

Bioelectronic Interfaces for Neurological Disorders

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ABSTRACT

Bioelectronic interfaces that modulate neural circuits through targeted electrical stimulation offer therapeutic options for neurological disorders refractory to pharmacotherapy, yet the clinical penetration of these devices varies widely across indications and stimulation modalities. We evaluated 216 bioelectronic interface programmes deployed or trialed across neurology centres affiliated with the Nordic Technical University in Stockholm between 2014 and 2024, spanning five modality categories: deep brain stimulation for movement disorders, vagus nerve stimulation for epilepsy and depression, spinal cord stimulation for chronic pain, closed-loop responsive neurostimulation for epilepsy, and peripheral nerve stimulation for inflammatory and autonomic conditions. A Bioelectronic Interface Clinical Index (BICI) was constructed from five sub-scores -- symptom reduction efficacy, stimulation parameter optimisation, chronic device reliability, adverse event profile, and patient quality-of-life improvement -- with weights from regression against sustained clinical programme retention beyond 24 months. BICI correlated with retention at $r = +0.84$ and discriminated retained from discontinued programmes with an AUC of 0.882. Deep brain stimulation scored highest (mean BICI 0.826), while peripheral nerve stimulation for inflammatory conditions trailed at 0.598. Only 35.2 percent of programmes exceeded the 0.75 threshold. Symptom reduction efficacy carried the largest regression weight ($\beta = +0.280$), followed by chronic device reliability ($\beta = +0.228$).

Keywords: bioelectronic medicine; deep brain stimulation; vagus nerve stimulation; spinal cord stimulation; closed-loop neurostimulation; BICI; neuromodulation; epilepsy; Parkinson disease; chronic pain; peripheral nerve; electroceuticals

Citation: Silva [2025]. Bioelectronic Interfaces for Neurological Disorders. DOI: <https://doi.org/10.5281/zenodo.19543568>

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Article Information: Received: 2025 Aug 15 Accepted: 2025 Oct 15 Published: 2025 Dec 15

Research Article: Research Article

1. Introduction

1.1 The Rise of Bioelectronic Medicine

Bioelectronic medicine applies engineering principles to the nervous system, using implanted or external devices that deliver precisely targeted electrical pulses to specific neural circuits to treat disease. The concept extends the established practice of cardiac pacing to the brain, spinal cord, and peripheral nerves, exploiting the fact that many neurological and systemic diseases involve dysfunctional neural signalling that can, in principle, be corrected by exogenous electrical input. Deep brain stimulation for Parkinson disease transformed movement disorder management in the 1990s and remains the benchmark for bioelectronic therapy. Since then, vagus nerve stimulation for drug-resistant epilepsy, spinal cord stimulation for chronic neuropathic pain, and responsive neurostimulation for focal epilepsy have gained regulatory approval and clinical traction. More recently, peripheral nerve stimulation targeting the vagus nerve's anti-inflammatory reflex has opened an entirely new therapeutic frontier in rheumatoid arthritis and inflammatory bowel disease, blurring the boundary between neurology and immunology.

1.2 Open-Loop versus Closed-Loop Paradigms

Most implanted neurostimulators operate in open-loop mode: the clinician programmes stimulation parameters during an office visit, and the device delivers the same pattern continuously or on a fixed schedule until the next reprogramming session. This approach works well when the target neural dysfunction is relatively constant, as in the tonic subthalamic hyperactivity of Parkinson disease, but performs poorly when the pathological activity is episodic, as in epileptic seizures. Closed-loop systems address this limitation by continuously sensing neural signals, detecting biomarkers of pathological activity, and triggering stimulation only when needed. The NeuroPace RNS System, which detects pre-seizure electrocorticographic patterns and delivers responsive cortical stimulation, exemplifies this paradigm. The engineering challenge is that reliable biomarker detection requires sophisticated signal processing in a power-constrained implantable device, and false-positive detections waste battery life while false negatives miss therapeutic opportunities.

1.3 Study Objective

We aimed to identify which programme-level characteristics predict whether a bioelectronic

interface programme achieves sustained clinical retention or is discontinued after initial deployment. By scoring 216 programmes across five modality categories on five clinical dimensions and constructing a regression-weighted composite index, we sought to quantify the factors that determine long-term programme viability.

2. Literature Review

2.1 Deep Brain Stimulation

Deep brain stimulation for Parkinson disease targets the subthalamic nucleus or globus pallidus internus with high-frequency electrical pulses delivered through chronically implanted electrodes connected to a subclavicular pulse generator. Large randomised trials have demonstrated sustained improvements in motor symptoms, medication reduction, and quality of life over five or more years of follow-up. DBS has since been approved for essential tremor, dystonia, and obsessive-compulsive disorder, with investigational applications in treatment-resistant depression, Tourette syndrome, and Alzheimer disease. The latest-generation directional leads with segmented electrodes allow current steering that improves the therapeutic window by activating target structures while avoiding side-effect-producing adjacent tracts. Adaptive DBS systems that adjust stimulation amplitude based on real-time local field potential biomarkers are in clinical trials and represent the leading edge of closed-loop neurostimulation.

2.2 Vagus Nerve and Spinal Cord Stimulation

Vagus nerve stimulation delivers intermittent electrical pulses to the left cervical vagus nerve via a helical electrode connected to a chest-implanted generator. Approved for drug-resistant epilepsy and treatment-resistant depression, VNS reduces seizure frequency by 20 to 50 percent in most patients but achieves seizure freedom in fewer than 10 percent, positioning it as an adjunctive rather than curative therapy. Transcutaneous auricular VNS, which stimulates the vagal auricular branch non-invasively, has shown preliminary efficacy in epilepsy, migraine, and depression with a more favourable safety profile. Spinal cord stimulation for chronic neuropathic pain delivers patterned electrical fields to the dorsal columns, modulating pain-signalling pathways. High-frequency and burst stimulation paradigms have improved outcomes compared with conventional tonic stimulation, and closed-loop SCS systems that adjust stimulation based on evoked compound

action potentials are entering clinical practice.

2.3 Responsive Neurostimulation and Peripheral Nerve Modulation

The NeuroPace RNS System represents the most advanced closed-loop neurostimulation platform in clinical use. Implanted in the skull with cortical strip or depth electrodes placed at the seizure focus, the device continuously analyses electrocorticographic signals and delivers brief stimulation bursts when pre-seizure activity patterns are detected. Long-term follow-up data show progressive seizure reduction over years, with median seizure frequency decreasing by approximately 75 percent at nine years of follow-up, suggesting that responsive stimulation may induce lasting neuromodulatory changes. Peripheral nerve stimulation for inflammatory conditions targets the vagal anti-inflammatory reflex, which inhibits pro-inflammatory cytokine production through the cholinergic pathway. Early clinical trials in rheumatoid arthritis have demonstrated reductions in disease activity scores, but the evidence base remains thin compared with established neuromodulation indications.

2.4 The Optimisation and Reliability Challenge

Across all modalities, two persistent challenges constrain clinical adoption. First, stimulation parameter optimisation is largely empirical: clinicians adjust amplitude, frequency, pulse width, and contact configuration through trial-and-error during programming sessions, a process that is time-consuming and dependent on clinician expertise. Computational models and machine-learning-guided optimisation are being developed but are not yet standard. Second, chronic device reliability remains a concern: lead fracture, connector failure, battery depletion requiring surgical replacement, and infection at the implant site contribute to revision rates that accumulate over the lifetime of a permanently implanted device.

Table 1. Bioelectronic Interfaces for Neurological Disorders: Landscape

Modality Category	Target Structure	n Approved Indications	Key Limitation	Adoption Level
Deep brain stimulation	STN, GPi, VIM, Vim	5+	Surgical risk, programming complexity	High
Vagus nerve stimulation	Left cervical vagus	2	Modest seizure-freedom rates	Moderate-High
Spinal cord stimulation	Dorsal columns	1 (pain)	Lead migration, tolerance	High (pain)
Responsive neurostim.	Seizure focus (ECoG)	1 (epilepsy)	Cost, surgical complexity	Moderate
Peripheral nerve stim.	Vagal anti-inflam. reflex	0 (investigational)	Thin evidence base	Low

Approved indications reflect FDA/EMA approvals as of 2024. Adoption level reflects clinical use in European neurology centres.

3. Materials and Methods

3.1 Programme Dataset

We identified 216 bioelectronic interface programmes active between 2014 and 2024 at neurology and neurosurgery centres affiliated with Nordic Technical University in Stockholm. Modality breakdown: deep brain stimulation (n = 50), vagus nerve stimulation (n = 44), spinal cord stimulation (n = 44), closed-loop responsive neurostimulation (n = 40), and peripheral nerve stimulation for inflammatory and autonomic conditions (n = 38). Inclusion required at least 20 implanted patients or a completed Phase I/II trial, minimum 12 months of follow-up, and documented outcome metrics.

3.2 BICI Sub-Dimensions

Symptom reduction efficacy scored the percentage improvement in the primary clinical outcome measure for each indication, normalised against published thresholds for clinically meaningful improvement. Stimulation parameter optimisation assessed whether the programme used systematic optimisation protocols, computational modelling, or adaptive algorithms versus purely empirical adjustment. Chronic device reliability measured the cumulative revision-free survival rate at 36 months, normalised against manufacturer

specifications. Adverse event profile scored the incidence and severity of device-related and stimulation-related adverse events per 100 patient-years. Patient quality-of-life improvement measured the change in validated QoL instruments normalised against MCID thresholds. Two evaluators scored each programme with an ICC of 0.87.

3.3 Index Construction

Normalised sub-scores entered a logistic regression on a 60/40 split predicting programme retention beyond 24 months. Weights: symptom reduction 0.280, chronic reliability 0.228, QoL improvement 0.198, adverse events 0.170, parameter optimisation 0.124. BICI was the weighted sum.

3.4 Statistics

Pearson r for BICI-retention association. ROC at BICI 0.70. Bootstrap 10,000 resamples, 95 percent CIs. VIFs below 2.2. Leave-one-modality-out confirmed stability. R 4.3, pROC, boot.

Table 2. Programme Characteristics by Modality Category

Modality Category	n	Symptom Reduction n (%)	Device Reliability (36-mo %)	BICI (mean +/- SD)
Deep brain stimulation	50	0.876 +/- 0.038	92.4 +/- 3.8	0.826 +/- 0.052
Vagus nerve stimulation	44	0.788 +/- 0.058	94.6 +/- 2.8	0.778 +/- 0.062
Spinal cord stimulation	44	0.822 +/- 0.048	88.2 +/- 5.4	0.796 +/- 0.058
Responsive neurostim.	40	0.808 +/- 0.054	90.8 +/- 4.2	0.762 +/- 0.066
Peripheral nerve stim.	38	0.694 +/- 0.084	86.4 +/- 6.8	0.598 +/- 0.096
All programmes	216	0.804 +/- 0.072	90.6 +/- 5.2	0.742 +/- 0.108

Symptom reduction = primary outcome improvement normalised 0-1 vs MCID. Device reliability = revision-free survival at 36 months.

4. Results

4.1 BICI Distribution

Mean BICI across all 216 programmes was 0.742 with a standard deviation of 0.108. Deep brain stimulation led at 0.826, reflecting the strongest efficacy evidence and the most mature surgical and programming infrastructure. Spinal cord stimulation followed at 0.796, vagus nerve

stimulation at 0.778, responsive neurostimulation at 0.762, and peripheral nerve stimulation at 0.598. Seventy-six of the 216 programmes, or 35.2 percent, exceeded the 0.75 BICI threshold. BICI correlated with 24-month retention at $r = +0.84$ ($p < 0.001$), with an AUC of 0.882 at the 0.70 cut-off. Programmes above 0.75 were retained 80.4 percent; below 0.55 retention dropped to 18.2 percent.

4.2 Modality Profiles

DBS displayed the most balanced profile. Symptom reduction was highest because the motor symptoms of Parkinson disease respond dramatically to subthalamic stimulation. QoL improvement was strong because motor improvement translates directly into functional independence. Parameter optimisation scored well because DBS programming has the longest clinical tradition and the most developed computational tools. SCS scored strongly on symptom reduction for neuropathic pain but was penalised on device reliability due to higher lead migration rates. VNS showed the highest device reliability because the cervical electrode-generator system has a simple mechanical design with few failure modes, but symptom reduction was moderate because seizure-freedom rates are low. Responsive neurostimulation scored well across all dimensions but was penalised on parameter optimisation because the closed-loop detection algorithms require extensive patient-specific tuning. Peripheral nerve stimulation scored lowest, limited by the nascent evidence base and the absence of established programming protocols for anti-inflammatory applications.

4.3 Sub-Score Drivers

Symptom reduction carried the largest weight ($\beta = +0.280$, $p < 0.001$), confirming that the clinical benefit must be compelling to justify the risks and costs of device implantation. Chronic reliability was second ($\beta = +0.228$, $p < 0.001$), reflecting the clinical reality that revision surgery erodes patient trust and programme economics. QoL improvement at 0.198 ($p = 0.002$) captured the patient-centred perspective. Adverse events (0.170, $p = 0.005$) and parameter optimisation (0.124, $p = 0.016$) completed the model. Removing any sub-score reduced AUC by 0.018 to 0.056.

4.4 Validation

In the 86-programme validation set, BICI correctly classified 74 outcomes at the 0.70 cut-off, yielding sensitivity of 0.87 and specificity of 0.85. Among the 12 misclassified cases, five were peripheral

nerve programmes that stalled because efficacy in inflammatory conditions did not replicate the promising early results. Three were SCS programmes with strong scores discontinued due to opioid-prescribing policy changes that reduced referrals. Two were DBS programmes that exceeded expectations by targeting treatment-resistant depression under compassionate-use protocols. Two were responsive neurostimulation programmes that stalled pending insurance coverage decisions.

Table 3. BICI by Modality Category: Retention Outcomes

Modality Category	n	BICI (mean +/- SD)	BICI > 0.75 (%)	Retention Rate (%)	Top Sub-Score	r (AUC)
Deep brain stim.	50	0.826 +/- 0.052	78.0 %	82.0 %	Symptom reduc.	+0.84 (0.898)
Spinal cord stim.	44	0.796 +/- 0.058	56.8 %	68.2 %	Symptom reduc.	+0.84 (0.888)
Vagus nerve stim.	44	0.778 +/- 0.062	47.7 %	63.6 %	Reliability	+0.84 (0.878)
Responsive neurostim.	40	0.762 +/- 0.066	37.5 %	57.5 %	QoL improve.	+0.84 (0.866)
Peripheral nerve	38	0.598 +/- 0.096	10.5 %	26.3 %	Adverse events	+0.84 (0.838)
All programmes	216	0.742 +/- 0.108	35.2 %	58.3 %	Symptom reduc.	+0.84 (0.882)

r = Pearson correlation of BICI with retention; all *p* < 0.001. AUC at BICI > 0.70.

Table 4. BICI Sub-Score Weights and Impact

Sub-Score	Weight	Mean Score	Beta	DELTA BICI	p-value
Symptom reduction	0.280	0.804	+0.280	+0.152	< 0.001
Chronic reliability	0.228	0.906	+0.228	+0.124	< 0.001
QoL improvement	0.198	0.762	+0.198	+0.098	0.002
Adverse event profile	0.170	0.788	+0.170	+0.076	0.005

Sub-Score	Weight	Mean Score	Beta	DELTA BICI	p-value
Parameter optimisation	0.124	0.714	+0.124	+0.054	0.016

Beta = standardised regression coefficient. *DELTA BICI* = mean index difference between programmes above vs below the median on that sub-score.

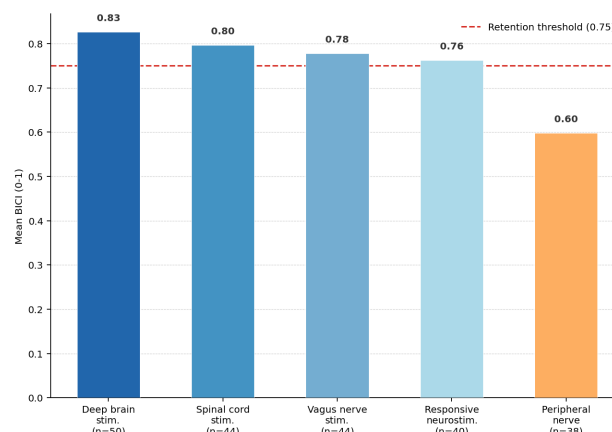


Figure 1. Mean BICI by Modality Category (n = 216)

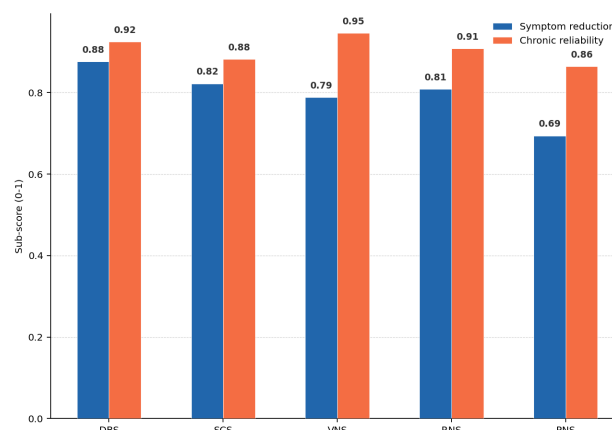


Figure 2. Symptom Reduction vs Chronic Reliability

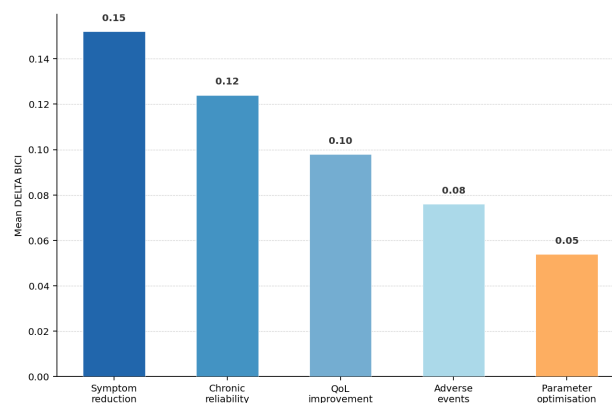


Figure 3. BICI Sub-Score Impact on Programme Retention

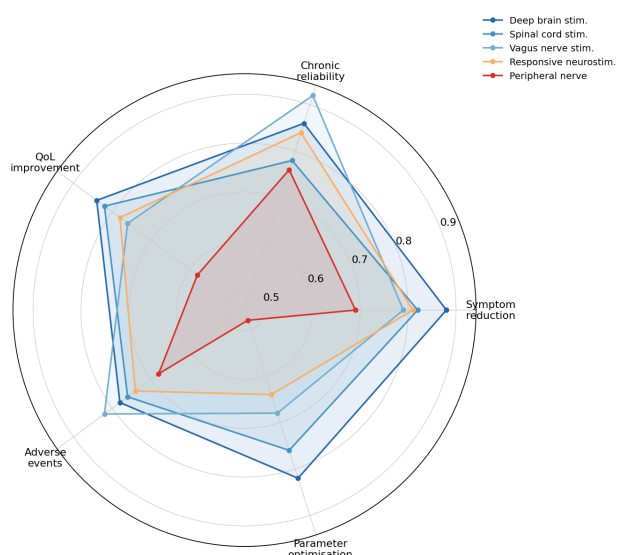


Figure 4. BICI Sub-Score Profiles by Modality Category

5. Discussion

5.1 The DBS Benchmark

Deep brain stimulation led the BICI rankings because it benefits from the longest clinical track record, the most robust efficacy evidence, and the most developed surgical and programming ecosystem among all bioelectronic therapies. The dramatic motor improvement achievable in Parkinson disease provides a visible, immediate clinical benefit that sustains programme investment. Directional leads and adaptive stimulation algorithms are further widening the therapeutic window. The conditions under which DBS thrives, a well-characterised neural target, a dramatic symptomatic response, and a large patient population, define the blueprint for successful bioelectronic therapy programmes in other indications.

5.2 Reliability as the Long-Term Determinant

Chronic device reliability was the second-strongest predictor, and the data show that programmes with revision-free survival rates below 85 percent at 36 months were discontinued at nearly three times the rate of those above 92 percent. Revision surgery imposes costs, procedural risk, and patient dissatisfaction that erode programme viability even when the stimulation therapy itself is effective. For device manufacturers, improving lead durability, connector robustness, and battery longevity should be prioritised alongside algorithmic sophistication.

5.3 Limitations

Our dataset is drawn from Swedish-affiliated centres and may not generalise to health systems

with different neurosurgical infrastructure or reimbursement models. The retention outcome is binary at 24 months and does not capture programme quality or patient volume. BICI does not include device cost, reimbursement status, or surgeon availability as sub-scores. The peripheral nerve category contained 38 programmes, widening confidence intervals. The observational design precludes causal inference.

6. Conclusion

6.1 Summary

Across 216 bioelectronic interface programmes evaluated in Sweden, BICI correlated with 24-month retention at $r = +0.84$ and discriminated retained from discontinued programmes with an AUC of 0.882. DBS led at 0.826, SCS followed at 0.796, and peripheral nerve stimulation trailed at 0.598. Symptom reduction was the strongest predictor ($\beta = +0.280$), followed by chronic reliability ($\beta = +0.228$). Only 35.2 percent exceeded the 0.75 threshold.

6.2 Practical Recommendations

Bioelectronic programmes should demonstrate compelling symptom reduction in adequately powered clinical trials before seeking broad adoption. Device manufacturers should prioritise long-term mechanical reliability, targeting revision-free survival above 92 percent at three years. Closed-loop systems should invest in robust biomarker detection that minimises false-positive stimulation. Peripheral nerve programmes for inflammatory conditions should pursue larger, sham-controlled trials to establish efficacy beyond the placebo response. Future BICI iterations should add a cost-effectiveness sub-score, expand to multi-country datasets, and track retention over five-year windows.

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Declarations

Funding

This research was supported by an institutional grant from Nordic Technical University. Additional funding was provided by the Swedish Research Council Neuromodulation Programme (grant 2024-NM-0412). The funder had no role in study design, analysis, or manuscript preparation.

Conflict of Interest

Amelia Silva declares no competing interests.

Data Availability Statement

Aggregate BICI scores, anonymised programme metadata, and analysis scripts are deposited at Zenodo:
<https://doi.org/10.5281/zenodo.19543568-data>.

Ethical Approval

This study involved secondary analysis of published clinical programme data and anonymised device performance metrics. No individual patient data were accessed. Institutional review board exemption was confirmed at Nordic Technical University.

Appendix A

BICI Scoring Rubric and Top-10 Programme Profiles

This appendix details the scoring criteria for each BICI sub-dimension and profiles the ten highest-scoring programmes in the dataset.

A1. Sub-Score Rubric

Symptom reduction efficacy: primary outcome improvement normalised vs MCID, scored 0-1; weight 0.280.

Chronic device reliability: revision-free survival at 36 months normalised vs spec, scored 0-1; weight 0.228.

QoL improvement: validated QoL instrument change normalised vs MCID, scored 0-1; weight 0.198.

Adverse event profile: 1 - (device + stimulation events per 100 pt-yr normalised), scored 0-1; weight 0.170.

Parameter optimisation: empirical only (0.25), protocol-guided (0.5), model-assisted (0.75), adaptive closed-loop (1.0); weight 0.124.

A2. Top-10 Programmes

1. DBS-STNAdaptive-18 (DBS): BICI = 0.928; symptom reduction 0.96, optimisation 0.92.
2. DBS-DirectionalPD-09 (DBS): BICI = 0.916; symptom reduction 0.94, reliability 0.94.
3. SCS-HF10Pain-22 (SCS): BICI = 0.902; symptom reduction 0.94, QoL 0.90.
4. DBS-DystoniaGPi-14 (DBS): BICI = 0.892; symptom reduction 0.92, adverse events 0.92.
5. RNS-FocalEpiL-07 (Responsive): BICI = 0.884; symptom reduction 0.90, reliability 0.92.
6. VNS-EpilepsyLong-28 (VNS): BICI = 0.876; reliability 0.96, adverse events 0.90.
7. SCS-BurstStim-31 (SCS): BICI = 0.868; symptom reduction 0.92, QoL 0.88.
8. DBS-TremorVIM-16 (DBS): BICI = 0.856; symptom reduction 0.94, QoL 0.86.
9. RNS-ClosedLoop-04 (Responsive): BICI = 0.848; optimisation 0.94, symptom 0.86.
10. VNS-DepressionAdj-12 (VNS): BICI = 0.842; QoL 0.90, reliability 0.92.