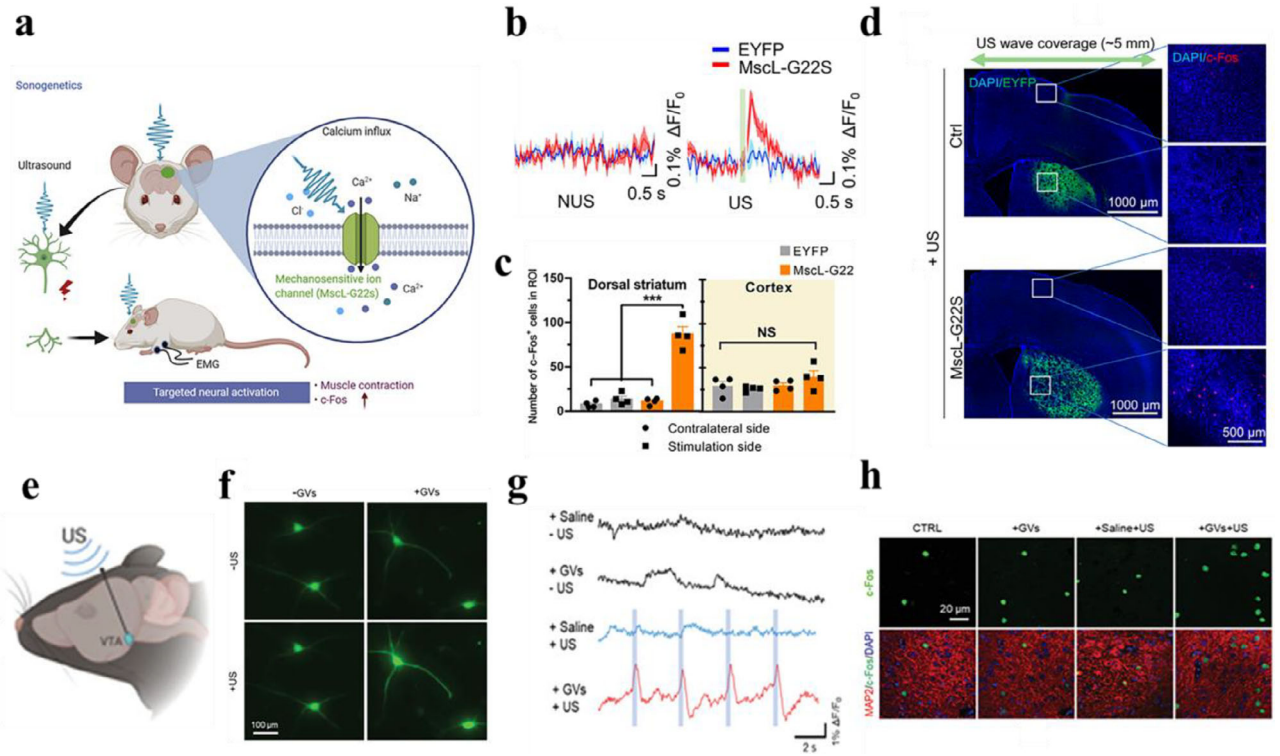

Figure 3. a) Schematic diagram of overexpression of mechanosensitive channel MscL-G22S and application of ultrasound to trigger muscular response and c-Fos expression. Reproduced with permission.[97] Copyright 2020, Cell Press. b) Changes of DA mean fluorescence signal after EYFP mice and MSCR-Expressing mice without ultrasound and 0.3 MPa ultrasonic stimulation (ΔF/F0). c) Ultrasonic stimulation of mouse dSTR and target region upper cortex nuclear c-Fos count in each layer. ***$p < 0.001$. d) Representative images of dSTR after ultrasonic stimulation. Reproduced with permission.[100] Copyright 2023, National Academy of Sciences. e) Schematic diagram of ultrasound stimulation plan. f) Representative images show GCaMP6s fluorescence in primary neurons, with/without GVs, before and after 0.20 MPa ultrasound. g) Representative gene encoding calcium sensor GCaMP6s fluorescence traces in mouse VTA before and after ultrasound. h) Representative c-Fos images of mouse VTA treated with or without ultrasound/GVs treatment. Reproduced with permission.[61]Copyright 2021, John Wiley and Sons.

demonstrating that inducing MscL expression enhances the ability of ultrasound to stimulate cells. This method can activate target neurons in different regions under the dorsal striatum (dSTR) (**Figure** 3a–d).[100] This method requires a viral vector or gene carrier for gene transfection in living organisms, but controlling gene expression precisely to avoid off-target effects is challenging. The process is also time-consuming, with potential issues like transgene instability affecting outcomes. Nanobubbles offer a solution by enhancing specificity and reducing invasiveness.[12,101,102] They can localize and amplify ultrasound effects, lowering the threshold for neuron stimulation and enabling precise targeting in the deep brain. The empty protein shells of gas vesicles (GVs) facilitate the transmission of acoustic oscillations to the surrounding medium, mimicking the behavior of microbubbles. This is attributed to the nonlinear signals that arise from the buckling effects driven by ultrasound.[103] Therefore, GV-mediated ultrasonic neuromodulation can be directly localized and has an amplified ultrasonic effect, which can reduce the threshold of ultrasonic stimulation neurons and thus perform spatially precise neuronal regulation of the deep brain target region.

Hou et al. obtained relatively stable and non-cytotoxic GV through centrifugation and found that it significantly enhanced the efficiency and precision of ultrasonic stimulation, successfully achieving selective activation of neurons in deep regions of the mouse brain (Figure 3e). GV was used to effectively stimulate the activation of primary neurons through short pulses of low-intensity ultrasound (Figure 3f). The researchers deduced that the primary cause of GV-mediated ultrasonic stimulation can activate the mechanosensitive ion channels. In addition, GV can enable low-intensity, noninvasive ultrasound to specifically stimulate VTA in mice and significantly increase c-Fos expression in the VTA brain region (Figure 3g,h). Under the stimulation of low-intensity ultrasound, the mice produced an obvious myoelectric response, significantly improved their motor ability, and caused a significant increase in c-Fos expression in the striatum region.[61]

Nanovesicles can enhance focused ultrasound by lowering the stimulation threshold, but they have limitations, such as low stimulation intensity, a narrow size range, and a short in vivo half-life, hindering long-term therapeutic effects. Additionally, ultrasound dissipates quickly after 5 s of stimulation, making it less effective for treating neurological diseases.[104]

3.2.2. Ultrasound-Electric Responsive Neuromodulation

Ultrasound-electric responsive neuromodulation is a technique that uses ultrasound waves to induce electrical responses in

neural tissues, thereby modulating neural activity. This method leverages the ability of ultrasound to penetrate deep tissues non-invasively and stimulate neurons or neural circuits by converting mechanical energy into electrical signals. It holds promise for precise control of neural functions and treatment of neurological disorders. Ultrasound-sensing nanoparticles can be used instead of mechanosensitive ion channels to enhance ultrasound-based neuromodulation. Piezoelectric materials can convert ultrasonic and mechanical energy into electrical energy and are ideal for this purpose due to their high piezoelectric coefficient and biocompatibility. Furthermore, our earlier studies demonstrate novel light emission and phototronic characteristics of the materials under the piezoelectric effect.[105–108] They are valuable in biomedical applications such as antitumor treatments and health monitoring.[109] These nanoparticles can be precisely targeted in tissues, including the brain.[110] Common piezoelectric materials possess perovskite-type ABO_3 structures, like BTO, or wurtzite structures like zinc oxide (ZnO). Additionally, 2D materials such as MoS_2, In_2Se_3, SnSe, MXene, and $CuInP_2S_6$ also exhibit piezoelectric effects, influenced by their layer structure.[89,111–115] These properties make piezoelectric materials promising for neurological disease applications.

Piezoelectric nanoparticles mediate STN-DBS, providing a new method for PD treatment and alleviating PD symptoms. The piezoelectric effect is defined as the phenomenon occurring in certain dielectric materials where internal polarization arises upon deformation along a specific direction induced by external forces, leading to the accumulation of positive and negative charges on opposing surfaces.[116] Piezoelectric nanomaterials, which integrate the piezoelectric effect with the unique properties of nanomaterials, facilitate the conversion of mechanical energy into electrical energy and have garnered considerable attention owing to their potential applications within the biomedical field.[117] Notably, barium titanate nanoparticles (BTNPs) are prominent candidates for biomedical applications due to their exceptional biocompatibility, superior piezoelectric properties, and intriguing nonlinear optical characteristics.[117,118] Consequently, they have been extensively investigated for use in antitumor therapies,[119,120] antibacterial treatments,[87] injury repair processes,[117] and neural modulation strategies.[117] BTNPs can induce calcium ion inflow in human neuroblastoma cells and electrophysiological responses in hippocampal neurons when exposed to ultrasound.[121] In our previous work, we designed a core–shell piezoelectric nanoparticle (C@BT) that generates an electromagnetic field under ultrasonic stimulation. The C@BT NPs can cause cell surface depolarization, thereby regulating intracellular calcium signals under a certain intensity of ultrasonic stimulation. At the same time, nanoparticles can improve the motor dysfunction of zebrafish and increase the time and distance of movement.[62] We then designed a multistructure nanocluster for piezoelectric power generation (Pep@BT NCs) that can electrically stimulate individual dopaminergic neurons under ultrasonic stimulation (**Figure 4a**). The nanoparticles are assembled into garnet-like piezoelectric nanoclusters, which can achieve higher electrical output at the same ultrasonic intensity, solving the problem of ultrasound focusing electricity deep into the brain nerve. With the increase of ultrasonic intensity, the discharge frequency of nanoclusters increased, and the inflow of Ca^{2+} in nerve cells was promoted by stimulating voltage-gated channels, thus increasing the fluorescence intensity of TH (Figure 4b). The Pep@BT NCs are injected into the SN area of mice, and with US stimulation, the movement disorders of PD mice were significantly improved (Figure 4c).[48]

Kim et al. designed a multifunctional system consisting of no-releasing N, N "-di-se-butyl-N, N"-dinitro-1, 4-phenylenediamine (BNN6) and piezoelectric Barium titanate nanoparticles (BTNP) coated with polydopamine (pDA).[122] The nanoparticles were stimulated by ultrasound to release NO, mediating the opening of the blood–brain barrier (Figure 4d). In the PD mouse model, the systemic administration of nanoparticles and high-intensity focused ultrasound (HIFU, 462.4 W cm^{-2}) increased the c-Fos content in the STN brain area and the instantaneous dopamine release in the dorsal striatum (Figure 4e). After 10 days of continuous ultrasonic stimulation, the movement ability of mice in the nanoparticle group was improved, and after 16 days of stimulation, the movement ability of mice in the piezoelectric nanoparticle group was almost completely restored. They hypothesize that the reason is that the ultrasonic drive of the current output of the nanoparticle opens a voltage-gated channel to promote nerve stimulation and then releases neurotransmitters. It was shown that ultrasonically induced piezoelectric nanoparticles can enhance the behavioral function of PD mice, including motor coordination and motor activity. In addition, more TH^+ neurons were observed in mice treated with HIFU-induced nanoparticles (Figure 4f). These results suggest that piezoelectric stimulation induces dopamine release by inhibiting the degeneration of dopaminergic neurons, thereby reducing the symptoms of PD.[63]

Ultrasound is a promising, minimally invasive tool for manipulating central nervous system functions. Combining ultrasound with piezoelectric materials could lead to advanced, targeted neuromodulation methods. Recently, piezoelectric magnetic Janus microparticles (PEMPs) have been designed for neural stimulation mediated by low-intensity focused ultrasound.[117] Half of the PEMPs act as piezoelectric electrodes by conjugated BT nanoparticles, inducing electrical stimulation, while half of the magnetic particles of the nickel–gold nanofilm coating provide spatial and directional control of the nerve stimulation through an external uniformly rotating magnetic field. In addition, through the surface functionalization of targeted antibodies, they can specifically bind/target and stimulate dopaminergic neurons. Utilizing these capabilities, PEMP is designed to provide unique functionality for wireless nerve stimulation for the minimally invasive treatment of neurological diseases. Modifying piezoelectric nanomaterials enables precise control of the temporal and spatial neuromodulation characteristics. However, due to the short distance of the internal electric field generated by piezoelectric nanoparticles and the occurrence of fluid erosion, the material loss of piezoelectric nanomaterials will occur. Therefore, the tight anchoring of piezoelectric nanoparticles and cell membranes is a necessary condition for realizing efficient electrical transmission. Zhang et al. modified cholesterol, a cell membrane affinity molecule, on the surface of high-performance lead-free potassium sodium niobate (KNN) piezoelectric nanoparticles to obtain cholesterol-modified KNN nanoparticles (KNNC) with cell anchoring function (Figure 4g). This nanoparticle can effectively resist fluid scour and can achieve radio stimulation at ultrasonic intensity <10 mW cm^{-2}. Moreover, the regulation of

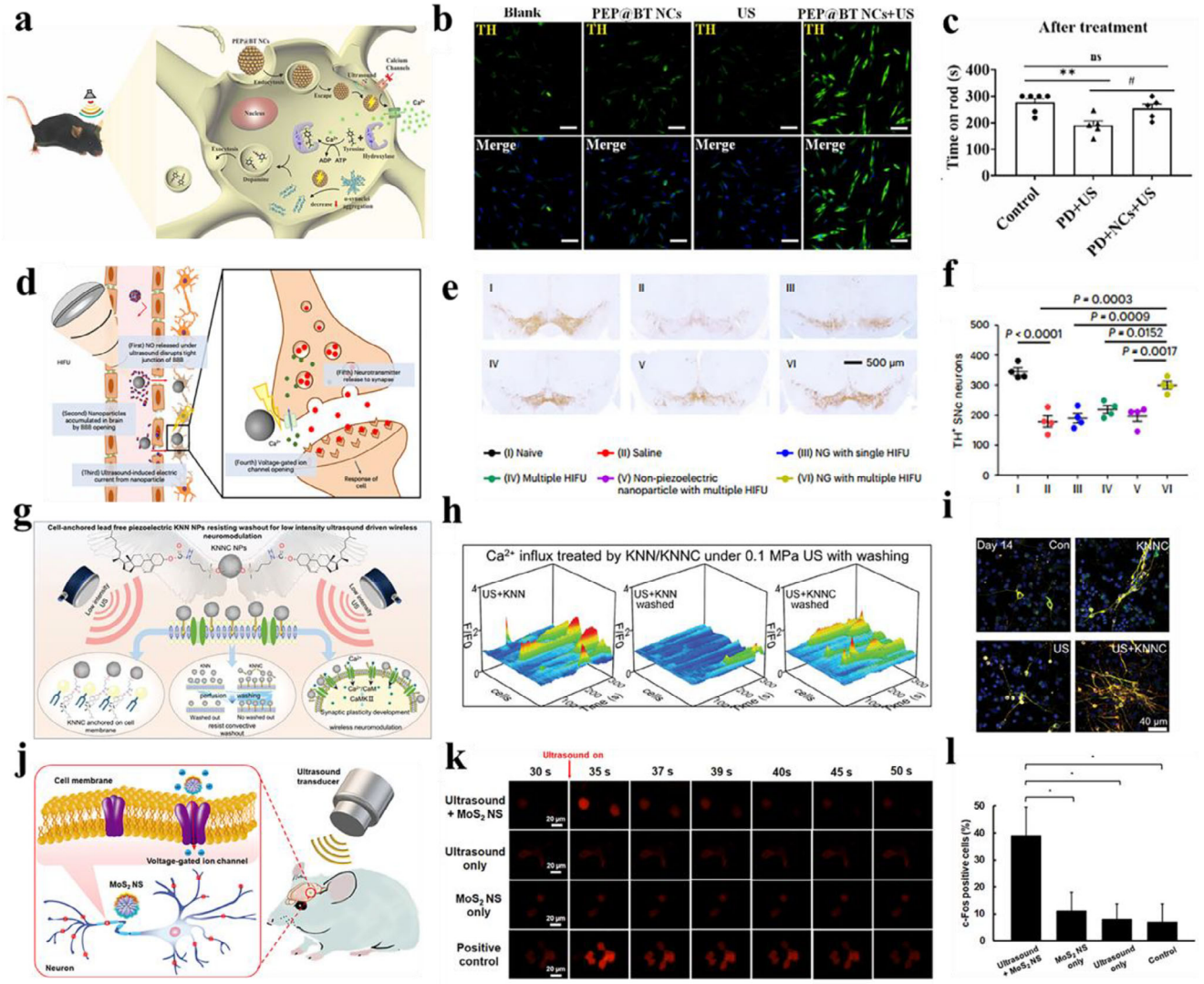

Figure 4. a) Schematic diagram of neuronal recovery in a PD model mouse facilitated by BTNP-mediated DBS. b) Immunofluorescence images of TH in PC12 cells under different treatments. Scale bar: 50 μm. c) The time on the rod of the different groups before and after the US treatment in the rotarod test. Reproduced with permission.[48] Copyright 2022, Springer Nature. d) Schematic diagram of the opening of the blood–brain barrier under ultrasonic stimulation and the stimulation of the STN brain region by nanoparticle combined with ultrasound. e) Representative immunohistochemical images of TH in SNc of mice in different treatment groups. f) The number of SNc TH^+ neurons in mice in different treatment groups. Reproduced with permission.[63] Copyright 2022, Springer Nature. g) Schematic diagram of piezoelectrical signal transmission in cell modulation by cell-anchored KNNC NPs. h) Time-related traces in Ca^{2+} influx of SH-SY5Y cells subjected to perfusion washing, indicating the KNN NPs attach to the cell membrane through electrostatic interactions, enabling wireless electrical stimulation of the cells. i) Representative immunofluorescent staining images for the neuronal cell markers Tuj1, MAP2, and nuclei on 14 days, indicating that radio stimulation of US+KNNC can lead to the production and maturation of more neurons. Reproduced with permission.[123] Copyright 2024, John Wiley and Sons. j) Schematic diagram illustrating the remote and selective method for modulating neuronal activity through the use of piezoelectric MoS_2 nanosheets and ultrasound. k) Time-lapse images of Ca^{2+} levels in SH-SY5Y cells under various stimulation conditions. l) Quantification of c-Fos-positive MoS_2 NS-positive cells (red) after ultrasound stimulation in the ROI ($*p < 0.05$). Reproduced with permission.[124] Copyright 2023, American Chemical Society.

intracellular calcium ion concentration induced by this electrical stimulation can effectively regulate the downstream signaling pathway and promote neural differentiation and the formation of synaptic structure (Figure 4h,i).[123]

Although the application of traditional piezoelectric materials to neural regulation has made great progress, inevitably, the ultrasonic transmission efficiency of ultrasound is largely influenced by the geometric characteristics of piezoelectric materials, such as structure, size, curvature, etc. The resonance frequency of ultrasound is greatly affected by the thickness of piezoelectric materials. The smaller the thickness, the higher the resonance frequency may be.[102] Therefore, 2D materials with smaller thickness, greater mechanical flexibility, and greater acoustic–electrical conversion capability are being investigated for neuroregulation.[114] Single-layer molybdenum disulfide nanosheets (MoS_2 NS) are 2D materials. Earlier reports

presented the method and possible mechanism of remote selective regulation of neuronal activity by MoS_2 NS combined with ultrasound in vitro and in vivo (Figure 4j). The research group applied monopulse ultrasound to SH-SY5Y cells surrounding MoS_2 NS to induce a significant calcium ion flux response without detecting cell damage (Figure 4k). When MoS_2 NS was injected into the septal nucleus of rats, the expression of c-Fos was three times that of the control group under ultrasonic stimulation (Figure 4l).[124] To improve the safety of piezoelectric materials and reduce their invasivity, new biodegradable piezoelectric materials are also gradually used for nervous system regulation.[13,55,125] Other research teams constructed a biodegradable piezoelectric scaffold with the ability to drive an ultrasonic discharge. The scaffold combines polylactic acid (PLA) nanofibers with piezoelectric potassium sodium niobate ($K_{0.5}Na_{0.5}NbO_3$, KNN) nanowires, allowing them to degrade naturally. Superstimulation of the stent can restore the motor ability of rats with spinal cord injury, promote the differentiation of neural stem cells in the lesion and endogenous angiogenesis, enhance the repair of spinal cord injury, and provide ultrasound-driven on-demand electrical stimulation for regenerative medicine.[126]

In addition to their application in nervous system-related regulation, piezoelectric nanomaterials also show great promise in the treatment and improvement of various clinical symptoms. For example, the use of ultrasound-mediated piezoelectric materials to cut off the generation and transmission of bone cancer pain from the source, to achieve strong, non-addictive analgesia based on peripheral nerves.[127]

At present, the technology of ultrasound-mediated piezoelectric materials regulating the nervous system has become increasingly mature and has achieved promising results. However, technical barriers still exist. For instance, the heat generated during ultrasonic stimulation may cause damage to the brain. Ensuring the long-term safety and efficacy of ultrasound-induced nanoparticles is critical for clinical application. Future research should focus on optimizing stimulus parameters, improving targeting accuracy, and combining real-time imaging with feedback to improve the accuracy and adaptability of DBS.

3.2.3. Ultrasound-Optical Response Materials

Ultrasound-optical response materials represent a novel class of smart materials enabling diagnostic and therapeutic functions through mechanical-to-optical energy conversion. Their design centers on functional units combining ultrasound-sensitive components with optically active elements like optogenetic proteins (ChR2, NpHR), upconversion nanoparticles ($NaYF_4$:Yb^{3+}/Er^{3+}), or fluorescent probes (CdSe/ZnS quantum dots, carbon dots).[128–132] In these materials, ultrasound-sensitive parts transduce mechanical stimuli while optical components generate or modulate light signals for diverse applications

Ultrasound-optical response materials function through direct energy conversion or indirect regulation. Direct conversion includes the piezoelectric–fluorescence effect, where ultrasound induces a polarized electric field in piezoelectric materials like ZnO nanowires, modulating carrier concentration and fluorescence in coupled emitters such as CdSe quantum dots[15] and mechanoluminescence, where stress-induced carrier release from crystal defects leads to light emission. Indirect regulation occurs through acoustic flow effects, where ultrasound-driven cavitation or microflow alters liquid crystal alignment or fluorophore aggregation,[133] and thermal/chemical activation, where cavitation-generated heat or reactive oxygen species (ROS) triggers responsive probes, as seen in nitroaromatic-loaded liposomes.[134] Recently, ultrasound-responsive optogenetic materials have emerged, combining deep tissue penetration with precise optical control for applications like neuromodulation.

Mechanical luminescent nanotransducers are a class of inorganic nanomaterials designed through defect engineering that store light energy through ultraviolet light pre-activation and release visible light under focused ultrasound (FUS) mechanical stimulation.[135] Jiang et al. utilized the "optical flow battery" mechanism to deliver mechanoluminescent nanotransducers (MLNTs) through the circulatory system. After the surface blood vessels were charged by external ultraviolet light, they migrated to the deep tissues along with the blood flow (**Figure 5a**). By systemic injection of MLNTs and targeted FUS stimulation, neurons expressing light-sensitive channel proteins can be non-invasively activated, successfully inducing limb motor behavior in mice.[64] Although MLNTs have shown potential in neural regulation, their half-life is relatively short, multiple injections are required to prolong the duration of action, and their therapeutic effect on neurodegenerative diseases is unknown. Researchers recently developed a sonosensitized Hydrogen-bonded organic framework (HOF) incorporating chemiluminescent L012 with high biocompatibility. The HOF-L012 system takes the sound-sensitive ligand H4TBAPy as the framework and loads the L012 chemical luminescent agent through π–π stacking. Under the ultrasonic trigger, the $^1O_2$ generated by the acoustic force reacts with L012 to form an excited-state intermediate, emitting 470 nm blue light (Figure 5b). In the 6-OHDA-induced PD rat model, this material improved the symptoms of bradykinesia by activating PV^+ neurons in the GPe (Figure 5c), and there was no gliosis caused by intracranial implantation.[135] While achieving neuron-specific regulation, the demand for dynamic monitoring of pathological markers has promoted the integration of imaging functions of acousto–optic materials. Researchers further developed multimodal probes with both therapeutic and diagnostic functions through the piezoelectric–chemiluminescence coupling mechanism. Nanoparticles based on trianthracene derivatives (TD NPs) achieve ultrasound-activated luminescence through a piezoelectric–chemiluminescence two-stage energy conversion mechanism: Ultrasonic vibration triggers the piezoelectric effect of TD NPs, triggering piezoelectric catalysis to generate ROS. ROS reacts with TD molecules to form chemiluminescent intermediates (such as dioxacyclobutane), and eventually releases photons (Figure 5d). TD NPs have been successfully used for tumor imaging and dynamic monitoring of the microenvironment. The granzyme B activation probe (TD-Grz-BHQ), designed through resonance energy transfer, can evaluate the stimulating effect on immunotherapy in real time (Figure 5e). After anti-PD-L1 treatment, the release of granzyme B in CT-26 tumors was significantly higher than that in 4T1 tumors, and the ultrasound-induced luminescence signal was significantly enhanced (Figure 5f). Furthermore, TD@IR780 NPs can

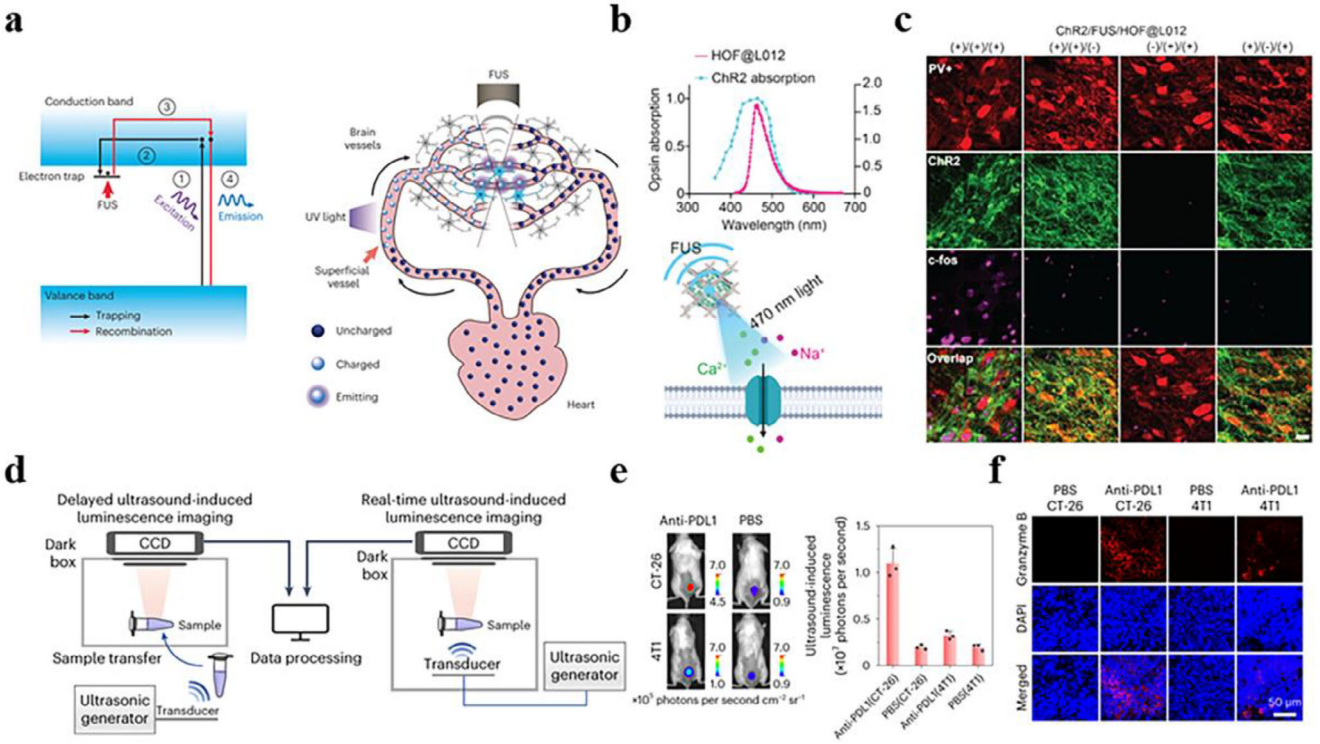

Figure 5. a) Schematic diagram of the luminescence mechanism of MLNTs under FUS stimulation and the photoexcitation and discharge (light emission) process of MLNTs during the cycling process. Reproduced with permission.[64] Copyright 2023, Springer Nature. b) Mechanical luminescence spectra of HOF@L012 nanoparticles, emission spectra of nanotransducers mainly covering ChR2 opsin absorption spectra (blue dot curve); Activation scheme of ChR2 opsin by mechanical luminescence HOF@L012 nanoparticles under ultrasonic activation. c) Mechanoluminescence HOF@L012 nanoparticles ultrasonic-activated ChR2 opsin activation protocol, confocal fluorescence image showing c-FOS expression in rat GPe under different conditions. Reproduced with permission.[135] Copyright 2025, Cold Spring Harbor Laboratory. d) Schematic diagrams of the experimental setup for the delayed ultrasound-induced luminescence imaging mode and the real-time ultrasound-induced luminescence imaging mode. e) Delayed ultrasound-induced luminescence images and intensity of mice in each group after injection of TD-Grz-BHQ. f) Confocal fluorescence images of tumour slices stained with granzyme B antibody. Reproduced with permission.[136] Copyright 2024, Springer Nature.

specifically detect the level of peroxynitrite in drug-induced liver injury, enabling early assessment of drug toxicity.[136] With the increase in the functional complexity of materials, the molecular design that precisely regulates the acousto–optic response has become the key. Supramolecular engineering constructs programmable templates through dynamic hydrogen bond networks, providing a new idea for high-precision energy conversion. The polymer system based on 1,3, 5-oxadiazine achieved the sub-nanometer arrangement of sonoluminescence sites through the self-assembly of the conjugated π system and the hydrogen bond network. Its molecular orbital overlap integration and wide bandgap characteristics enable the material to exhibit outstanding stability in triplet energy level regulation, laying the foundation for acousto–optic logic circuits driven by deep blue OLeds.[137]

Ultrasound-optical materials have made remarkable progress, but their clinical transformation still has problems such as low energy conversion efficiency, poor long-term biocompatibility, and the lack of precise dynamic regulation.[134] In the future, programmable acousto–optic switches can be further designed in combination with optogenetic modules to achieve gene editing targeting the pathological microenvironment, opening up new ideas for precise intervention of neurodegenerative diseases.

3.3. Magnetically Responsive Material Deep-Brain Stimulation

Nowadays, noninvasive neural stimulation methods like transcranial magnetic stimulation and transcranial direct current stimulation have shown the ability to modulate neural activity. Yet, they are constrained by their limited spatial resolution and depth of penetration. Functional materials in conjunction with external stimuli offer a promising alternative. This presents a significant step forward in replacing larger medical devices that can cause patient discomfort, tissue damage, and post-surgical complications. However, achieving an optimal balance between penetration depth and the power required for light and ultrasound stimulation remains challenging. Optogenetics utilizes light to stimulate opsins in specific cell types; however, light is susceptible to scattering and absorption by biological tissues. Alternatively, acoustic methods, including sonogenetics and focused ultrasound stimulation, can regulate neuronal activities without the necessity for hardware implantation. Nonetheless, ultrasound waves may experience scattering, reflection, and distortion upon interaction with the skull and bones. Among various physical stimuli, magnetic fields stand out as they can penetrate the brain without significant absorption or scattering.[49] Consequently, magnetic stimulation is emerging as a

promising method for deep tissue stimulation without invasive procedures, positioning it as a leading candidate for neural activation. Due to differences in stimulation parameters, material composition, and material shape, magnetic conversion materials can convert magnetic energy into different types of energy, such as heat, electricity, machinery, and light,[78,138,139] making them more promising for development. Magnetocaloric DBS utilizes magnetic nanoparticles (MNPs) to generate heat under the action of an alternating magnetic field (AMF), activating thermosensitive ion channels such as TRPV1 in the brain. This technology was initially validated as effective in vitro and C. elegans, and has been successfully applied to mice in recent years.[66] Compared with magnetocaloric genetics, magneto–mechanical genetics provides unique advantages for wireless DBS, including long-distance working distances with cellular and anatomical specificity, while avoiding potential thermally induced tissue damage.[67] Studies have proved that magnetite nanodiscs (MNDs) can activate neurons through transient receptor potential canonical (TRPC) channels.[49] Magnetoelectric nanoparticles have also been employed for remote neuromodulation, as it is believed that this class of material can convert an external magnetic field into an electric field, thereby directly activating voltage-gated ion channels. Materials designed with this concept have been proven effective in neuromodulation on rodents.[140] More promising is that some materials have been proven to have therapeutic effects on diseases, such as Fe_3O_4@$BaTiO_3$ Nanochain (FBC) can be used for epilepsy treatment,[27] while bismuth ferrite ($BiFeO_3$, BFO) coated with cobalt ferrite ($CoFe_2O_4$, CFO) can be used for AD treatment.[68] Currently, the application of magnetically responsive materials in neural regulation has shown good prospects in preclinical experiments, and relevant research has been conducted in the brain, spinal cord, and peripheral nerve tissues.[13] In the field of brain science, magnetically responsive materials have not only achieved wireless brain stimulation in rodents[141,142] but have also shown promising effects in neural differentiation, providing a novel perspective for neural repair.[143] Furthermore, in the context of spinal cord and peripheral nervous system, these materials have exhibited remarkable efficacy in motor function recovery.[13,52,144]

3.3.1. Magnetothermal Responsive Neuromodulation

The magnetic stimulation of gene-encoded neurons, known as magnetogenetics, has become a powerful alternative to wireless DBS.[67] When the neurons are transfected with TRPV1, emitting heat could trigger the reversible discharge of neurons expressing TRPV1. Hescham et al. developed a wireless magnetocaloric method of DBS using MNPs to achieve comparable therapeutic results in two PD mouse models induced by MPTP and 6-OHDA (**Figure 6a**). MNPs consist of an iron oxide core capable of magnetic-to-thermal conversion, which is encapsulated by a polyethylene glycol-poly (maleic anhydride-alt-1-octadecene) polymeric shell, a design intended to enhance their biocompatibility and maintain colloidal stability. Within an AMF operated at a therapeutically pertinent frequency of f = 160 kHz and a field amplitude of H_0 = 30 kA m^{-1}, these MNPs display a specific loss of power. This remarkable heating capability can induce a temperature elevation of 6 °C, thereby triggering the reversible activation of neurons expressing the TRPV1 ion channel. Open field test indicates that the motor function of all MPTP-induced PD mice can be improved after injecting MNPs into STN and transfecting TRPV1 with AMF stimulation for 3 min. (Figure 6b). In the 6-OHDA model, magnetic stimulation on various gait and balance-related parameters, such as accelerated run duration and increased regularity index in step sequence, were detected (Figure 6c). It should be noted that MNPs will cool back to physiological temperature after leaving the magnetic field. The precise heating rate in brain tissue is still unknown, and the delay in effectively heating brain tissue remains an issue.[66] The precise temporal modulation of neural activity is under further investigation. Sebesta et al. have generated sub-second behavioral responses in *Drosophila melanogaster* by integrating magnetic nanoparticles with rate-sensitive thermoreceptors (TRPA1-A).[145] In addition, the damage to brain tissue caused by gene transfection and increased temperature should also be considered. To avoid such damage, using non-transfection methods and wireless stimulation methods that convert magnetic energy into other forms of energy may be a good approach.

3.3.2. Magneto–Mechanical Responsive Neuromodulation

In addition to magnetothermal conversion, magneto–mechanical stimulation employs the mechanical force exerted by magnetic nanoparticles within low-intensity magnetic fields to elicit neuronal activation. The TRPC family comprises non-selective cation channels that are abundantly expressed across various brain regions, with TRPC1, 5, and 6 exhibiting mechanosensitivity and contributing to the cellular response to stretch stimuli. Su et al. demonstrated that the torque generated by magnetic nanoparticles (MNDs) can activate neurons via endogenous TRPC channels under conditions of weak alternating magnetic fields (Figure 6d). The main component of MNDs is magnetite Fe_3O_4 nanodiscs sized between 200–300 nm. When MNDs are applied to primary cultured hippocampal neurons, magnetic stimulation at an AMF (10 Hz and 50 mT) can induce Ca^{2+} responses in neurons (Figure 6e). Unilateral injection of MND into the STN area of mice can cause a significantly higher expression of c-Fos in STN compared to the non-injected groups, indicating this method can modulate neuronal activity in vivo (Figure 6f). Although this experiment does not require transfection and the regulation of TRPC is associated with PD,[146] depression,[147] AD,[93] etc. Unfortunately, the precise functional contribution of TRPC in the majority of brain areas remains elusive. The variability in the functional roles exhibited by TRPC across diverse brain regions and cellular types hinders its utilization.[49] Similarly, Shin et al. have designed a nanoscale magnetic force actuator (m-Torquer) that utilizes transduced mechanically sensitive Piezo1 ion channels for magnetic–mechanical transduction material-mediated DBS, aiming to improve motor activities and balance in PD mouse models.[67] Choi et al. also achieved cell-type-specific magnetic modulation for remote and spatiotemporally precise control of deep brain neural activity across various behavioral models, such as bidirectional feeding control, by selectively activating

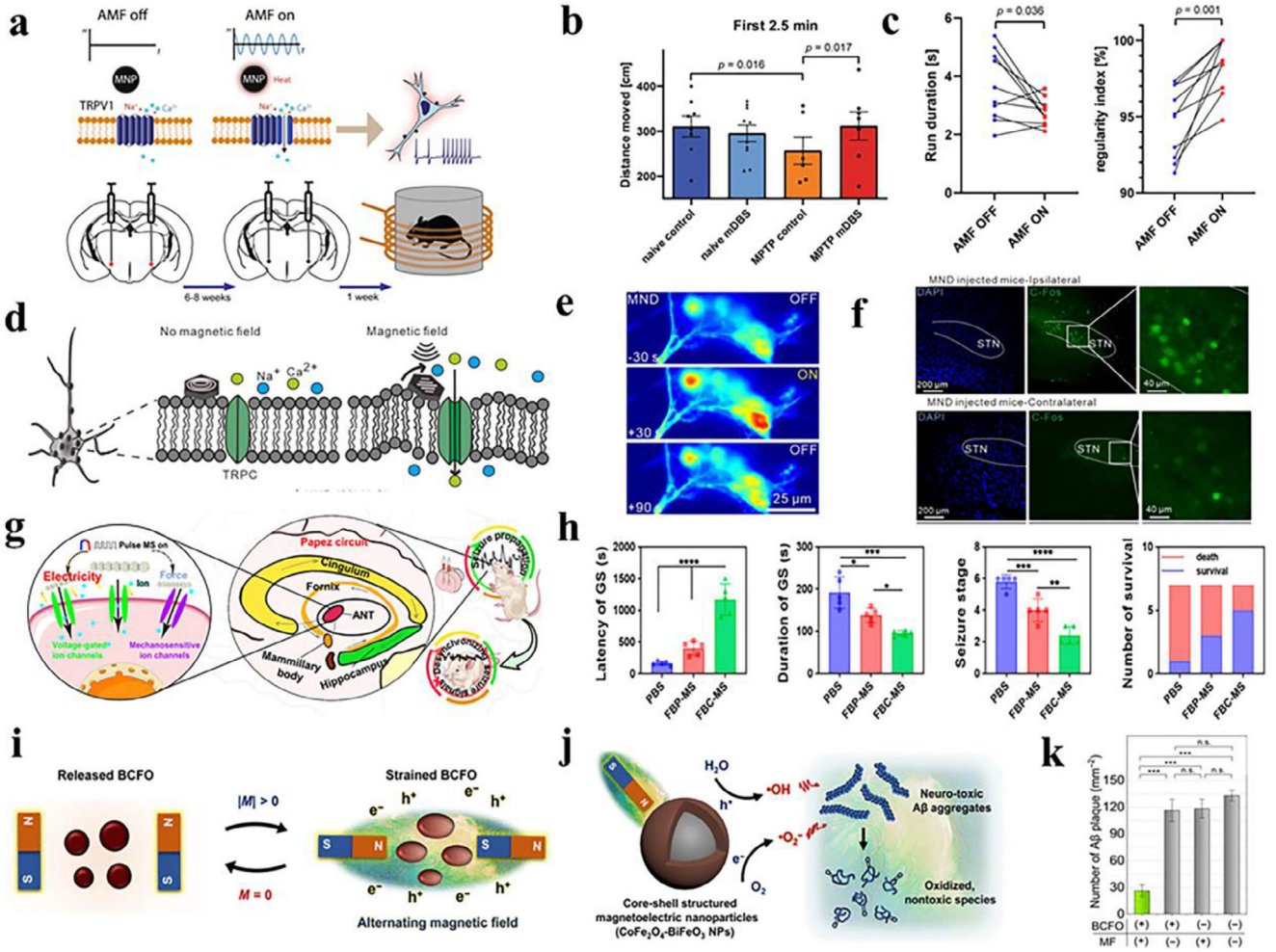

Figure 6. The representatives of magnetically responsive material DBS. a) The experimental scheme of magnetic field stimulation causes heat generation in MNP, leading to membrane depolarization. The figure below shows the experimental steps. b) The total distance of mice moving in the open field within the first 2.5 min. c) Mice in CatWalk showed faster running duration ($p = 0.036$) and increased step regularity (%) ($p = 0.001$). Reproduced with permission.[66] Copyright 2021, Springer Nature. d) Diagram illustrating the application of magneto–mechanical stimulation through MND. e) Color map of neuronal fluorescence intensity when MND is applied to primary cultured neurons. f) Images of the ipsilateral and contralateral STN of mice injected with MND. Reproduced with permission.[49] Copyright 2022, Springer Nature. g) Schematic diagram of wireless DBS platform. h) The latency of generalized ankylosing colon seizures in the treatment group was prolonged, the duration and seizure stage decreased, and the survival rate increased. Reproduced with permission.[30] Copyright 2023, American Chemical Society. i) Schematic illustration depicting the generation of charge carriers excited by strain in BCFO nanoparticles upon exposure to a low-frequency magnetic field. j) Schematic representation of magnetoelectric dissociation of AD Aβ aggregate structures using magnetoelectric nanoparticles and low-frequency magnetic fields. k) Aβ plaque density in brain slices from the magnified region after 6 h treatment with BCFO nanoparticles and low-frequency magnetic fields. Reproduced with permission.[68] Copyright 2022, American Association for the Advancement of Science.

genetically encoded Piezo1 ion channels in targeted neuronal populations.[148]

3.3.3. Magnetoelectric Responsive Neuromodulation

Magnetoelectric materials can transform magnetic fields into electric fields[140] and have been used for remote neural regulation, effectively promoting intracellular calcium ion influx[30] and directly activating voltage-gated ion channels.[144] Compared to TRPC, voltage-gated ion channels have been more clearly characterized and widely used in neural regulation research. Magnetoelectric nanomaterials can generate charge separation under magnetic stimulation by the interplay between the magnetostrictive and piezoelectric phases, enabling noninvasive microscale neural stimulation. The core–shell-like Fe_3O_4@$BaTiO_3$ nanoparticles are capable of generating electrical signals. However, the limited coupling area between the magnetostrictive core and the piezoelectric shell in this material restricts the further development of the magnetoelectric effect.[149] In contrast, 1D nanochains, with their larger contact areas and shape anisotropy, are potential solutions to enhance magnetoelectricity. In a previous investigation, Fe_3O_4@$BaTiO_3$ nanochain (FBC) with 270 nm in height and 2 μm in length was used to treat epilepsy by pulsed magnetic stimulation.[30] FBC is a 1D chain-like structure that can enhance the magnetoelectric effect and wirelessly

regulate neuronal activity by activating voltage-gated ion channels (Figure 6g). FBC was stereotactically injected into the anterior thalamic nucleus (ANT) as a wireless DBS platform for in vivo epileptic electrical stimulation. It achieves the inhibition of epileptic seizures and neuroprotection of the hippocampus mediated by the Papez circuit (Figure 6h).[30] The magnetoelectric nanodiscs (MENDs) with a Fe_3O_4-$CoFe_2O_4$-$BaTiO_3$ core–shell structure are designed for a minimally invasive DBS method. These MENDs convert magnetic fields into electric potentials, enabling remote neuromodulation. Injected into brain regions like the ventral tegmental area or subthalamic nucleus, MENDs allow precise control of reward or motor behaviors in mice without genetic modification.[150]

The application of the wireless magnetoelectric deep brain therapy platform in epilepsy management streamlines the process of delivering stimulation to specific target areas and enables convenient, on-demand, long-term wireless electrical stimulation. BFO and CFO are commonly used single-phase magnetoelectric materials for manufacturing electronic products such as sensors. This system exhibits stronger magnetoelectric coupling due to lattice matching and piezoelectric effects. Recent studies have shown that CFO coated with BFO (BCFO) can effectively excite charge carriers under low-frequency magnetic fields[68,151–153] and exhibit biocompatibility with biological cells and mice models.[68,154,155] On the other hand, magnetoelectric nanomaterial under a low-frequency magnetic field was designed, which can reduce the Aβ in the brain tissue of AD mice models in vitro.[68] The atypical aggregation of β-amyloid (Aβ) peptides and their accumulation in the brain represent a significant pathological characteristic of AD. In this research, $CoFe_2O_4$ nanoparticles coated with magnetoelectric $BiFeO_3$ at ≈33.2 nm respond to low-frequency magnetic fields (1 kHz and 13.6 mT) and emit stimulated charge carriers (Figure 6i). They found that BCFO nanoparticles can generate charges in a magnetic field, causing dissolved oxygen molecules to produce free radical substances • OH and • O^{2-} (Figure 6j). The BCFO can effectively dissociate the Aβ Plaques and directly decompose the substances that cause diseases through redox reactions.[68] Kozielski et al designed a two-phase design of magnetostrictive $CoFe_2O_4$ nanoparticles coated with magnetoelectric nanoparticles (MENPs). This material modulates subthalamic regions, influencing basal ganglia circuits and altering mouse behavior.[69] In addition, Lu et al. established a combined magnetic stimulation system treatment (c-MSST), and discovered that magnetoelectric conversion materials can influence synaptic plasticity through neuromodulation, exerting an antidepressant effect in a mouse model of depression.[70] Furthermore, some researchers believe that existing magnetoelectric nanoparticles exhibit relatively long latency periods (ranging from hundreds of milliseconds to a few seconds) in neural stimulation, which limits their ability to directly drive action potentials on demand, and propose magnetoelectric nonlinear metamaterials that can achieve millisecond-long neural stimulation.[140]

Magnetic stimulation is emerging as a promising method for achieving deep tissue stimulation without invasive procedures, positioning it as a leading candidate for radio-frequency-based neural activation. In a manner akin to light and ultrasound stimulation, magnetic stimulation materials can be implanted completely into the brain by simple injection, which is minimally invasive, has a long life span, and has good biocompatibility, so it can reduce patient discomfort, tissue damage, and postoperative complications. Compared to other stimuli, the significant advantage of magnetism lies in its outstanding penetration ability and the characteristic of not being absorbed or scattered. In addition, a low-frequency magnetic field has a much lower risk of causing damage to the outer tissues (e.g., scalp and skull) for deep brain treatment in patients.[68] The TRPV1 channel utilized by magnetocaloric materials has been widely used in neural regulation research, and although most studies rely on exogenous expression of TRPV1, this channel is endogenously expressed in neurons and glial cells in certain regions of the mammalian central nervous system.[66] However, the thermal energy generated by materials may cause tissue damage, so a balance between effectiveness and damage is still needed in material design. Therefore, compared to high-frequency magnetic fields that induce a large amount of heat generation, low-frequency magnetic fields with nonthermal effects may have greater potential for development in medicine. Compared with magneto-thermal materials, magneto mechanical materials and magneto electric materials can perform precise targeted operations at a long distance at the cellular and anatomical levels while avoiding the risk of tissue damage caused by heat generation. For magneto mechanical materials, regulating TRPC has been proposed for the treatment of PD and ischemic stroke. However, the functional role of TRPC in most brain regions remains unclear, necessitating consideration of its regional and cellular variability for future applications and further translational research.[49] For magneto electric materials, the widespread distribution of voltage-gated ion channels has excellent benefits for their use in treating diseases. Although magnetoelectricity can achieve remote stimulation of neural tissue, the optimal resonance frequency is usually too high to stimulate neural activity.[140] How to achieve millisecond level time precision stimulation is still a problem that the magneto electric material design needs to face. In addition, utilizing magnetic electrolysis to decompose major disease biomarkers such as Aβ in AD may become a promising new approach for material design. Additionally, providing long-term use of magnetic fields is necessary to maintain the therapeutic effect on patients. Scaling the coil to the volume required for neural regulation in human patients is also a daunting challenge, as it requires achieving unity of established power and portability.

4. Mechanisms of Transducer Material-Mediated Neuromodulation

4.1. Multiscale Coupling Mechanisms Between Physical Stimuli and Ion Channels

The study of the physical mechanisms underlying neuromodulation has revealed the complex coupling relationships between external stimuli and the electrophysiological properties of neurons, with the core process being the precise regulation of transmembrane ion dynamics. This process involves the coordinated action of voltage-gated ion channels, dynamic changes in membrane capacitance, and the spatiotemporal reconfiguration of ion concentration gradients. When external physical stimuli (such as electrical, optical, thermal, or mechanical forces) act on neurons, they can induce the transmembrane migration of ions

such as sodium, potassium, and calcium by altering the membrane potential or directly modulating the conformation of ion channels, thereby triggering the cascade propagation of action potentials.[13,156] Different stimulation modalities, through their specific physical parameters (such as electric field strength, rate of temperature change, and mechanical stress), interact with the neuronal membrane system to form differentiated pathways for electrical signal transduction, ultimately achieving multiscale regulation of neuronal excitability.[14] This physical–biological coupling mechanism provides a quantitative basis for understanding neural information encoding and establishes a key theoretical framework for developing targeted neuromodulation technologies. Research on the physical mechanisms of neural modulation has revealed complex coupling relationships between external stimuli and neuronal electrophysiological properties.

The Hodgkin–Huxley model is the classical framework for describing action potential generation and propagation in neurons. This model is based on three ionic currents: sodium current (I_{Na}), potassium current (I_K), and leakage current (I_L), with its core equation expressed as:

$$C \cdot dV/dt = I_{ext^-} \cdot I_{Na^-} \cdot I_{k-} \cdot I_L \quad (1)$$

C represents membrane capacitance, V denotes membrane potential, and Iext signifies external current.

The regulation of neuronal excitability fundamentally relies on the dynamic equilibrium of intracellular–extracellular ionic concentration gradients and their transmembrane transport. According to the Hodgkin–Huxley model, the generation and propagation of neuronal electrical activity are primarily determined by the kinetic properties of voltage-gated ion channels, which are directly influenced by variations in ion concentrations. Different ions exhibit distinct migratory behaviors due to their physicochemical characteristics: monovalent ions (K^+, Na^+), with their smaller ionic radii and single charges, demonstrate significantly higher migration rates compared to divalent ions (Ca^{2+}, Mg^{2+}). This differential ion migration establishes specific spatial distribution patterns that subsequently influence neuronal structure and function. The accumulation of K^+ leads to axonal swelling and increased membrane permeability, promoting depolarization and enhanced excitability; whereas Ca^{2+} aggregation induces axonal constriction, inhibits K^+ influx, and consequently reduces excitability.[13] These findings provide a crucial theoretical foundation for deepening our understanding of the relationship between ion dynamics and neuronal excitability, while also pointing the way toward developing ion-modulation-based strategies for neural function intervention.

Dynamic modeling of ion channels based on Hodgkin–Huxley-type equations demonstrates that the activation functions of voltage-gated Na^+/K^+ channels exhibit pronounced nonlinear responses to transmembrane potential variations.[157] Transducer-converted stimuli of different modalities can interact with ion channels by modulating specific parameters, thereby influencing neuronal excitability. Electrical stimulation induces membrane depolarization by altering the membrane potential. Experimental data demonstrate that neuronal excitation is typically triggered when the membrane depolarization reaches a threshold range of 15–30 mV.[150] Additionally, electrical stimulation modulates the opening of voltage-gated ion channels, including calcium channels. Fan et al. discovered that the combination of MoS_2 and ultrasound could induce Ca^{2+} responses in human neuroblastoma cells and primary cultured hippocampal neurons via voltage-gated ion channels.[124] Thermal stimulation, on the other hand, modulates sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) currents by affecting their respective ion channels.[55,66] For instance, the magnetothermal conversion material designed by Hescham et al. activates TRPV1 under a magnetic field, altering the transmembrane migration of Na^+ and Ca^{2+} and thereby triggering reversible firing in TRPV1-expressing neurons. Additionally, temperature fluctuations influence the activation and inactivation of multiple ion channels, ultimately affecting action potential generation.[158] Optical and mechanical stimulation can activate corresponding photosensitive[55,159] and mechanosensitive channels,[49,160] thereby modulating sodium and calcium ion channels. The upconversion materials designed by Sun et al. significantly activated the extracellular sodium current in Neuro2a cells expressing the ChR2 ion channel under 980 nm irradiation.[49] The magnetomechanical conversion materials designed by others can induce Ca^{2+} responses in primary cultured neurons under a 50 mT magnetic stimulation.[55] Additionally, ultrasound-induced mechanical strain has been demonstrated to modify membrane capacitance,[161] while externally applied pressure increases membrane tension, consequently affecting the open probability of mechanosensitive ion channels.[162] Plaksin et al. proposed a "neuronal bilayer sonophore" model, which predicts the emergence of pulsating nanobubbles induced by ultrasound within the neuronal bilayer membrane and ultimately leads to the generation of action potentials.[161]

Localized stimuli can modulate neuronal electrical activity through mechanisms such as regulating ion channel activity or altering membrane capacitance, thereby achieving therapeutic effects. These findings provide crucial guidance for transducer selection and optimization: clinical applications should comprehensively consider the transducer's modulation characteristics for specific ion channels, electrical signal transduction mechanisms, and pathological features of target diseases to establish precise and efficient neural modulation strategies. Future studies should further elucidate the neural modulation mechanisms mediated by transducer materials, which will open new research avenues for precision treatment of neurological disorders.

4.2. Synergistic Material-Channel-Pathway Interventions for Neural Repair

The innovation in neuromodulation technology is propelling a paradigm shift in the treatment of neurological diseases, from "symptom management" to "precision repair." Transducer materials, through their precise interactions with ion channels via multi-physical field coupling mechanisms, have emerged as the core driving force to realize this transition. As molecular switches for neuronal electrical activity, the spatiotemporal-specific regulation of voltage-gated, mechanosensitive, and thermosensitive ion channels not only directly determines neuronal excitability but also influences key physiological processes such as neuroplasticity and synaptic remodeling through downstream cascades like calcium signaling and the MAPK pathway.[13,156] The

development in this field will not only accelerate therapeutic innovations for intractable conditions such as neurodegenerative diseases and spinal cord injuries but may also redefine the intervention models of future neuromedicine.

Piezoelectric materials generate surface charges during mechanical deformation that modulate voltage-gated calcium channels (VGCCs).[163,164] Photothermal nanoparticles induce localized surface plasmon resonance under NIR excitation, triggering the opening of thermosensitive TRPV1 channels.[90] Photoconversion materials capture NIR light and transform it into UV/visible wavelengths, thereby activating conjugated photochemical ligands to facilitate TRPA1 channel photostimulation.[83] Magnetoelectric nanomaterials achieve neural stimulation via charge separation generated through magnetostrictive–piezoelectric coupling under magnetic fields, influencing calcium channel proteins such as L-type VGCCs.[149] Under low-frequency weak magnetic fields, magnetomechanical transducers produce torque-derived mechanical forces that activate mechanosensitive TRPC channels on cell membranes.[49] For magnetothermal nanoparticles, magnetic field application induces rapid magnetization flipping, generating heat to open thermosensitive channels like TRPV1.[66] Elucidation of these physio–biological coupling mechanisms provides a theoretical foundation for developing precision neuromodulation technologies. Studies reveal that these modulations further influence downstream signaling pathways, yielding therapeutic effects for neurological disorders.

Electrical stimulation, as an important neuromodulation technique, is capable of regulating the activity and signaling pathways of nerve cells through a variety of mechanisms, thereby playing a significant role in the treatment of nervous system diseases. Research has shown that electrical stimulation can not only modulate the charge balance of the extracellular matrix to trigger ion transport across the cell membrane, but also influence neuroplasticity and synaptic remodeling through downstream signaling transduction mechanisms such as the calcium signaling pathway and MAPK pathway. During electrically triggered calcium influx, kinases in MAPK pathway exhibit significant concentration alterations.[13] Cellular studies demonstrate that Kawamura et al. observed electrical stimulation promoting neurite outgrowth and survival in PC12 cells via p38 MAPK pathway activation.[165] Wang et al. reported that electrical stimulation enhances BDNF expression in spinal neurons through Ca^{2+} and Erk-dependent signaling.[166] Additionally, Wen et al. discovered that electrical stimulation mediates axonal repulsion by downregulating Netrin-1/DCC via Rho GTPase signaling, thereby guiding axonal growth.[167] In animal models, Wang et al. demonstrated that electrical stimulation rapidly directs neural stem cell (NSC) differentiation into dopaminergic neurons by activating calcium and MAPK pathways, exerting therapeutic effects in PD mice.[168]

Thermal stimulation, as an emerging neuromodulation technique, possesses the advantages of high tissue penetrability and spatial selectivity, enabling precise regulation of neural activity in target regions. Studies have shown that thermal stimulation can modulate the concentration of intracellular calcium ions and the levels of ROS by regulating temperature-sensitive ion channels and associated signaling pathways within cells. This regulatory mechanism not only alleviates neuroinflammation but also promotes the construction and enhancement of neural networks by modulating neuronal excitability.[169] Li et al. designed photothermal nanoparticles that effectively cross the blood–brain barrier (BBB) under 808 nm laser irradiation, reducing Aβ aggregation and facilitating extracellular disaggregation. Concurrently, these nanoparticles mitigate Aβ42-associated neurotoxic signaling by modulating ROS and Ca^{2+} levels, alleviating neuroinflammation.[170]

Optical stimulation, as a noncontact, noninvasive, and highly precise neuromodulation technique, can precisely regulate the activity of nerve cells through optogenetic techniques or photosensitive materials. Studies have shown that optical stimulation can trigger ion transport across the cell membrane and intracellular signal transduction by activating photosensitive proteins (such as ChR2) or modulating intracellular photochemical reactions. Zhang et al. developed an upconversion nano-reactor that scavenges excess ROS and attenuates tau hyperphosphorylation via the Akt/GSK3β pathway under NIR excitation, preventing neuronal apoptosis and improving cognitive function in AD model mice.[144]

Mechanical stimulation, by directly acting on the mechanical properties of cells, is capable of modulating the activity and signaling transduction of nerve cells. Studies have demonstrated that mechanical stimulation can influence intracellular calcium ion concentrations and cytoskeletal reorganization by activating mechanosensitive ion channels on the cell membrane and the downstream RhoA signaling pathway. This regulatory mechanism promotes the differentiation of neurons and the extension of axons. Mechanical stimulation, another critical modality, directly targets cellular biomechanics to exert neuromodulatory effects. Oh et al. confirmed that mechanical forces promote human iPSC differentiation into neurons via RhoA signaling and ciliary neurotrophic factor regulation.[171]

Transducer materials enable precise neural activity control through multifaceted interactions with ion channels, while their therapeutic effects on neurological disorders are mediated via downstream signaling pathways. These advancements not only provide theoretical support for neuromodulation technologies but also offer novel therapeutic strategies for neurological diseases.

5. Conclusion and Outlook

The use of transducer materials for brain stimulation presents a promising frontier for the treatment of neurodegenerative diseases. These materials offer the potential for less invasive, more precise, and self-powered stimulation methods. Currently, DBS mediated by transducer materials has demonstrated remarkable potential in the treatment of various neurological disorders, including PD,[63,66] epilepsy,[30,59] AD,[68] and mood disorders.[70] Recent advancements in nanotechnology have opened new avenues for brain stimulation, potentially overcoming some limitations of traditional DBS, such as the need for invasive surgery and hardware-related complications. As mentioned, piezoelectric materials can convert the mechanical energy contained in ultrasound into electrical energy. When applied to brain stimulation, these materials can be engineered to respond to natural physiological activities, such as blood flow or breathing, to generate electrical stimulation without needing external power sources. This could lead to less invasive and self-powered DBS

systems. Photothermal materials can convert light energy into thermal energy, thereby generating neural stimulation to regulate neural activity. When targeted to specific brain regions, these nanoparticles can be activated by external light sources to modulate neuronal activity through localized heating. However, balancing the power of ultrasound with the wavelength and penetration depth of light is not an easy task. Compared to ultrasound and light stimulation, magnetic stimulation has the advantage of penetrating the brain with little absorption or scattering.[172] By targeting these materials in the brain and applying an external magnetic field, it is possible to induce localized electrical stimulation. This method could provide a noninvasive means of deeper brain stimulation. The development of novel energy-converting nanomaterials for the treatment of neurological disorders such as PD, depression, and anxiety represents a promising and innovative research direction. This approach leverages advancements in nanotechnology to create materials that can interact with specific brain regions targeted by clinical electrical stimulation. By functionalizing the surface of these materials with specific neuron markers, such as GAD67 for GABAergic neurons, tyrosine hydroxylase antibody for dopaminergic neurons, synapsin I antibody for general neurons, and vesicular glutamate transporter-1 antibody for glutamatergic neurons, this method can achieve enhanced neuron targeting for different situations. Besides targeting, interfacing with, or triggering neuronal cells, other cell types like astrocytes can also be regulated by the transducer materials.[173]

Noninvasive neuroregulatory delivery technology, through innovative material design and delivery methods, can break through the limitations of the blood–brain barrier (BBB) and has significant potential in the field of neurological disease treatment. Current research focuses on two core directions. One is to utilize the anatomical advantages of the olfactory nerve/trigeminal nerve pathway to achieve efficient local brain entry. For example, the nucleic acid framework tFNAs (≈10 nm), due to its small size, high negative charge density and biomimetic structure, can penetrate the mucus layer and be transported along axons, achieving whole-brain distribution;[174] Hydrogel can prolong the nasal retention time and enhance drug accumulation through temperature response.[175] In addition, the targeted BBB penetration strategy optimizes the drug delivery efficiency through bionic materials and intelligent response carriers.

Bionic membrane coatings (PLGA nanoparticles loaded with Dex) target and penetrate the BBB through surface markers to induce apoptosis of tumor cells.[176] ROS/enzyme-responsive nanocarriers utilize the microenvironment of the lesion to trigger drug release and simultaneously achieve oxidative stress regulation.[177]

The core advantages of such technologies encompass three principal aspects: noninvasive administration for reducing systemic toxicity and enhancing patient compliance, precision-targeted delivery systems that minimize off-target effects on healthy tissues, exemplified by RVG peptide-modified exosomes and transferrin receptor-mediated targeting strategies.[176,178] and multifunctional synergistic therapeutic approaches, including the co-delivery of miRNA-124 and curcumin to concurrently suppress amyloid-β production and mitigate neuroinflammatory responses.[168]

Current transducer materials still face critical bottlenecks, including insufficient stability, limited targeting specificity, and difficulties in scalable fabrication. For neurodegenerative disease treatment, future breakthroughs should focus on developing dynamic response systems integrating spatiotemporal modulation, optimizing ligand-receptor targeting to enhance BBB penetration, and adopting advanced manufacturing like microfluidics for standardized biomimetic material production. Through cross-modal precision regulation, this technology holds promise as a next-generation noninvasive therapeutic platform for PD and other neurodegenerative disorders, accelerating the translation from bench to bedside.

Stimulation targeting different brain regions can elicit distinct therapeutic effects, and the newly identified brain targets and associated mechanisms in traditional DBS research are further advancing the development of transducer materials for disease treatment. However, there are significant challenges to overcome before these technologies can be translated into clinical practice. These include ensuring biocompatibility, achieving targeted delivery and activation, and understanding the long-term effects of nanomaterials within the brain. DBS remains a valuable tool for managing symptoms of neurodegenerative diseases, and emerging nanomaterial-mediated stimulation techniques hold the potential to revolutionize this field. As research progresses, these novel approaches may provide more effective, less invasive, and personalized treatment options for patients suffering from these debilitating conditions. This offers great potential for future brain–computer interfaces and human–machine interfaces, such as electronic skins and wearable devices. By precisely coupling the nanotransducer network with the neural microcircuit, a bidirectional interactive neural interface can be established: it can not only decode the discharge characteristics of specific neural nuclei in real time but also achieve dynamic neural coding reconstruction through local field regulation. This system overcomes the inherent limitation of unidirectional signal transmission in conventional brain–computer interfaces through closed-loop intervention mechanisms while offering innovative therapeutic solutions for neurodegenerative disorders such as PD and AD. Crucially, the biohybrid interface establishes adaptive coupling channels between cerebral neural networks and external artificial intelligence systems via synergistic integration of nanotransducer arrays with synaptic plasticity. This neural–artificial hybrid technology not only expands the boundaries of human perception and cognition but may also catalyze a human–machine symbiosis paradigm.

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Conflict of Interest

The authors declare no conflict of interest.

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