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REVIEW

Electroceuticals in Neuromodulation: Mechanisms, Clinical Applications, and Future Directions

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ABSTRACT

Electroceuticals have emerged as an innovative therapeutic approach that employs targeted electrical stimulation to modulate neural circuits and restore physiological balance. Unlike conventional pharmacological treatments, which act through systemic biochemical pathways, electroceuticals enable precise spatial and temporal control of neural activity. The rapid proliferation of electroceutical devices across clinical and investigational settings, combined with accelerating advances in artificial intelligence, closed-loop engineering, and bioelectronic interface design, has generated an urgent need for rigorous, critically appraised synthesis to guide evidence-based clinical adoption and inform future research priorities. This review addresses the rapidly expanding field of bioelectronic medicine by providing a critical synthesis of existing data, moving beyond simple descriptions to analyze the scientific robustness and maturity of contemporary clinical and translational interventions. A literature search was conducted across electronic databases focusing on peer-reviewed articles published between January 2010 and March 2026. Articles were screened hierarchically by title, abstract, and full text to extract data regarding stimulation modalities, evidence levels, and therapeutic outcomes. Electroceuticals modulate neural function through mechanisms such as the regulation of neuronal excitability, synaptic transmission, neuroimmune signaling, and activity-dependent neuroplasticity. Established clinical evidence supports the therapeutic utility of deep brain stimulation for movement disorders and vagus nerve stimulation for drug-resistant epilepsy, while emerging, early-phase data suggest potential applications in neuropsychiatric and neuroinflammatory conditions. Advances in device engineering, including miniaturized implants, improved electrode biomaterials, and closed-loop stimulation systems, have enhanced treatment precision, though challenges regarding interpatient variability, tissue-device impedance mismatch, and translational scaling remain. Electroceuticals represent a structural shift toward circuit-based therapy in modern medicine. While technological and translational advancements continue to broaden their clinical reach, establishing standardized methodological frameworks, defining objective biomarkers, and balancing optimistic translational claims with evidence-based limitations are necessary steps to support widespread clinical adoption.

Keywords: Electric stimulation therapy, Neuromodulation, Neuroplasticity, Artificial intelligence

1. Introduction

Neuromodulatory electroceuticals represent a paradigm shift in therapeutic strategies for a wide range of chronic and complex diseases by leveraging precise electrical modulation of neural circuits rather than traditional pharmacological mechanisms. The term electroceutical, a synthesis of "electronic" and "pharmaceutical", was popularized in the early 2010s to describe therapies that use targeted electrical

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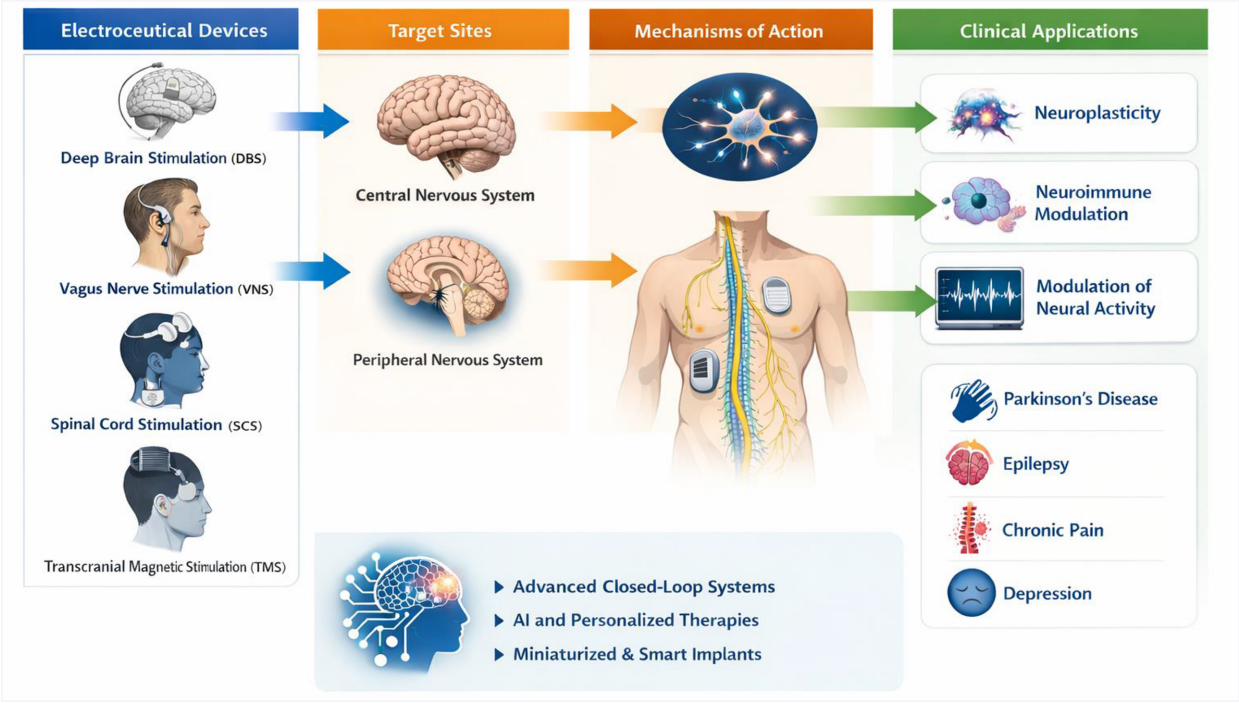

Fig. 1. Graphical overview of electroceuticals in neuromodulation.

impulses to regulate biological function at the level of neural signalling rather than systemic biochemical pathways [1]. Electroceuticals encompass a broad range of devices and techniques, from deep brain stimulation (DBS) and vagus nerve stimulation (VNS) to spinal cord stimulators, wearable neuromodulation systems, and emerging closed-loop technologies that collectively aim to correct dysfunctional neural circuits underlying pathological conditions [2] (Fig. 1).

The concept of using electricity for healing is not new; primitive applications of electrical stimulation were observed as far back as ancient Rome, and scientific interest in bioelectrical phenomena can be traced to Luigi Galvani's 18th-century demonstration that electrical currents could induce muscle contraction [3]. However, it was only with the advent of modern electronics, implantable devices, and an improved understanding of neural circuitry that electrical medicine matured into a clinically viable field with therapeutic precision [4]. In contrast to conventional pharmacotherapy, which often distributes drugs systemically and can cause widespread off-target effects, electroceuticals aim to modulate specific neural pathways that underlie disease mechanisms. By delivering controlled electrical stimuli to defined anatomical targets, such as the vagus nerve, subthalamic nucleus, or dorsal columns of the spinal cord, electroceuticals can influence physiological processes with high spatial and temporal resolution [5]. This localized modulation holds several theoretical advantages, including reduced systemic toxicity, real-time adjustability of treatment parameters, and the possibility of closed-loop control guided by physiological feedback signals [2].

The clinical application of electrical stimulation evolved substantially in the mid-20th century with the development of fully implantable devices. The first modern neurostimulation devices were applied for pain control, with Norman Shealy implanting the first prototype spinal cord stimulator in 1967, followed by Medtronic's commercial release in 1968. These systems evolved rapidly into treatments for movement disorders via DBS and for epilepsy through VNS, the latter receiving regulatory approval in the 1990s [6]. With advancing technology and accumulating clinical evidence, neuromodulation has expanded beyond symptom management toward potentially disease-modifying interventions that engage endogenous neuroplastic processes [7].

A key rationale for neuromodulatory electroceuticals arises from the recognized limitations of pharmacological therapies in treating disorders with neural circuit dysfunction. Conditions such as Parkinson's disease (PD), treatment-resistant depression, and chronic pain syndromes are frequently characterized by circuit-level dysregulation that is either insufficiently responsive or refractory to drug treatment. In such contexts, electrical stimulation offers

a means to directly influence dysfunctional neural activity and restore homeostatic function [1, 2]. Additional pharmacological limitations include off-target effects, poor blood–brain barrier (BBB) penetration, drug resistance, and interindividual variability in drug response [1].

Despite this promising landscape, important evidence gaps and translational challenges remain. The maturity of clinical evidence varies substantially across modalities and indications, and many emerging applications lack robust randomized controlled trial data. Furthermore, questions of long-term safety, optimal patient selection, and the mechanisms underpinning clinical benefit remain incompletely resolved. This review, therefore, aims not only to synthesize the current mechanistic and clinical landscape of electroceuticals but also to critically appraise the quality of existing evidence and highlight areas where further rigorous investigation is required. In the subsequent sections, we detail the neurobiological foundations, classifications, mechanisms of action, clinical applications, engineering advancements, and ethical and regulatory considerations that together define the current state and future trajectory of neuromodulatory electroceuticals.

2. Methodology

A literature search was performed using PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar databases to identify relevant peer-reviewed publications from January 2010 to March 2026. Search terms included combinations of keywords such as “electroceuticals,” “neuromodulation,” “deep brain stimulation,” “spinal cord stimulation,” “vagus nerve stimulation,” “responsive neurostimulation,” “transcranial magnetic stimulation,” “transcranial direct current stimulation,” “focused ultrasound neuromodulation,” “closed-loop stimulation,” “adaptive neuromodulation,” “bioelectronic medicine,” “neuroplasticity,” “brain–computer interface,” and “artificial intelligence in neuromodulation.” Boolean operators (AND, OR) were utilized to refine search combinations.

Studies were included if they were peer-reviewed, published in English, and addressed mechanisms of action, device engineering, clinical efficacy, or safety profiles of electroceutical interventions. Reviews, meta-analyses, randomized controlled trials, prospective cohort studies, and foundational preclinical studies were considered eligible. Conference abstracts, editorials without supporting data, and non-peer-reviewed sources were excluded. Duplicate results across databases were manually removed.

Given the narrative nature of this review, formal quality assessment tools were not applied systematically. However, study design, sample size, follow-up duration, and level of evidence were considered when interpreting findings. Throughout the manuscript, a deliberate effort has been made to distinguish between well-established clinical evidence, preliminary findings from early-phase or single-arm trials, and mechanistic insights derived primarily from preclinical models. The authors acknowledge that this approach is subject to inherent selection bias and that the review does not claim exhaustive coverage of all available literature.

3. Neurobiological basis of neuromodulation

A mechanistic understanding of neuromodulation requires a clear grasp of how electrical fields interact with neural elements at multiple scales, from ion channels and membrane potentials to synaptic networks and large-scale circuits. This section examines these interactions by exploring the electrical properties of neural tissue, the mechanisms by which applied electrical signals influence neurons and synapses, and the circuit-level consequences that underlie therapeutic electroceutical effects.

3.1. Electrical properties of neural tissue

Neurons maintain a resting membrane potential (~ -70 mV) through differential ion distributions, regulated by Na^+/K^+ ATPase pumps and voltage-gated ion channels. Voltage-gated Na_v and K_v channels determine neuronal excitability, shaping action potential speed, amplitude, and threshold. External electrical stimulation alters membrane potential, modulating channel gating states; efficacy depends on ion channel density, kinetics, and plasticity influenced by disease states [8]. Action potentials are triggered when depolarization reaches threshold, driving rapid Na^+ influx followed by K^+ efflux-mediated repolarization. Signal propagation velocity varies with axon diameter and myelination [9]. External electrical fields directly depolarize neural membranes, initiating action potentials without synaptic input, a principle underlying DBS for target activation or inhibition [10]. Chemical synaptic transmission initiates with presynaptic action potential arrival, triggering Ca^{2+} entry and quantal neurotransmitter release. Postsynaptic ligand-gated receptors generate excitatory/inhibitory potentials that integrate with intrinsic electrical activity, determining firing patterns and

network dynamics. This electrical-chemical interplay provides the substrate for neuromodulatory interventions [11, 12].

3.2. Mechanisms of electrical signal interaction with neurons

Applied electrical fields modulate neuronal excitability by depolarizing or hyperpolarizing membranes, thereby lowering or raising action potential thresholds depending on stimulation parameters (amplitude, duration, pulse shape) and ion channel states [8]. Electrical stimulation also alters presynaptic neurotransmitter release: high-frequency protocols elevate presynaptic Ca^{2+}, enhancing vesicle fusion and transmitter output per action potential, while others suppress release or bias excitatory-inhibitory balance to remodel aberrant circuits [11, 12]. Beyond acute effects, stimulation can induce long-term synaptic plasticity, either long-term potentiation (LTP) via high-frequency protocols or long-term depression (LTD) via low-frequency stimulation, through Ca^{2+} influx, AMPA/NMDA receptor trafficking, and downstream signalling cascades [12, 13]. These activity-dependent changes underpin durable therapeutic neuromodulation effects, although the clinical significance of individual mechanistic pathways remains an area of ongoing investigation.

3.3. Network and circuit-level effects

Neuromodulation can reshape pathological network states by altering neuronal firing patterns and connectivity. In Parkinson's disease, for example, subthalamic nucleus DBS is thought to reduce pathological beta-band oscillations and disrupt maladaptive synchrony, restoring more physiological basal ganglia–thalamocortical activity; however, the exact mechanisms linking network-level changes to clinical benefit remain an active area of research [14]. Neural circuits exhibit oscillatory patterns reflecting population synchrony, and dysregulated rhythms contribute to conditions such as epilepsy, depression, and chronic pain. Electrical stimulation may entrain or desynchronize these oscillations depending on frequency and target. Transcranial alternating current stimulation (tACS), for instance, has been shown in experimental studies to modify cortical synchrony, though the translation of these effects to consistent clinical benefit requires further validation [15]. Long-term neuromodulation may also drive lasting connectivity changes through synaptic plasticity and intrinsic excitability shifts, potentially enabling adaptive network rewiring in states of impaired plasticity [13, 16].

4. Classification of neuromodulatory electroceuticals

Neuromodulatory electroceuticals can be systematically classified according to degree of invasiveness, anatomical target, and mode of electrical or energy delivery. This classification is clinically relevant because therapeutic efficacy, safety profile, regulatory burden, and patient acceptance vary substantially across modalities. Broadly, neuromodulatory electroceuticals are grouped into invasive, minimally invasive/semi-implantable, and non-invasive systems, each occupying a distinct niche in contemporary bioelectronic medicine. Table 1 summarizes the principal neuromodulatory electroceutical modalities, their anatomical targets, key clinical indications, and proposed mechanisms of action.

4.1. Invasive neuromodulation techniques

Invasive neuromodulation involves surgically implanted electrodes that directly interface with central or peripheral neural structures. These approaches provide the highest degree of anatomical specificity and stimulation precision and are typically reserved for severe or treatment-refractory conditions.

4.1.1. Deep brain stimulation (DBS)

DBS is the most extensively studied and clinically established invasive neuromodulatory electroceutical. DBS involves stereotactic implantation of electrodes into specific deep brain nuclei, most commonly the subthalamic nucleus (STN), globus pallidus internus (GPi), or ventral intermediate nucleus of the thalamus (VIM), connected to an implantable pulse generator [18]. DBS is approved for and widely used in Parkinson's disease, essential tremor, and dystonia, with expanding investigational indications in neuropsychiatric disorders such as obsessive–compulsive disorder (OCD) and treatment-resistant depression. Mechanistically, DBS modulates pathological circuit dynamics, disrupts abnormal oscillatory activity, and reshapes information flow within distributed neural networks [14, 17]. A notable advantage of DBS is its programmability and reversibility, allowing stimulation parameters to be individualized and adjusted over time [36].

4.1.2. Spinal cord stimulation (SCS)

SCS involves implantation of electrodes in the epidural space, typically over the dorsal columns, to modulate ascending sensory pathways. SCS is primarily indicated for chronic neuropathic pain, including failed back surgery syndrome, complex regional pain syndrome, and ischemic limb pain. The gate control

Table 1. Classification and summary of neuromodulatory electroceutical modalities.

Modality	Invasiveness	Principal Anatomical Targets	Primary Clinical Indications	Primary Proposed Mechanisms	Source(s)
Deep Brain Stimulation (DBS)	High (Invasive)	Subthalamic Nucleus (STN), Globus Pallidus internus (GPi), Ventral Intermediate Thalamic Nucleus (VIM)	Parkinson's Disease, Essential Tremor, Dystonia, Obsessive-Compulsive Disorder (OCD)	Disruption of pathological oscillations (e.g., beta-band); modulation of basal ganglia-thalamocortical loops; high-frequency feed-forward inhibition.	[14, 17, 18]
Spinal Cord Stimulation (SCS)	High (Invasive)	Epidural space over the dorsal columns of the spinal cord	Chronic neuropathic pain, Failed Back Surgery Syndrome (FBSS), Complex Regional Pain Syndrome (CRPS)	Activation of large myelinated Aβ fibers to suppress nociceptive transmission via Aδ and C fibers; dorsal horn GABA/serotonin modulation.	[19, 20]
Vagus Nerve Stimulation (VNS)	Moderate (Invasive)	Cervical vagus nerve trunk (afferent and efferent axons)	Drug-Resistant Epilepsy, Treatment-Resistant Depression	Activation of the nucleus tractus solitarius; enhancement of norepinephrine and serotonin release; anti-inflammatory reflex activation.	[21–23]
Peripheral Nerve Stimulation (PNS)	Moderate (Invasive)	Localized peripheral nerve trunks (e.g., occipital, tibial nerves)	Localized neuropathic pain syndromes, headache disorders, overactive bladder	Afferent signaling modulation; localized sensory block; reduction of peripheral nociceptive excitability.	[24–26]
Transcranial Magnetic Stimulation (TMS)	Non-Invasive	Cortical tissue (e.g., Dorsolateral Prefrontal Cortex)	Major Depressive Disorder (MDD), localized cortical pain processing syndromes	Frequency-dependent induction of localized electrical currents; modification of cortical excitability and LTP/LTD plasticity.	[27, 28]
Transcranial Direct Current Stimulation (tDCS)	Non-Invasive	Cortical surfaces via scalp electrodes	Cognitive enhancement (investigational), stroke rehabilitation, mood disorders	Sub-threshold biasing of neuronal membrane potentials; modulation of cortical network excitability threshold.	[29, 30]
Transcutaneous Electrical Nerve Stimulation (TENS)	Non-Invasive	Superficial peripheral nerve paths	Acute and chronic pain management	Non-invasive peripheral activation of large-diameter afferents; segmental spinal inhibition of pain transmission.	[31, 32]
Focused Ultrasound Neuromodulation	Non-Invasive	Variable deep and superficial brain structures	Experimental target modulation, blood-brain barrier opening	Acoustic energy mechanical perturbation; alteration of mechanosensitive ion channels and endothelial tight junctions.	[33–35]

theory of pain historically explained the analgesic effects of SCS [20, 37]. However, contemporary evidence indicates more complex mechanisms involving modulation of dorsal horn excitability, descending inhibitory pathways, and supraspinal network effects [19]. Recent innovations such as high-frequency (10 kHz) stimulation and burst stimulation have improved efficacy, and SCS is considered a mature, evidence-supported clinical platform [38].

4.1.3. Vagus nerve stimulation (VNS)

VNS involves implantation of a cuff electrode around the cervical vagus nerve, delivering intermittent electrical impulses to modulate afferent and efferent vagal signalling. Initially approved for drug-resistant epilepsy, VNS is now also indicated for treatment-resistant depression and is under active investigation for inflammatory and cardiovascular disorders, applications that remain at earlier stages of clinical validation [21]. VNS exemplifies the concept of electroceutical modulation of systemic physiology, as vagal afferents project widely to brainstem nuclei and influence mood, autonomic balance, and immune regulation. The activation of the vagal "inflammatory reflex" positions VNS at the intersection of neuromodulation and immunotherapy, though much of the supporting mechanistic evidence derives from preclinical studies [22].

4.1.4. Peripheral nerve stimulation (PNS)

PNS targets specific peripheral nerves using implanted electrodes to modulate sensory or motor signalling. PNS is used for localized pain syndromes, headache disorders (e.g., occipital nerve stimulation),

and is being explored for functional rehabilitation. Compared with central neuromodulation, PNS offers greater anatomical selectivity and lower surgical risk [24]. Despite limited evidence from large randomized trials for several applications, advances in electrode miniaturization and ultrasound-guided implantation have expanded the clinical feasibility of PNS [25].

4.2. Minimally invasive and semi-implantable systems

4.2.1. Implantable pulse generators

Implantable pulse generators (IPGs) form the core of many invasive and semi-invasive neuromodulatory systems [39]. Technological evolution has produced smaller, longer-lasting, and MRI-conditional IPGs with rechargeable batteries and wireless programming capabilities. While many such advanced features remain under clinical evaluation, modern IPGs can support complex stimulation waveforms, adaptive algorithms, and closed-loop functionality, enabling real-time adjustment based on physiological feedback, [40].

4.2.2. Leadless and micro-implant devices

Leadless and micro-implant neuromodulation systems represent a technological advance aimed at minimizing complications associated with leads and surgical pockets. These devices can be wirelessly powered and controlled. While some leadless systems have achieved regulatory approval in cardiac pacing [41], their application in neuromodulation remains largely investigational, and the long-term safety and efficacy data needed to support widespread clinical adoption are still being established [26].

4.3. Non-invasive neuromodulation modalities

4.3.1. Transcranial magnetic stimulation (TMS)

TMS uses rapidly changing magnetic fields to induce electrical currents in cortical tissue. Repetitive TMS (rTMS) is FDA-approved for major depressive disorder and has demonstrated efficacy in several other neuropsychiatric and neurological conditions [28]. It modulates cortical excitability and plasticity in a frequency-dependent manner. However, evidence quality varies across indications, and the durability of therapeutic effects often requires ongoing maintenance treatment [27].

4.3.2. Transcranial direct current stimulation (tDCS)

tDCS delivers low-intensity direct current via scalp electrodes, subtly shifting neuronal membrane potentials without directly eliciting action potentials. Although its effects are more modest than invasive techniques, tDCS can bias cortical networks toward excitation or inhibition and facilitate plasticity [30]. Its low cost and portability have supported widespread exploratory use for cognitive enhancement, stroke rehabilitation, and mood disorders. However, variability in individual response, limited spatial specificity, and methodological inconsistencies across studies remain significant challenges for clinical standardization [29].

4.3.3. Transcutaneous electrical nerve stimulation (TENS)

TENS applies electrical stimulation through surface electrodes to activate peripheral nerves, primarily for pain relief. It represents one of the earliest and most accessible forms of electroceutical therapy. While TENS lacks the precision of implanted systems, evidence supports its utility in certain pain conditions, and it demonstrates how peripheral neuromodulation can engage central pain processing networks [31, 32].

4.3.4. Focused ultrasound neuromodulation

Although not purely electrical, focused ultrasound neuromodulation is increasingly discussed alongside electroceuticals due to its ability to modulate neural activity non-invasively with high spatial resolution. Low-intensity focused ultrasound can alter neuronal excitability and synaptic transmission. Its mechanisms and long-term safety profiles remain under active investigation, and clinical applications are predominantly at the exploratory stage [33, 34].

5. Molecular and cellular mechanisms of electroceutical action

At the molecular and cellular levels, electroceuticals exert their therapeutic effects by modulating neuronal excitability, synaptic signaling, neurochemical balance, and non-neuronal cellular responses. Unlike pharmacological agents that act through ligand–receptor interactions, electrical stimulation influences electrophysiological states, intracellular signaling cascades, and gene expression, resulting in both acute and long-term biological effects. This multiscale mode of action underpins the durability and adaptability of neuromodulation-based therapies. It is important to note, however, that many of the detailed molecular mechanisms described below derive primarily from preclinical studies and may not fully recapitulate the human disease context.

5.1. Neurochemical and neurotrophic effects

Neuromodulation alters neurotransmitter dynamics in ways that may relieve neurological and psychiatric

symptoms. In Parkinson's disease, DBS of the STN or GPi modulates basal ganglia–cortical circuits, with evidence suggesting enhancement of downstream dopaminergic signaling despite ongoing neurodegeneration [42]. VNS targets limbic and cortical regions, boosting locus coeruleus and dorsal raphe nucleus activity via nucleus tractus solitarius projections, acutely elevating norepinephrine and serotonin in prefrontal and limbic areas; chronic VNS has also been associated with increased BDNF expression and synaptic plasticity, contributing to its antidepressant effects [21, 43].

GABAergic modulation is thought to restore inhibitory control in epilepsy and movement disorders. Anterior thalamic nucleus DBS has been associated with enhanced hippocampal interneuron activity and reduced temporal lobe seizure severity in experimental models [44]. In Parkinson's disease and dystonia, GPi DBS may trigger GABA release from afferents, inhibiting hyperactive thalamocortical pathways, although the precise contribution of individual neurotransmitter changes to clinical outcomes remains incompletely characterized [45].

Neuromodulation may also upregulate neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF), via Ca^{2+}-dependent TrkB signalling, promoting synaptic growth and long-term plasticity [46]. Rodent studies of DBS in Parkinson's disease models have demonstrated elevations in striatal BDNF and TrkB expression, supporting neuroprotective hypotheses [47, 48]. However, whether such neurotrophic effects translate meaningfully to human clinical outcomes remains to be established through prospective clinical research.

5.2. Neuroimmune and neurovascular interactions

Electrical neuromodulation acts within a complex neuroimmune environment involving glial and immune cells. Stimulation can shift microglia from pro-inflammatory to neuroprotective phenotypes, thereby attenuating neuroinflammation. VNS activates the cholinergic anti-inflammatory pathway through α7-nicotinic acetylcholine receptors, suppressing NF-κB signalling and reducing pro-inflammatory cytokines while promoting anti-inflammatory mediators [21, 23]. These immunomodulatory effects may contribute to neuroprotection, although much of the mechanistic evidence remains preclinical.

Neuromodulation may also transiently influence BBB physiology. Experimental studies suggest that tDCS and focused ultrasound can temporarily alter endothelial signalling and tight-junction organization [35, 49]. The reproducibility, spatial precision, and long-term safety of such BBB modulation remain active areas of investigation and should not yet be extrapolated to clinical practice without supporting human data. Neuromodulation additionally affects neurovascular coupling: clinical imaging studies show region-specific perfusion changes with DBS and rTMS consistent with altered neuronal metabolism, though their direct contribution to therapeutic outcomes remains incompletely understood [46, 50].

6. Clinical applications of neuromodulatory electroceuticals

Neuromodulatory electroceuticals are applied across a range of neurological and psychiatric disorders, particularly where conventional pharmacotherapy shows limited efficacy or tolerability. Table 2 summarizes the clinical advantages, limitations, major risks, and key patient-selection considerations associated with currently available neuromodulatory modalities. Throughout this section, a deliberate distinction is drawn between modalities with established evidence from randomized controlled trials and those supported primarily by observational data or preliminary findings.

6.1. Movement disorders

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by bradykinesia, rigidity, tremor, and postural instability. Deep brain stimulation targeting the STN or GPi is a well-established therapy for patients with medication-refractory motor fluctuations and dyskinesias; randomized trials have demonstrated significant improvements in motor scores, reduced dopaminergic medication requirements, and enhanced quality of life compared with best medical therapy [53]. Emerging adaptive DBS systems that adjust stimulation based on beta-band local field potentials have shown encouraging results in early trials; however, their superiority over conventional DBS in large randomized comparisons remains to be conclusively established. Non-invasive approaches, including TMS, tDCS, and transcutaneous VNS (tVNS), have been explored for PD with preliminary evidence of modest cortical network modulation, though the clinical magnitude and durability of benefit require further characterization [61, 62].

Essential tremor represents another movement disorder in which neuromodulation has proven highly effective, with DBS of the ventral intermediate nucleus of the thalamus consistently reducing tremor severity and improving functional

Table 2. Comparative analysis of clinical maturity, advantages, and risks.

Modality	Maturity Level	Primary Advantages	Major Clinical Risks & Limitations	Patient Selection Considerations	Source(s)
DBS	Established Clinical	Reversible, highly programmable; significantly reduces motor fluctuations and medication dependence in PD.	Invasive surgical risks (1-2% hemorrhage risk); cognitive/mood changes (apathy, depression); high device and maintenance costs.	Medication-refractory motor complications; preserved cognitive function; strict neuropsychological screening required.	[51–53]
SCS	Established Clinical	Effective for localized neuropathic pain; modern high-frequency (10 Hz) paradigms eliminate paresthesia.	Lead migration or fracture; localized infection; potential loss of efficacy over time due to fibrotic encapsulatio.	Refractory neuropathic pain (e.g., FBSS, CRPS); positive response during a temporary stimulation trial phase.	[38, 54, 55]
VNS	Established Clinical	Broad systemic and central regulatory effects; progressive reduction in seizure frequency over time.	Surgical risks of neck implantation; voice alteration, cough, and dyspnea during stimulation pulses.	Drug-resistant epilepsy (focal or generalized) where surgical resection is contraindicated or has failed.	[21, 56]
RNS	Established Clinical	Highly specific, responsive, closed-loop mechanism; preserves eloquent cortex; low side-effect profile.	Invasive cranial surgery; requires extensive data review and optimization of automated algorithms.	Focal, drug-resistant epilepsy originating from up to two well-defined eloquent or bilateral seizure foci.	[57–59]
TMS	Established Clinical	Non-invasive; favorable safety profile; no surgical or anesthesia risks; effective for treatment-resistant MDD.	Transient scalp discomfort or headache; low but non-zero risk of inducing localized seizures; requires frequent visits.	Major depressive disorder that has failed to respond to at least one adequate antidepressant trial.	[28, 60]
tDCS	Experimental/ Investigational	Low-cost, highly portable; safe with minimal side effects (mild tingling or erythema).	High interpatient variability in response; limited spatial focaity and penetration depth; lacks standardized protocols.	Primarily investigated in clinical trials for neurorehabilitation, cognitive training, or adjunctive mood stabilization.	[29, 30]

performance across long-term follow-up studies [63]. For dystonia, DBS of the GPi produces clinically meaningful reductions in motor disability, particularly in primary generalized or segmental forms; however, clinical response is more variable in secondary or acquired dystonic syndromes, and patient selection criteria continue to evolve [64].

6.2. Neuropsychiatric disorders

Neuromodulation has expanded therapeutic options for refractory psychiatric disorders, though the strength of evidence varies considerably across applications. In Major Depressive Disorder (MDD), rTMS targeting the dorsolateral prefrontal cortex is an approved non-invasive therapy with demonstrated efficacy in patients who have failed conventional antidepressants; its favourable safety profile supports use as an adjunctive treatment [60]. Investigational use of DBS targeting the subcallosal cingulate has shown potential in open-label studies, but clinical outcomes remain variable, and optimal patient selection criteria are still being defined through ongoing trials [65].

For obsessive–compulsive disorder (OCD), DBS received a US Humanitarian Device Exemption in 2009 for treatment-refractory cases. Stimulation of the ventral capsule/ventral striatum or anterior limb of the internal capsule produces clinically meaningful symptom reductions in approximately 40–70% of carefully selected patients in available series, with long-term follow-up demonstrating sustained benefit in responders [66–68]. These estimates, however, are derived largely from single-centre experiences and may not reflect broader clinical populations. Evidence for neuromodulation in anxiety disorders is still emerging; preliminary studies with rTMS and VNS suggest potential benefit in subsets of treatment-resistant patients, but robust randomized clinical validation remains limited.

6.3. Chronic pain syndromes

Chronic neuropathic pain frequently remains refractory to conventional pharmacotherapy, affecting an estimated 25% of the global population [69]. Neuromodulatory electroceuticals have emerged as important therapeutic options in this context, with

analgesic effects largely attributed to modulation of neurotransmission and activation of descending inhibitory pathways consistent with the Gate Control Theory of Pain [54, 69].

SCS is a well-established therapy for chronic refractory neuropathic pain. Randomized controlled trials and systematic reviews support efficacy in conditions such as failed back surgery syndrome, complex regional pain syndrome, and painful diabetic neuropathy, with high-frequency (10 kHz) stimulation and closed-loop systems often achieving ≥50% pain reduction [55, 70]. Dorsal root ganglion stimulation (DRG-S), by targeting sensory ganglia responsible for dermatomal pain transmission, has demonstrated efficacy for localized neuropathic pain in randomized trials and is increasingly explored in combination strategies for complex pain syndromes [54]. Non-invasive approaches such as rTMS can reduce pain intensity through cortical modulation; however, effects are typically modest and transient, requiring maintenance protocols, and comparative effectiveness data remain limited [71].

6.4. Epilepsy and seizure disorders

Neuromodulation has become an important therapeutic strategy for drug-resistant epilepsy (DRE), which affects approximately 30% of individuals with epilepsy who fail conventional antiepileptic drugs [72]. Two major paradigms have emerged: open-loop neuromodulation and closed-loop responsive control [73].

VNS, approved in 1997, is an open-loop strategy with a substantial evidence base from controlled trials. Clinical studies report ≥50% seizure reduction in approximately 26–40% of patients within the first year, with efficacy often improving over longer follow-up periods [56]. Responsive neurostimulation (RNS), the first clinically deployed closed-loop brain stimulation system for epilepsy (approved in 2013), uses implanted electrodes to continuously record electrocorticographic activity and deliver stimulation upon detection of early epileptiform patterns [59, 74]. Long-term prospective studies demonstrate progressive seizure reduction, likely reflecting both acute interruption of abnormal activity and activity-dependent neuroplastic changes [57, 75]. This modality is particularly relevant for focal epilepsy where resective surgery is not feasible [58]. Emerging evidence also suggests potential benefits from targeting thalamocortical circuits or combining approaches in complex multifocal epilepsy, though large-scale comparative trials are needed to define their relative effectiveness [76–78].

6.5. Neurorehabilitation and neuroplasticity

Electroceuticals are increasingly integrated into neurorehabilitation strategies aimed at enhancing neuroplasticity and functional recovery after CNS injury. Non-invasive approaches such as TMS and tDCS, when combined with conventional physiotherapy, have shown benefit in motor recovery after stroke in several randomized trials; however, effect sizes are generally modest and patient selection criteria require further refinement [71].

Neuromodulation for functional restoration following spinal cord injury, including SCS-assisted facilitation of volitional movement, has generated encouraging proof-of-concept data in selected patients, but current evidence remains preliminary and insufficient to guide broad clinical implementation [69, 71]. Investigational applications of DBS in traumatic brain injury also warrant cautious interpretation, as existing data derive largely from small case series. Overall, the therapeutic rationale of these interventions lies in their ability to reshape maladaptive neuroplasticity, though continued rigorous evaluation is required to define the patient populations most likely to benefit and to establish cost-effectiveness [71].

7. Device engineering and technological advances

The evolution of electroceutical devices is profoundly shaped by advances in materials science, bioelectronics, and computational engineering. These modern systems aim to improve safety, efficacy, and usability through innovative electrode designs, energy solutions, and adaptive stimulation algorithms. Key emerging device technologies and the integration of artificial intelligence in neuromodulation systems are summarized in Table 3.

7.1. Electrode design and biomaterials

The electrode–tissue interface critically determines the efficiency, selectivity, and longevity of neuromodulation. Biocompatible materials such as platinum–iridium, titanium, and conductive polymers minimize inflammatory responses and fibrotic encapsulation that can increase impedance and reduce therapeutic efficacy over time [91]. Surface engineering strategies, including micro-roughening and coatings with conductive polymers such as PEDOT or hydrogel layers, enhance charge transfer and reduce electrochemical stress, particularly important in chronic implants such as DBS, SCS, and PNS [92]. Flexible and stretchable electrode systems have been developed to

Table 3. Summary of engineering innovations and AI integration.

Technology Area	Current Innovation	Functional Benefit	Unresolved Engineering/ Clinical Challenge	Source(s)
Advanced Biomaterials	Conductive polymers (PEDOT), hydrogel coatings, flexible thin-film metal elastomers.	Reduces electrochemical impedance; improves charge injection capacity; minimizes mechanical mismatch with soft neural tissue.	Long-term material degradation; risk of delamination or pinhole defects under chronic electrical stress in vivo.	[80–82]
Energy Management	Wireless inductive coupling, high-energy micro-batteries, experimental biomechanical harvesters.	Eliminates or extends the interval between surgical battery replacements; allows smaller device form factors.	Efficiency loss during transcutaneous power transfer; heat dissipation; early developmental stage of autonomous harvesters.	[83–85]
Closed-Loop Sensing	Local Field Potential (LFP) feedback, real-time electrocorticography (ECoG) sensing algorithms.	Shifts therapy from continuous to on-demand; reduces power consumption; minimizes overstimulation side effects.	Artifact filtering during simultaneous sensing and stimulation; identifying reliable, cross-patient electrophysiological biomarkers.	[86–88]
AI Parameter Optimization	Machine learning decoding models, Bayesian optimization, reinforcement learning.	Replaces manual trial-and-error parameter adjustment with dynamic, automated tuning of amplitude and frequency.	Computational latency; high power demands for on-device processing; lack of large-scale clinical validation for predictive models.	[89–91]

reduce mechanical mismatch with soft neural tissue [80], while emerging nanoengineered interfaces incorporating carbon-based materials such as graphene further enhance charge injection capacity and enable high-density electrode arrays [79]. Many of these advanced biomaterial approaches, however, remain at the preclinical or early clinical evaluation stage.

7.2. Power sources and energy management

Traditional electroceuticals rely on implantable batteries that necessitate careful balance between device size, operational longevity, and patient safety. Rechargeable batteries now support multi-year operation with wireless recharging, reducing surgical replacement burden [84]. Wireless power delivery through inductive coupling and resonant magnetic resonance allows further miniaturization and enables remote programming [82, 83]. Emerging energy-harvesting approaches using piezoelectric and triboelectric materials represent a promising but largely experimental area, with self-sustaining microimplants powered by biomechanical motion remaining a future goal rather than a current clinical reality [93].

7.3. Closed-loop and adaptive neuromodulation

Next-generation electroceuticals are moving beyond traditional open-loop stimulation by integrating sensing and closed-loop adaptive capabilities. These systems monitor neural and physiological signals in real time and modulate stimulation parameters accordingly [86, 87]. A well-studied example is adaptive DBS for Parkinson's disease, which adjusts stimulation based on beta-band oscillations; an initial randomized feasibility trial demonstrated improvements in motor control with reduced energy use compared with conventional stimulation, though definitive large-scale evidence is still accruing [85, 89]. Similarly, responsive neurostimulation for epilepsy and adaptive SCS for chronic pain represent established or emerging closed-loop platforms with growing clinical evidence bases [86]. Future devices incorporating AI and neuromorphic computing for real-time processing represent a paradigm shift in precision bioelectronic medicine, though their clinical deployment remains prospective [86, 87].

8. Artificial intelligence and precision neuromodulation

The integration of artificial intelligence (AI) into neuromodulation is an area of rapid development, with potential to transform how stimulation parameters are selected, adjusted, and individualized. It is important, however, to distinguish between AI applications with current clinical deployment and those that remain primarily in the research and development phase.

8.1. Machine learning in signal interpretation

Machine learning (ML) and AI are increasingly applied to decode complex neural signals and guide electroceutical therapies. Supervised, unsupervised, and deep learning models analyze high-dimensional

neurophysiological data such as electroencephalography (EEG), intracranial EEG (iEEG), electrocorticography (ECoG), and local field potentials (LFPs), to detect pathological oscillations, seizure precursors, or aberrant motor activity [94–96]. This enables earlier intervention and more targeted therapy. AI-driven predictive models integrating longitudinal neural, behavioural, and physiological data have shown promise in research settings; for example, ML algorithms have been developed to anticipate tremor severity or motor fluctuations in PD, and seizure prediction models have been explored for pre-emptive closed-loop stimulation [97, 98]. The translation of these research-grade tools into clinically validated, reliable systems for routine use remains an active area of development.

8.2. AI-driven optimization of stimulation parameters

Conventional neuromodulation relies on iterative, clinician-guided adjustment of stimulation parameters, a process that can be time-consuming and suboptimal [88]. AI-driven approaches aim to transform this process by integrating real-time neural feedback and biomarker trends to dynamically optimize amplitude, frequency, and pulse width [89]. Reinforcement learning and Bayesian optimization have been explored for adaptive DBS, with early studies suggesting improved motor outcomes with lower cumulative stimulation than fixed-parameter protocols; however, these findings are based on small-scale or feasibility trials and require confirmation in larger, controlled studies before clinical recommendations can be made [90]. Machine learning also shows promise in enhancing movement decoding from multi-channel cortical recordings, potentially reducing the need for frequent clinician intervention while maintaining therapeutic precision [95].

8.3. Brain–computer interfaces (BCIs) and hybrid systems

Hybrid systems integrating BCIs with electroceuticals represent an emerging frontier in neuromodulation. BCIs decode voluntary or pathological neural signals and translate them into commands for external devices or direct stimulation [99]. Current clinical applications remain limited but include motor BCIs in spinal cord injury and closed-loop seizure suppression systems [51]. These hybrid approaches hold considerable theoretical promise for enhancing therapeutic specificity and supporting functional recovery, but long-term clinical evidence from adequately powered trials is still limited, and the practical challenges of system reliability, patient burden, and regulatory approval remain substantial.

9. Safety, ethical, and regulatory considerations

The rapid expansion of electroceuticals into clinical practice and research necessitates careful evaluation of safety, ethical implications, and regulatory frameworks. While neuromodulation offers therapeutic advantages in treatment-refractory disorders, it carries unique risks and societal challenges that require multidisciplinary oversight.

9.1. Adverse effects and risk profiles

Invasive neuromodulation techniques such as DBS, SCS, and implantable VNS involve surgical intervention, exposing patients to risks including haemorrhage, infection, device migration, and hardware failure [89]. For DBS, haemorrhagic complications occur in approximately 1–2% of cases, with permanent deficits being uncommon but clinically significant [51]. SCS carries risks including lead displacement, wound infection, and inadvertent neural injury Beyond surgical risks, stimulation of central neural circuits can alter cognition, mood, or behaviour: subthalamic nucleus DBS in PD may precipitate depression, apathy, or impulse-control disorders in some patients, underscoring the importance of preoperative neuropsychological assessment and ongoing monitoring [52, 100]. Chronic stimulation may also induce unintended network remodelling, and long-term studies, particularly in paediatric populations or patients with early-stage neurodegenerative disorders, are needed to characterize such outcomes [101, 102].

9.2. Ethical issues in neuromodulation

Electroceuticals raise important ethical concerns regarding personal identity, autonomy, and cognitive liberty. Modulating mood, behaviour, or decision-making can impact selfhood, particularly in psychiatric or neuroenhancement contexts, requiring ethical frameworks that safeguard patient agency [103]. Informed consent is especially challenging when patients have impaired decisional capacity, as in severe depression or OCD, and must be treated as an ongoing process given the potentially transformative effects of chronic neuromodulation [104].

Neuroenhancement applications, using neuromodulation to improve cognition or motor function in healthy individuals, introduce further ethical

dilemmas, including concerns about equitable access, societal pressures, and the potential widening of social disparities [105, 106]. Direct-to-consumer neurotechnologies exacerbate these challenges by bypassing medical oversight, raising concerns about unvalidated claims and unforeseen risks [107]. Additional complexities arise in contexts such as addiction therapy or potential military applications, where coercion or dual loyalty may compromise voluntary and beneficent use [108, 109].

9.3. Regulatory pathways and clinical adoption

Electroceutical devices are regulated as medical devices, requiring evaluation of safety, efficacy, and manufacturing quality. In the United States, the FDA oversees premarket approval (PMA) or 510(k) clearance based on device risk classification, while in Europe, devices are evaluated under the Medical Device Regulation (MDR) framework [110]. For novel AI-driven and adaptive devices, regulatory frameworks are still evolving, and the absence of clear adaptive-device approval pathways represents a practical translational challenge. Post-marketing surveillance is essential for monitoring long-term safety and performance [110, 111]. High implantation and maintenance costs continue to limit accessibility, particularly in low- and middle-income regions, and cost-effectiveness analyses are needed to inform reimbursement policies and support equitable adoption [109].

10. Challenges and limitations

Despite remarkable progress, multiple scientific, technical, and translational challenges continue to limit the precision, efficacy, and broader adoption of electroceutical therapies. Addressing these limitations is critical to advancing bioelectronic medicine from proof-of-concept studies to widely applicable, patient-specific interventions.

10.1. Precision targeting of neural circuits

Precise modulation of pathological neural circuits remains a major challenge. Even with advanced imaging and stereotactic guidance, electrode placement deviations at the micrometre scale can reduce efficacy or induce off-target effects, as observed in DBS where minor misplacement may cause suboptimal symptom control or neuropsychiatric adverse effects [110]. Non-invasive techniques such as TMS and tDCS are further limited by penetration depth and focality, restricting selective modulation of deep structures. Emerging approaches including high-density electrode arrays, multi-contact leads, and computational electric-field modelling aim to enhance spatial precision, but inter-individual anatomical and connectivity variability complicates standardization [109]. Ethically, enhanced precision targeting also raises concerns about personal identity, cognitive liberty, and agency that must be addressed in parallel with technical development [111, 112].

10.2. Interpatient variability

Response to neuromodulation is highly heterogeneous, influenced by age, disease stage, genetic background, and neural plasticity. In Parkinson's disease, some patients achieve robust motor improvement with DBS while others experience minimal benefit despite accurate targeting [113]. In depression, rTMS efficacy varies due to differences in cortical excitability, network connectivity, and medication history [114]. Consequently, a "one-size-fits-all" approach to neuromodulation often leads to suboptimal outcomes, necessitating the development of personalized and adaptive stimulation strategies.

10.3. Long-term durability and device failure

Long-term durability and device reliability remain major challenges for implantable electroceuticals. Mechanical mismatch between rigid implants and soft neural tissues can induce chronic inflammation and micromotion, contributing to glial scarring, fibrotic encapsulation, increased impedance, and reduced stimulation efficiency [115, 116]. Material degradation through electrochemical corrosion, thin-film delamination, and electrode deterioration further compromises device longevity [117]. Battery limitations necessitate periodic surgical replacement. Emerging solutions, including wireless power transfer and energy-harvesting technologies, hold promise for extending device longevity, though their clinical implementation at scale requires further validation [118].

10.4. Translational gaps between preclinical and clinical findings

Despite valuable mechanistic insights from preclinical models, translating electroceutical therapies to humans remains challenging due to differences in brain anatomy, circuit organization, and disease heterogeneity [119]. Major gaps include scaling stimulation parameters from rodents or non-human primates, replicating complex behavioural and cognitive outcomes, and the limited availability of reliable

biomarkers to guide therapy. The lack of objective, quantifiable biomarkers forces parameter optimization to rely on empirical approaches. Bridging these gaps requires integrated approaches combining computational modelling, advanced imaging, and real-time neural monitoring [120]. Importantly, this review itself is subject to inherent selection bias as a narrative synthesis, and the evidence presented should be interpreted with the understanding that not all available literature was systematically reviewed.

11. Future directions and translational potential

Electroceuticals hold substantial promise for advancing precision medicine beyond conventional pharmacology, though realizing this potential will require addressing the mechanistic, technical, and clinical evidence gaps outlined in this review. Future directions appropriately focus on enhancing specificity, adaptability, and patient-centricity, leveraging advances in materials science, bioelectronics, AI, and clinical neuroscience. Innovations in electrode design are expected to enable higher-resolution, multichannel stimulation with improved chronic stability and reduced tissue reactivity. Wireless, minimally invasive micro-implants may broaden accessibility and reduce surgical burden, though realizing these goals will require demonstration of long-term safety and efficacy in clinical trials. The integration of AI and closed-loop sensing holds promise for predictive, adaptive modulation that dynamically adjusts to disease state; however, the development of clinically validated, regulatory-cleared AI-driven systems represents a substantial translational challenge that current early-phase data do not yet resolve.

Emerging applications in neurodegenerative diseases (e.g., Alzheimer's disease, Huntington's disease), neuroinflammatory and autoimmune disorders, and treatment-resistant psychiatric conditions are at varied stages of clinical investigation, and the evidence base for most of these applications remains preliminary. Digital health integration through smartphone connectivity, cloud analytics, and telemedicine offers opportunities for remote monitoring and large-scale data collection, though data governance, privacy, and regulatory frameworks for such systems require careful development.

Translational success will require bridging preclinical–clinical gaps through multi-scale modelling, advanced imaging, and biomarker-guided interventions; ensuring cost-effectiveness and equitable access across healthcare settings; harmonizing regulatory pathways for adaptive and AI-driven devices; and maintaining robust ethical oversight regarding cognitive liberty and patient autonomy. Multidisciplinary collaboration among neuroscientists, engineers, clinicians, ethicists, and policymakers is essential to translate these innovations into therapies that are safe, effective, and widely adoptable.

12. Limitations

This review has limitations that should be considered when interpreting its findings. As a narrative review, although a comprehensive literature search was conducted, the possibility of omitting relevant studies cannot be completely excluded. Also, the evidence base for many electroceutical interventions remains heterogeneous, with substantial variation in study design, patient populations, stimulation parameters, outcome measures, and follow-up duration, limiting direct comparisons across studies. Furthermore, several emerging technologies discussed in this review are supported primarily by preclinical investigations or early-phase clinical trials, and therefore, their long-term efficacy, safety, and real-world applicability remain uncertain.

13. Conclusion

Electroceuticals are transforming modern medicine by enabling precise, adaptive, circuit-targeted interventions that complement or surpass conventional pharmacotherapy. Advances in device engineering, bioelectronic interfaces, closed-loop systems, and AI-guided optimization have demonstrated efficacy across movement disorders, neuropsychiatric conditions, chronic pain, epilepsy, and neurorehabilitation. Key challenges remain, including precision targeting, interpatient variability, long-term device durability, and bridging preclinical-clinical translational gaps. Ethical, safety, and regulatory considerations are critical, especially as AI and hybrid brain–computer interface systems are integrated into therapy. The convergence of bioelectronics, computational neuroscience, and digital health promises expanded efficacy, personalization, and accessibility. Future research should prioritize: (i) development of validated, objective biomarkers to guide patient selection and adaptive parameter optimization; (ii) large-scale, multicenter randomized controlled trials for emerging indications such as treatment-resistant psychiatric disorders and neuroinflammatory conditions; (iii) harmonized regulatory frameworks that address the unique adaptive and AI-driven characteristics of next-generation devices; and (iv) cost-effectiveness

and equity analyses to support accessible implementation across healthcare settings. With continued interdisciplinary collaboration among neuroscientists, engineers, clinicians, ethicists, and policymakers, and with rigorous translational research grounded in clinical evidence, electroceuticals are poised to become a cornerstone of next-generation precision medicine, redefining treatment strategies for complex neurological and systemic disorders.

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The authors declare that there is no conflict of interest.

Ethical statement

Not applicable.

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References

1. Jung B, Yang C, Lee SH. Electroceutical and bioelectric therapy: Its advantages and limitations. *Clin Psychopharmacol Neurosci*. 2023 Feb 28;21(1):19–31. doi:10.9758/cpn.2023.21.1.19.
2. Mishra I, Chaudhary K, Sharma V, Krishna G, Mishra R. Electroceuticals: Unlocking the promise of therapies. *DARU J Pharm Sci*. 2024 Dec 19;33(1):7. doi:10.1007/s40199-024-00549-4.
3. Mishra S. Electroceuticals in medicine – the brave new future. *Indian Heart J*. 2017 Sep 1;69(5):685–6. doi:10.1016/j.ihj.2017.10.001.
4. Garg I, Verma M, Kumar H, Maurya R, Negi T, Jain P. Bioelectronic therapeutics: A revolutionary medical practice in health care. *Bioelectricity*. 2025 Mar 18;7(1):2–28. doi:10.1089/bioe.2024.0039 PubMed PMID: 40342937; PubMed Central PMCID: PMC12054615.
5. Ziesel D, Nowakowska M, Scheruebel S, Kornmueller K, Schäfer U, Schindl R, *et al.* Electrical stimulation methods and protocols for the treatment of traumatic brain injury: A critical review of preclinical research. *J NeuroEngineering Rehabil*. 2023 Apr 25;20(1):51. doi:10.1186/s12984-023-01159-y.
6. Due B, Farooq Anwar M, Vorenkamp K. Electrical neuromodulation – past, present, and future directions. *ASRA News*. 2022 Aug 1;46(3). doi:10.52211/asra080122.031.
7. Gkintoni E, Vassilopoulos SP, Nikolaou G, Vantarakis A. Neurotechnological approaches to cognitive rehabilitation in mild cognitive impairment: A systematic review of neuromodulation, EEG, virtual reality, and emerging AI applications. *Brain Sci*. 2025 May 28;15(6):582. doi:10.3390/brainsci15060582.
8. Ye H, Hendee J, Ruan J, Zhirova A, Ye J, Dima M. Neuron matters: Neuromodulation with electromagnetic stimulation must consider neurons as dynamic identities. *J NeuroEngineering Rehabil*. 2022 Nov 3;19(1):116. doi:10.1186/s12984-022-01094-4.
9. Grider MH, Jessu R, Kabir R. Physiology, Action potential. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2026 Feb 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK538143/PubMed PMID: 30844170.
10. Balbinot G, Milosevic M, Morshead CM, Iwasa SN, Zariffa J, Milosevic L, *et al.* The mechanisms of electrical neuromodulation. *J Physiol*. 2025 Jan;603(2):247–84. doi:10.1113/JP286205.
11. Borroto-Escuela DO, Gonzalez-Cristo E, Ochoa-Torres V, Serra-Rojas EM, Ambrogini P, Arroyo-García LE, *et al.* Understanding electrical and chemical transmission in the brain. *Front Cell Neurosci*. 2024 Jun 26;18:1398862. doi:10.3389/fncel.2024.1398862.
12. Wang B, Dudko OK. A theory of synaptic transmission. *eLife*. 2021 Dec 31;10:e73585. doi:10.7554/eLife.73585.
13. Tan X, Zhong Y, Li R, Chang C. Neuromodulation of chemical synaptic transmission driven by THz photons. *Research*. 2022 Jan;2022:0010. doi:10.34133/research.0010.
14. McIntyre CC, Anderson RW. Deep brain stimulation mechanisms: The control of network activity via neurochemistry modulation. *J Neurochem*. 2016 Oct;139(S1):338–45. doi:10.1111/jnc.13649.
15. Sveva V, Mancuso M, Cruciani A, Casula EP, Leodori G, Selvaggi SA, *et al.* Cellular and molecular mechanisms of non-invasive brain stimulation techniques: A systematic review on the implications for the treatment of neurological disorders. *Cells*. 2025 Dec 15;14(24):1996. doi:10.3390/cells14241996.
16. Cao H, Shang L, Hu D, Huang J, Wang Y, Li M, *et al.* Neuromodulation techniques for modulating cognitive function: Enhancing stimulation precision and intervention effects. *Neural Regen Res*. 2026 Feb;21(2):491–501. doi:10.4103/NRR.NRR-D-24-00836.
17. Neumann WJ, Steiner LA, Milosevic L. Neurophysiological mechanisms of deep brain stimulation across spatiotemporal

resolutions. *Brain*. 2023 Nov 2;146(11):4456–68. doi:10.1093/brain/awad239.
18. Sandoval-Pistorius SS, Hacker ML, Waters AC, Wang J, Provenza NR, de Hemptinne C, *et al.* Advances in deep brain stimulation: From mechanisms to applications. *J Neurosci*. 2023 Nov 8;43(45):7575–86.
19. Caylor J, Reddy R, Yin S, Cui C, Huang M, Huang C, *et al.* Spinal cord stimulation in chronic pain: Evidence and theory for mechanisms of action. *Bioelectron Med*. 2019 Dec;5(1):12. doi:10.1186/s42234-019-0023-1.
20. Sdrulla AD, Guan Y, Raja SN. Spinal cord stimulation: Clinical efficacy and potential mechanisms. *Pain Pract*. 2018 Nov;18(8):1048–67. doi:10.1111/papr.12692.
21. Austelle CW, Cox SS, Wills KE, Badran BW. Vagus nerve stimulation (VNS): Recent advances and future directions. *Clin Auton Res*. 2024 Dec;34(6):529–47. doi:10.1007/s10286-024-01065-w.
22. Fang YT, Lin YT, Tseng WL, Tseng P, Hua GL, Chao YJ, *et al.* Neuroimmunomodulation of vagus nerve stimulation and the therapeutic implications. *Front Aging Neurosci*. 2023 Jul 6;15:1173987. doi:10.3389/fnagi.2023.1173987.
23. Wang W, Li R, Li C, Liang Q, Gao X. Advances in VNS efficiency and mechanisms of action on cognitive functions. *Front Physiol*. 2024 Oct 9;15:1452490. doi:10.3389/fphys.2024.1452490 PubMed PMID: 39444752; PubMed Central PMCID: PMC11496278.
24. Ong Sio LC, Hom B, Garg S, Abd-Elsayed A. Mechanism of Action of Peripheral Nerve Stimulation for Chronic Pain: A Narrative Review. *Int J Mol Sci*. 2023 Feb 25;24(5):4540. doi:10.3390/ijms24054540.
25. Mao Z, Lv J, Sun Y, Shen J, Gao Y, Sun S, *et al.* Peripheral nerve stimulation for neuropathic pain management: A narrative review. *Pain Ther*. 2024 Sep 28;13(6):1387–406. doi:10.1007/s40122-024-00659-6.
26. Nyan TH, Park E. Emerging implantable tibial nerve stimulation devices for overactive bladder. *Int Neurourol J*. 2025 Sep 30;29(3):146–56. doi:10.5213/inj.2550162.081.
27. Lee J, Lee AY. Transcranial magnetic stimulation parameters as neurophysiological biomarkers in Alzheimer's disease. *Ann Clin Neurophysiol*. 2021 Apr 30;23(1):7–16. doi:10.14253/acn.2021.23.1.7.
28. Mann SK, Malhi NK. Repetitive transcranial magnetic stimulation. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2026 Feb 2]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK568715/ PubMed PMID: 33760474.
29. Kazinczi C, Szepfalusi N, Nemeth VL, Holczer A, Jakab K, Vecsei L, *et al.* The effect of transcranial direct current stimulation and inhibitory control training on depression and anxiety among post-stroke individuals. *BMC Neurol*. 2025 Jan 27;25(1):38. doi:10.1186/s12883-025-04042-6.
30. Lewis A, Rattray B, Flood A. Understanding the effects of transcranial direct current stimulation on the neurovascular unit: A narrative review. *Front Neurosci*. 2025 Oct 1;19:1667100. doi:10.3389/fnins.2025.1667100.
31. Patel P, Green M, Tram J, Wang E, Murphy M, Abd-Elsayed AA, *et al.* Latest advancements in transcutaneous electrical nerve stimulation (TENS) and electronic muscle stimulation (EMS): Revisiting an established therapy with new possibilities. *J Pain Res*. 2025 Jan;18:137–53. doi:10.2147/JPR.S493162.
32. Teoli D, Dua A, An J. Transcutaneous electrical nerve stimulation. In. StatPearls Publishing; 2024 [cited 2026 Feb 2]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537188/.
33. Fomenko A, Neudorfer C, Dallapiazza RF, Kalia SK, Lozano AM. Low-intensity ultrasound neuromodulation: An overview of mechanisms and emerging human applications. *Brain Stimulat*. 2018 Nov;11(6):1209–17. doi:10.1016/j.brs.2018.08.013.
34. Matt E, Radjenovic S, Mitterwallner M, Beisteiner R. Current state of clinical ultrasound neuromodulation. *Front Neurosci*. 2024 Jun 19;18:1420255. doi:10.3389/fnins.2024.1420255.
35. Wu CC, Szalontay L, Pouliopoulos AN, Bae S, Berg X, Wei HJ, *et al.* Blood-brain barrier opening with neuronavigation-guided focused ultrasound in pediatric patients with diffuse midline glioma. *Sci Transl Med*. 2025 Nov 12;17(824):eadq6645. doi:10.1126/scitranslmed.adq6645.
36. Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, *et al.* Deep brain stimulation: Current challenges and future directions. *Nat Rev Neurol*. 2019 Mar;15(3):148–60. doi:10.1038/s41582-018-0128-2.
37. Dua A, Collier SA, Garcia K, Kumar S. Spinal cord stimulation. In. StatPearls Publishing; 2025 [cited 2026 Feb 2]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553154/.
38. Ravikumar S, Stevens B, Mehreteab T, Erdek M. Use of high-frequency 10-kHz spinal cord stimulation in the treatment of persistent spinal pain syndrome type 2: A systematic review. *Neuromodulation Technol Neural Interface*. 2026 Jan;29(1):15–25. doi:10.1016/j.neurom.2025.08.417.
39. Sarica C, Iorio-Morin C, Aguirre-Padilla DH, Najjar A, Paff M, Fomenko A, *et al.* Implantable pulse generators for deep brain stimulation: Challenges, complications, and strategies for practicality and longevity. *Front Hum Neurosci*. 2021 Aug 26;15:708481. doi:10.3389/fnhum.2021.708481.
40. Attilio DT, Domenico LT, Giusy G, Giorgio V, Angelo L. Innovative developments in deep brain stimulation devices. *Interdiscip Neurosurg*. 2025 Jun 1;40:102035. doi:10.1016/j.inat.2025.102035.
41. Antoun I, Alkhayer A, Somani R, Antoun I, Alkhayer A, Somani R. Leadless pacemakers: Clinical advances, outcomes, and comparison with conventional systems. *Br J Hosp Med*. 2026 Jan 22;87(1). doi:10.31083/BJHM50278.
42. Bano I, Jeevanandam J, Tsenov G. Advances in therapeutic hybrid neuromodulation for Parkinson's disease. *3 Biotech*. 2026 Jan;16(1):58. doi:10.1007/s13205-025-04681-z.
43. Hulsey DR, Shedd CM, Sarker SF, Kilgard MP, Hays SA. Norepinephrine and serotonin are required for vagus nerve stimulation directed cortical plasticity. *Exp Neurol*. 2019 Oct;320:112975. doi:10.1016/j.expneurol.2019.112975.
44. Bae S, Lim HK, Jeong Y, Kim SG, Park SM, Shon YM, *et al.* Deep brain stimulation of the anterior nuclei of the thalamus can alleviate seizure severity and induce hippocampal GABAergic neuronal changes in a pilocarpine-induced epileptic mouse brain. *Cereb Cortex*. 2022 Dec 8;32(24):5530–43. doi:10.1093/cercor/bhac033.
45. Mina F, Benquet P, Pasnicu A, Biraben A, Wendling F. Modulation of epileptic activity by deep brain stimulation: A model-based study of frequency-dependent effects. *Front Comput Neurosci*. 2013;7. doi:10.3389/fncom.2013.00094.
46. Binns TS, Köhler RM, Vanhoecke J, Chikermane M, Gerster M, Merk T, *et al.* Shared pathway-specific network mechanisms of dopamine and deep brain stimulation for the treatment of Parkinson's disease. *Nat Commun*. 2025 Apr 15;16(1):3587. doi:10.1038/s41467-025-58825-z.
47. Faust K, Vajkoczy P, Xi B, Harnack D. The effects of deep brain stimulation of the subthalamic nucleus on vascular endothelial growth factor, brain-derived neurotrophic factor, and glial cell line-derived neurotrophic factor in a rat

model of parkinson's disease. *Stereotact Funct Neurosurg*. 2021;99(3):256–66. doi:10.1159/000511121.
48. Knorr S, Musacchio T, Paulat R, Matthies C, Endres H, Wenger N, *et al.* Experimental deep brain stimulation in rodent models of movement disorders. *Exp Neurol*. 2022 Feb 1;348:113926. doi:10.1016/j.expneurol.2021.113926.
49. Chu PC, Liu HL, Lai HY, Lin CY, Tsai HC, Pei YC. Neuromodulation accompanying focused ultrasound-induced blood-brain barrier opening. *Sci Rep*. 2015 Oct 22;5(1):15477. doi:10.1038/srep15477.
50. Kahan J, Mancini L, Urner M, Friston K, Hariz M, Holl E, *et al.* Therapeutic subthalamic nucleus deep brain stimulation reverses cortico-thalamic coupling during voluntary movements in parkinson's disease. Baron JC, editor, in PLoS ONE. 2012 Dec 26;7(12):e50270. doi:10.1371/journal.pone.0050270.
51. Calderone A, Latella D, Bonanno M, Quartarone A, Mojdehdehbaher S, Celesti A, *et al.* Towards transforming neurorehabilitation: The impact of artificial intelligence on diagnosis and treatment of neurological disorders. *Biomedicines*. 2024 Oct 21;12(10):2415. doi:10.3390/biomedicines12102415.
52. Cyron D. Mental side effects of deep brain stimulation (DBS) for movement disorders: the futility of denial. *Front Integr Neurosci*. 2016 Apr 20;10. doi:10.3389/fnint.2016.00017.
53. Lefaucheur JP, Moro E, Shirota Y, Ugawa Y, Grippe T, Chen R, *et al.* Clinical neurophysiology in the treatment of movement disorders: IFCN handbook chapter. *Clin Neurophysiol*. 2024 Aug;164:57–99. doi:10.1016/j.clinph.2024.05.007.
54. Da Silva MDV, Martelossi-Cebinelli G, Yaekashi KM, Carvalho TT, Borghi SM, Casagrande R, *et al.* A narrative review of the dorsal root ganglia and spinal cord mechanisms of action of neuromodulation therapies in neuropathic pain. *Brain Sci*. 2024 Jun 9;14(6):589. doi:10.3390/brainsci14060589.
55. Wang D, Lee KY, Kagan ZB, Bradley K, Lee D. Frequency-dependent neural modulation of dorsal horn neurons by kilohertz spinal cord stimulation in rats. *Biomedicines*. 2024 Jun 18;12(6):1346. doi:10.3390/biomedicines12061346
56. Pérez-Carbonell L, Faulkner H, Higgins S, Koutroumanidis M, Leschziner G. Vagus nerve stimulation for drug-resistant epilepsy. *Pract Neurol*. 2020 May;20(3):189–98. doi:10.1136/practneurol-2019-002210.
57. Geller EB. Responsive neurostimulation: Review of clinical trials and insights into focal epilepsy. *Epilepsy Behav*. 2018 Nov;88:11–20. doi:10.1016/j.yebeh.2018.06.042.
58. Inaji M, Yamamoto T, Kawai K, Maehara T, Doyle WK. Responsive neurostimulation as a novel palliative option in epilepsy surgery. *Neurol Med Chir (Tokyo)*. 2020;61(1):1–11. doi:10.2176/nmc.st.2020-0172.
59. Jarosiewicz B, Morrell M. The RNS system: Brain-responsive neurostimulation for the treatment of epilepsy. *Expert Rev Med Devices*. 2021 Feb 1;18(2):129–38. doi:10.1080/17434440.2019.1683445.
60. Alfihed S, Majrashi M, Ansary M, Alshamrani N, Albrahim SH, Alsolami A, *et al.* Non-invasive brain sensing technologies for modulation of neurological disorders. *Biosensors*. 2024 Jul 9;14(7):335. doi:10.3390/bios14070335.
61. Guidetti M, Bertini A, Pirone F, Sala G, Signorelli P, Ferrarese C, *et al.* Neuroprotection and non-invasive brain stimulation: Facts or fiction? *Int J Mol Sci*. 2022 Nov 9;23(22):13775. doi:10.3390/ijms232213775.
62. Moshayedi AJ, Mokhtari T, Emadi Andani M. Brain stimulation techniques in research and clinical practice: A comprehensive review of applications and therapeutic potential in parkinson's disease. *Brain Sci*. 2024 Dec 27;15(1):20. doi:10.3390/brainsci15010020.
63. Yu CH, Lench DH, Cooper C, Rowland NC, Takacs I, Revuelta G. Deep brain stimulation for essential tremor versus essential tremor plus: Should we target the same spot in the thalamus? *Front Hum Neurosci*. 2023 Oct 31;17:1271046. doi:10.3389/fnhum.2023.1271046.
64. Hussein AFA, Imran WM, Serag I, Abbas A, Mohamed Hammad E, Pastrana-Brandes S, *et al.* Deep brain stimulation (DBS) in movement disorders management: exploring therapeutic efficacy, neurobiological mechanisms, and clinical implications. *Ann Med Surg*. 2025 Apr;87(4):2163–79. doi:10.1097/MS9.0000000000003096.
65. Johnson KA, Okun MS, Scangos KW, Mayberg HS, De Hemptinne C. Deep brain stimulation for refractory major depressive disorder: A comprehensive review. *Mol Psychiatry*. 2024 Apr;29(4):1075–87. doi:10.1038/s41380-023-02394-4.
66. Pinckard-Dover H, Ward H, Foote KD. The decline of deep brain stimulation for obsessive–compulsive disorder following FDA humanitarian device exemption approval. *Front Surg*. 2021 Mar 12;8:642503. doi:10.3389/fsurg.2021.642503.
67. Greenberg BD, Gabriels LA, Malone DA, Rezai AR, Friehs GM, Okun MS, *et al.* Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: Worldwide experience. *Mol Psychiatry*. 2010 Jan;15(1):64–79. doi:10.1038/mp.2008.55.
68. Karas PJ, Lee S, Jimenez-Shahed J, Goodman WK, Viswanathan A, Sheth SA. Deep brain stimulation for obsessive compulsive disorder: Evolution of surgical stimulation target parallels changing model of dysfunctional brain circuits. *Front Neurosci*. 2019 Jan 8;12:998. doi:10.3389/fnins.2018.00998.
69. Zhong B, Shi X, Yuan X, Liu Y. Mechanisms and clinical progress of spinal cord stimulation in refractory chronic pain: An overview. *Front Neurol*. 2026 Jan 16;16:1687276. doi:10.3389/fneur.2025.1687276.
70. Zhao Y. A systematic review on high-frequency spinal cord stimulation therapy for neuropathic pain. *Sci Technol Eng Chem Environ Prot*. 2024 Dec 31;1(10). doi:10.61173/e0rer980.
71. Jayathilake NJ, Phan TT, Kim J, Lee KP, Park JM. Modulating neuroplasticity for chronic pain relief: Noninvasive neuromodulation as a promising approach. *Exp Mol Med*. 2025 Mar 3;57(3):501–14. doi:10.1038/s12276-025-01409-0.
72. De Oliveira TVHF, Cukiert A. How neuromodulation changed the landscape of epilepsy surgery. *Stereotact Funct Neurosurg*. 2025 Sep 24;103(5):436–69. doi:10.1159/000548581.
73. Markert MS, Fisher RS. Neuromodulation - science and practice in epilepsy: Vagus nerve stimulation, thalamic deep brain stimulation, and responsive neurostimulation. *Expert Rev Neurother*. 2019 Jan 2;19(1):17–29. doi:10.1080/14737175.2019.1554433.
74. Kusyk DM, Meinert J, Stabingas KC, Yin Y, Whiting AC. Systematic review and meta-analysis of responsive neurostimulation in epilepsy. *World Neurosurg*. 2022 Nov;167:e70–8. doi:10.1016/j.wneu.2022.07.147.
75. Roa JA, Marcuse L, Fields M, Vega-Talbott ML, Yoo JY, Wolf SM, *et al.* Long-term outcomes after responsive neurostimulation for treatment of refractory epilepsy: A single-center experience of 100 cases. *J Neurosurg*. 2023 Nov 1;139(5):1463–70. doi:10.3171/2023.2.JNS222116.
76. Fields MC, Eka O, Schreckinger C, Dugan P, Asaad WF, Blum AS, *et al.* A multicenter retrospective study of patients

treated in the thalamus with responsive neurostimulation. *Front Neurol*. 2023 Sep 8;14:1202631. doi:10.3389/fneur.2023.1202631.
77. Nanda P, Walton A, Sisterson N, Richardson RM. 194 responsive neurostimulation targeting the centromedian nucleus of the thalamus improves seizure control in idiopathic generalized epilepsy and select multifocal disease. *Neurosurgery*. 2024 Apr;70(Supplement_1):50–50. doi:10.1227/neu.0000000000002809_194.
78. Beaudreault CP, Spirollari E, Naftchi AF, Sukul V, Das A, Vazquez S, *et al.* Safety of vagus nerve stimulation and responsive neurostimulation used in combination for multifocal and generalized onset epilepsy in pediatric patients. *J Neurosurg Pediatr*. 2023 Jun 1;31(6):565–73. doi:10.3171/2023.1.PEDS22486.
79. Hejazi M, Tong W, Ibbotson MR, Prawer S, Garrett DJ. Advances in carbon-based microfiber electrodes for neural interfacing. *Front Neurosci*. 2021 Apr 12;15:658703. doi:10.3389/fnins.2021.658703.
80. Maiolo L, Polese D, Convertino A. The rise of flexible electronics in neuroscience, from materials selection to in vitro and in vivo applications. *Adv Phys X*. 2019 Jan 1;4(1):1664319. doi:10.1080/23746149.2019.1664319.
81. Niemiec M, Kim K. Lifetime engineering of bioelectronic implants with mechanically reliable thin film encapsulations. *Prog Biomed Eng*. 2024 Jan 1;6(1):012001. doi:10.1088/2516-1091/ad0b19.
82. Aboualalaa M, Mansour M, Mansour I. Wireless power transfer for biomedical implants. *Int J Circuit Theory Appl*. 2025 Jul 30;cta.70080. doi:10.1002/cta.70080.
83. Park W, Lee J, Chung WG, Jeong I, Kim E, Kwon YW, *et al.* Recent advances in wireless energy transfer technologies for body-interfaced electronics. *Nano Energy*. 2024 Jun;124:109496. doi:10.1016/j.nanoen.2024.109496.
84. Zhai L, Duan J, Lin T, Shao H. Recent advances in implantable batteries: Development and challenge. *J Alloys Compd*. 2024 Apr;979:173551. doi:10.1016/j.jallcom.2024.173551.
85. Cho J, Seong G, Chang Y, Kim C. Energy-efficient integrated circuit solutions toward miniaturized closed-loop neural interface systems. *Front Neurosci*. 2021 May 31;15:667447. doi:10.3389/fnins.2021.667447.
86. Contreras LFH, Truong ND, Eshraghian JK, Xu Z, Huang Z, Nikpour A, *et al.* Neuromorphic neuromodulation: Towards the next generation of on-device AI-revolution in electroceuticals [Internet]. arXiv; 2023 [cited 2026 Mar 4]. Available from: https://arxiv.org/abs/2307.12471 doi:10.48550/ARXIV.2307.12471.
87. Magisetty R, Park SM. New era of electroceuticals: Clinically driven smart implantable electronic devices moving towards precision therapy. *Micromachines*. 2022 Jan 22;13(2):161. doi:10.3390/mi13020161.
88. Chandrabhatla AS, Pomeraniec IJ, Horgan TM, Wat EK, Ksendzovsky A. Landscape and future directions of machine learning applications in closed-loop brain stimulation. *NPJ Digit Med*. 2023 Apr 27;6(1):79. doi:10.1038/s41746-023-00779-x.
89. Oehrn CR, Cernera S, Hammer LH, Shcherbakova M, Yao J, Hahn A, *et al.* Chronic adaptive deep brain stimulation versus conventional stimulation in Parkinson's disease: A blinded randomized feasibility trial. *Nat Med*. 2024 Nov;30(11):3345–56. doi:10.1038/s41591-024-03196-z.
90. Oliveira AM, Coelho L, Carvalho E, Ferreira-Pinto MJ, Vaz R, Aguiar P. Machine learning for adaptive deep brain stimulation in Parkinson's disease: Closing the loop. *J Neurol*. 2023 Nov;270(11):5313–26. doi:10.1007/s00415-023-11873-1.
91. Zhou Y, Burgoyne Morris GH, Nair M. Current and emerging strategies for biocompatible materials for implantable electronics. *Cell Rep Phys Sci*. 2024 Aug 21;5(8):101852. doi:10.1016/j.xcrp.2024.101852.
92. Abouelleil M, Deshpande N, Ali R. Emerging trends in neuromodulation for treatment of drug-resistant epilepsy. *Front Pain Res*. 2022 Mar 21;3:839463. doi:10.3389/fpain.2022.839463.
93. Jeon J, Kang D, Kim SW. Electrotherapy and health monitoring with piezoelectric and triboelectric technologies. *Biomaterials*. 2025 Dec;323:123425. doi:10.1016/j.biomaterials.2025.123425.
94. Mirchi N, Warsi NM, Zhang F, Wong SM, Suresh H, Mithani K, *et al.* Decoding intracranial EEG with machine learning: A systematic review. *Front Hum Neurosci*. 2022 Jun 27;16:913777. doi:10.3389/fnhum.2022.913777.
95. Peterson V, Merk T, Bush A, Nikulin V, Kühn AA, Neumann WJ, *et al.* Movement decoding using spatio-spectral features of cortical and subcortical local field potentials. *Exp Neurol*. 2023 Jan;359:114261. doi:10.1016/j.expneurol.2022.114261.
96. Saeidi M, Karwowski W, Farahani FV, Fiok K, Taiar R, Hancock PA, *et al.* Neural decoding of EEG signals with machine learning: A systematic review. *Brain Sci*. 2021 Nov 18;11(11):1525. doi:10.3390/brainsci11111525.
97. Anthonisamy A, Srivel R. Next-generation parkinson's disease management: The perform of machine learning in early diagnosis and tailored treatments. In: 2025 11th International Conference on Communication and Signal Processing (ICCSP) [Internet]. Melmaruvathur, India: IEEE; 2025 [cited 2026 Mar 5]. p. 431–5. Available from: https://ieeexplore.ieee.org/document/11088520/doi:10.1109/ICCSP64183.2025.11088520.
98. Georgis-Yap Z, Popovic MR, Khan SS. Supervised and unsupervised deep learning approaches for EEG seizure prediction. *J Healthc Inform Res*. 2024 Jun;8(2):286–312. doi:10.1007/s41666-024-00160-x.
99. Ajirak M, Adali T, Sanei S, Grosenick L, Djurić PM. Exploring synergies: Advancing neuroscience with machine learning. *Signal Process*. 2026 Jan;238:110116. doi:10.1016/j.sigpro.2025.110116.
100. Zarzycki MZ, Domitrz I. Stimulation-induced side effects after deep brain stimulation – A systematic review. *Acta Neuropsychiatr*. 2020 Apr;32(2):57–64. doi:10.1017/neu.2019.35.
101. Kawabata S. Excessive/aberrant and maladaptive synaptic plasticity: A hypothesis for the pathogenesis of alzheimer's disease. *Front Aging Neurosci*. 2022 Jul 5;14:913693. doi:10.3389/fnagi.2022.913693.
102. Puderbaugh M, Emmady PD. Neuroplasticity. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2026 Mar 5]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK557811/PubMed PMID: 32491743.
103. Woopen C. Ethical aspects of neuromodulation. In: International Review of Neurobiology [Internet]. Elsevier; 2012 [cited 2026 Mar 5]. p. 315–32. https://linkinghub.elsevier.com/retrieve/pii/B9780124047068000164 doi:10.1016/B978-0-12-404706-8.00016-4.
104. Smith JN, Dorfman N, Hurley M, Cenolli I, Kostick-Quenet K, Storch EA, *et al.* Adolescent OCD patient and caregiver perspectives on identity, authenticity, and normalcy in potential deep brain stimulation treatment. *Camb Q Healthc Ethics*. 2024 Oct;33(4):507–20. doi:10.1017/S0963180124000203.

105. Gordon EC, Seth AK. Ethical considerations for the use of brain–computer interfaces for cognitive enhancement. *PLOS Biol*. 2024 Oct 28;22(10):e3002899. doi:10.1371/journal.pbio.3002899.
106. Jwa AS. Regulating the use of cognitive enhancement: An Analytic Framework. *Neuroethics*. 2019 Oct;12(3):293–309. doi:10.1007/s12152-019-09408-5.
107. Wild V, Nijsingh N, Hendl T. Taking a step back: The ethical significance of DTC neurotechnology. *AJOB Neurosci*. 2019 Oct 2;10(4):170–2. doi:10.1080/21507740.2019.1665139.
108. Boyle Q, Illes J. Neuromodulation and opioid use disorder: Ethical opportunities for Canada. *Can J Neurol Sci J Can Sci Neurol*. 2023 Jun;50(s1):s26–33. doi:10.1017/cjn.2022.328.
109. Lo C, Mane M, Kim JH, Berk M, Sharp RR, Lee KH, *et al.* Treating addiction with deep brain stimulation: Ethical and legal considerations. *Int J Drug Policy*. 2023 Mar;113:103964. doi:10.1016/j.drugpo.2023.103964.
110. Zuk P, Torgerson L, Sierra-Mercado D, Lázaro-Muñoz G. Neuroethics of neuromodulation: An update. *Curr Opin Biomed Eng*. 2018 Dec;8:45–50. doi:10.1016/j.cobme.2018.10.003.
111. Goering S, Klein E, Specker Sullivan L, Wexler A, Agüera Y, Arcas B, Bi G, *et al.* Recommendations for responsible development and application of neurotechnologies. *Neuroethics*. 2021 Dec;14(3):365–86. doi:10.1007/s12152-021-09468-6.
112. Muñoz JM, Bernácer J, Güell F. A conceptual framework to safeguard the neuroright to personal autonomy. *Neuroethics*. 2023 Oct;16(3):18. doi:10.1007/s12152-023-09523-4.
113. França C, Carra RB, Diniz JM, Munhoz RP, Cury RG. Deep brain stimulation in Parkinson's disease: State of the art and future perspectives. *Arq Neuropsiquiatr*. 2022 May;80(5 suppl 1):105–15. doi:10.1590/0004-282x-anp-2022-s133.
114. Chen D, Lei X, Du L, Long Z. Use of machine learning in predicting the efficacy of repetitive transcranial magnetic stimulation on treating depression based on functional and structural thalamo-prefrontal connectivity: A pilot study. *J Psychiatr Res*. 2022 Apr 1;148:88–94. doi:10.1016/j.jpsychires.2022.01.064.
115. Bjånes DA, Kellis S, Nickl R, Baker B, Aflalo T, Bashford L, *et al.* Quantifying physical degradation alongside recording and stimulation performance of 980 intracortical microelectrodes chronically implanted in three humans for 956-2130 days. *Acta Biomater*. 2025 May;198:188–206. doi:10.1016/j.actbio.2025.02.030.
116. Dalrymple AN, Jones ST, Fallon JB, Shepherd RK, Weber DJ. Overcoming failure: Improving acceptance and success of implanted neural interfaces. *Bioelectron Med*. 2025 Mar 14;11(1):6. doi:10.1186/s42234-025-00168-7.
117. Koo JH, Song JK, Kim DH, Son D. Soft implantable bioelectronics. *ACS Mater Lett*. 2021 Nov 1;3(11):1528–40. doi:10.1021/acsmaterialslett.1c00438.
118. Gao Z, Zhou Y, Zhang J, Foroughi J, Peng S, Baughman RH, *et al.* Advanced energy harvesters and energy storage for powering wearable and implantable medical devices. *Adv Mater*. 2024 Oct;36(42):2404492. doi:10.1002/adma.202404492.
119. Shen K, Chen O, Edmunds JL, Piech DK, Maharbiz MM. Translational opportunities and challenges of invasive electrodes for neural interfaces. *Nat Biomed Eng*. 2023 Apr 20;7(4):424–42. doi:10.1038/s41551-023-01021-5.
120. Chakrabarty S, Loeb G, Malliaras G, Yin H. How do we ensure that bioelectronic devices revolutionize medicine and healthcare? *Res Dir Bioelectron*. 2023;1:e1. doi:10.1017/bel.2023.1.