RJNMSR
Review Journal of Neurological & Medical Sciences Review

Volume 4, Issue 2, 2026

NEUROMODULATION IN BRAIN FUNCTIONAL DISORDERS: TECHNOLOGICAL FRONTIERS, CLINICAL PARADIGMS, AND THE FUTURE OF NEURAL CIRCUIT INTERVENTIONS: A NARRATIVE REVIEW

Eeman Salam[1], Hafsa Asif[2], Ayesha Javaid Baig[3], Laheem Ullah Khan[4], Alina Hamid[5], Sameer Ali[6], Mohsin Mushtaq Ali[7], Mubashir Raza[*8]

[1,2,3,4,5,6,7,*8]*Department of Medicine, Baqai Medical University, Karachi, Pakistan*

[1]eemans9@gmail.com, [2]asifhafsa373@gmail.com, [3]ayeshajavaidbg@gmail.com, [4]laheemullah@gmail.com, [5]alinahamid245@gmail.com, [6]drsameer442@gmail.com, [7]drmohsinmushtaqali@gmail.com, [*8]mubashir19raza@gmail.com

[*8]https://orcid.org/0009-0007-3041-2099

Corresponding Author: *
Mubashir Raza

DOI: https://doi.org/10.5281/zenodo.18871292

Received	Accepted	Published
29 December 2025	13 February 2026	28 February 2026

ABSTRACT

Introduction

Neurological disorders affect over 3 billion people globally and represent the leading cause of disability and mortality worldwide. Conventional pharmacotherapies often fail in treatment-resistant cases, necessitating innovative circuit-based interventions. Neuromodulation, including deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), spinal cord stimulation (SCS), vagus nerve stimulation (VNS), and responsive neurostimulation (RNS) has emerged as a transformative therapeutic paradigm for brain functional disorders.

Methods

This narrative review synthesizes recent clinical trials, systematic reviews, and technological advancements (2024–2026) in invasive and non-invasive neuromodulation. Emphasis was placed on adaptive closed-loop systems, personalized targeting strategies, waveform innovations, and integration of artificial intelligence (AI) in therapeutic modulation across movement disorders, depression, chronic pain, epilepsy, and systemic inflammatory conditions.

Results

Adaptive DBS demonstrated significant improvements in "on" time without dyskinesia and reduced energy consumption compared to conventional stimulation. Functional magnetic resonance imaging (fMRI) guided TMS improved response rates in treatment-resistant depression (77.5% vs. 62.2% with standard targeting). Closed-loop SCS using Evoked Compound Action Potential (ECAP) sensing provided stable pain control, while novel waveforms such as Differential Target Multiplexed (DTM) enhanced modulation of neuron–glial interactions. Non-invasive VNS showed promising anti-inflammatory and analgesic effects. In epilepsy, RNS achieved progressive seizure reduction up to 75% over long-term follow-up. AI-driven closed-loop systems and neuromorphic computing enabling real-time signal decoding and personalized stimulation adjustments.

Conclusion

Neuromodulation is transitioning from static, symptom-based therapy to precision, adaptive circuit intervention. Integration of closed-loop technology and AI promises improved efficacy, reduced *adverse effects, and expanded indications. Ensuring equitable access and ethical oversight will be essential as these technologies redefine the future of brain disorder management.*

Keywords: *Neuromodulation; Chronic Pain; Vagus Nerve Stimulation; Movement disorders; Deep Brain Stimulation; Brain disorders; Epilepsy; Seizures*

1. INTRODUCTION

The global health landscape is currently confronting an unprecedented crisis regarding the prevalence and management of neurological conditions. According to the 2024 and 2025 reports from the World Health Organization (WHO), neurological disorders have emerged as the leading cause of illness and disability worldwide, affecting over one-third of the global population, approximately 3.4 billion individuals [World Health Organization Report, 2025]. This staggering figure underscores a profound public health challenge, as the total health burden linked to these conditions has risen by 18% since 1990, a trend driven largely by demographic shifts and an aging global population [Shu Wang et al., 2025]. The socioeconomic implications are equally severe, with neurological conditions responsible for over 11 million deaths annually and a massive loss of human capital and economic productivity [World Health Organization 11 million lives lost each year, 2025].

The burden is not distributed equitably across the globe. Low and middle-income countries experience over 80% of neurological-related deaths and health loss, yet they face a critical shortage of specialists [World Health Over 1 in 3 people affected with neurological conditions, 2024]. High income nations possess up to 82 times more neurologists per 100,000 people compared to low-income regions [World Health Organization Report, 2025]. This disparity means that for billions, timely diagnosis, effective treatment, and ongoing care remain structurally inaccessible. Furthermore, less than one in three countries possesses a national policy to address the growing burden, and only 25% of WHO member states include neurological care within their universal health coverage benefit packages [World Health Organization 11 million lives lost each year, 2025]. In response to this escalating crisis, the intersectoral global action plan on Epilepsy and other neurological disorders 2022–2031 (IGAP) was adopted to improve prevention, identification, and treatment [World Health Organization Report, 2025]. Within this context, neuromodulation has emerged as a transformative therapeutic paradigm. By modulating neural circuits to restore normal function, techniques such as deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), and spinal cord stimulation (SCS) offer alternatives to traditional pharmacological therapies that are often inadequate for treatment-resistant cases [Davidson et al., 2024].

The urgency of this situation is mirrored in regional initiatives, such as the Spanish Brain Plan, which seeks to synthesize evidence on the burden of brain disorders in Spain, where approximately 43% of the population lives with a neurological disorder and 29% experience mental health problems [Robles et al., 2025]. Overall epidemiology across the globe has been shown in **Table 1.** These plans prioritize neuroscience research and the implementation of integrated care pathways, emphasizing the need for translational and evidence-based medicine and the adoption of cutting-edge technologies like closed-loop neuromodulation [Robles et al., 2025].

Table 1: Epidemiological profile of global neurological health

Metric	Global Status (2021-2025 Baseline)	Key Drivers and Barriers
Total Affected Population	> 3 billion (approx. 43% in certain regions)	Aging population, demographic shifts, COVID-19 complications
Annual Mortality	11 million deaths globally	Lack of national policies; limited specialist access
Leading Causes of DALYs	Stroke, Neonatal Encephalopathy, Migraine, Dementia	Lifestyle factors (smoking, high blood glucose, lead exposure)
Specialist Density (High-Income)	~70-82 neurologists per 100k people	Concentration in urban centers
Specialist Density (Low-Income)	< 1 neurologist per 100k people	Severe workforce training gaps
Burden Growth (since 1990)	18% increase in absolute Disability-Adjusted Life Years (DALYs)	Diabetic neuropathy identified as fastest-growing condition

2. Deep Brain Stimulation: Technological Evolution and the Move Toward Adaptive Personalization

Deep brain stimulation (DBS) has served as a cornerstone for managing medication-refractory movement disorders, including Parkinson's disease (PD), essential tremor (ET), and dystonia [Zaib et al., 2025]. The procedure involves the implantation of a neurostimulator that delivers electrical impulses to specific brain regions, typically the subthalamic nucleus (STN) or the globus pallidus internus (GPi) effectively modulating pathological neural network activity. While traditional continuous DBS (cDBS) has provided relief for decades, it is fundamentally limited by its static nature. Parkinson's symptoms are inherently dynamic, fluctuating based on medication cycles, sleep patterns, and physical activity. Delivering a constant electrical current can lead to overstimulation, causing side effects such as dyskinesia or speech impairment, or under stimulation, leaving the patient in an "off" state.

3. The ADAPT-PD Trial and BrainSense™ Technology

The most significant recent advancement in this field is the development of adaptive deep brain stimulation (aDBS), as evidenced by the results of the Medtronic Adaptive DBS Algorithm for Personalized Therapy in Parkinson's Disease (ADAPT-PD) trial [Peprah et al., 2021; Bronte-Stewart et al., 2025]. Published in JAMA Neurology in late 2025, this trial evaluated the world's first closed-loop DBS system, utilizing BrainSense™ technology to sense and respond to unique brain activity in real time [Bronte-Stewart et al., 2025].

The technology identifies local field potentials (LFPs), specifically beta-band oscillations, which serve as biomarkers for motor dysfunction. When the system detects high beta activity, it automatically increases stimulation; as beta activity subsides, the stimulation is dialed back. Refer to **Table 2.**

Table 2: Clinical efficacy and patient outcomes in deep brain stimulation

Outcome Metric	Result (aDBS vs. cDBS)	Clinical Implication
"On" Time without Dyskinesia	Significant improvement (Primary Endpoint met)	Enhanced motor control without adverse movements
Additional "On" Time (Dual Mode)	+1.3 hours average	Clinically meaningful extension of functional time
Reduction in "Off" Time	-1.6 hours average	Reduced periods of being undertreated
Patient Preference	98% (44/45 participants)	High subjective preference for adaptive therapy
Energy Consumption	Reduced Total Electrical Energy Delivered (TEED)	Potential for increased battery longevity

This evolution toward a "smart" pacemaker for the brain allows for a degree of personalization previously unattainable. Beyond the ADAPT-PD trial, research at institutions UCSF [accessed on 2026] is exploring a DBS for a broader range of functional disorders, including treatment-resistant depression, bipolar disorder, obsessive-compulsive disorder (OCD), and even opioid use disorder. By combining behavioral tasks with neural recordings, researchers aim to uncover the neurophysiological underpinnings of motivation and value-based decision-making in Parkinson's patients, further refining stimulation targets.

4. Surgical Innovations and Global Accessibility

Technological breakthroughs are not confined to algorithms. The physical components of DBS are also evolving. Directional leads now allow clinicians to focus on electrical current more precisely, minimizing stimulation of adjacent structures that cause side effects. Furthermore, robotic-assisted lead placement and multimodal imaging have refined the surgical target accuracy, reducing the variability of outcomes [Zaib et al., 2025]. In a global context, the expansion of DBS centers is being supported by telemedicine-enabled remote programming. This is particularly vital in countries like China, where large populations and vast distances make frequent in-person clinic visits impractical. However, emerging programs in Africa still face substantial resource limitations, highlighting the need for equitable access strategies to ensure that these precision neuromodulation therapies do not remain limited to high-income settings.

5. Transcranial Magnetic Stimulation: Personalization through Functional Connectivity

Transcranial magnetic stimulation (TMS) represents a non-invasive frontier in the treatment of major depressive disorder (MDD) and other neuropsychiatric conditions. By utilizing electromagnetic induction to stimulate neuronal depolarization, rTMS modulates cortical excitability [Liu et al., 2025]. Despite its approval, variability in patient response has historically hindered its broader application, with conventional targeting relying on anatomical landmarks (the "5 cm rule" or Beam F3) that do not account for individual structural and functional differences.

6. Functional Magnetic Resonance Imaging Guided Targeting and the Subgenual Cingulate Connection

A paradigm-shifting study published in 2025 provides evidence that personalizing TMS targets via functional magnetic resonance imaging (fMRI) dramatically improves response rates [Ha et al., 2025; Jiang et al., 2026]. The core of this approach lies in identifying the point in the left dorsolateral prefrontal cortex (L-DLPFC) that shows the strongest negative functional connectivity with the subgenual cingulate cortex (SGC) [Ha et al., 2025]. The SGC is known to be overactive in patients with depression. By stimulating the L-DLPFC target that is most strongly 'anti-correlated' with the SGC, clinicians can more effectively downregulate the overactive emotional processing regions. Refer to **Table 3** for relative comparison in efficacy between fMRI guided and standard TMS.

Table 3: Comparative efficacy between fMRI-Guided vs. Standard TMS

Parameter	**fMRI-Guided rTMS**	**Non-fMRI Guided rTMS**	**Significance**
Response Rate (Matched Analysis)	77.5%	62.2%	p = 0.035; OR = 2.30
Overall Remission Rate (aTMS)	51.8%	N/A	Highly effective in treatment-resistant cases
Predictive Value	Identified as the only independent predictor	N/A	Validates the network-based approach
Number Needed to Treat (NNT)	6.5	N/A	Benefit of fMRI over standard care
Common Side Effects	Headache, site pain, transient anxiety	Similar, but often less frequent	Precision targeting affects specific circuits

7. Accelerated TMS (aTMS) Protocols

The evolution of TMS is further characterized by the adoption of accelerated protocols (aTMS), which condense a traditional six-week treatment course into just five days by delivering multiple sessions (up to 10) per day using intermittent theta-burst stimulation (iTBS). This acceleration leverages neuroscience principles of neuroplasticity, inducing physical rewiring of neural connections in response to concentrated stimulation [Ha et al., 2025, DeSouza et al., 2025].

Research is now moving toward high-risk populations, such as adolescents with suicidal ideation, where the fast-acting nature of aTMS could provide a critical life-saving intervention [ClinicalTrials.gov NCT07025720, 2025; Ha et al., 2025]. Preliminary results from trials like PATH-RAD at UC Davis aim to determine if aTMS can reduce the incidence of hospitalization and improve daily functioning in young adults with MDD.

8. Spinal Cord Stimulation: Innovative Waveforms and Closed-Loop Control

Spinal cord stimulation (SCS) has traditionally been used to manage chronic intractable pain by delivering tonic stimulation to the dorsal columns, creating paresthesia (a tingling sensation) that masks pain. However, the field has undergone a rapid shift toward paresthesia-free strategies and adaptive, closed-loop systems [Zeng and Bhatia, 2025].

9. Closed-Loop SCS (CL-SCS) and ECAP Sensing

One of the primary challenges in SCS is 'overstimulation' or 'under-stimulation' caused by changes in patient posture. When a patient lies down or coughs, the distance between the spinal cord and the lead decreases, causing the electrical current to feel significantly stronger [Zeng and Bhatia, 2025]. Closed-loop systems, currently offered by companies like Saluda and Medtronic, address this by measuring Evoked Compound Action Potentials (ECAPs). It represents the cumulative electrical response of the sensory neurons in the spinal cord. By monitoring these responses in real-time, the pulse generator can automatically adjust its intensity to maintain a constant level of neural activation, providing stable pain relief regardless of the patient's movement.

10. Waveform Innovations: DTM and High-Frequency

Modern SCS systems utilize complex waveforms designed to exert specific biological effects. Differential target multiplexed (DTM) SCS, for instance, targets the neuro-inflammatory state of the spinal cord by modulating both neurons and glial cells. Glial cells outnumber neurons 6:1 and play a central role in maintaining neuropathic pain; DTM uses coordinated signals at varying frequencies to modulate glial activation [Zeng and Bhatia, 2025]. Refer to **Table 4** for further information.

Table 4: Mechanism of action, ranges in frequency, and clinical indication of spinal cord stimulation waveforms.

SCS Waveform	Frequency Range	Mechanism of Action	Clinical Indication
Tonic (PB-SCS)	30–80 Hz	Paresthesia-based; dorsal column gate control	Traditional PSPS, CRPS
High-Frequency (10 kHz)	10,000 Hz	Paresthesia-free; activation of inhibitory interneurons	Axial back pain; sub-perception relief
Burst SCS	~40 bursts/sec	Intermittent high-frequency packets	Targets medial pain pathways; paresthesia-free
DTM-SCS	20–1200 Hz	Multiplexed signals; modulates neuron-glial pathways	Axial back pain; neuroinflammation
FAST Therapy	Proprietary	Rapid-onset sub-perception stimulation	Immediate pain relief needs

These advancements allow for more personalized care. For example, active patients may benefit more from the stability of CL-SCS, while patients with significant axial back pain may find superior relief with DTM waveforms. Expansion of indications has now moved beyond post-laminectomy syndrome to include painful diabetic neuropathy and refractory non-surgical low back pain [Lam et al., 2023; Lempka et al., 2018].

11. Vagus Nerve Stimulation: A Multimodal Approach to Systemic Dysfunction

Vagus nerve stimulation (VNS) has long been recognized for its role in the "anti-inflammatory reflex." As the primary component of the parasympathetic nervous system, the vagus nerve coordinates autonomic function and immune response through its bidirectional communication along the brain-gut axis [Sun et al., 2025].

11.1. Mechanisms of Action and Central Modulation

VNS achieves its therapeutic effects through several interrelated pathways. It activates the cholinergic anti-inflammatory pathway, decreasing the production of pro-inflammatory cytokines such as TNF and IL-6 [Sun et al., 2025; Veldman et al., 2025]. Additionally, it modulates the "pain matrix" in the brain, including the periaqueductal gray (PAG) and the nucleus of the solitary tract (NTS) [Zhang et al., 2026]. Imaging studies confirm that VNS can remodel the PAG network, enhancing its connectivity with the amygdala and sensorimotor cortex, which suggests that VNS modulates not only the intensity of pain but also its emotional and sensory dimensions [Zhang et al., 2026].

11.2. Non-Invasive Vagus Nerve Stimulation (nVNS/taVNS)

The development of non-invasive devices, such as the GammaCore Sapphire or transcutaneous auricular VNS (taVNS), has expanded the reach of this therapy. taVNS targets the auricular branch of the vagus nerve at the cymba concha of the ear [ClinicalTrials.gov NCT07409363, 2026; NCT06912399, 2025]. Now, national Institute of health funded research are currently exploring more precise methods of VNS using specialized devices that can selectively activate specific fibers within the vagus nerve [Feinstein Institutes for Medical Research Report, 2025]. This selectivity aims to maximize therapeutic efficacy for conditions like heart failure and inflammatory bowel disease while minimizing side effects like hoarseness or cardiac changes.

11.3. Neuromodulation in Epilepsy: From Detection to Interdiction

Epilepsy remains a common and disabling condition, with approximately 30% of patients failing to achieve seizure control with anti-seizure medications [Catherine Joachin 2025]. Neuromodulation offers a critical alternative for those who are not candidates for resective surgery due to the seizure focus located in eloquent cortex [Sloka Iyengar and Patricia O. Shafer, 2017].

11.4. Responsive Neurostimulation (RNS) and Closed-Loop Systems

The RNS® System is a prime example of a closed-loop device that continuously monitors brain activity. When it detects patient-specific seizure patterns (ictal electrocorticography), it delivers small electrical pulses to stop the seizure before it spreads [Catherine Joachin 2025]. Unlike VNS or DBS for epilepsy, which deliver stimulation at set intervals, RNS is purely responsive. Clinical outcomes for RNS demonstrate progressive improvement over time. Adults with drug-resistant focal epilepsy have reported a 44% reduction in seizures after one year, rising to 75% after nine years of treatment. Beyond seizure reduction, RNS is associated with improved quality of life, including better cognitive function, memory, and mood.

Recent meta-analyses in 2025 have compared various non-invasive neurostimulation techniques for drug-resistant epilepsy, evaluating their responder rates (the percentage of participants with a >50% decrease in seizure frequency) [Premaratne et al., 2026]. Further findings of the analyses have been shown through **Table 5.**

Table 5: Types of interventions for non-invasive neurostimulation for drug-resistant epilepsy.

Intervention	Responder Rate (RR)	Seizure Frequency Change	Certainty of Evidence
rTMS	33% - 38%	-30.2%	Strongest evidence for effectiveness
tDCS	41% - 49%	-46.9%	Strong evidence; no serious adverse events
tVNS	29% - 34%	-49.2%	Promising but requires more study
TNS	42%	Data limited	Shows promise for seizure control
LI-FUS	Inadequate data	Inadequate data	Emerging; requires further investigation

The ongoing revolution in diagnostic workup, including high-resolution MRI, magnetoencephalography, and stereoencephalography (SEEG)—allows for more precise seizure localization, enabling these neuromodulatory interventions to be tailored to each individual's unique brain network [Ryan Gallagher and Aria Fallah, 2025].

11.5. The Convergence of Artificial Intelligence and Neuromodulation

The future of neuromodulation is inextricably linked to advances in artificial intelligence (AI) and machine learning (ML). These technologies are being integrated into closed-loop systems to decode complex neural signals and provide adaptive feedback [Luis Fernando Herbozo Contreras et al., 2024; Calderone et al., 2025]. AI serves as the "decoding engine" for brain-computer interfaces (BCIs), translating brain signals into commands or therapeutic adjustments [Williams C et al., 2025]. Different ML algorithms offer varying strengths in this context. Refer to **Table 6.**

Table 6: Machine Learning Techniques in Brain Computer Interfaces and Closed-Loop Systems

Algorithm / Technique	Accuracy / Error Rate	Key Strength	Challenge
Convolutional Neural Nets (CNN)	> 90%	High adaptability to complex patterns	High processing cost/latency (~300-500ms)
Support Vector Machines (SVM)	78% - 90%	Efficient for real-time binary tasks	Sensitive to inter-subject variability
Transfer Learning (TL)	Reduces error up to 15%	Ideal for cross-subject adaptation	Moderate training cost
Linear Discriminant Analysis (LDA)	75% - 85%	Very low latency (< 100ms)	Limited to simpler signal types

Recurrent Neural Nets (RNN)	85% - 90%	Effective for time-series EEG data	Computationally intensive

12. Neuromorphic Neuromodulation

A significant bottleneck in current implantable devices is the power consumption and heat constraints of real-time processing. Researchers are now proposing Neuromorphic Neuromodulation, a new breed of responsive feedback systems that utilize hardware designed to mimic biological neural structures [Luis Fernando Herbozo Contreras et al., 2024; Calderone et al., 2025]. These systems could enable continuous, low-power learning on-chip, allowing devices to adapt to a patient's neurophysiology over years without exhausting the battery or causing thermal injury to the brain. The integration of multimodal AI combining neuroimaging, clinical data, and multi-omics will facilitate the identification of novel biomarkers, shifting neuromodulation from a "one-size-fits-all" model to a truly personalized approach [Fang SJ et al., 2025].

13. Socioeconomic Implications and Ethical Considerations in Neuromodulation

The rapid advancement of neuromodulation raises several ethical and practical concerns. As therapies become more personalized and technologically complex, the cost of specialized imaging (like fMRI-guided TMS) and surgical procedures may widen the 'treatment gap' between high-income and low-income populations [World Health Organization 11 million lives lost each year, 2025]. Moreover, the move toward 'intelligent' devices that can alter brain states autonomously require careful ethical oversight. Issues regarding patient agency, the privacy of neural data (neuro-privacy), and the long-term effects of chronic brain circuit intervention must be addressed through robust philosophical and medical inquiry.

Finally, the sustainability of these healthcare interventions depends on a well-trained workforce. With high-income countries facing a shortage and low-income countries facing a crisis, the global medical community must invest in specialized training for neurologists, neurosurgeons, and technicians capable of managing these advanced neuromodulation systems [Shu Wang et al., 2025].

14. Conclusion and Future Recommendation

The current state of research suggests that we are entering a new era of precision medicine for brain functional disorders. Neuromodulation has transitioned from a palliative option of last resort to a sophisticated, adaptive, and highly effective primary therapy for a wide range of debilitating conditions. The integration of closed-loop systems, such as the BrainSense™ aDBS for Parkinson's and the RNS® for epilepsy, demonstrates that real-time responsiveness is key to optimizing patient outcomes. Meanwhile, the success of personalized targeting in TMS and the innovative waveforms in SCS highlight the importance of understanding the underlying neural network dynamics rather than focusing solely on anatomical landmarks.

As the global burden of neurological disease continues to grow, the upcoming decade will likely see the maturation of neuromorphic computing, the expansion of non-invasive therapies like taVNS into broader clinical practice, and the development of AI-driven tools that will further enhance the precision and efficacy of these life-changing treatments. By restoring functions to dysfunctional circuits, neuromodulation offers not just management of symptoms, but a revolution in the quality of life for billions worldwide.

Abbreviations

DBS: Deep brain stimulation. TMS: Transcranial magnetic stimulation. SCS: Spinal cord stimulation. VNS: Vagus nerve stimulation. RNS: Responsive microsimulation. AI: Artificial intelligence. fMRI: Functional magnetic resonance imaging. ECAP: Evoked Compound Action Potential. DTM: Differential Target Multiplexed. WHO: World Health Organization.

Availability of data and materials

No datasets were generated or analysed during the current study

Funding

The authors received no extramural funding for the study.

Conflict of Interest

The authors report there are no competing interests to declare.

AUTHOR CONTRIBUTION

Eeman Salam conceptualized the study. **Hafsa Asif, Ayesha Javaid Baig, Laheem Ullah Khan, Alina Hamid, and Sameer Ali** conducted the literature review and drafting while editing and supervision were performed by **Eeman Salam, Hafsa Asif, Mohsin Mushtaq Ali, and Mubashir Raza.** The final version of this manuscript has been read and approved by the authors.

15. REFERENCES

WHO Report Finds Neurological Conditions Now Affect Over One-Third of the World's Population, accessed on February 14, 2026. https://wfneurology.org/activities/news-events/archived-news/2025-10-17-wcn2025-who-report-1-in-3-neurological-conditions

Shu Wang , Yin Jiang , Anchao Yang , Fangang Meng , Jianguo Zhang. The Expanding Burden of Neurodegenerative Diseases: An Unmet Medical and Social Need. *Aging and disease*. 2025, 16(5): 2937-2952 https://doi.org/10.14336/AD.2024.1071

11 million lives lost each year: urgent action needed on neurological care, accessed on February 14, 2026. https://www.who.int/news/item/14-10-2025-11-million-lives-lost-each-year-urgent-action-needed-on-neurological-care

Over 1 in 3 people affected by neurological conditions, the leading cause of illness and disability worldwide - World Health Organization (WHO), accessed on February 14, 2026. https://www.who.int/news/item/14-03-2024-over-1-in-3-people-affected-by-neurological-conditions--the-leading-cause-of-illness-and-disability-worldwide

Davidson B, Bhattacharya A, Sarica C, Darmani G, Raies N, Chen R, Lozano AM. Neuromodulation techniques–From non-invasive brain stimulation to deep brain stimulation. Neurotherapeutics. 2024 Apr 1;21(3):e00330. https://doi.org/10.1016/j.neurot.2024.e00330.

Robles V, Valentí M, Mendibe M, Hidalgo Á, Albamonte F, Berrocoso E, Lara M, Calvo R, López C, Deshpande O, Palma-Gudiel H, Benito G, Díaz Marsa M, Parellada M, Dierssen M; Spanish Brain Council. Promoting brain health across the lifespan: Socioeconomic burden, global recommendations, and the Spanish national plan. Neurosci Appl. 2025 Dec 17;5:106879. https://doi.org/10.1016/j.nsa.2025.106879

Zaib M, Khizar M, Ali Q, Mahato RK. Advances in deep brain stimulation for movement disorders. Ann Med Surg (Lond). 2025 Nov 10;88(1):951-952. https://doi.org/10.1097/MS9.0000000000004268

Peprah K, Horton J; Authors. Adaptive Deep Brain Stimulation for the Treatment of Parkinson Disease and Essential Tremor: CADTH Horizon Scan [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2021 Dec. Available from: https://www.ncbi.nlm.nih.gov/books/NBK591048

Bronte-Stewart HM, Beudel M, Ostrem JL, Little S, Almeida L, Ramirez-Zamora A, Fasano A, Hassell T, Mitchell KT, Moro E, Gostkowski M. Long-term personalized adaptive deep brain stimulation in Parkinson disease: a nonrandomized clinical trial. JAMA neurology. 2025 Nov;82(11):1171-80.

UCSF Deep Brain Stimulation Clinical Trials — San Francisco Bay Area, accessed on February 14, 2026, https://clinicaltrials.ucsf.edu/deep-brain-stimulation

Liu B, Hu C, Bao P. Precision TMS through the integration of neuroimaging and machine learning: optimizing stimulation targets for personalized treatment. Front Hum Neurosci. 2025 Sep 29;19:1682852. https://doi.org/10.3389/fnhum.2025.1682852.

Jiang L, Fung CCS, Cheng CPW. Research advances in neuronavigated target localization for repetitive transcranial magnetic stimulation in depression: from standardization to individualized neuromodulation. Front Neuroimaging. 2026 Jan 12;4:1703198. https://doi.org/10.3389/fnimg.2025.1703198.

Ha T, Jakimier K, O'Sullivan S. The Use of MRI and TMS in Treatment-Resistant Depression: Advances in Pediatric Applications. Brain Sciences. 2025 Feb 14;15(2):194. https://doi.org/10.3390/brainsci15020194.

DeSouza, Danielle & Meng, Nathan & DeGaetano, Noah & Nakano, Erica & Hoang, Vivian & Nguyen, Teresa & Ling, David & Carreon, David & Siddiqi, Shan. (2025). Naturalistic Outcomes with fMRI-Guided and Non-fMRI-Guided Accelerated TMS for Depression. https://doi.org/10.1101/2025.09.03.25334813.

Study Details | NCT07025720 | Personalized Accelerated TMS for High-Risk Adolescent Depression | ClinicalTrials.gov, accessed on February 14, 2026, https://clinicaltrials.gov/study/NCT07025720

Zeng Y, Bhatia A. New modes of spinal cord stimulation for pain syndromes - Similar yet different approaches to improving outcomes. Indian J Anaesth. 2025 Dec;69(12):1256-1259. https://doi.org/10.4103/ija.ija_976_25.

Lam CM, Latif U, Sack A, Govindan S, Sanderson M, Vu DT, Smith G, Sayed D, Khan T. Advances in spinal cord stimulation. Bioengineering. 2023 Feb 1;10(2):185. https://doi.org/10.3390/bioengineering10020185.

Lempka SF, Patil PG. Innovations in spinal cord stimulation for pain. Curr Opin Biomed Eng. 2018 Dec;8:51-60. doi: 10.1016/j.cobme.2018.10.005. Epub 2018 Nov 12. https://doi.org/10.1016/j.cobme.2018.10.005.

Sun H, Hu H, Bian Z, Liu H, Huang M, Chen S, Wang L, Xiao W, Zhang Y, Fang J, Shao X. Evaluating the efficacy and safety of transcutaneous vagus nerve stimulation for systemic lupus erythematosus: a protocol for a systematic review and meta-analysis. BMJ Open. 2025 Oct 21;15(10):e098576. https://doi.org/10.1136/bmjopen-2024-098576.

Veldman F, Hawinkels K, Keszthelyi D. Efficacy of vagus nerve stimulation in gastrointestinal disorders: a systematic review. Gastroenterol Rep (Oxf). 2025 Jan 26;13:goaf009. https://doi.org/10.1093/gastro/goaf009

NIH awards Feinstein Institutes $3 million grant to develop devices for precision vagus nerve stimulation with imec, accessed on February 14, 2026, https://feinstein.northwell.edu/news/the-latest/nih-grant-vagus-nerve-stimulation-devices-imec

Zhang J, Zhang Y, Zhao J, Sun J and Zhang X (2026) The role of transcutaneous auricular vagus nerve stimulation in chronic pain: from neurobiological mechanisms to clinical applications. Front. Pain Res. 7:1733445. doi: 10.3389/fpain.2026.1733445

Study Details | NCT07409363 | Non-invasive Vagus Nerve Stimulation for Chronic Musculoskeletal Pain | ClinicalTrials.gov, accessed on February 14, 2026, https://clinicaltrials.gov/study/NCT07409363

Study Details | NCT06912399 | Effect of Transauricular Vagus Nerve Stimulation on Postoperative Pain Management in Video Assisted Thoracic Surgery | ClinicalTrials.gov, accessed on February 14, 2026, https://clinicaltrials.gov/study/NCT06912399

Catherine Joachin. Responsive Neurostimulation (RNS) - The Defeating Epilepsy Foundation, accessed on February 14, 2026. https://www.defeatingepilepsy.org/treatment-for-epilepsy/responsive-neurostimulation/

Premaratne S, Zoghi M, Antonic-Baker A, Chen Z, Chen L, Hamer R et al. Non-invasive neurostimulation for drug-resistant epilepsy: systematic review and meta-analysis of effectiveness, safety, and optimal stimulation parameters. Journal of Neurology. 2026 Jan;273(1):7. doi: 10.1007/s00415-025-13522-1

Sloka Iyengar and Patricia O. Shafer. Epilepsy Foundation-Responsive Neurostimulation (RNS). November 28th, 2017. https://www.epilepsy.com/treatment/devices/responsive-neurostimulation

Responsive Neurostimulation (RNS) for Epilepsy | Duke Health, accessed on February 14, 2026, https://www.dukehealth.org/treatments/neurological-disorders/epilepsy/neuromodulation-epilepsy?utm_campaign=dukehealth&utm_source=youtube&utm_medium=video

Ryan Gallagher and Aria Fallah. Innovations in Less-Invasive Epilepsy Surgery - - Practical Neurology. November 11th, 2025. https://practicalneurology.com/diseases-diagnoses/epilepsy-seizures/innovations-in-less-invasive-epilepsy-surgery/39963/

Luis Fernando Herbozo Contreras, Nhan Duy Truong, Jason K Eshraghian, Zhangyu Xu, Zhaojing Huang, Thomas Vincenzo Bersani–Veroni, Isabelle Aguilar, Wing Hang Leung, Armin Nikpour, Omid Kavehei, Neuromorphic neuromodulation: Towards the next generation of closed-loop neurostimulation, *PNAS Nexus*, Volume 3, Issue 11, November 2024, pgae488, https://doi.org/10.1093/pnasnexus/pgae488

Fang SJ, Yin ZD, Cai Q, Li LF, Zheng PF, Chen LZ. Harnessing artificial intelligence for brain disease: advances in diagnosis, drug discovery, and closed-loop therapeutics. Front Neurol. 2025 Jul 28;16:1615523. doi: 10.3389/fneur.2025.1615523.

Calderone, A., Latella, D., La Fauci, E., Puleo, R., Sergi, A., De Francesco, M., Mauro, M., Foti, A., Salemi, L., & Calabrò, R. S. (2025). Artificial Intelligence-Driven Neuromodulation in Neurodegenerative Disease: Precision in Chaos, Learning in Loss. *Biomedicines*, *13*(9), 2118. https://doi.org/10.3390/biomedicines13092118

Williams C, Anik FI, Hasan MM, Rodriguez-Cardenas J, Chowdhury A, Tian S, He S, Sakib N. Advancing Brain-Computer Interface Closed-Loop Systems for Neurorehabilitation: Systematic Review of AI and Machine Learning Innovations in Biomedical Engineering. JMIR Biomed Eng. 2025 Nov 5;10:e72218. https://doi.org/10.2196/72218