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Review of Neuromodulation Techniques: Mechanisms, Applications and Future Directions

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Abstract

Objectives: This review aims to offer an in-depth primer on neuromodulation, a medical field focused on altering nerve activity through specific stimuli. It seeks to analyze the mechanisms, principal clinical applications, benefits, limitations, recent advancements, and available simulation tools for effective treatment management. **Methods:** The article consolidates contemporary literature on both invasive techniques, such as Deep Brain Stimulation (DBS), Spinal Cord Stimulation (SCS), Vagus Nerve Stimulation (VNS), and Responsive Neurostimulation (RNS), as well as non-invasive methods, including Transcranial Magnetic Stimulation (TMS), Transcranial Direct Current Stimulation (tDCS), and Focused Ultrasound (FUS). **Findings:** Neuromodulation operates on the premise that many neurological and psychiatric disorders stem from abnormal electrical or chemical activity within specific neural circuits. These devices can modulate neurological tissue function similarly to a cardiac pacemaker, applying targeted stimulation to suppress hyperactive signals (as seen in chronic pain) or to activate hypoactive regions (as in depression). **Novelty:** This review presents a timely and organized analysis of the intricate neuromodulation landscape, discussing the mechanisms of action, established clinical applications, associated risks and benefits, and an overview of innovative approaches and simulation tools essential for improving treatment management in chronic and treatment-resistant neurological and mental disorders.

Keywords: Neuromodulation techniques; Simulation tools; Invasive and Non-invasive approaches; Transcranial electrical stimulation (tES); Spinal cord stimulation (SCS)

1 Introduction

The nervous system serves as the body's command center and communication network. It regulates all bodily functions and emotions. The central nervous system (CNS) and the peripheral nervous system (PNS) constitute its two primary components. The central nervous system comprises the brain and spinal cord. They acquire and analyze information. The peripheral nervous system (PNS) comprises a network of nerves that link to the central nervous system (CNS) and transmit messages to and from the body.

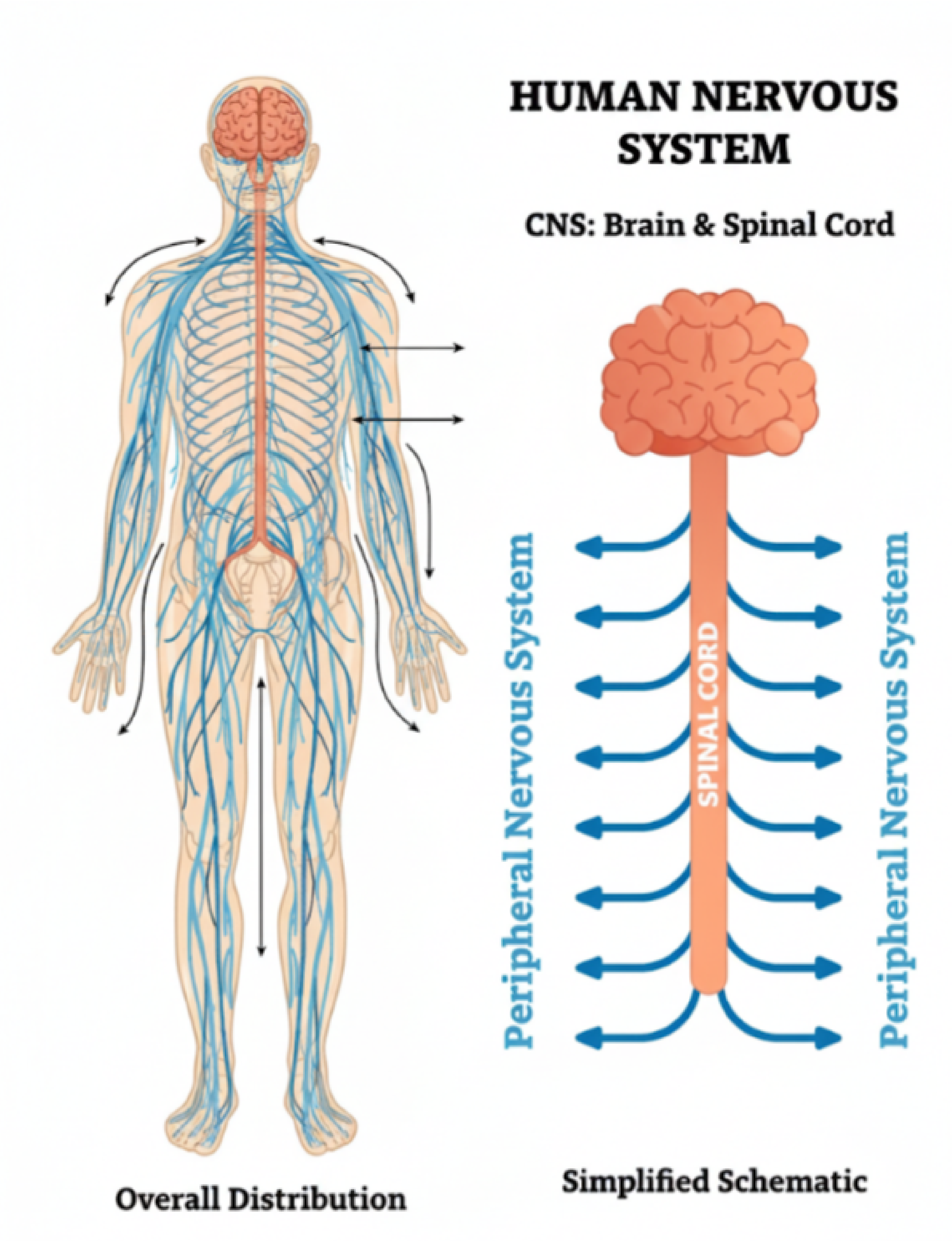

Fig 1. Human Nervous System

The nervous system comprises two primary cell types: Neurons: The essential components of the nervous system convey electrical and chemical messages. Each neuron comprises a cell body, dendrites (which receive information), and an axon (which transmits impulses). Action potentials propagate along the axon to the synapse, facilitating communication between two neurons. Neurotransmitters enable transmission in this setting. Glial cells enhance neuronal function. They safeguard neurons, produce myelin (an insulating sheath encasing axons that enhances signal transmission), and maintain equilibrium throughout the nervous system. Neuromodulation is the technique of altering nerve function through certain stimulation. This can be accomplished by administering electrical stimulation or pharmacological agents to specific regions of the nervous system. It resembles adjusting a radio to achieve a clearer reception. In conventional synaptic transmission, neurons engage in rapid, direct communication. In neuromodulation, neurons communicate in a more extensive and diffuse manner.

Neuromodulators are a class of chemical messengers distinct from conventional neurotransmitters. A neurotransmitter directly influences a synapse to either stimulate or suppress a particular postsynaptic neuron. A neuromodulator can influence several neurons across an extensive region, altering the overall excitability and functionality of a neural circuit. They do not merely "fire" or "inhibit" a neuron; they alter the manner in which neurons react to other signals. A neuromodulator can alter a neuron's resting membrane potential, its responsiveness to neurotransmitters, or the efficacy of synaptic connections. This occurs when they attach to receptors, initiating a cascade of intracellular alterations. Dopamine, serotonin, and norepinephrine serve as prevalent examples of neuromodulators. They are recognized for significantly influencing mood, attentiveness, and motivation[(1)]. Neuromodulation is essential for the nervous system's flexibility and adaptability, enabling the reconfiguration of circuits to accommodate various behavioral states, such as transitioning from a tranquil state to one of increased arousal[(2)].

Neuromodulators are often released into the extracellular fluid or cerebrospinal fluid, enabling them to spread over a wide area and interact with several neurons[(3)]. Neuromodulators alter the collective state of a neuronal ensemble, hence affecting their responsiveness to external stimuli[(4)]. They can alter the ease with which a neuron discharges, the strength of its synaptic connections, or the patterns of its firing. Neuromodulators demonstrate effects that often initiate more slowly and endure longer than traditional neurotransmitters, spanning from hundreds of milliseconds to several minutes or beyond. Neuromodulators generally attach to G-protein coupled receptors (GPCRs) located on the neuronal membrane. This initiates a cascade of alterations within the cell, resulting in enduring and extensive modifications in cerebral function. Dopamine, serotonin, and norepinephrine are prevalent neuromodulators essential for regulating mood, sleep, attention, and motivation.

Neuromodulation therapies are essential for numerous conditions where conventional treatments, such as pharmacotherapy or surgical intervention, are ineffective, induce considerable adverse effects, or are unfeasible. These therapies can directly influence the neurological system to alleviate symptoms and significantly enhance quality of life.

The clinical requirement for neuromodulation in Parkinson's disease (PD) stems from its progressive, motor-symptom-focused characteristics. Initial pharmaceutical therapies, such as levodopa, are beneficial; however, their efficacy frequently diminishes with time or results in significant adverse effects, including dyskinesia (involuntary movements)[(5)]. For some patients, neuromodulation, particularly deep brain stimulation (DBS), represents a significant alternative. Deep Brain Stimulation (DBS) is a process involving the implantation of a device that transmits electrical impulses to targeted regions of the brain, such as the sub-thalamic nucleus, to modify the function of aberrant neural circuits and alleviate tremors, rigidity, and other motor symptoms[(6)].

Approximately 30% of individuals with epilepsy exhibit a drug-resistant or "refractory" variant of the condition, indicating that their seizures remain uncontrolled by pharmacological treatment. For these individuals, neuromodulation offers a non-invasive option to surgery, which may be unfeasible if the seizure center is located in a vital brain region. Implantable devices such as vagus nerve stimulation (VNS) and responsive neurostimulation (RNS) deliver electrical impulses to prevent seizures or terminate them promptly upon onset[(7)].

Chronic pain, characterized by its persistence beyond 12 weeks, is a multifaceted condition frequently resistant to standard therapies such as opioids, which pose risks of addiction and other consequences. Neuromodulation provides a non-pharmacological option. Spinal cord stimulation (SCS) is a prevalent therapeutic intervention that entails the implantation of a device that transmits electrical impulses to the spinal cord. This inhibits the transmission of pain signals to the brain. This is particularly beneficial for illnesses such as complex regional pain syndrome (CRPS), failed back surgery syndrome, and diabetic neuropathy[(8)].

For certain patients with severe depressive disorders, conventional therapies such as antidepressants and psychotherapy are inadequate. This disorder is referred to as treatment-resistant depression. Neuromodulation provides a distinct method by directly modifying cerebral function. Transcranial magnetic stimulation (TMS) employs magnetic fields to activate brain regions responsible for mood regulation without the need for surgical intervention. Vagus nerve stimulation (VNS) and deep brain stimulation (DBS) are invasive interventions for cases unresponsive to other therapies. These therapies can restore dysfunctional brain networks, proving beneficial when alternative methods have failed.

2 Review Methodology

Neuromodulation Techniques:

Neuromodulation is a treatment approach that modifies nerve activity via electrical or chemical agents, categorized into two main types: invasive and non-invasive approaches.

2.1 Invasive Neuromodulation

Invasive techniques require surgical procedures to implant a device that directly interfaces with the nervous system. Deep Brain Stimulation (DBS) is a technique that involves the implantation of electrodes into targeted regions of the brain via stereotactic methods. This transmits high-frequency electrical impulses to specific regions, aiding in the regulation of aberrant neuronal pathways associated with movement disorders[9]. Spinal Cord Stimulation (SCS) utilizes electrodes surgically positioned in the epidural space near the spinal cord to deliver electrical currents that disrupt and mask chronic pain signals prior to their transmission to the brain[10]. Vagus Nerve Stimulation (VNS) is a recognized invasive procedure that entails the implantation of a device in the chest, which connects to the vagus nerve and transmits electrical impulses to modulate mood and seizure activity. Sacral Nerve Stimulation (SNS) entails the implantation of a device to activate the sacral nerves, essential for regulating bladder and bowel function, hence offering an effective remedy for disorders such as incontinence[11].

Deep Brain Stimulation (DBS): Deep Brain Stimulation (DBS) is a significant surgical procedure that entails the implantation of electrodes into specific deep brain regions utilizing stereotactic techniques. The subthalamic nucleus (STN) is the predominant region utilized for the treatment of Parkinson's disease. The electrodes are linked to an implanted pulse generator (IPG) via a wire that traverses subcutaneously. The IPG, analogous to a pacemaker, is typically situated beneath the skin in the thoracic region, as illustrated in figure 2. This IPG emits continuous electrical impulses believed to assist abnormal brain activity associated with movement disorders. The precise mechanisms remain inadequately comprehended; nevertheless, they are believed to be non-exclusive and encompass local and network-wide electrical and neurochemical effects, alterations in oscillatory activity, and synaptic plasticity.

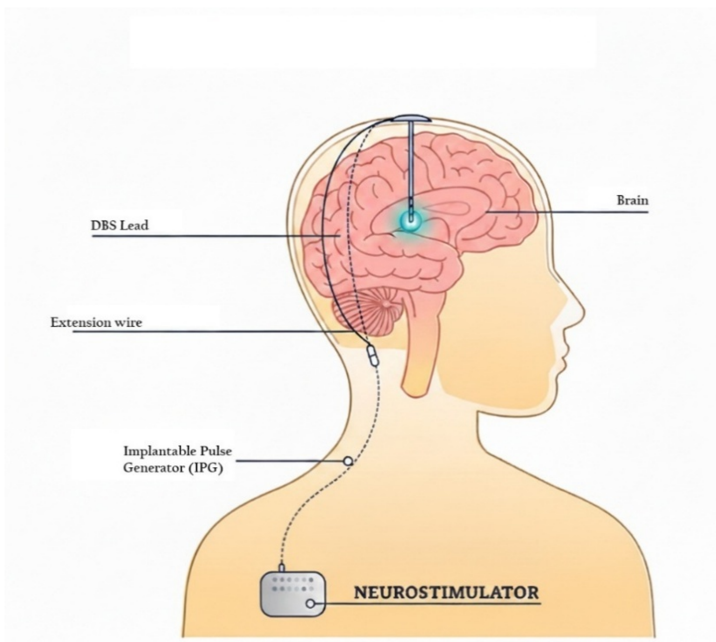

Fig 2. Deep Brain Stimulation

Deep brain stimulation (DBS) is a recognized and efficacious intervention for the motor manifestations of Parkinson's disease (PD), essential tremor, and dystonia. Deep brain stimulation can substantially enhance motor function in appropriate Parkinson's disease patients, with 70% to 80% seeing considerable symptom alleviation[12]. The beneficial effects on motor symptoms last for a minimum of 5 to 10 years. A notable benefit of DBS is its capacity to diminish the necessity for medication, thus mitigating prevalent adverse effects including uncontrollable movements and nausea. The FDA has sanctioned its use for obsessive-compulsive disorder (OCD) and is currently investigating its efficacy for various other neuropsychiatric illnesses[13].

This treatment mostly facilitates long-term symptom management rather than providing a definitive cure. For instance, DBS does not remedy Parkinson's disease; rather, it assists individuals in managing the symptoms more effectively. This distinction is crucial for patient expectations and underscores the necessity of a comprehensive, long-term care plan that frequently incorporates additional therapies for support.

Deep Brain Stimulation (DBS), a significant neurosurgical intervention, entails associated hazards. The surgical hazards encompass a 1% probability of cerebral hemorrhage, potentially resulting in a stroke, alongside the possibilities of infection and device malfunction. The hazards escalate for individuals aged 70 and above, as well as for those with pre-existing diseases such as hypertension and cerebrovascular disease [14]. Patients may encounter transient adverse effects during stimulation, including facial or limb tingling, muscular contractions, speech or visual impairments, and balance disturbances. The effects are typically minimal and may frequently be reversed by adjusting the stimulation parameters.

The efficacy of DBS treatment relies not solely on technology but also on a meticulous patient selection process. Candidates must exhibit a significantly diminished quality of life due to their symptoms, an inadequate response to pharmacological treatment, and the capacity to endure the surgical intervention. This comprehensive assessment, frequently encompassing mental evaluations and imaging, is essential to enhance outcomes and ensure the operation is appropriate for the individual.

Spinal Cord Stimulation (SCS): Spinal Cord Stimulation (SCS) is an implanted neuromodulatory apparatus utilized for the management of chronic pain. The method entails the insertion of electrodes into the epidural space (the region between the spinal cord and the vertebrae) and the implantation of the IPG subcutaneously, typically in proximity to the buttocks or abdomen, as illustrated in figure 3. The gadget transmits a low-voltage electrical current through the body, intended to obstruct the pain impulses that traverse between the brain and the spinal cord. This is accomplished by stimulating large-diameter afferent fibers, which then activate spinal neuronal networks and produce inhibitory neurotransmitters that obstruct the neural impulses responsible for pain. Conventional spinal cord stimulation methods substitute pain with a tingling sensation known as paresthesia. Nevertheless, contemporary technologies provide "sub-perception" stimulation that the patient cannot perceive [15].

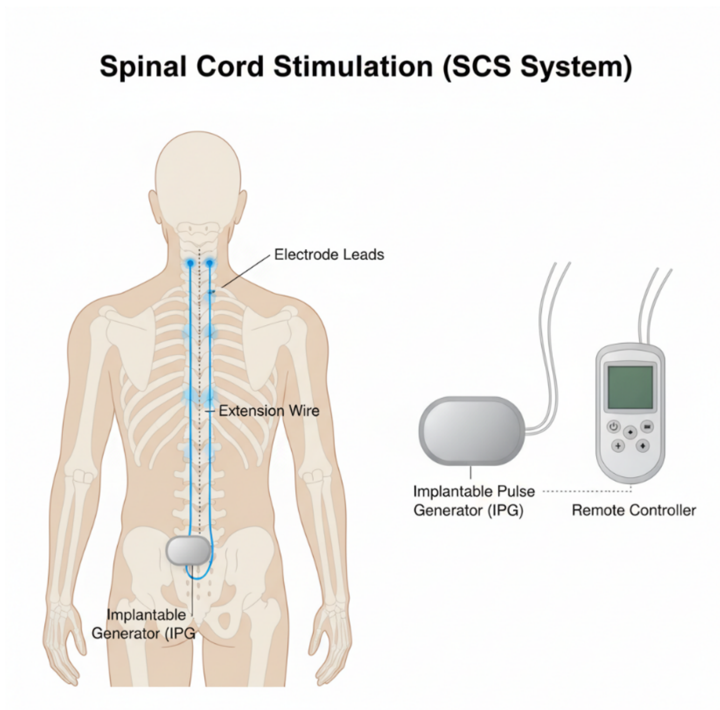

Fig 3. Spinal cord stimulation

SCS is typically regarded for those who have not attained adequate relief from other conservative or surgical treatments. It is effective for various illnesses, including Failed Back Surgery Syndrome (FBSS) and Complex Regional Pain Syndrome (CRPS). The treatment is a recognized, long-term method to enhance an individual's quality of life and functional capacity, potentially reducing the necessity for oral opioids [16].

Selecting appropriate candidates for SCS therapy is crucial. It typically entails imaging and psychological assessments to ensure the patient is suitable. The procedure commences with a trial duration ranging from three to seven days. During this period, temporary leads are inserted using a needle and linked to an external generator. A trial is deemed effective if the patient has a minimum 50% reduction in pain and an enhancement in function. This trial functions as a crucial, reversible diagnostic approach enabling the patient to assess the therapy's effects prior to committing to a permanent implant.

There are three primary categories of spinal cord stimulation (SCS) devices: a conventional implantable pulse generator (IPG) requiring surgical battery replacement, a rechargeable IPG that allows for non-surgical recharging, and a radiofrequency stimulator with an external battery, which is increasingly rare. Lead migration, which may be rectified with reprogramming or surgical intervention, and lead fracture are two prevalent issues.

Vagus Nerve Stimulation (VNS): Vagus Nerve Stimulation (VNS) is a neuromodulatory treatment that entails the surgical implantation of a compact pulse generator on the left side of the thorax. This gadget transmits low-level electrical impulses via the vagus nerve to the brain consistently. The vagus nerve is a crucial conduit influencing the brain's regulation of mood and seizures. VNS is believed to function by altering neurotransmitter release and influencing cerebral blood flow[17].

The FDA has sanctioned VNS as an adjunctive treatment for adults and children (ages 4 and older) with drug-resistant epilepsy (DRE) who have not adequately responded to antiepileptic drugs. It is additionally sanctioned for those with chronic depression who have undergone four or more unsuccessful treatments, including medication and electroconvulsive therapy. VNS frequently provides enduring advantages, unlike numerous other pharmaceuticals.

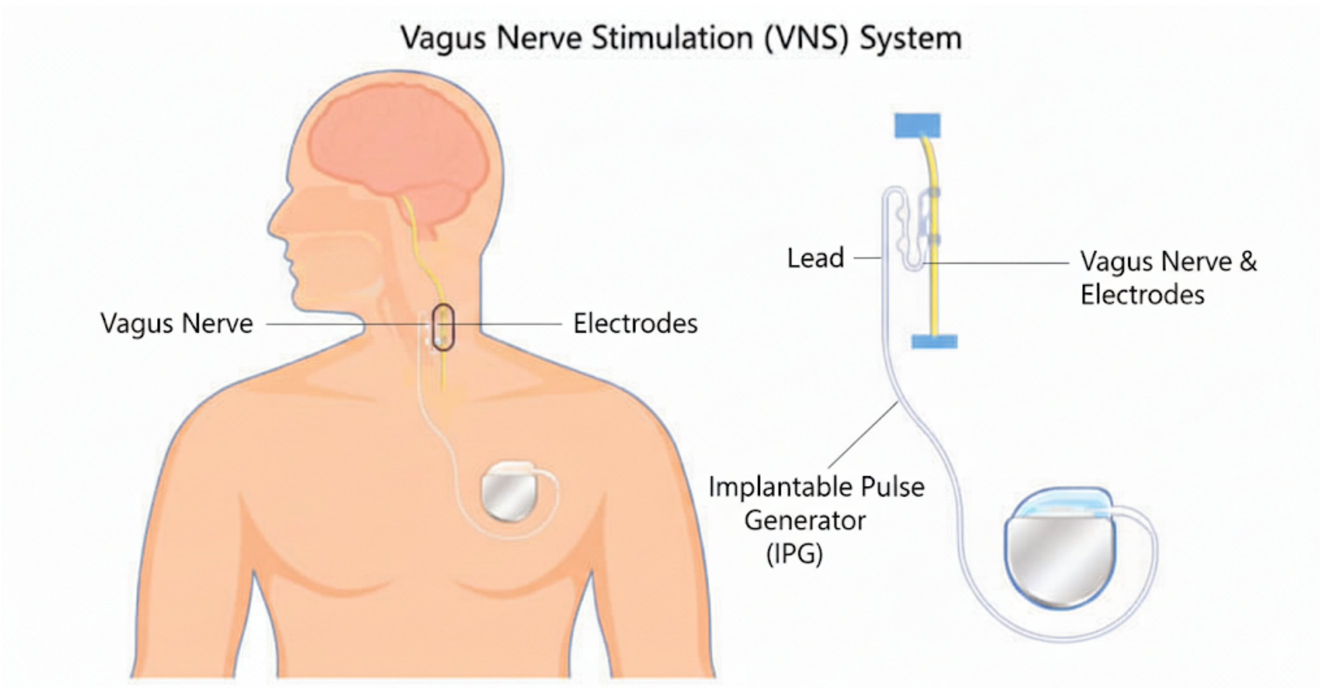

Fig 4. Vagus nerve stimulation

Implanted VNS surgical devices may induce discomfort at the incision site, infection, and dysphagia. Stimulation induces adverse consequences that typically resolve independently or through modifications to the device. Symptoms include hoarseness, throat pain, coughing, and dyspnea[18].

Sacral Nerve Stimulation (SNS): Sacral Nerve Stimulation (SNS) is a recognized, minimally invasive neuromodulatory procedure targeting the afferent and efferent pathways of the sacral nervous system. This therapeutic technique is the insertion of an electrode lead through the dermis, typically into the S3 foramen, to establish an electrical connection with the sacral nerve roots[19]. The leads are subsequently linked to an implanted pulse generator (IPG), often situated in the upper buttock or abdominal region, as seen in Figure 5.

The mechanism of action entails administering low-amplitude electrical impulses that regulate neuronal activity in the sacral plexus. This neuromodulation is thought to reinstate normal reflex arcs associated with urine and feces, thereby enhancing bladder and bowel storage and evacuation capabilities[20]. The expected outcomes comprise the suppression of detrusor

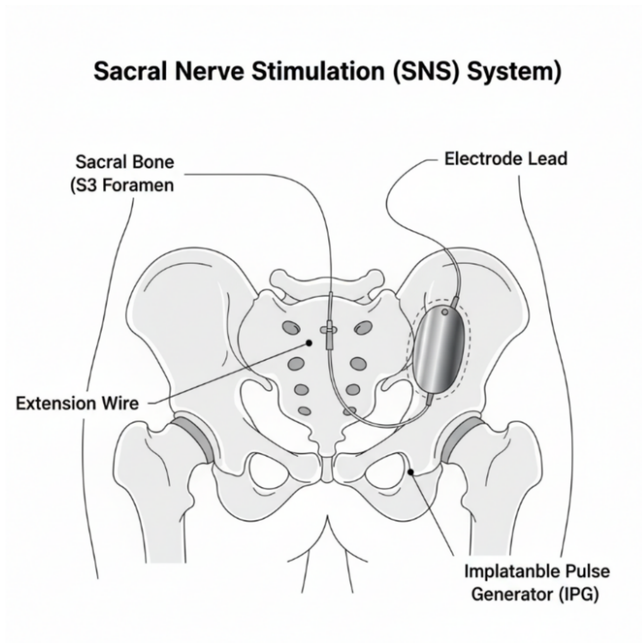

Fig 5. Sacral nerve stimulation

overactivity, enhancement of bladder capacity, augmentation of urethral sphincter tone, and reinstatement of colorectal motility and feeling [11].

SNS is clinically indicated for the management of refractory lower urinary tract symptoms, including overactive bladder (OAB) with urge incontinence, urinary urgency-frequency, non-obstructive urinary retention, chronic fecal incontinence, and specific types of chronic pelvic pain, following the failure of conservative treatments [21]. The efficacy is often evaluated during an initial peripheral nerve examination (PNE) or a staged implant procedure, confirming symptomatic improvement prior to the permanent implantation of the IPG.

2.2 Non-Invasive Neuromodulation

Non-invasive neuromodulation techniques do not require surgical intervention. Transcranial Magnetic Stimulation (TMS) utilizes a powerful, pulsed magnetic field generated by an external coil to induce an electrical current in specific brain regions, thereby modulating neuronal activity and proving useful in the treatment of illnesses such as depression [22]. Transcranial Direct Current Stimulation (tDCS) administers a mild, continuous electrical current through electrodes placed on the scalp to modulate cortical excitability [23]. Peripheral Nerve Stimulation (PNS) is the use of electrodes on the skin to deliver electrical stimulation to nerves in the extremities or torso, promoting pain relief and muscle regulation without necessitating an implanted device [24]. These non-invasive techniques are more secure and accessible than their intrusive alternatives.

Transcranial Magnetic Stimulation (TMS): Transcranial magnetic stimulation (TMS) is a non-invasive therapy that employs a magnetic coil placed on the scalp to provide brief, targeted magnetic pulses. This technique entails generating a time-varying magnetic field within brain tissue through the application of an electric field, grounded on Faraday's law of electromagnetic induction. Neurons in the neocortex generate an action potential when the intracranial electric field induces depolarization. The treatment coil is the essential component of a TMS system. It typically contains a wire coil that rapidly transmits a high-current electrical pulse, as illustrated in figure 6. This rapid discharge generates a potent magnetic field that last briefly and can penetrate the scalp and skull with minimal attenuation of strength. The induced electric field generates an electrical current that traverses the neuronal cell membrane. This current induces a modification in the transmembrane potential (membrane polarization), which may result in either depolarization or hyperpolarization of the neuron. If the induced current is sufficiently strong and appropriately directed, it can lead to the depolarization of the neuron and the generation of an action potential. The induced electric field is most effective in stimulating neurons with axons aligned parallel to the direction of the induced current. The modified neuronal activity, especially by rTMS, is believed to facilitate the modulation and release of several neurotransmitters (such as serotonin, norepinephrine, and dopamine), which is essential for its therapeutic efficacy in disorders like depression. Transcranial magnetic stimulation (TMS) is thought to provide therapeutic benefits by modulating cortical excitability; low-frequency TMS (1 Hz or less) inhibits cortical firing, while high-frequency TMS (>1 Hz) facilitates it [25].

The Food and Drug Administration (FDA) has sanctioned transcranial magnetic stimulation (TMS) for the treatment of migraines, major depressive disorder (MDD), and various other mental health conditions. It is also utilized to aid folks in quitting smoking when other methods have been unsuccessful. The medication is thought to mitigate depression by stimulating the dorsolateral prefrontal cortex (DLPFC), a brain area commonly hypoactive in individuals with depression, yet essential for mood regulation. In addition to approved applications, rTMS has been explored as a potential treatment for many neurological and psychiatric illnesses, including Tourette's syndrome, chronic pain syndrome, and some movement disorders like Parkinson's disease [26].

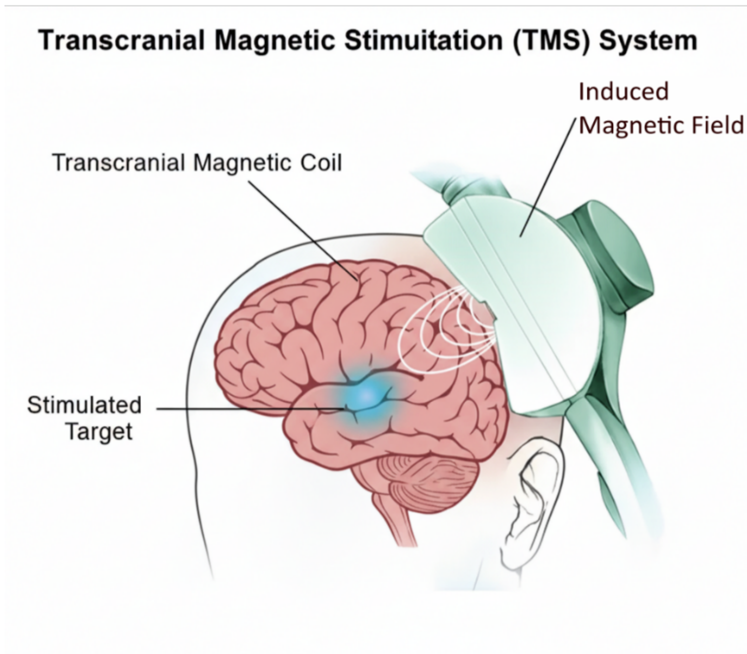

Fig 6. Transcranial Magnetic Stimulation System

Transcranial Direct Current Stimulation (tDCS): Transcranial Electrical Stimulation (tES) encompasses non-invasive methods for brain stimulation utilizing electrical currents. Transcranial direct current stimulation (tDCS) utilizes electrodes to administer a continuous, low direct current to the skull, as depicted in figure 7. This modification alters the neuron's resting membrane potential, hence affecting its excitability [27]. Cathodal (negative) stimulation hyperpolarizes the neuron, while anodal (positive) stimulation depolarizes it and elevates the firing rate. Changes in the cortex may endure beyond the stimulation period, potentially promoting long-term potentiation and depression, the mechanisms by which the brain undergoes transformation. Extended tDCS can elicit alterations akin to long-term potentiation (LTP) and long-term depression (LTD) of synaptic connections. Anodal tDCS is often linked to an increase in glutamate (or Glx: glutamate + glutamine) activity in the stimulated cortex. Anodal tDCS generally associates with a decrease in gamma-aminobutyric acid (GABA) levels, leading to heightened cortical excitability. The effects of cathodal tDCS on GABA are intricate, although it can also reduce GABA levels in interconnected areas.

Transcranial Direct Current Stimulation (tDCS) was originally developed for the treatment of brain injuries and neuropsychiatric disorders. It now exhibits promise in treating mild, severe, and treatment-resistant depression. It also exhibits potential for the treatment of schizophrenia, anxiety, and post-traumatic stress disorder (PTSD) [28].

Research demonstrates that tDCS improves cognitive function and aids recovery from impairments beyond the field of psychiatry. When integrated with intense rehabilitation, tDCS can aid stroke patients in improving their motor skills and speech therapy for aphasia [29]. Transcranial Direct Current Stimulation (tDCS) enhances memory in Alzheimer's disease via regulating hippocampal activity [23]. It enhances executive function and decision-making in patients with traumatic brain injury and addiction.

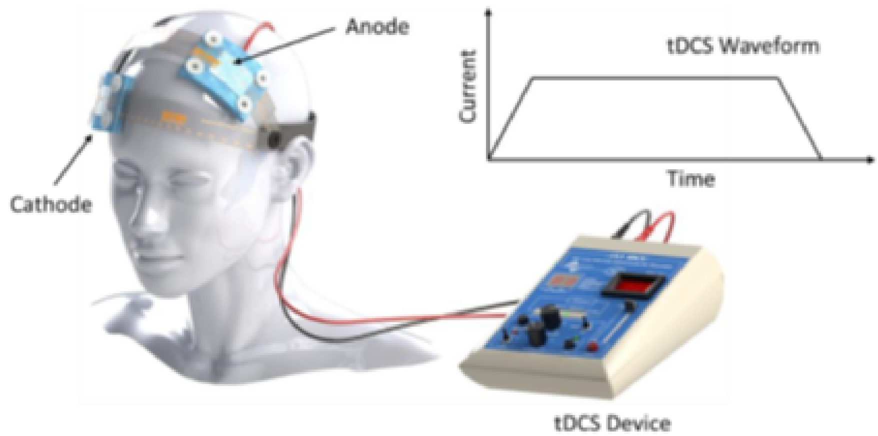

Fig 7. tDCS device and associated waveform (Source: Soterix Medical devices)

Peripheral Nerve Stimulation (PNS): Peripheral nerve stimulation (PNS) mitigates chronic pain. Figure 8 demonstrates that an implantable electrical device delivers mild electrical impulses to a peripheral nerve outside the brain and spinal cord. The peripheral nervous system obstructs the transmission of pain signals from nerves to the brain. This modifies the perception of pain and its effects on you. The device delivers a mild electrical current throughout the body, mitigating pain by eliciting sensations of tingling or pleasure [30]. This disruption hinders the brain's capacity to interpret pain signals, leading to pain relief. Temporary systems utilize a simple outpatient procedure to place a slender, wire-like electrode in proximity to the nerve. A minimally intrusive technique ensures patient comfort and convenience. Electrodes powered by batteries are attached to the body. A 60-day trial is conducted before the placement of a permanent implant to assess therapeutic efficacy. After a successful trial, permanent implantable systems must enter a crucial phase. A surgeon will subcutaneously implant a pulse generator and connect it to the electrode. The individual controls the entire system with a tiny device. PNS targets localized chronic pain that has not responded to medication or physical therapy. Diabetic neuropathy causes chronic nerve pain [31]. This illness causes chronic discomfort and reduces quality of life

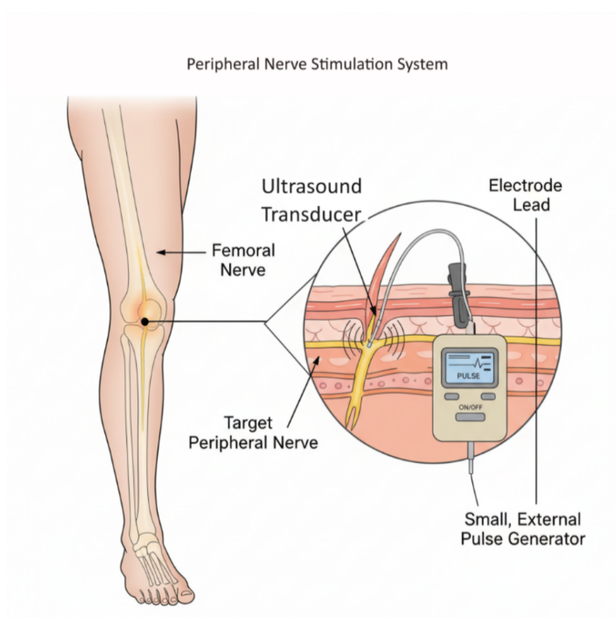

Fig 8. Peripheral Nerve Stimulation Device

2.3 Comparison of Techniques

Table 1 shows the comparative analysis of different Neuromodulation techniques, indicating its invasiveness level, applications, efficacy/remission rate and key side effects with potential risks.

Table 1. Comparative analysis of different Neuromodulation Techniques

Technique	Invasiveness Level	Primary Applications	Typical Efficacy/Remission Rate	Key Side Effects and Risks
Deep Brain Stimulation (DBS)	Invasive	Parkinson's disease, essential tremor, dystonia, OCD	70-80% symptom improvement in well-selected PD patients	1% risk of stroke/hemorrhage, infection, device malfunction, speech/balance problems
Spinal Cord Stimulation (SCS)	Invasive	Chronic pain (FBSS, CRPS, neuropathic pain) [32]	50%+ pain reduction	Lead migration, lead fracture, infection, loss of effectiveness [33]
Vagus Nerve Stimulation (VNS)	Invasive	Drug-resistant epilepsy, treatment-resistant depression [17]	Significant seizure reduction, sustained benefits	Voice changes, cough, throat pain, trouble swallowing [34]
Transcranial Magnetic Stimulation (TMS)	Non-Invasive	Major depression, OCD, migraines.	50% response, 30%+ remission (rTMS) up to 86% response, 79% remission (SAINT)	Scalp discomfort, headache, rare seizure risk (0.1%)
Transcranial Direct Current Stimulation (tDCS)	Non-Invasive	Depression, cognitive enhancement, stroke rehabilitation [35] [36]	Moderate benefit for depression; promising for other conditions	Tingling/itching on scalp, nausea
Transcutaneous Electrical Nerve Stimulation (TENS)	Non-Invasive	Short-term & long-term pain relief [37]	Temporary relief; does not work for everyone	Tingling sensation (paresthesia)

2.4 Simulation tools and their importance

Simulation tools are essential for neuromodulation technologies enumerated in Table 2 because of the invisible, complex, and individualized effects of electrical or magnetic stimulation on the nervous system. These tools provide critical information into the mechanism of action, enabling optimization, customization, and safety assessment.

Predicting the Field and Target Engagement: The primary objective of simulation is to predict the Volume of Tissue Activated (VTA) or the produced Electric Field (E-field). Deep Brain Stimulation (DBS) and Spinal Cord Stimulation (SCS): The effectiveness of these interventions depends on the accurate positioning of the electrode and the adjustment of stimulation parameters to target a specific, minute brain region (e.g., the subthalamic nucleus for Parkinson's disease or specific spinal pathways for pain management). Simulation techniques, including Finite Element Modeling, are crucial for defining the electrical environment around the implanted electrode and predicting the neural pathways that are either stimulated or inhibited. This is crucial for optimizing programming, improving treatment efficacy, and minimizing undesirable effects. [38], [39], [40]

TMS and tDCS: Since the stimulation is non-invasive, the current or magnetic field must penetrate the scalp, skull, and cerebrospinal fluid. Simulation (SimNIBS, ROAST) is the exclusive technique for accurately calculating the intensity and dispersion of the electric field that successfully reaches the designated brain area, enabling personalized electrode or coil placement.

Enabling Personalized and Precise Therapy: Neural anatomy, encompassing brain size, skull thickness, spinal cord geometry, and nerve placement, demonstrates significant variability among people.

Patient-Specific Modeling: Simulation programs create customized models with MRI or CT data. This allows physicians and researchers to account for individual variability, which is especially crucial for implantable devices (DBS, SCS, VNS) to ensure precise lead placement and accurate current supply [38]

High-Definition/Directional Stimulation: Recent advancements, like directional DBS leads and high-definition tDCS, provide a wide range of potential stimulation settings. Simulation is crucial for the rapid and secure assessment of diverse options, progressing beyond tedious "trial-and-error" clinical programming to efficiently optimize parameters.

Safety and Mechanism of Action (Research & Development): Simulation is crucial for the research and commercialization of devices and protocols. These devices focus on peripheral nerves, specifically the vagus nerve or peripheral sensory nerves. Simulation enables researchers to examine the correlation between electrode design, stimulation parameters (waveform, frequency), and selective activation of nerve fibers (e.g., A, B, or C fibers) to elucidate the mechanism of therapy and guarantee safe physiological stimulation [38].

Evaluating Novel Waveforms: Prior to expensive and hazardous human trials, it is essential to model brain tissue to assess new stimulation protocols such as high-frequency spinal cord stimulation and burst stimulation.

Training and Surgical Planning: Invasive treatments like as DBS and SCS require extraordinary precision. Surgical simulators, like the SCS Module of SPINE Mentor, are employed to educate surgeons on the complex techniques of lead insertion inside a safe virtual environment.

Trajectory Planning: Simulation software aids the neurosurgeon in identifying the safest and most efficient route for Deep Brain Stimulation (DBS), guaranteeing the avoidance of critical structures such as blood vessels.

Table 2. Simulation tools available for Neuromodulation techniques: Description, features and system requirements

Technique	Simulation tool Description	Importance of Simulation	Name of Simulation Tool	Specification and minimum requirement for simulation setup
Deep Brain Stimulation (DBS)	Programming software that integrates patient anatomy and the visual effect map to assist physicians in linking stimulated structures to clinical outcomes.	• It selects targeted anatomy and avoids other regions. • Algorithm generated patient- specific stimulation plan.	Illumina 3D Technology	Dedicated embedded software for Vercise Deep Brain Stimulation System
Spinal Cord Stimulation (SCS)	The SPINE Mentor simulator integrates synthetic soft tissues, a 3D-printed spinal model, and sophisticated virtual reality technology to facilitate training with exceptional tactile precision and visual authenticity.	• It facilitates the execution of a comprehensive spinal intervention under real-time fluoroscopic supervision, encompassing palpation, needle placement utilizing the loss-of-resistance approach, and puncture. Prompt feedback directs the trainee until a successful puncture is achieved.	SPINE Mentor	The core gear, including the computer and graphics card, is pre-configured by Surgical Science to satisfy the simulator's performance requirements

Continued on next page

Table 2 continued

Vagus Nerve Stimulation (VNS)	A commercial platform enabling the development of functionalized vagus nerve models integrated within authentic human anatomical models. It is employed to examine neurostimulation, encompassing electromagnetic (EM) simulations, to forecast E-field dispersion and fiber recruitment.	• Trainees practice the insertion of percutaneous electrodes into the epidural space, employing the loss of resistance approach and dynamic force feedback. The section encompasses cases featuring various anatomical variances.	Sim4Life (with T-NEURO feature)	• CPU: x64 architecture with sufficient PCIe lanes to handle multiple GPUs. • RAM: 128 GB. • GPU: Up to 8x of NVIDIA RTX 3080 or RTX 4080 or higher. • Storage: 2 TB NVMe storage for working projects and calculated results. • GPU Support: For CUDA-based solvers (P-EM-FDTD, P-THERMAL, P-ACOUSTICS), Sim4Life supports NVIDIA GPU models with CUDA compute capability 5.0 and above, and requires device drivers that support the CUDA toolkit 11.0 and above
Transcranial Magnetic Stimulation (TMS)	NeMo-TMS denotes the Neuron Modeling for TMS toolbox. This is an open-source, multi-scale computational modeling toolbox utilized by researchers to examine the effects of Transcranial Magnetic Stimulation (TMS) at cellular and subcellular levels.	• Multi-scale Simulation: Facilitates the simulation of TMS effects from the entire head's electric field to individual neuron firing and calcium signaling. • Realistic Modeling: Facilitates the implementation of morphologically precise neuron models featuring intricate dendritic and axonal structures. • Open-Source: The toolkit and guidelines are accessible at no cost to the research community, often hosted on sites such as GitHub. • Protocol Simulation: Accommodates both single-pulse and repeated TMS protocols.	NeMo-TMS (Neuron Modeling for TMS toolbox)	• Operating System: It has been evaluated and is compatible with Microsoft Windows and Ubuntu. • Dependencies/Environment: A functional installation of the NEURON simulation environment is necessary for resolving the cable equation and channel dynamics, and MATLAB is frequently utilized for specific scripts or analyses. • Required Software: The toolbox is intended to be used in conjunction with whole-head modeling software, such as SimNIBS, to deliver macro-scale electric field data.

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Table 2 continued

Transcranial Direct Current Stimulation (tDCS)	An extensively utilized, complimentary, and open-source software suite that employs patient-specific MRI data to produce high-fidelity head models for accurate finite element method (FEM) computations of the induced electric field for both TMS and tDCS.	• SimNIBS is an open-source software available under the GPL 3 license. It comprises automated instruments for picture segmentation, meshing, and electric field modeling.	SimNIBS, ROAST, BONSIA, SPHERES	64-bit Windows 10/11, Linux (e.g., Ubuntu, CentOS), or macOS (Apple Silicon supported)
Transcutaneous Electrical Nerve Stimulation (TENS)	TENS simulation primarily concentrates on simulating the electric field distribution in peripheral tissues (skin, muscle, fat) to comprehend how the location of surface electrodes and stimulation patterns activate the underlying peripheral nerves.	• The procedure entails constructing the anatomical geometry, assigning tissue-specific electrical characteristics, modeling the electrodes, and subsequently calculating the electric potential distribution.	COMSOL	Model Size (Degrees of Freedom) Approximate RAM Requirement ∼1 million DOF (coarse model) 8 GB – 16 GB ∼5 million DOF (detailed limb/organ) 32 GB – 64 GB ∼10 million+ DOF (high-resolution model), 128 GB+ (often requiring an HPC or server)

3 Discussion

Success in Deep Brain Stimulation (DBS) is characterized by a substantial and enduring decrease in the primary motor symptoms of Parkinson's disease (PD), Essential Tremor, or Dystonia, frequently enabling a reduction in medication and enhancement of quality of life. Patients who exhibit a favorable response to medicine yet experience debilitating side effects such as dyskinesia are the most suitable candidates. Unfavorable results often arise from improper patient selection, especially in those with significant cognitive impairment, dementia, or predominant non-motor complaints (such as gait or speech difficulties) that deep brain stimulation cannot adequately address. Additional causes of failure encompass improper lead positioning during surgery or insufficient post-operative device programming.

In Spinal Cord Stimulation (SCS), success is often defined as a minimum 50% decrease in chronic intractable pain, particularly for Failed Back Surgery Syndrome (FBSS) and Complex Regional Pain Syndrome (CRPS), facilitating enhanced functionality and less dependence on opioids. Conversely, failure frequently results from a deficiency or deterioration of pain relief over time, or hardware issues, such as the migration of the stimulating lead from its optimal position, necessitating additional surgical intervention. Active psychological problems, such as severe, untreated depression or anxiety, are significantly associated with adverse SCS results.

Vagus Nerve Stimulation (VNS) is deemed successful when it effectively complements treatment for refractory epilepsy by markedly decreasing seizure frequency or severity, and for treatment-resistant depression (TRD) by delivering a gradual, modest, yet enduring antidepressant effect over time. Unsuccessful VNS applications typically pertain to patients who fail to attain a significant clinical response. Moreover, intolerable side effects such as hoarseness, coughing, or throat pain, which frequently arise from the nerve's role in vocal cord function, can lead to treatment failure, prompting some patients to cease usage or undergo device explantation.

For Sacral Nerve Stimulation (SNS) to work, it has to help people with conditions that don't respond to other treatments, like Overactive Bladder (OAB) and Fecal Incontinence (FI). A successful outcome is when symptoms improve by at least 50% (for example, when there are fewer leaks or voids). The main problem that keeps people from succeeding is that the temporary trial phase, in which the device is tested for a short time before being permanently implanted, doesn't work. Long-term failure can also happen with SCS when the electrode lead moves too close to the sacral nerves, which can cause problems like infection or pain at the implant site.

Table 2 delineates the function of simulation and computational modeling in diverse neuromodulation techniques, such as Deep Brain Stimulation (DBS), Spinal Cord Stimulation (SCS), Vagus Nerve Stimulation (VNS), Transcranial Magnetic Stimulation (TMS), Transcranial Direct Current Stimulation (tDCS), and Transcutaneous Electrical Nerve Stimulation (TENS).

The data unequivocally illustrates the escalating sophistication and vital significance of these tools in clinical practice (planning and training) and research (comprehending mechanisms of action).

For implanted techniques such as DBS, Illumina 3D Technology is recognized for its capacity to create patient-specific stimulation plans by amalgamating patient anatomy with visual effect maps. This enables surgeons to accurately identify target anatomy and circumvent unwanted areas, thereby enhancing clinical outcomes and minimizing side effects. Likewise, VNS modeling with Sim4Life facilitates the prediction of E-field distribution and fiber recruitment, essential for optimizing stimulation parameters prior to implantation.

The SPINE Mentor for SCS exemplifies a sophisticated virtual reality platform designed to facilitate training with remarkable tactile accuracy and visual realism. It enables the performance of intricate spinal procedures under simulated real-time fluoroscopic oversight, providing immediate feedback until accurate needle placement is accomplished. This high-fidelity simulator significantly mitigates the risks linked to first human procedures and expedites learner proficiency. Implanted devices frequently depend on specialized commercial software, such as Illumina 3D Technology for the Vercise DBS system, which is intricately linked to the device's working specifications. SPINE Mentor constitutes a specialized, integrated platform dedicated to procedural instruction.

Sim4Life and COMSOL, utilized for TENS, are sophisticated commercial tools adept at intricate electromagnetic (EM) and multi-physics simulations. The elevated specifications and minimum requirements for Sim4Life, which include up to 8 high-performance GPUs and 128 GB of RAM, highlight the computing demands necessary for precise, high-resolution electromagnetic simulations in heterogeneous biological tissues.

Computational tools facilitate a comprehensive understanding of the biological impacts of non-invasive procedures. NeMo-TMS enables multi-scale simulation, modeling TMS effects from the comprehensive electric field of the head to the specific firing of individual neurons and calcium signaling. This is essential for creating realistic, morphologically accurate neuron models and evaluating various stimulation regimes. Similarly, SimNIBS for tDCS utilizes patient-specific MRI data to generate high-fidelity head models for precise finite element method (FEM) calculations of the induced electric field, which is essential for optimizing electrode placement and current dose.

The prevalence of open-source tools such as NeMo-TMS and SimNIBS (including ROAST, BONSIA, and SPHERES) is markedly significant. The open-source characteristics of NeMo-TMS and the provision of SimNIBS under the GPL 3 license facilitate equitable access to advanced modeling for the research community. These technologies depend on external software such as the NEURON simulation environment (for NeMo-TMS) and whole-head modeling software (for SimNIBS), underscoring a network of specialized, interrelated computing resources. SimNIBS's extensive interoperability with Windows, Linux, and macOS facilitates its widespread use.

4 Future Directions and Challenges

The field of neuromodulation is transitioning from fixed, anatomical targeting to personalized, dynamic, and network-focused therapy. Future success hinges on overcoming numerous essential scientific and engineering challenges.

Parameter Optimization: The primary challenge in optimizing neuromodulation is the considerable variability in patient responses, often due to the standardization of current device parameters (e.g., amplitude, frequency, pulse width).

Responsive neuromodulation: Real-time biomarkers, such as aberrant neural oscillations and local field potentials, autonomously modify stimulation parameters. Targeted stimulation may enhance efficacy, minimize side effects, and conserve battery life. Creating personalized computational models requires patient-specific imaging data, including fMRI and DTI, in conjunction with machine learning and AI methodologies. These models forecast the ideal stimulation aim and parameters for dysfunctional brain circuits, rather than exclusively depending on physical landmarks.

4.1 Mechanism of Action: Bridging the Micro and Macro Scales

Despite the efficacy of neuromodulation, its cellular and network mechanisms remain unidentified. Research must delineate acute effects (e.g., local neuronal inhibition or excitation and transiting fibers) resulting from the neuroplastic changes (synaptogenesis, gene expression, neurotransmitter release) induced by chronic stimulation. The brain constitutes a dynamic network rather than discrete entities. The effects of stimulation will be examined to determine its impact on the restoration of brain networks, namely the cortico-basal ganglia-thalamic loop associated with Parkinson's disease. Functional neuroimaging and sophisticated electrophysiology are necessary.

4.2 Expanded Clinical Indications

With advancements in technology and an enhanced understanding of brain networks, neuromodulation is being investigated for both neurological and psychological illnesses. Research on Alzheimer's Disease (AD) and dementia concentrates on memory circuits, including the fornix and the nucleus basalis of Meynert, to improve cognitive function. DBS and tDCS/TMS trials have shown promise in improving memory and verbal learning.

Neuromodulation is being explored to disrupt reward and executive control circuits (Nucleus Accumbens, Dorsolateral Prefrontal Cortex) to diminish cravings and drug-seeking behavior in addiction and substance use disorders. Targeting the amygdala and ventromedial prefrontal cortex by invasive and non-invasive techniques may mitigate hyperarousal and fear-conditioning symptoms associated with post-traumatic stress disorder.

4.3 Technological Progress: Miniaturization and Accuracy

Advanced hardware is necessary to make neuromodulation safer, more effective, and more accessible. Compact, rechargeable, and computationally robust devices are essential for closed-loop operation. Examples encompass high-density electrode arrays for precise stimulation and cordless, battery-free implants operated externally. Advanced non-invasive therapies, such as Focused Ultrasound (FUS), provide exact spatial accuracy for the temporary or permanent modification of deep brain regions without surgical intervention. Furthermore, improving TMS coil designs will yield more profound and targeted non-invasive stimulation.

The use of biosensors will allow future implanted devices to employ multimodal sensors for the real-time monitoring of electrical activity, neurochemistry (including neurotransmitter levels), temperature, and pH to enable therapeutic modifications.

5 Conclusion

Neuromodulation, which includes methods like Deep Brain Stimulation (DBS) and Transcranial Magnetic Stimulation (TMS), is a major step forward in treating neurological and psychiatric disorders that don't respond to other treatments. This review synthesized the current landscape, showing that these electrical and magnetic therapies provide a targeted approach for directly modulating diseased brain circuits with greater spatial and temporal specificity than conventional pharmacotherapy.

The logical and technological advancement in this domain is the shift from static, open-loop stimulation to adaptive, closed-loop neuromodulation (c-LNM) systems. To move forward with c-LNM, we need to do focused research in three related areas: Finding and validating biomarkers: Progress depends on the reliable discovery and real-time sensing of validated electrophysiological biomarkers (such as specific oscillatory activity) that strongly correlate with therapeutic efficacy, allowing for true on-demand and responsive therapy.

Hardware Evolution and Accessibility: Improving minimally invasive delivery systems like Focused Ultrasound (FUS) and creating very small, wirelessly powered implantable devices are important steps to make surgery less painful, lower costs, and make treatment for common conditions like Alzheimer's and chronic pain more widely available.

Data Science and Precision Dosing: To turn complex neural sensing data into personalized and optimized dosage plans for each patient, it is important to use standardized, large-scale data collection and strict AI-driven algorithms.

There are still a lot of big problems that make it hard for c-LNM to be widely used, even though it has a lot of potential as a treatment. Some of these problems are that there aren't any standardized protocols for collecting data from multiple centers, that current invasive DBS systems are expensive and invasive at first, and that it is hard to get adaptive, non-deterministic devices approved by regulators. Additionally, a more profound comprehension of the specific cellular and molecular mechanisms that facilitate long-term neuroplasticity and therapeutic efficacy constitutes a significant scientific deficiency.

In conclusion, the effectiveness of neuromodulation in accurately altering dysfunctional brain activity guarantees its ongoing significance as a primary conduit for clinical innovation. By systematically integrating advanced neurology, biomedical engineering, and data science to overcome these recognized constraints, the field is poised to fully implement closed-loop control and deliver a new generation of adaptive therapies.

6 Appendix 1

7 Financial Disclosure/Conflict of Interest:

The authors declare that there was no financial aid received, and no conflict of interest associated with this research work.

Sr. No	Abbreviation	Description
1	AD	Alzheimer's Disease
2	CNS	Central nervous system
3	CRPS	Complex regional pain syndrome
4	DBS	Deep Brain Stimulation
5	DLPFC	Dorsolateral prefrontal cortex
6	DRE	Drug-resistant epilepsy
7	DTI	Diffusion-Tensor Imaging
8	FBSS	Failed Back Surgery Syndrome
9	FDA	Food and drug administration
10	fMRI	Functional Magnetic Resonance Imaging
11	FUC	Focused Ultrasound
12	GPCRs	G-protein coupled receptors
13	Hz	Hertz
14	IPG	Implantable pulse generator
15	MDD	Major depressive disorder
16	OAB	Overactive bladder
17	OCD	Obsessive-compulsive disorder
18	PD	Parkinson's disease
19	PNE	Peripheral nerve evaluation
20	PNS	Peripheral nervous system
21	RNS	Responsive Neurostimulation
22	ROAST	Realistic, Volumetric Approach to Simulate Transcranial Electric Stimulation
23	SCS	Spinal Cord Stimulation
24	SimNIBS	Simulation of Non-invasive brain stimulation
25	SNS	Sacral Nerve Stimulation
26	STN	Subthalamic nucleus
27	tDCS	Transcranial Direct Current Stimulation
28	tES	Transcranial Electrical Stimulation
29	TMS	Transcranial Magnetic Stimulation
30	VNS	Vagus Nerve Stimulation

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