

Emerging techniques for precision neuromodulation: A comparative framework from bench to bedside

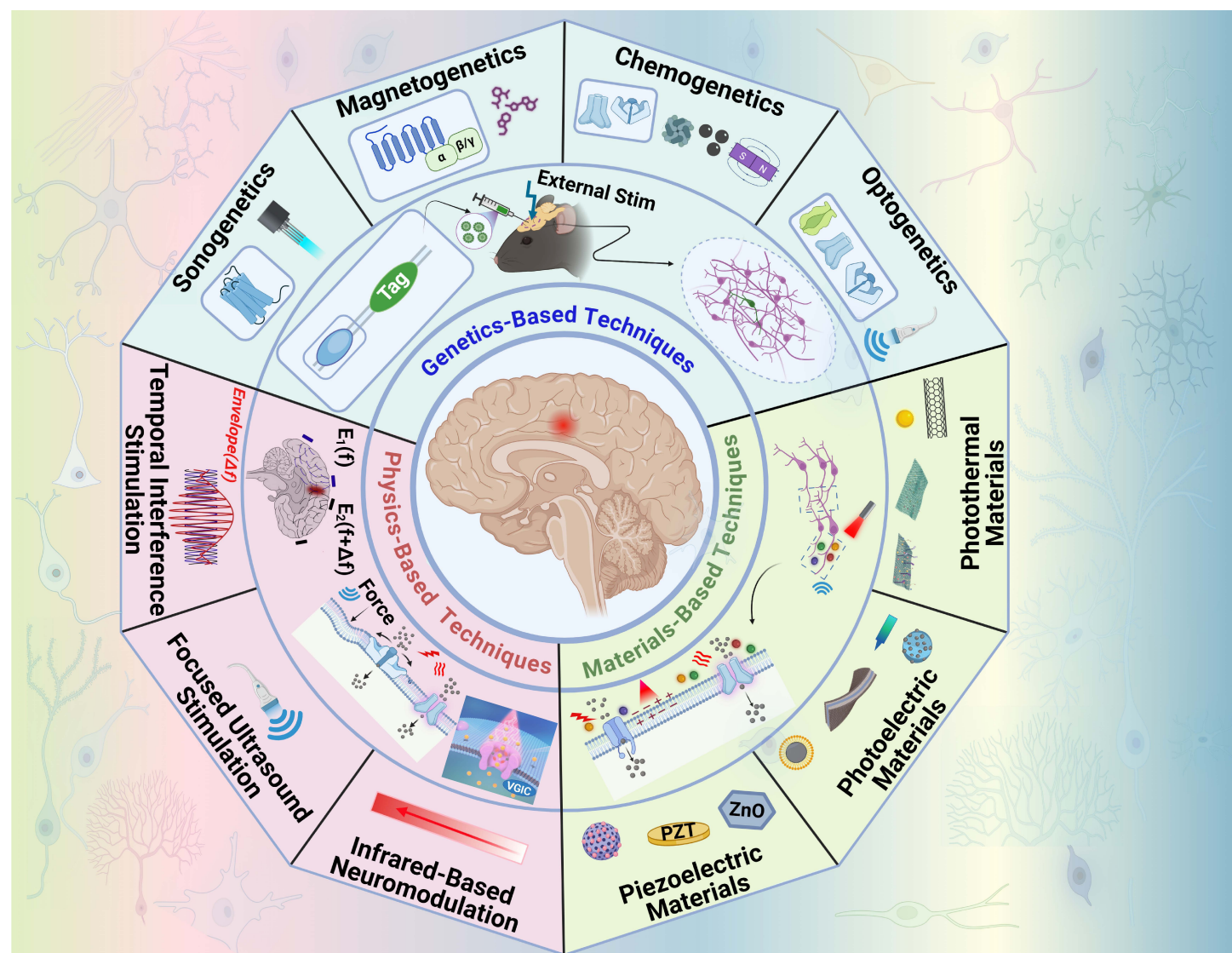
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Classical neuromodulation techniques lack precision in targeting specific neuronal subtypes or circuits.
- Emerging genetics-, material-, physics-based neuromodulation techniques offer promise for enhancing precision.
- Six-dimensional analyses reveal trade-offs in spatial/temporal resolution, specificity, biosafety, depth, feasibility.
- This review offers a framework matching precision neuromodulation methods with scientific and clinical demands.

Emerging techniques for precision neuromodulation: A comparative framework from bench to bedside

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Precision neuromodulation has emerged as a transformative field in neuroscience, enabling both targeted treatment of neurological disorders and mechanistic dissection of brain function. While classical techniques like deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS) are widely used in clinical practice, they lack the fine-scale specificity required for precise control of specific neuronal subtypes or neural circuits. In contrast, emerging strategies, including genetics-based (optogenetics, chemogenetics, sonogenetics, magnetogenetics), materials-based (photothermal, photoelectric, piezoelectric), and physics-based (infrared, ultrasound, temporal interference) neuromodulation techniques, hold the potential for enhancing spatiotemporal resolution, cell-type specificity, and novel delivery mechanisms. Here, we systematically compare classical and emerging neuromodulation techniques across six critical dimensions: spatial resolution, temporal resolution, cell-type specificity, biosafety, depth of stimulation, and clinical feasibility. We highlight the divergent precision requirements of basic research and clinical applications and categorize all methods by actuator type and stimulation modality to guide practical use. We further examine translational strategies for integrating advanced tools into human therapies. While no single method satisfies all criteria, complementary approaches can be tailored to meet distinct goals of precision in experimental neuroscience and clinical applications. This review provides a conceptual and practical roadmap for selecting and optimizing precision neuromodulation strategies, offering insights that bridge mechanistic research and clinical translation.

INTRODUCTION

Neuromodulation refers to the targeted regulation of nervous system activity and has long served as both a therapeutic modality and a tool for probing brain function. Classical techniques, such as deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS), have shown efficacy in treating neurological and psychiatric conditions including Parkinson's disease, depression, and epilepsy.¹⁻⁴ However, these approaches typically act on relatively broad brain regions, lacking the ability to selectively target specific neuronal subtypes or neural circuits, thereby limiting both their therapeutic precision and interpretative value in neuroscience research.

In recent years, the emergence of precision neuromodulation techniques has begun to address these limitations. Enabled by advances in genetic engineering, materials science, and biophysics, these emerging techniques, involving genetics-based (optogenetics, chemogenetics, magnetogenetics and sonogenetics),⁵⁻⁸ materials-based (photothermal, photoelectric, and piezoelectric materials),^{9,10} and physics-based methods (infrared light, focused ultrasound and temporal interference stimulations),¹¹⁻¹⁴ hold the potential to improve spatial and temporal resolution, enhance cell-type specificity, and offer greater adaptability for modulating defined neuronal subtypes or circuits.

This review provides a comprehensive and structured comparison of both classical and emerging neuromodulation techniques. We systematically evaluate each method across six key dimensions: spatial resolution, temporal resolution, cell type specificity, biosafety, depth of stimulation, and clinical

feasibility. We then examine the differing demands for precision in basic research versus clinical applications, assessing how well each method addresses the specific demands of these domains. Finally, we highlight current technical challenges, suggest strategies for translating emerging techniques from laboratory research to clinical use, and offer forward-looking perspectives on the future of precision neuromodulation.

CLASSICAL NEUROMODULATION TECHNIQUES

Overview of DBS, TMS, and tDCS

DBS is an invasive procedure that involves implanting electrodes into deep brain structures such as the subthalamic nucleus or globus pallidus. It delivers continuous electrical pulses to modulate pathological neural activity and has demonstrated robust clinical efficacy in treating Parkinson's disease, essential tremor, dystonia, and obsessive-compulsive disorder (OCD), all of which have received regulatory approval in multiple countries (Figure 1A).^{2,15-19}

TMS is a non-invasive technique that uses rapidly changing magnetic fields to induce localized electrical currents in cortical regions. It has been FDA-approved for treatment-resistant major depressive disorder, and is being actively explored for anxiety, schizophrenia, and post-traumatic stress disorder (PTSD) (Figure 1B).^{3,20-24}

tDCS is another widely used non-invasive neuromodulation technique that involves applying a low, constant electrical current to the scalp to modulate neuronal excitability. It has shown promise in enhancing motor recovery following stroke, treating depression, anxiety, and schizophrenia, and supporting cognitive enhancement in both healthy individuals and those with cognitive impairments (Figure 1C).^{4,25-29}

Cross-dimensional evaluation of classical methods

The comparison is summarized in Table 1 and visualized in Figures 1D-F.

GENETICS-BASED NEUROMODULATION TECHNIQUES: A PARADIGM SHIFT FOR PRECISION NEUROMODULATION

From a clinical standpoint, classical neuromodulation techniques are valued for their established safety profiles, regulatory approvals, and proven therapeutic efficacy. However, in basic neuroscience research, these methods exhibit significant limitations in spatial resolution, cell-type specificity, and circuit-level targeting. Such constraints reduce their utility in dissecting fine-scale mechanisms underlying neural computation and behavior. Recent technical refinements, such as directional DBS leads, adaptive closed-loop stimulation, and high-definition tDCS, represent meaningful advancements but also highlight the inherent constraints of these approaches in achieving precision neuromodulation.^{35,40}

These challenges have fueled the development of genetics-based techniques, which harness genetic engineering to introduce actuator proteins, such as ion channels or receptors, into specific neuronal populations. These methods enable targeted neuronal control in response to external stimuli, including light (optogenetics), chemicals (chemogenetics), magnetic fields (magnetogenetics), and ultrasound (sonogenetics). By allowing precise and cell-type specific activation or inhibition, genetics-based neuromodulation has transformed basic research, enabling causal interrogation of defined neural circuits and their roles in behavior and pathology. In clinical contexts,

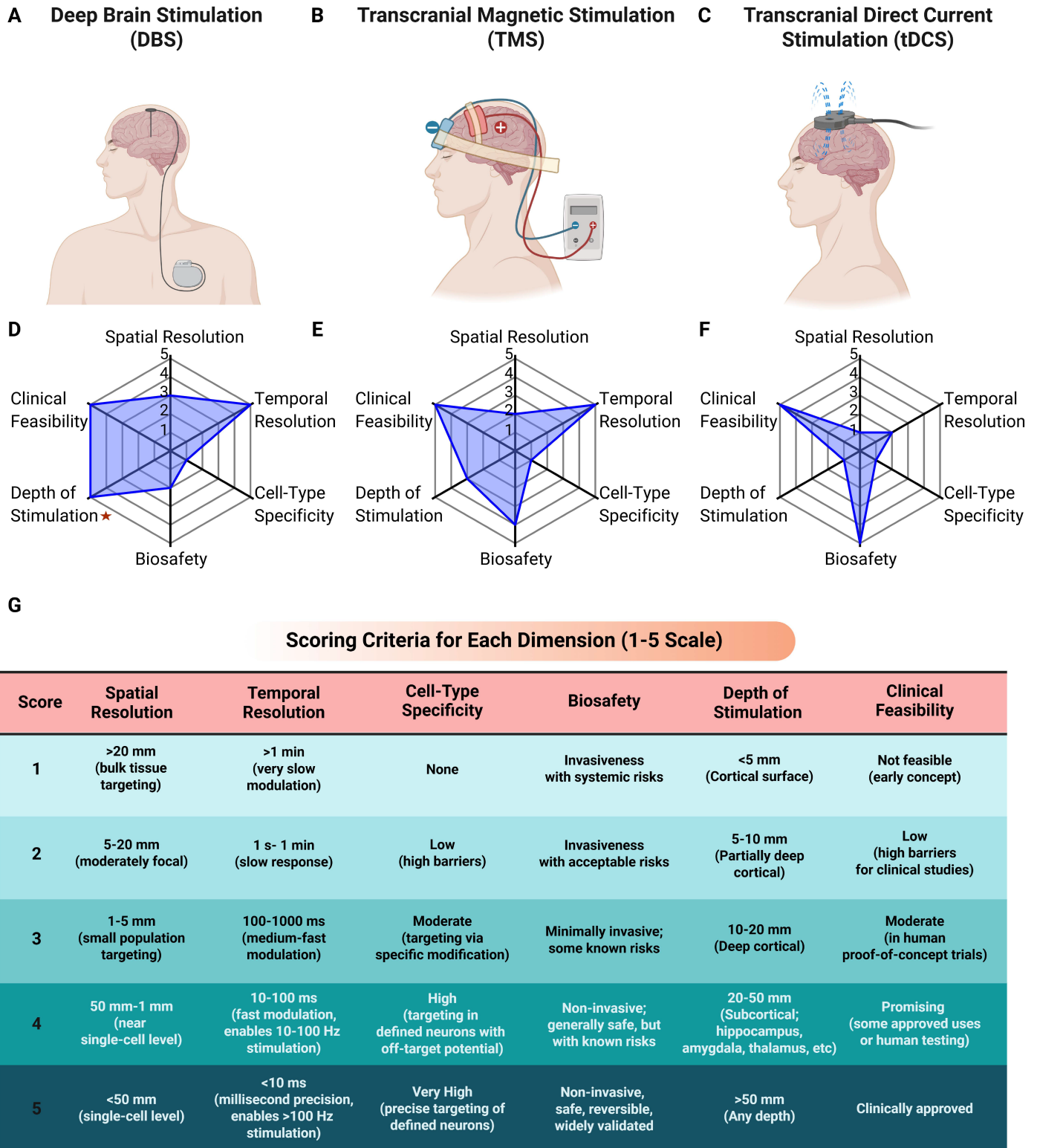


Figure 1. Summary and evaluation of the classical neuromodulation techniques (A) DBS involves the surgical implantation of electrodes into specific regions of the brain, such as the subthalamic nucleus and the globus pallidus. These electrodes are connected to a pulse generator that emits continuous or responsive electrical impulses to modulate neural activity. (B) TMS is a non-invasive neuromodulation technique that uses time-varying magnetic fields to penetrate the cerebral cortex and induce electrical currents, thereby modulating neural activity. (C) tDCS is a non-invasive neuromodulation technique that modulates the excitability of the cerebral cortex. This modulation is achieved through the placement of electrodes on the scalp and the delivery of a weak direct current through them. Anodal (positive) stimulation typically facilitates the activation of neurons, increasing their excitability, while cathodal (negative) stimulation may decrease neural excitability. (D-F) Evaluation of DBS (D), TMS (E), and tDCS (F) across six dimensions: spatial resolution, temporal resolution, cell-type specificity, biosafety, depth of stimulation, and clinical feasibility. *Note: For DBS, depth of stimulation is assessed based on invasive access, unlike other non-invasive methods. (G) Scoring criteria for each dimension. The figure was created using BioRender.

these technologies hold promise for future interventions that precisely modulate dysfunctional circuits with high specificity, minimal invasiveness, and reduced side effects.

Principles and applications of genetics-based neuromodulation techniques

Optogenetics. Optogenetics integrates genetic engineering with optical

Table 1. Comparative evaluation of classical neuromodulation techniques.

Dimension	DBS	TMS	tDCS
Spatial resolution	~2 mm radius (~4 mm diameter) around the electrode. Current spreads over several millimeters, limiting single-neuron targeting precision. ^{30,31}	~15 mm focality using standard figure-8 coil. Typically targets ~1–2 cm cortical regions; focality varies with coil shape and intensity. ^{20,21,32,33}	Broad (~50–70 mm) due to use of large sponge electrodes. High-definition tDCS improves resolution but remains less focal than DBS and TMS. ³⁴
Temporal resolution	Millisecond precision. Delivers high-frequency pulses (e.g., ~60–100 μ s pulse width at ~130–185 Hz). Adaptive DBS allows closed-loop modulation. ^{19,31,35}	Millisecond precision. Single-pulse TMS achieves ~100 μ s resolution. Repetitive protocols vary (typically 1–20 Hz). ^{20,32,33}	Low temporal resolution. Effects accumulate over seconds to minutes. Lacks precise onset/offset control. ²⁷ Some studies report effects at ~100 ms scale. ³⁴
Cell-type specificity	None.	None.	None.
Biosafety (invasiveness & risks)	Invasive. Involves neurosurgery with associated risks (infection, hemorrhage, lead migration). Long-term safety generally well-documented. ³⁶	Non-invasive. Considered safe with low risk; rare reports of seizures in vulnerable populations. ³⁷ Standard coils reach ~20 mm depth; deep TMS (H-coil) extends to ~50 mm. Cannot access deep structures as directly as DBS. ^{38,39}	Non-invasive. Well-tolerated with minimal side effects (e.g., mild scalp discomfort, itching, redness). ²⁷
Depth of stimulation	Capable of directly reaching deep brain nuclei and subcortical targets invasively.		Most current is limited to surface cortex; ineffective for deep brain targets. ²⁷
Clinical feasibility	Clinically approved. Widely used in movement disorders (e.g., Parkinson's disease) and certain psychiatric conditions; well-established protocols.	Clinically approved for depression; used extensively in both research and clinical settings.	Clinically approved. Low-cost, portable, and suitable for outpatient or at-home therapy; increasingly used for cognitive enhancement and rehabilitation.

control to modulate neuronal activity using light-sensitive ion channels or pumps such as Channelrhodopsin-2 (ChR2) for depolarization and Halorhodopsin (NpHR) for hyperpolarization. When expressed in specific neurons, these opsins enable temporally precise activation or inhibition upon illumination with wavelength-specific light (Figures 2A-B).⁵

Optogenetics is unparalleled in its temporal resolution (millisecond-scale) and spatial precision (single-cell or even subcellular resolution), owing to continual advancements in optical hardware. Tools such as implantable optical fibers, gradient index (GRIN) lenses, and wireless micro-LEDs enable deep-brain photo-stimulation in freely moving animals with submillimeter targeting and millisecond precision.^{41,42} Additionally, holographic two-photon stimulation systems support three-dimensional, patterned activation of multiple neurons simultaneously, allowing for cellular and circuit-level interrogation.⁴³ Parallel progress in opsin engineering has yielded variants with accelerated kinetics and red-shifted activation spectra, enabling high-frequency stimulation (≥ 100 Hz) with sub-millisecond spike timing and enhanced penetration through brain tissue due to reduced scattering.^{5,44,45}

Optogenetics has been used to dissect neural circuits involved in fear memory, sleep, reward, and locomotion.^{46,47} Clinically, a landmark study demonstrated partial visual restoration in a blind patient with retinitis pigmentosa using optogenetic therapy.⁴⁸ Despite these breakthroughs, clinical translation remains limited by the need for invasive gene delivery and challenges in delivering light to deep brain structures, often requiring surgically implanted optical fibers.

Chemogenetics. Chemogenetics uses engineered receptors (e.g., Designer Receptors Exclusively Activated by Designer Drugs, DREADDs) that are activated by otherwise inert synthetic ligands (e.g., clozapine-N-oxide, CNO). Upon ligand binding, these GPCRs trigger excitatory or inhibitory intracellular signaling cascades that either excite or inhibit neuronal activity (Figures 2C-D).⁴⁹ Major limitations of chemogenetics involve slow onset due to pharmacokinetics, limited spatiotemporal control, and potential confounds arising from CNO metabolism to clozapine in humans.^{5,49}

While chemogenetics lacks the rapid kinetics of optogenetics, it enables prolonged modulation (minutes to hours), systemic delivery of ligands, and non-invasive reactivation. It has been widely applied to study motivation, learning, memory, epilepsy, and neurodegenerative diseases.^{6,50-53}

Magnetogenetics. Magnetogenetics aims for non-invasive control by using genetically encoded thermosensitive (e.g., TRPV1) or mechanosensitive proteins (e.g., Piezo1, TRPV4) that are activated by magnetic nanoparticles (MNPs) or magnetically sensitive protein fusions (e.g., ferritin⁵⁴).⁸ External magnetic fields generate local heating (magneto-thermogenetics⁵⁵⁻⁵⁷) or mechanical forces (magneto-mechanogenetics^{58,59}), leading to neuronal acti-

vation (Figures 2E-F). In addition to these established approaches, a third approach aims to simplify the configuration of magnetogenetics by using a polymeric magnetosensitive rod-shaped protein complex (Drosophila CG8198, iron chaperone ISCA1, or MagR).^{60,61}

A key advantage of magnetogenetics is deep tissue penetration without implants. However, reproducibility remains a major concern, especially with approaches such as MagR/ISCA1, whose mechanism remains debated.⁶² Additionally, concerns about the biosafety and delivery of magnetic nanoparticles and the efficiency of in vivo magnetic force transduction limit clinical readiness. Despite this, magnetogenetics represents a promising route for wireless, minimally invasive or noninvasive neuromodulation.

Sonogenetics. Sonogenetics uses focused ultrasound to stimulate neurons expressing mechanosensitive ion channels like TRPV1, MscL, Piezo1, or TRPA1 (Figures 2G-H).^{7,63,64} Ultrasound offers high penetration and can be focused on deep brain regions with millimeter-level resolution. Thus, sonogenetics enables remote, non-invasive neuromodulation without the need for implants. It has been used to modulate sensory, motor, and limbic circuits in various model organisms.⁷ Nonetheless, several challenges remain. Chief among them is the potential for off-target effects caused by activation of endogenous mechanosensitive proteins.⁶⁵⁻⁶⁸ Furthermore, the need to optimize ultrasound parameters to minimize thermal or mechanical tissue damage and the development of synthetic, highly specific sonosensitive actuators are ongoing areas of investigation.

Gene delivery strategies for genetics-based neuromodulation

The success of genetics-based neuromodulation techniques critically depends on the ability to deliver exogenous genes encoding actuator proteins into specific neuronal populations with high cell-type specificity.

Currently, Adeno-associated viruses (AAVs) and lentiviruses remain the most widely used vectors for delivering genes encoding optogenetic, chemogenetic, magnetogenetic, or sonogenetic actuators.^{69,70} These vectors enable long-term expression in neurons with relatively low immunogenicity. Cell-type specificity is enhanced by using specific promoters (e.g., CaMKII α , GAD67) or Cre-dependent systems. However, high viral titers may raise concerns about immune responses, expression stability, and unintended off-target expression.^{59,71,72}

Genome editing technologies such as CRISPR/Cas9 allow for stable and precise insertion of genetic constructs into the host genome, improving expression fidelity and enabling conditional activation in specific developmental or pathological states.⁷³ However, concerns remain about off-target effects, long-term genotoxicity, and ethical issues.⁷⁴

Efforts are also underway to develop non-viral platforms that minimize

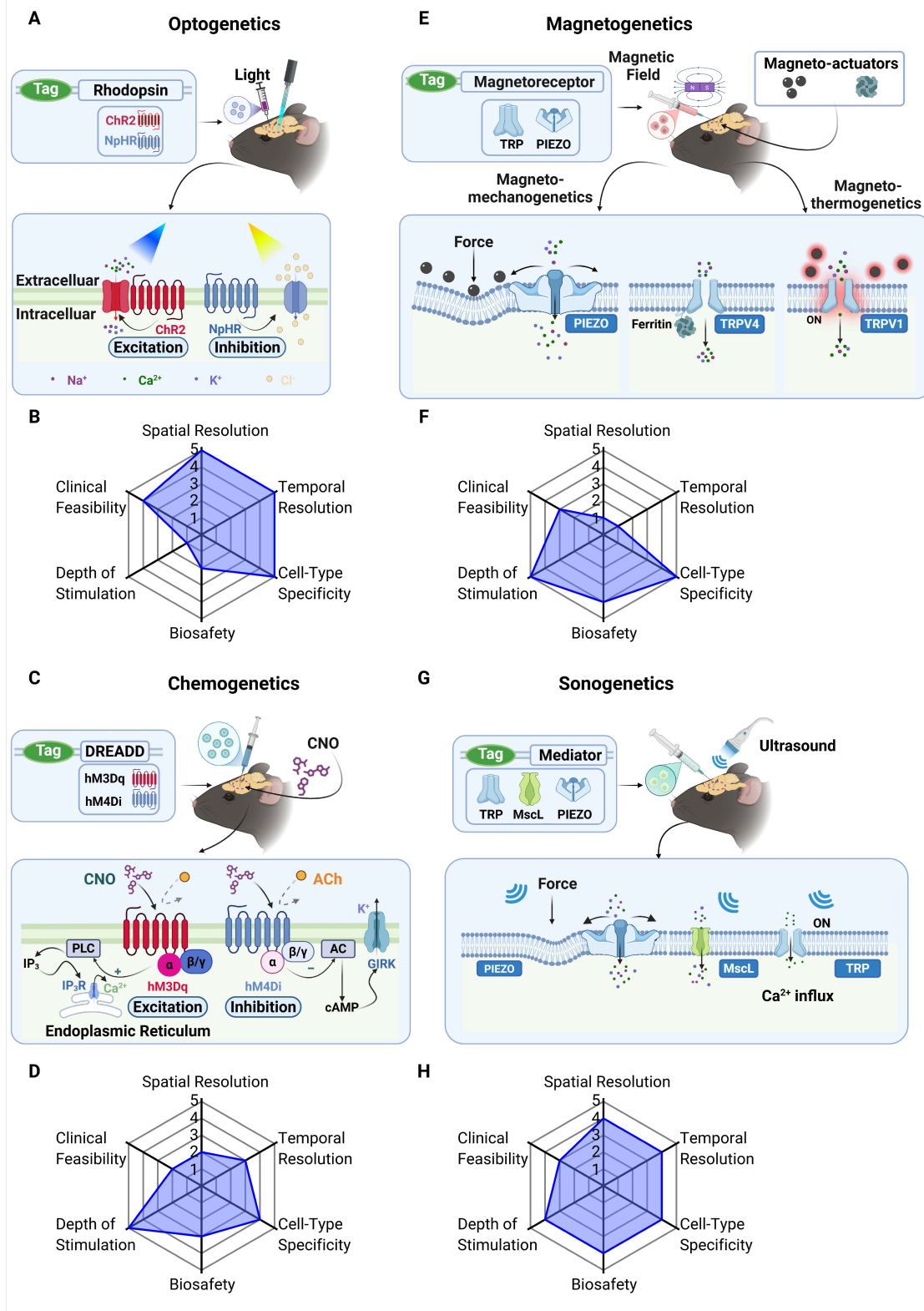


Figure 2. Summary and evaluation of genetics-based neuromodulation techniques (A) Optogenetics is a technique that employs light to achieve spatiotemporal control over neural activity. Genetic methods introduce light-sensitive proteins, such as Channelrhodopsin-2 (ChR2) and Halorhodopsin (NpHR), into target neurons. ChR2 is activated by blue light, allowing cation influx to depolarize the cell and trigger action potentials. Conversely, NpHR is activated by yellow light, enabling anion influx to hyperpolarize the neuron and silence its activity. (B) Evaluation of optogenetics. (C) Chemogenetics (DREADD) is a technique that combines genetic engineering with pharmacology. Neurons are engineered to express designer receptors (e.g., hM3Dq or hM4Di) that respond specifically to the ligand clozapine-N-oxide (CNO) while remaining unresponsive to endogenous acetylcholine (ACh). Upon CNO binding, hM3Dq activates the Gq protein signaling pathway, leading to phospholipase C (PLC) activation, production of inositol triphosphate (IP₃) and diacylglycerol (DAG), and the release of intracellular calcium. This cascade depolarizes the membrane and induces burst-like firing, effectively activating the neuron. Conversely, hM4Di activates the Gi protein-coupled inwardly rectifying potassium channel (GIRK), resulting in hyperpolarization and neuronal inhibition. (D) Evaluation of chemogenetics. (E) Magnetogenetics involves encoding magnetic nanoparticles or magnetic response proteins into target cells. The applied magnetic field induces magneto-thermal or magneto-mechanical effects that activate or inhibit ion channels, such as TRP or Piezo channels, on specific cells, enabling precision neuromodulation. (F) Evaluation of magnetogenetics. (G) Sonogenetics employs genetic engineering techniques to express ultrasound-sensitive proteins (TRP, PIEZO, and MscL channels) in target neurons, which can activate or inhibit specific cellular activities when these neurons are stimulated by ultrasound, thereby achieving precise regulation of neural activity. (H) Evaluation of sonogenetics. The figure was created using BioRender.

immune activation and enhance safety. Nanoparticles and liposomes capable of crossing the blood-brain barrier (BBB) offer promising routes for systemic and minimally invasive gene delivery. These technologies aim to improve the translational potential of genetics-based neuromodulation, especially for clinical applications requiring broader distribution or repeated dosing.⁷⁵

The choice of delivery route further influences the balance between precision and practicality. Stereotactic injection allows highly localized and circuit-specific expression, making it ideal for basic research. In contrast, systemic administration, particularly when combined with BBB-penetrating capsids or targeted ligands, offers a more clinically viable alternative. Additionally, retrograde transport vectors such as modified rabies virus or herpes simplex virus (HSV) have shown effectiveness in labeling and manipulating specific neural projections, expanding the toolkit for projection-specific circuit modulation.⁷⁶

MATERIALS-BASED TECHNIQUES

Clinically, implantable neurostimulators with specific material design (such as DBS electrodes) have been in use for decades. However, advancements in nanotechnology have led to the development of multifunctional materials that have transformed the field of neuromodulation.⁹ These materials, owing to their unique properties, offer various mechanisms to modulate neuronal activity, such as photothermal, photoelectric, and piezoelectric effects. Here we only discuss the novel material-based techniques that employ stimulus-responsive materials. This section is organized into subgroups based on the different effects exhibited by these materials.

Photothermal materials. Photothermal materials absorb light and convert it into localized heat, which activates thermosensitive ion channels and depolarizes neurons (Figure 3A). Gold nanorods, carbon nanotubes (CNTs), and NIR-absorbing polymer composites are common platforms. For instance, gold nanorods or nanoparticles modulate neuronal activity via targeted heating, while composite polymers achieve deep-brain stimulation in freely behaving mice using NIR-II light (1064 nm).^{77,78} Polydopamine-coated nanoparticles further support wireless stimulation.⁷⁹ These approaches have been applied to disorders such as Parkinson's disease and epilepsy.^{80,81}

Photoelectric materials. Photoelectric materials transduce light energy into electrical currents, mimicking natural neuronal activation through localized depolarization (Figure 3B). These include silicon-based bioresorbable diodes,⁸² azobenzene-modified small molecules,⁸³ and Au-TiO₂ nanowire arrays for vision restoration.⁸⁴ These systems offer millisecond temporal control and can be designed for transient therapeutic use.⁸⁵

Piezoelectric materials. Piezoelectric materials convert mechanical energy (typically ultrasound) into electrical signals that stimulate neurons (Figure 3C). Barium titanate nanoparticles (BTNPs) and lead zirconate titanate (PZT) are popular choices.^{9,86-90} Recent studies demonstrated ultrasound-triggered dopamine release from NO-piezoelectric hybrids in a mouse Parkinson's model.⁹¹ These materials allow deep, non-invasive stimulation with minimal thermal effects.

PHYSICS-BASED NEUROMODULATION TECHNIQUES

Recent advances in physics-based neuromodulation methods, particularly those leveraging infrared light (IR), focused ultrasound (FUS), and temporal interference (TI), have enabled non-genetic and non-material control of neural activity with high precision. These approaches rely on physical fields and forces to modulate excitability, offering rapid, reversible, and deep brain stimulation with minimal biological burden. Their high safety profile and flexibility make them attractive tools for both mechanistic studies and clinical interventions.

Infrared-based neuromodulation. Infrared-based neuromodulation utilizes light in the near- or mid- spectrum to influence neuronal excitability (Figure 4A).

Near-infrared (NIR, 0.78–2.5 μm) light modulates neurons via photothermal effects and possibly alters membrane capacitance, though the exact mechanisms remain under investigation.⁹²⁻⁹⁶ While effective, thermal buildup requires careful dose control. Additionally, functional near-infrared spectroscopy (fNIRS) enables hemodynamic monitoring, offering closed-loop opportunities.^{97,98}

Mid-infrared (MIR, 2.5–25 μm) light enables nonthermal neuromodulation,

addressing the heat-related limitations of near-infrared (NIR) stimulation. It has been demonstrated that 5.6 μm (53.7 THz) MIR can modulate neuronal activity via nonlinear resonance with bond vibrations at the potassium channel's selectivity filter, enabling ion channel-specific, nonthermal neuromodulation.⁹⁹ Subsequent studies confirmed both theoretically and experimentally that 7.05 μm (42.5 THz) light can selectively activate Ca_v channels, thereby inducing neuronal activation in a wavelength-dependent manner.¹⁰⁰ MIR-based neuromodulation has been used to modulate behavior in zebrafish, enhance learning and memory in mice, relieve neuropathic pain, and control optokinetic nystagmus in pigeons.¹¹ Its nonthermal, minimally invasive nature makes MIR a promising candidate for precision neuromodulation with clinical potential.

Focused ultrasound. Focused Ultrasound (FUS) delivers mechanical energy at frequencies of 250 kHz–25 MHz to modulate neural activity (Figure 4B). The primary mechanisms can be described in greater detail as: (1) activation of mechanosensitive ion channels, (2) thermal effects to activate the thermosensitive ion channels, (3) indirect neuromodulation mediated by astrocytes, and (4) modulation of the capacitance of the neuronal membrane. These mechanisms provide a comprehensive understanding of how ultrasound influences neural activity.^{63,68,101,102} FUS can both excite and inhibit brain circuits in a location-specific manner, as demonstrated in animal models.¹⁰³ High spatial precision is attainable with devices like the SOAP pad (resolution ~83 μm),¹⁰⁴ and FUS is already used clinically for essential tremor and under study for depression and epilepsy.^{63,101,105,106} It also enables neuromodulation in deep brain structures noninvasively, bridging fundamental research and translational potential.

Temporal Interference. Temporal Interference (TI) Stimulation offers a novel alternative to invasive deep brain stimulation. By overlapping two or more high-frequency electric fields at distinct frequencies, a low-frequency envelope is generated within deep brain regions, enabling targeted stimulation without affecting superficial cortex (Figure 4C).¹⁴ TI stimulation has been shown to enhance hippocampal function and memory in healthy humans and shows therapeutic promise for Parkinson's, epilepsy, and depression.¹⁰⁷⁻¹⁰⁹ While cell-type specificity is lacking, TI offers high temporal resolution and the unique advantage of deep, noninvasive stimulation using conventional electrode setups.

CROSS-DIMENSIONAL EVALUATION OF EMERGING NEUROMODULATION TECHNIQUES

The comparison is summarized in Table 2.

PRECISION NEUROMODULATION IN BASIC RESEARCH VS. CLINICAL PRACTICE

General differences of demands for precision neuromodulation

The pursuit of precision in neuromodulation is not a singular goal but one shaped by the divergent demands of basic research and clinical practice.

In basic neuroscience, precision enables causal mapping of neural circuits, dissecting how specific cell types and networks drive behavior, cognition, or pathology.¹²⁰ The emphasis is on mechanistic insight, requiring high spatial and temporal resolution, cell-type specificity with minimal off-target effects, and compatibility with circuit-level interrogation tools such as calcium imaging and electrophysiology.^{121,122}

In contrast, clinical neuromodulation prioritizes therapeutic effectiveness, safety, and scalability while minimizing side effects. Here, precision refers not only to anatomical targeting but also to the ability to adjust stimulation non-invasively and adaptively across patient populations. Clinical techniques must balance efficacy with biosafety, depth of stimulation, and long-term feasibility, even at the cost of reduced spatial or temporal resolution. Classical neuromodulation techniques (DBS, TMS, tDCS) have been highly effective but relatively coarse, stimulating bulk tissue regions.¹²³

Recent technical advances attempt to bridge this gap. For instance, directional DBS leads and adaptive DBS systems have enhanced spatial and temporal targeting while maintaining clinical reliability.^{35,124,125} Similarly, non-invasive brain stimulation methods such as TMS and tDCS are being refined to improve their depth and focus.^{38,40} However, current clinical approaches still fall short of the resolution and specificity routinely achieved in research

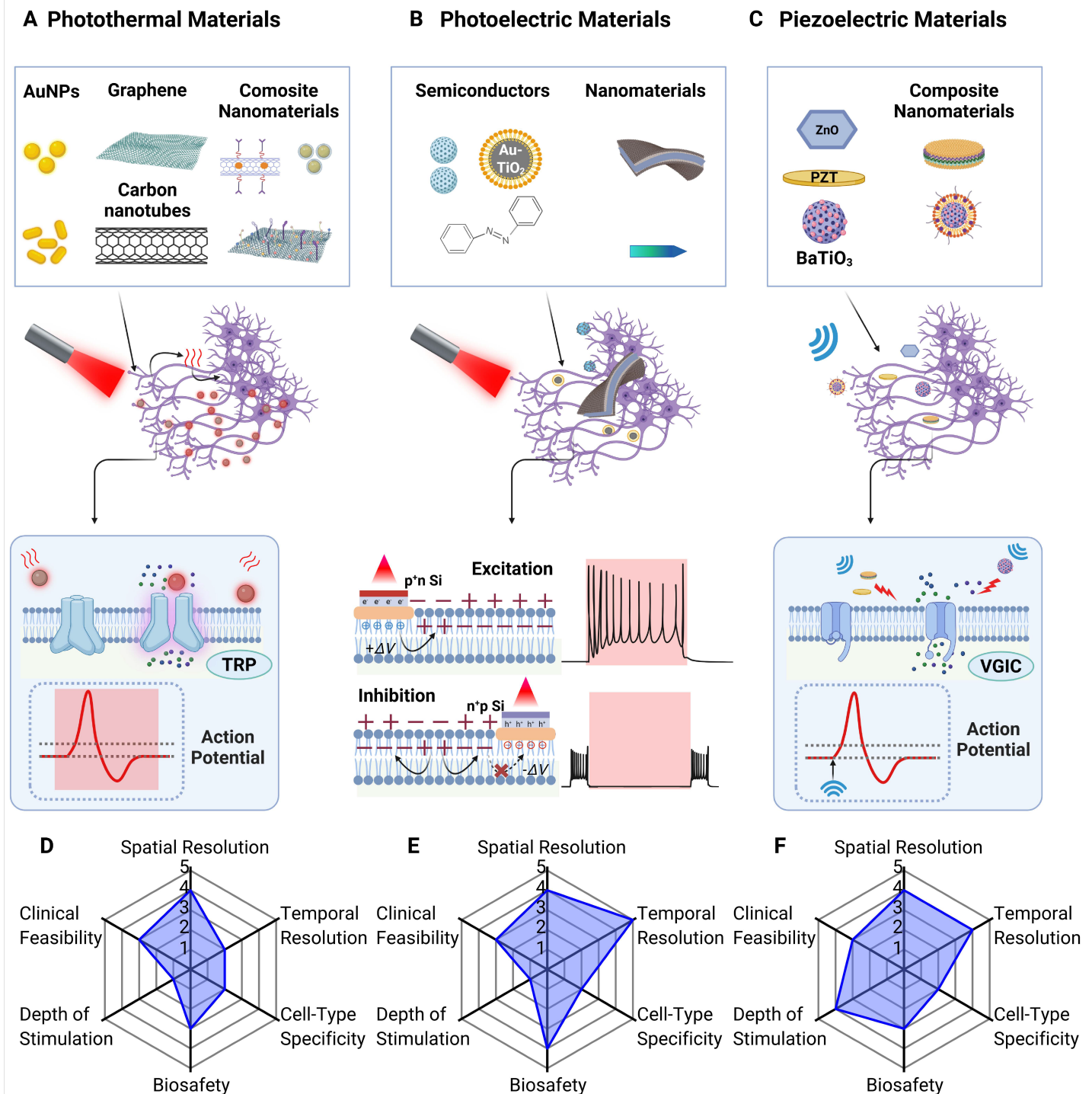


Figure 3. Summary and evaluation of the materials-based neuromodulation techniques (A) Photothermal materials, such as gold nanomaterials, carbon-based nanomaterials and composite nanomaterials, utilize photothermal effects to precisely control neural activity. When exposed to infrared light, they generate localized thermal energy, which activates temperature-sensitive ion channels (e.g., TRP channels). This activation leads to neuronal depolarization and action potential generation, enabling precision neuromodulation. (B) Photoelectric materials, including semiconductors and nanomaterials, are capable of converting light energy into electrical signals, which can be used to activate or inhibit neurons, providing a pathway for precision neuromodulation. (C) Piezoelectric materials, such as BaTiO₃ (barium titanate), PZT (lead zirconate titanate), and ZnO (zinc oxide), convert ultrasonic energy into electrical signals. These electrical signals can modulate neuronal activity through the voltage-gated ion channels (VGICs), providing a versatile approach to neuromodulation. (D-F) Evaluation of photothermal (D), photoelectric (E), and piezoelectric (F) materials. The figure was created using BioRender.

settings, underscoring the translational tension between precision and practicality.

Targeting neural circuits through precision neuromodulation

A fundamental goal of modern neuromodulation is to modulate specific neural circuits that underlie distinct functions and behaviors, rather than merely targeting individual neurons or broad brain regions. Neural circuits, comprising defined populations of interconnected neurons, serve as the

computational backbone of the nervous system and represent the most functionally meaningful unit for modulation in both basic research and clinical interventions.¹²⁰

In basic neuroscience, genetics-based approaches have facilitated unprecedented precision at the circuit level. For instance, Cre-dependent viral vectors combined with retrograde tracers (e.g., AAV-retro, canine adenovirus) allow bidirectional manipulation of pathways such as the hippocampal-prefrontal or thalamo-cortical circuits.¹²⁶ Optogenetic stimulation of an

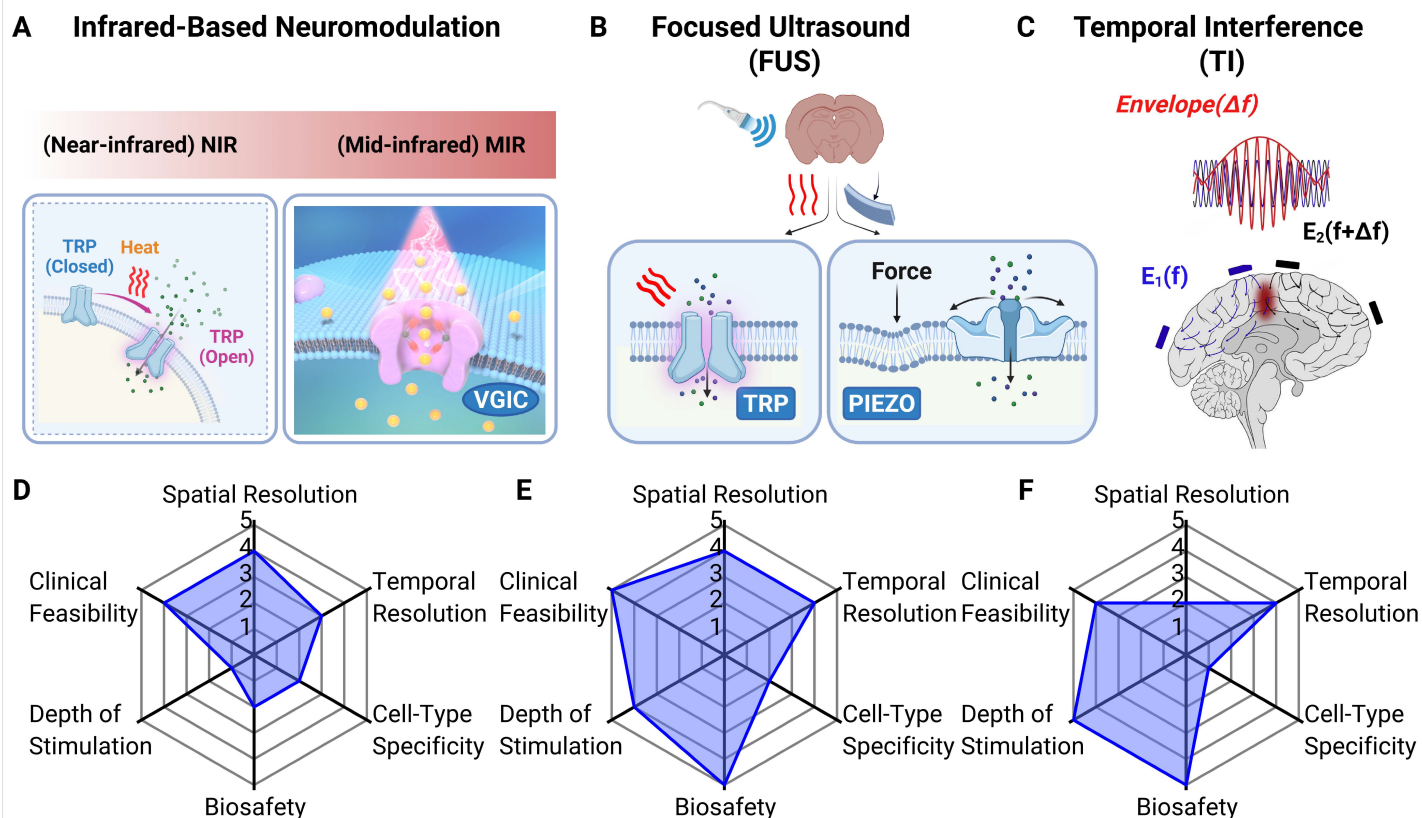


Figure 4. Summary and evaluation of the physics-based neuromodulation techniques (A) Infrared-based neuromodulation uses the unique properties of infrared light to influence neuronal activity. Near-infrared (NIR) stimulation activates neurons through a variety of mechanisms. One of the key mechanisms is its ability to activate temperature-sensitive ion channels, such as TRP channels. Mid-infrared (MIR) stimulation resonates with chemical bond vibrations at ion channel selectivity filters (e.g., K_v , Na_v , and Ca_v channels), enhancing ion permeability to non-thermally modulate neuronal activity.¹⁰⁰ Reprinted with permission from Sun et al. Copyright© 2024 Wiley - VCH GmbH. (B) Focused ultrasound (FUS) modulates neural activity through multiple mechanisms. Key mechanisms include modulating mechanosensitive ion channels (e.g., Piezo channels) and temperature-sensitive ion channels (e.g., TRP channels) via mechanical stress and thermal effects. FUS enables precise spatial targeting and non-invasive deep brain penetration, allowing for the activation or inhibition of neurons. (C) Temporal interference (TI) stimulation is a non-invasive deep brain stimulation method that delivers multiple high-frequency electrical fields through scalp-placed electrodes. While each field is too rapid to directly activate neurons, their intersection deep in the brain generates a low-frequency envelope capable of selectively modulating neuronal activity within targeted regions.¹⁴ (D-F) Evaluation of NIR/MIR (D), FUS (E), and TI (F) stimulation. Reprinted with permission from Grossman et al. Copyright© 2017 Elsevier. The figure was created using BioRender.

orbitofrontal cortex-to-dorsal striatum circuit has been shown to improve cognitive flexibility in mice with prefrontal dysfunction.¹²⁷ Similarly, optogenetic or chemogenetic stimulation of cortico-limbic pathways has been demonstrated to reverse depression-like behaviors in rodents, highlighting how targeting precise neural pathways can modulate mood circuits.¹²⁸ Moreover, sonogenetic activation of mechanosensitive ion channel-expressing ventral tegmental area (VTA) neurons has been found to increase nucleus accumbens dopamine levels and modify reward-related behaviors in mice.¹²⁹

In clinical research, direct targeting of neural circuits presents greater complexity. DBS often affects multiple interconnected pathways, not all of which contribute to therapeutic effects.¹³⁰ TMS has been proven to modulate abnormal functional connectivity across multiple cortico-cortical circuits in depression.¹³¹ Emerging physics-based methods, such as FUS and TI, offer high non-invasive spatiotemporal resolution, but without genetic targeting, they stimulate all neurons in the beam path, limiting circuit specificity.^{108,132}

Nevertheless, incorporating circuit-level insights into clinical neuromodulation holds immense potential. It could reduce side effects, increase efficacy, and align therapies more closely with disease mechanisms.¹³³⁻¹³⁵ Translating circuit-specific neuromodulation techniques from basic research to clinical applications holds the potential to revolutionize treatment strategies and improve patient outcomes.

Translating emerging neuromodulation techniques from lab to clinic

Genetics-based approaches: from lab to clinic. Genetics-based neuromodulation offers unrivaled cell-type and projection specificity, making it a powerful tool for modulating specific neural circuits or defined neuronal subtypes. Translating these genetics-based neuromodulation tools to the clinic is

underway, albeit gradually, via targeted gene therapies. Notably, an optogenetic therapy for retinitis pigmentosa has shown partial vision restoration in humans.⁴⁸ The retina provides a uniquely accessible CNS region, but translating optogenetics to the brain remains complex due to challenges in delivering genes and light to deep structures. Future strategies may involve combining gene delivery with implantable devices, such as opto-DBS systems tested in non-human primates.¹³⁶ Chemogenetic tools have shown promise in preclinical models of epilepsy and chronic pain.¹³⁷ However, the major challenge bottleneck still remains the efficient and targeted delivery of genetic material. One emerging strategy involves using focused ultrasound to transiently open the blood-brain barrier, thereby facilitating the delivery of viral or non-viral vectors.^{75,76} In addition to delivery challenges, genetic approaches must also address concerns related to viral vector immunogenicity, precise control of actuator expression levels, and the long-term persistence of transgene expression. Sonogenetics and magnetogenetics share similar issues, but offer non-invasive stimulation modalities. Among the two, sonogenetics is gaining more traction due to more consistent results and fewer controversies than magnetogenetics.⁶²

Once these challenges are addressed, genetics-based neuromodulation is expected to advance toward clinical trials for conditions inadequately treated by conventional therapies. Early applications will likely focus on localized, severe disorders like blindness, where targeted gene delivery is practical and the benefits of precision outweigh procedural complexity.

Materials-based approaches: from lab to clinic. Materials-based approaches have demonstrated their ability to transduce external energy into local stimuli in animal studies and hold the potential for targeting neural circuit through surface modifications or ligand-functionalized nanoparticles.

Table 2. Comparative Evaluation of Emerging Neuromodulation Techniques.

Dimension	Genetics-Based Neuromodulation				Materials-Based Neuromodulation			Physics-Based Neuromodulation		
	Optogenetics	Chemogenetics	Magnetogenetics	Sonogenetics	Photothermal	Photoelectric	Piezoelectric	NIR & MIR	FUS	TI
Spatial resolution	≈μm level. Single-cell precision with targeted light delivery. ¹¹⁰	>cm level. Broad modulation in receptor-expressing regions. ⁶	≈cm level. Regional activation; limited targeting precision. ⁵⁹	≈μm-mm level. FUS focal spot ~2 mm; can reach μm level with high frequency, at the cost of penetration depth. ^{111,112}	≈μm level. Lower than optogenetics due to the diffusive heat zone. ⁷⁷	≈μm level. Lower than optogenetics due to the limitation in nanorod or pixel scale. ^{113,114}	≈μm-mm level. Focus ultrasound alone produces a focal spot of roughly ~mm level in brain. But nanoparticles hold the potential to push the spatial resolution to sub-millimeter level. ¹¹⁵	≈μm level. Comparable to optogenetics. Hold the potential to achieve single-cell resolution. ⁹⁶	≈μm-mm level. Resolution can reach ~83 μm with advanced configurations. ¹⁰⁴	≈mm-cm level. TI stimulation creates an electric-field "hotspot" where two high-frequency currents interfere. The spatial resolution is coarser than invasive DBS or FUS. ¹⁰⁹
Temporal resolution	≈1-10 ms. Sub-10 ms control with fast opsins. ¹¹⁰	≈mins-hours. Slow onset and long duration. ^{6,49}	≈100 ms. Typically slower than optogenetics. Activation requires heating or mechanical force. ⁵⁹	≈100 ms. Typically slower than optogenetics. Activation of mechanosensitive channels may require tens to hundreds of milliseconds. ⁷	≈1 s onset due to the heat latency, seconds decay due to the slow heat dissipation. ⁷⁷	≈ms level onset and offset, comparable to electrodes. ^{82,113}	≈ms onset, depending on US and material setup. ^{86,91,115}	≈ms-second level. Sub-second for both NIR (photothermal) and MIR (nonthermal). ^{9,6,116}	≈100ms level. Described and discussed in sonogenetics. ¹⁰⁷⁻¹⁰⁹	Determined by the envelope frequency (e.g., 5-80 Hz demonstrated in humans). ¹⁰⁷⁻¹⁰⁹
Cell-type specificity	Very high. Only cells expressing the light-gated opsins respond to light, allowing very specific targeting of genetically defined neuron populations.	Very high. Similar to optogenetics.	Moderate. MNP targeting and endogenous channels limit specificity.	High. Similar to optogenetics, but pose the risks for off-target effects due to endogenous sonosensitive channels. ⁶⁵⁻⁶⁸	None inherently. Potential via thermosensitive channels overexpression or with ligand-functionalized nanoparticles. ^{77,117}	Typically none. Potential via functionalized nanoparticles. ¹⁷	None inherently. Potential with surface modifications or ligand-functionalized nanoparticles. ^{91,115}	Low. MIR may allow indirect cell-type targeting by selectively modulating specific ion channels or receptors. ¹¹	Low. Parameter tuning (duty cycle, intensity) can bias towards net excitation or inhibition of a region, but no cell-type exclusivity is achieved by FUS alone. ¹⁰³	None.
Biosafety	Requires gene delivery of opsins and typically an implanted fiber or LED for deep brain light delivery. High-power illumination can cause local heating. Long-term fiber implants can induce tissue reaction, but well-tolerated in animals.	Involves gene delivery, but no permanent implants are required. The ligands are often designed from FDA-approved drugs. However, care is needed with drug dosing and off-target metabolites. ⁴⁹	Involves gene and nanoparticle delivery. Nanoparticle safety remains a concern if used. Stimulation is remote and noninvasive via magnetic fields.	Involves gene delivery, but no permanent implants are required. Noninvasive ultrasound at low intensity is generally safe. ⁷	Minimally invasive (no permanent implant, just external light and injected nanoparticles). Risk of overheating; long-term nanoparticle accumulation. ^{11,8}	Minimally invasive. It avoids photothermal damage; bioresorbable materials and wireless options exist. ⁸²	Minimally invasive. Noninvasive low-intensity ultrasound is generally safe; ⁷ risk of long-term nanoparticle accumulation.	Invasive or minimally invasive. Low energy (≤0.5 J/cm ²) pulses caused no observable damage, while high energy pulse (0.8-1.0 J/cm ²) may induce damage. ⁹⁶	Noninvasive. FUS has shown a favorable safety profile in preclinical and human studies. ^{101,102}	Noninvasive. TI has been well-tolerated in recent human experiments without serious adverse effects. ¹⁰⁷⁻¹⁰⁹

Table 2. (Continued)

Dimension	Genetics-Based Neuromodulation				Materials-Based Neuromodulation			Physics-Based Neuromodulation		
	Optogenetics	Chemogenetics	Magnetogenetics	Sonogenetics	Photothermal	Photoelectric	Piezoelectric	NIR & MIR	FUS	TI
Depth of stimulation	≈1–2 mm. Limited by light penetration in tissue. Reaching deep structures requires invasive solutions (implanting optical fibers or micro-LED devices close to the target).	Not Limited. ligands reach deep targets via bloodstream.	Not Limited. Magnetic fields penetrate tissue freely.	≈mm to cm. Focused ultrasound can penetrate the skull and reach deep brain areas. Deep targets accessible with lower-frequency ultrasound. ¹¹¹	~1–5 mm tissue penetration with NIR. ⁷⁷ Reaching deep brain structures typically requires invasive implants.	~1–5 mm with visible light or NIR. ^{82,113} Reaching deep brain structures typically requires invasive implants.	High. Deep brain targets accessible via focused ultrasound. ⁹¹	~1–5 mm with NIR/MIR if without fiber implantation. Deeper penetration possible with implants.	High. Deep brain accessible; described and discussed in sonogenetics.	Any depth in principle. Deep brain accessible using surface electrodes and field interference. ¹⁰⁷
Clinical feasibility	Moderate to promising. Early clinical trials in retinal therapy, ⁴⁸ brain applications remain experimental due to the limitation of gene therapy and implants.	Moderate/Future potential. No human clinical applications of chemogenetics exist yet, but promising for future translation using drug-based delivery. ¹¹⁹	Low. Far from clinical use; further research is required to ensure reliable, safe activation in humans.	Moderate/Future Potential. While clinical trials are lacking, the approved use of focused ultrasound for brain stimulation suggests that sonogenetics could become clinically viable once gene delivery barriers are overcome.	Moderate. No clinical trials; requires improvement in thermal management and delivery strategies.	Moderate to promising. Especially for the non-thermal, wireless and bioresorbable neural interfaces.	Moderate to promising. Especially for noninvasive deep brain stimulation; blood-brain-barrier-crossing delivery shown feasible. ⁹¹	NIR is highly promising and has been tested in human cortex studies. ⁹⁶ MIR has not yet been evaluated in humans. ¹¹	FUS has been widely used in healthy and clinical populations. ^{102,106}	Highly promising. Demonstrated in healthy human brain; clinical applications remain experimental. ^{107,108}

These approaches do not require gene delivery, making them attractive for clinical translation. Moreover, the intrinsic properties of nanoparticles can substantially enhance the spatiotemporal resolution of external stimuli such as light, ultrasound, or magnetic fields, enabling more precise control over neural activity. However, implanted materials raise concerns about biosafety and long-term tissue compatibility. For nanoparticles, clearance and toxicity are major concerns, the body must be able to safely sequester or eliminate them after they have served their purpose. Bioresorbable stimulators (made of materials that dissolve after use) are being explored for temporary neuromodulation after injury or surgery, eliminating the need for removal surgery.⁸²

Despite these challenges, materials-based systems offer scalable precision and are increasingly integrated into therapeutic device development.⁹ While circuit-level targeting remains conceptually feasible through functionalized nanoparticle strategies, current experimental evidence supporting this application is limited. Substantial technological refinement is therefore required to realize this potential; without such advances, the comparative advantage of materials-based approaches may be diminished.

Physics-based approaches: from lab to clinic. Physics-based methods, including the NIR/MIR, FUS, and TI, offer the most immediate translational readiness due to their non-genetic and non-material nature. FUS has already entered clinical trials for conditions including essential tremor, depression, and Alzheimer's disease.^{102,103,106} TI and NIR stimulation have demonstrated brain modulation in human studies.^{96,107,108} Although MIR-based approaches are less clinically mature, they offer unique advantages in terms of spatial and temporal resolution. Importantly, MIR holds theoretical potential for achieving cell-type specificity without genetic manipulation. By exploiting the wavelength-dependent resonance with molecular vibrations of ion channels or receptors,¹¹ MIR may enable selective modulation of defined neuronal subtypes or specific neural circuits in a non-genetic and non-material manner. This distinguishing feature positions MIR as a rare candidate for achieving high-precision, circuit-level neuromodulation with minimal biological intervention.

Overall, physics-based techniques offer a favorable balance of safety and effectiveness, but improving their specificity and integrating them into closed-loop clinical systems will be essential for next-generation therapies.

STRATEGIC COMPARISON AND USE RECOMMENDATIONS OF NEUROMODULATION TECHNIQUES

This review provides a comprehensive analysis of a broad spectrum of neuromodulation techniques, ranging from classical approaches such as DBS, TMS, and tDCS to cutting-edge genetics-based, materials-based, and physics-based methods, evaluated across six key dimensions. For strategic comparison, we categorize all techniques along two complementary axes, actuator type and stimulation modality, to highlight their underlying mechanisms and application contexts. In addition, we offer brief use recommendations for each method, as summarized in Table 3.

Each modality is associated with specific advantages and limitations, which are concisely summarized in Table 4. Light-based techniques excel in spatial and temporal resolution but face challenges in achieving deep brain penetration and avoiding photothermal effects. Ultrasound-based methods achieve good spatial and temporal resolution with excellent penetration but are constrained by concerns such as stimulating dose and potential off-target effects. Electrical stimulation provides excellent temporal control but suffers from low spatial resolution and challenges in achieving non-invasiveness without sacrificing precision. Magnetic and drug-based modalities exhibit moderate to low spatial and temporal resolution but are highly safe and effective in penetrating deep brain regions.

Furthermore, the evaluation of actuators extends to their cell-type specificity for basic research and clinical feasibility, as detailed in Table 5. Genetics-based methods offer exceptional cell-type specificity but are hindered by limitations in gene delivery and moderate clinical feasibility. Materials-based techniques strike a balance, providing possibility in cell-type specificity and clinical feasibility, though challenges in material metabolism and biosafety

Table 3. Strategic comparison and use recommendation of neuromodulation techniques

Modalities Actuators	Light	Ultrasound	Electrics	Magnetics	Drugs
Genetics	Optogenetics (enables cell-type specific, millisecond-precision neural control; ideal for precise circuit mapping and potential targeted therapies.)	Sonogenetics (enables deep, non-invasive neuronal control; ideal for precision neuromodulation without implants.)		Magnetogenetics (enables wireless, cell-specific neuronal stimulation using magnetic fields; ideal for deep-brain neuromodulation without invasive hardware.)	Chemogenetics (enables targeted, long-lasting neuromodulation; ideal for chronic neurological and psychiatric conditions.)
Materials	Photothermal materials (enables non-contact stimulation through light-to-heat conversion; ideal for spatially confined neuromodulation.) Photoelectric materials (enables light-induced electrical activation of neurons; ideal for minimally invasive and spatially precise stimulation.)	Piezoelectric materials (enables ultrasound-triggered electrical stimulation through mechanotransduction, ideal for deep-brain modulation without direct electrodes.)			
Physics	NIR/MIR (enables contact-free infrared stimulation via wavelength-specific photothermal or nonthermal effects; ideal for spatially confined neuromodulation without implants.)	FUS (enables non-invasive stimulation of neural tissue; ideal for deep-brain targeting with high spatial precision in clinical applications.)	DBS (invasive, chronic electrical stimulation; ideal for deep-brain targets and medication-resistant neurological disorders) tDCS (enables weak, non-invasive current delivery across the scalp; ideal for stimulation of cortex) TI (enables non-invasive deep brain stimulation via overlapping high-frequency electric fields, ideal for modulating subcortical circuits without affecting the cortex.)	TMS (non-invasive, magnetic stimulation; ideal for superficial cortical modulation in clinical applications.)	

persist. Physics-based methods excel in clinical feasibility due to their non-invasive, non-genetic, and non-material nature but lack inherent cell-type specificity.

Together, it has become increasingly clear that no single method can satisfy all demands. Instead, each technique brings unique strengths and limitations, making it essential to strategically match methods to the demands of either basic research or clinical practice. These tables illustrate the trade-offs between precision, biosafety, and feasibility across neuromodulation modalities and actuator types.

CONCLUSION

The landscape of neuromodulation is rapidly evolving, transitioning from coarse, region-level interventions to increasingly precise, circuit- and cell-type-specific strategies. This review provides a comprehensive comparative framework that evaluates classical and emerging neuromodulation techniques across six critical dimensions. By categorizing methods by actuator types and stimulation modalities, we provide actionable insights for selecting the most suitable technique for either basic research or clinical applications. Genetics-based approaches excel in specificity but face delivery and safety challenges. Materials-based techniques offer non-genetic precision but require further validation in biosafety and targeting. Physics-based methods stand out for their non-invasive, clinically compatible features, though they currently lack cell-type specificity.

An emerging strategy to further enhance precision is the integration of neuromodulation with real-time neuroimaging to establish closed-loop feedback systems. By combining neural stimulation with simultaneous recording, these platforms enable dynamic, adaptive adjustments that optimize spatial,

temporal, and physiological precision.¹²⁵ Such closed-loop frameworks not only improve therapeutic efficacy but also provide a foundation for the next generation of brain-computer interfaces, where bidirectional communication between the brain and external devices can be achieved with high specificity and responsiveness.¹³⁸ While this review does not delve into such systems due to space constraints, they represent a crucial direction for advancing both basic circuit analysis and individualized therapeutic interventions.

In summary, the next frontier in precision neuromodulation lies not in pursuing a universal method, but in refining, combining, and deploying tools that meet the specific precision demands of neuroscience and the practical constraints of medicine. By embracing these complementary strategies, the field is well-positioned to develop individualized, mechanism-informed interventions that both reveal how the brain works and restore its function when it fails.

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Table 4. Comparative analysis of stimulation modalities.

Evaluation Modality	Spatial resolution	Temporal resolution	Biosafety	Depth of stimulation	Concerns
Light	Excellent (<10 µm with optics)	Excellent (<1 ms)	Moderate; challenging to achieve non-invasiveness without sacrificing precision	Low (if non-invasive); deeper access requires implantation	Photothermal effects; limitations in light delivery
Ultrasound	Good (µm-mm level)	Good (ms level, limited by responses of proteins)	Excellent; easily non-invasive when operated within safe parameters	Excellent; capable of targeting deep brain regions	Stimulating dose; potential off-target effects
Electrics	Low (mm-cm level)	Excellent (<1 ms)	Moderate; non-invasiveness is difficult without sacrificing precision (e.g., TI)	Excellent (invasive DBS, and non-invasive TI); or low (tDCS)	Implantation (DBS); off-target effects.
Magnetics	Moderate (cm level)	Good (ms level, limited by responses of proteins)	Excellent; non-invasive and well-tolerated	Excellent; unaffected by tissue depth	Limited stimulation efficacy; unclear mechanisms in some approaches
Drugs	Low (>cm level)	Low (minutes level)	Excellent; systemic delivery is safe and well-established	Excellent; wide distribution via bloodstream	Drug metabolism; off-target effects

Table 5. Comparative analysis of actuator types.

Evaluation Actuator Types	Cell-type specificity for basic research	Clinical feasibility	Note
Genetics	Excellent	Low	Restricted by gene delivery
Materials	Moderate	Moderate	Restricted by material metabolism and biosafety
Pure physics	Low	Excellent	Restricted by cell-type specificity

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Y.Y. and N.L. supervised the project and wrote the manuscript. Y.L. and Y.Y. created the figures. Y.L., X.S. and N.L. helped to revised the manuscript. All authors contributed to the final content and approved the submitted version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Not applicable

DATA AND CODE AVAILABILITY

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