Peripheral Nerve Injuries: Impact, Solutions and Innovation

Antonio Coviello[1*] & Giulio Franceschini[1*], Davide Scazzoli[1], Manuela Crocco[1], Silvia Mura[1], Paolo Motto Ros[2], Danilo Demarchi[2], Federica Burinato[1], Anna Simeone[1], Virginia Tasso[1], Chiara Cavigliano[1], Andrea Cerutti[1], Yeshua Giacalone[1], Umberto Spagnolini[1], and Maurizio Magarini[1]

[1]Politecnico di Milano, Piazza Leonardo da Vinci, 32, 20133, Milano (MI), Italy
[2]Politecnico di Torino, Corso Duca degli Abruzzi, 24, 10129, Torino (TO), Italy
[*] Both authors contributed equally
antonio.coviello@polimi.it
giulio.franceschini@mail.polimi.it

Abstract. Peripheral nerve injuries (PNIs) remain a significant clinical challenge, impacting both patients' quality of life and healthcare systems globally. This paper examines the individual and societal burdens of PNIs, reviewing current therapeutic strategies, including pharmacology, neuromodulation, surgery, and rehabilitation. Despite advancements, these approaches often fail to restore complex nerve functions, particularly in severe cases. We propose a novel implantable system that bypasses nerve lesions by recording neural activity proximally, processing the signals externally, and delivering precise stimulation distally. The system integrates multi-contact cuffs for both sensing and stimulation, ensuring minimal invasiveness and enhanced safety. We present a detailed analysis of the system's signal processing techniques, including noise reduction and feature extraction, and its potential for motor and sensory restoration. Furthermore, we explore the translational path for this technology, focusing on clinical trials, regulatory approval, and stakeholder alignment, including patients, clinicians, manufacturers, and payers. This solution aims to bridge existing gaps in PNI treatment by providing a functional bypass that restores nerve function while reducing long-term healthcare costs.

Keywords: Peripheral Nerve Injuries · Implantable Device · Stakeholder Engagement · Functional Bypass.

1 Introduction

The peripheral nervous system is a crucial component of the human body, responsible for bidirectional communication between the brain and the rest of the organism. Through this network, peripheral nerves transmit electrical and chemical signals that regulate not only movement but also sensory perception, allowing the body to interact with the surrounding environment. Since these structures are among the most delicate and vulnerable, they are particularly prone to trauma such as crushing, compression, and other forms of physical damage. These injuries disrupt communication between the brain and target organs, compromising vital motor and sensory functions. When a peripheral nerve injury (PNI) occurs, caused by various types of trauma, the disruption of signals between the brain and the body prevents proper motor and sensory function, severely impairing the patient's autonomy, Fig. 1. Given the significant impact of PNIs, both on patients' quality of life and healthcare costs, further research into these injuries is essential [1].

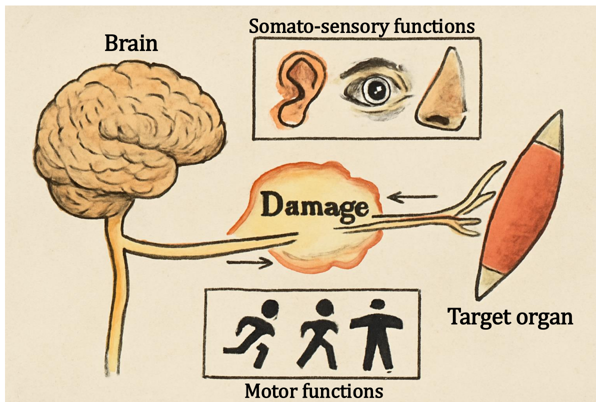


Fig. 1. Pictorial depiction of PNI showing how nerve damage disrupts the conduction of signals, impairing motor and somatosensory functions [3].

When nerves are damaged, Wallerian degeneration rapidly degrades the affected part, enabling surviving neurons to regenerate [2]. However, regeneration is often incomplete, with outcomes depending on factors such as age, injury severity, and neuronal survival. PNIs have a profound impact on both the physical and psychological health of patients, impairing motor skills, sensory perception, and independence, while often leading to anxiety, depression, and social isolation [4,5]. At a societal level, prolonged rehabilitation, long-term care, and reduced work capacity impose substantial economic costs on patients, families, and healthcare systems [6]. Given all those impacts, advancing treatment requires collaborative efforts among healthcare professionals, patients, caregivers, policymakers, and manufacturers to develop effective, sustainable solutions that restore function and quality of life.

This review synthesizes recent advances in diagnosis and treatment of PNIs, with emphasis on implantable technologies and future translational directions. Individually, it examines motor and sensory impairments, pain, and psychological consequences such as anxiety, depression, and reduced quality of life. Societally, it considers healthcare utilization, long-term care, productivity losses, and impacts on labor participation and tax contributions. The study reviews current diagnostic and therapeutic technologies, focusing on implantable solutions, analyzing their principles, mechanisms, advantages, and limitations. It also maps the stakeholder landscape—patients, caregivers, clinicians, payers, policymakers, regulators, manufacturers, and researchers—to identify challenges, innovation opportunities, and strategies for coordinated action to enhance outcomes and reduce costs.

The paper is organised as follows: Section 2 examines the physical and psychological effects of PNIs. Section 3 analyzes the socio-economic burden, including direct and indirect costs as well as impacts on labor participation and tax contributions. Section 4 reviews current diagnostic and therapeutic solutions. Section 5 focuses on implantable devices, outlining their operating principles, benefits, and limitations. Finally, Section 6 synthesizes the findings and discusses future developments, with particular attention to stakeholder perspectives and market considerations.

2 Individual impact

PNIs can have a profound impact on patients, often leading to persistent and debilitating symptoms. These may include sensations such as tingling, paresthesia ("pins and needles"), and chronic pain. Depending on the severity of the injury, PNIs can also cause loss of somatosensation and dexterity, and in some cases, complete paralysis [7]. Such debilitating symptoms can severely affect patients' ability to perform daily activities and have a long-lasting impact on their overall well-being.

The most common effects of PNIs are outlined in Table 1 [4,8,9,10,11]. These outcomes underscore the devastating toll of PNIs on patients' physical, emotional, and psychological well-being, severely diminishing their quality of life and often leading to long-lasting personal and societal consequences.

Given the profound physical impact of peripheral nerve injuries, they also give rise to significant psychological challenges, affecting both traumatic and

Table 1. Physical consequences and associated risks in patients affected by PNIs.

Possible PNI effects	**Percentage of affected PNI patients (%)**
Loss of sensation	95–100
Muscle weakness/paralysis	80–90
Neuropathic/acute pain	40–70
Autonomic dysfunctions*	5–15
Long-term disability**	25–50
Suicidal ideation	33.3
Suicide Risk	1.7x the general population

*Autonomic manifestations such as abnormal sweating, gastrointestinal disturbances, and blood pressure alterations.
.**The risk of long-term disability varies greatly according to location, severity, treatment efficacy, and patient characteristics.

non-traumatic cases. Patients often experience high levels of anxiety, depression, and post-traumatic stress, as evidenced by various studies, as shown in Fig. 2 a.

In [12], a study that followed patients with median and ulnar nerve injuries in the forearm reported that early post-traumatic stress symptoms were present in 92% of patients at 1 month and 83% at 3 months. Among these patients, 24.6% and 13.3% met the thresholds for psychological treatment at 1 and 3 months, respectively.

Similarly, in [13], a database study of 1843 adults undergoing surgery for brachial plexus injury (BPI) found that preoperative depression and anxiety were present in 38% and 42% of patients, with new-onset depression and anxiety occurring within 12 months in 12% and 20%, respectively. Furthermore, the risk of developing depression and anxiety in patients with PNIs has been quantified using hazard ratios. Specifically, the hazard ratio for new-onset depression was found to be 1.3, indicating that patients with PNIs have a 30% higher risk of developing depression compared to matched controls. Similarly, the hazard ratio for new-onset anxiety was 2.1, meaning these patients are more than twice as likely (a 110% increased risk) to develop anxiety compared to the control group.

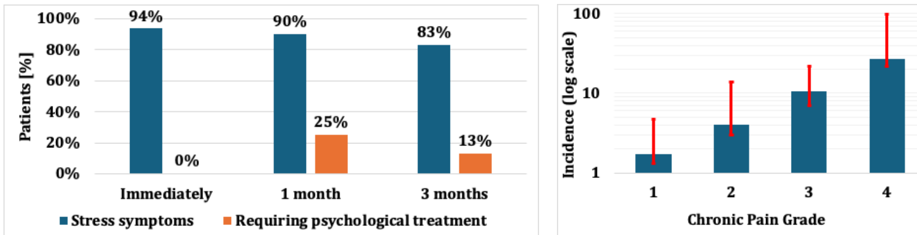
In [11], a clinical series of traumatic BPI cases was studied. 19% of patients met the criteria for Post-Traumatic Stress Disorder (PTSD), 19% for clinical depression, and 33% reported suicidal ideation. Focusing on suicidal ideation, it is evident that PNIs impose a severe psychological burden on patients. Alarmingly, 33.3% of PNI patients report suicidal ideation, which underscores the extreme emotional toll these injuries can take. In addition, patients with chronic pain are more likely to experience co-morbid depression and anxiety, with prevalence sharply increasing as the Chronic Pain Grade (CPG) worsens [5], as shown in Fig. 2 b. The psychological impact of PNIs—particularly the risk of suicide—is as critical as the physical consequences and demands urgent attention.

A study of 246 patients with cubital tunnel syndrome (CTS) [14] reported that depression and anxiety were found in 17.9% and 14.2% of the cases, respectively, as measured by the Hospital Anxiety and Depression Scale (HADS). The HADS is a widely used tool for assessing anxiety and depression in patients, consisting of 14 questions that evaluate emotional distress, with separate subscales for anxiety and depression.

Together, these findings quantify the high burden of PTSD, depression, anxiety, and stress responses in PNI patients, highlighting the urgent need for routine psychological screening and support alongside surgical and rehabilitative care.

3 Social impact

The social impact of PNIs extends far beyond the physical and psychological consequences, influencing patients' ability to work, engage in daily activities, and maintain financial independence. Given the significant healthcare utilization and long-term care requirements, it is crucial to quantify the public cost of PNIs, highlighting the importance of investing in effective treatments to identify more cost-effective solutions.



(a) (b)

Fig. 2. Psychological burden of PNIs: (a) results of a prospective cohort of forearm median/ulnar PNIs [5]; (b) CPG correlation with co-morbid depression and anxiety, normalized to the general population incidence [5].

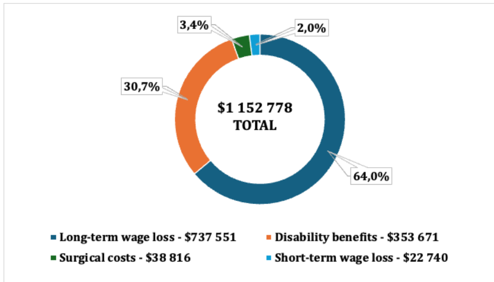
Across trauma populations worldwide, PNIs disproportionately affect working-age adults, with a strong male predominance. These injuries are most commonly caused by sharp trauma and motor vehicle accidents, particularly motorcycle crashes.

In [4], a study from the national Canadian trauma registry reports on 335 cases of PNIs and 64 cases of BPIs. The sex distribution of PNI cases was significantly male-skewed, with 81% of cases being male and 19% female. These data provide insight into the gender breakdown of nerve injuries in a contemporary trauma population, highlighting that PNIs and BPIs predominantly affect men in early-to-mid adulthood.

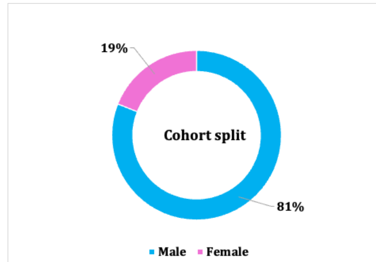
Contemporary registry and claims analyses [15] report cumulative PNI diagnoses following extremity trauma in $\sim$2.3% of cases overall (2.6% upper limb; 1.2% lower limb) in the United States and, in [4] a large Canadian trauma cohort (n=24,905), sharp injuries accounted for 39.4% of PNIs while motorcycle accidents were the leading cause of brachial plexus injury (32.8%). These epidemiologic profiles translate into substantial direct medical spending and even larger productivity losses borne by patients, employers, and public payers.

Direct acute and rehabilitation costs increase with the severity and complexity of the injury. In a nationwide workers' compensation cohort from Germany [6], which included 268 cases of upper-extremity PNIs (mean age 39.9 years; 85% male), mean in-patient reimbursement ranged from €3,418 to €5,360 per case, depending on the injury's location (distal to proximal). Additionally, 16% of patients required inpatient rehabilitation, averaging 41 $\pm$ 21 days, with €5,842 in extra costs. Sick leave averaged 147 days (range 11–1,109 days), with insurers covering €197 per day (€17,640 per case), and 26% of patients required a structured return-to-work program (mean duration: 21 days), highlighting the significant rehabilitation burden.

Procedure-specific studies show a similar cost gradient [16]: for surgically treated adult traumatic BPI in the USA, median 1-year direct payments amounted to $38,816 (IQR $18,209–$72,411), representing only a fraction of the long-term costs.



(a)



(b)

Fig. 3. Socio-economic aspects of PNIs: (a) breakdown of the lifetime cost for a traumatic brachial plexus injury in the USA [18]; (b) gender distribution of patients with PNIs [4].

In contrast, CTS incur much smaller direct costs. A Monte Carlo analysis in [17] estimated the mean total societal cost for operative CTS management at approximately $3,537, with surgery proving more cost-effective than nonoperative care. For patients with chronic nerve pain or injury, the financial burden is also significant: a cross-sectional USA study found considerable out-of-pocket expenses, missed workdays, and medical debt among individuals seeking surgery for chronic peripheral nerve injuries [18].

Indirect costs, including productivity loss and fiscal transfers, represent a significant portion of the overall economic burden of major PNIs. In particular, a USA lifetime BPI patient for a 26-year-old male manual laborer (base case) was estimated to incur substantial short-term and long-term financial losses [19]. These included short-term wage loss of $22,740, long-term wage loss of $737,551, and disability benefits amounting to $353,671, leading to a mean total indirect cost of $1,113,962 per patient (median $801,723), as shown in Fig. 3. This highlights the significant economic impact on individuals and society, underscoring the need for effective interventions to reduce long-term costs.

Crucially, this model demonstrated the sensitivity of indirect costs to return-to-work (RTW) outcomes. By doubling the probability of RTW into lower-paying employment, the model estimated a reduction in per-patient indirect costs to $867,987, resulting in savings of approximately $246,000 [19]. From a public payer perspective, disability transfers represent a significant fiscal expenditure. The same model attributed $353,671 to disability benefits alone [19]. Data from European insurers similarly reflect persistent public costs: in the German cohort, 30% of patients qualified for a work-disability pension, with an average annual payout of €3,187, leading to a projected lifetime liability of approximately €102,167 per recipient [6].

Broader social costs from upper-limb trauma—where PNIs are most commonly found—are substantial, even when averaged across a range of different injuries. In [20], a national study, hand and wrist injuries alone accounted for

$740 million annually, with productivity losses making up 56% of the total costs. While these studies include various non-nerve injuries, they help contextualize the societal burden of upper-extremity morbidity. Taken together, contemporary evidence highlights the following key points:

– PNIs primarily affect men in their most productive years, with the injuries often resulting from motor vehicle accidents or sharp tools [15,4];
– While direct acute, surgical, and rehabilitation costs are significant, the long-term impact of productivity loss and disability payments outweighs these immediate expenses [19,16,6];
– Policies and treatments that yield even modest improvements in return-to-work (RTW) rates can result in large, quantifiable savings—both in terms of societal costs (hundreds of thousands of dollars per patient for major injuries) and government budgets through reduced disability transfers [19,6].

Consequently, timely referral, evidence-based surgical reconstruction, and access to rehabilitation and vocational reintegration should be viewed not only as clinical imperatives, but also as fiscal policy strategies with measurable returns on investment.

4 Current therapeutic solutions

Given the significant social and economic burden of PNIs, effective therapeutic strategies are essential not only for improving patient outcomes but also for reducing long-term healthcare costs and productivity losses. Currently, available solutions span pharmacology, noninvasive and implanted neuromodulation, manual neurodynamics, acupuncture, robotic exoskeletons, and surgery [1]. In this section, we provide an analysis of each modality, summarizing its mechanism, historical introduction, efficacy, adverse events (AEs), and innovation status. Fig. 4 illustrates the trade-off between effectiveness and adverse effects for the existing solutions. In short, safety (low adverse effects) generally opposes efficacy across PNI solutions, with invasiveness and systemic exposure being the main drivers of adverse events.

Pharmacological therapies Drug strategies aim to enhance regeneration or control neuropathic pain. Following the discovery of nerve growth factor (NGF) and other neurotrophins such as brain-derived neurotrophic factor (BDNF) (mid-20th century), agents including tacrolimus (FK506; identified for neurite outgrowth in the 1990s) have shown regeneration benefits (e.g., $\sim$12–15% axon-growth increases and faster reinnervation in preclinical/early studies) [21,22]. Clinical translation remains limited: no disease-modifying medication reliably restores nerve function; efforts now emphasize localized delivery (to mitigate systemic toxicities like infection risk, nephrotoxicity, seizures) and combination approaches [21,22]. Following the advances of the early 2000s, progress has been incremental [21,22].

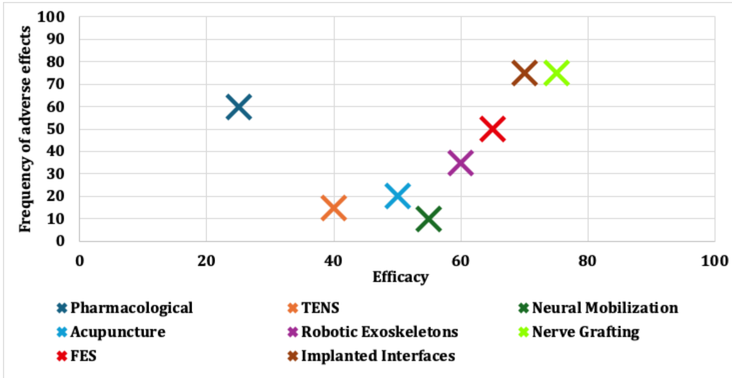


Fig. 4. Efficacy (higher is better) and adverse effects (higher is worse) trade-off, measured heuristically [1].

Transcutaneous electrical nerve stimulation (TENS) TENS (modern form late 1960s) delivers cutaneous pulses that activate large afferents and modulate pain pathways (gate-control and endogenous opioids) [23]. Evidence syntheses report modest-to-moderate pain reductions versus placebo with an excellent safety profile (mainly mild skin irritation); technology matured by the 1970s–1980s with subsequent incremental refinements [23].

Neural mobilization (neurodynamics) Formalized in the 1980s–1990s, nerve "gliding" seeks to restore excursion, reduce edema/adhesions, and down-modulate mechanosensitivity. A 2024 systematic review and meta-analysis showed short-term physiological gains — motor conduction velocity (MCV) 3 m/s and sensory conduction velocity (SCV) 11 m/s — alongside symptom improvements in entrapment neuropathies [24]. AEs are rare; in one randomized clinical trial (RCT), mobilization had no reported side effects while 3/31 patients on ibuprofen discontinued for AEs [25]. Core methods have remained stable since the early 2000s [24].

Acupuncture for painful diabetic peripheral neuropathy (pDPN) Applied to neuropathic pain with proposed effects on microcirculation, neurotrophic signaling, and central neuromodulation, acupuncture has gained supportive evidence: recent reviews/meta-analyses report significant pain reduction and improvements in nerve conduction metrics (MCV, SCV) with favorable safety (no excess serious AEs) [26,28]. The technique is longstanding; contemporary work focuses on dosing/standardization rather than new procedural paradigms [26,28].

Exoskeletons for motor rehabilitation After early concepts in the 1960s, clinically used lower-limb robotic exoskeletons emerged circa 2012–2015. In a 2023 randomized controlled trial (RCT) for incomplete spinal cord injury (SCI), exoskeleton training improved the Walking Index for Spinal Cord Injury II (WISCI-II) by ~ 3.5 points after 15 sessions versus < 1 in controls, with low serious-AE rates under supervision [29]. Devices restore task ability (gait practice, standing) and second-order benefits (conditioning, mood) but do not biologically repair nerves; innovation since the mid-2010s has been largely iterative (lighter frames, better control) [29].

Nerve grafting and surgical repair When tension-free neurorrhaphy is not possible, gaps are bridged with grafts. Decellularized allografts (introduced clinically in the late 2000s) preserve guidance architecture without chronic immunosuppression and now approach autograft sensory outcomes for moderate gaps: $\sim$ 87% meaningful sensory recovery (Medical Research Council, MRC, sensory scale $S \geq 3$) for $\leq$ 50 mm, and $\sim$ 69% for 50–70 mm [27]. Donor-site morbidity limits autografts; typical surgical risks (infection, scarring) apply [27]. Major innovation plateaued after the adoption of processed allografts; current work explores adjuncts (bioactive cargos, tissue engineering) [27].

Electrical stimulation and neural interfaces Functional electrical stimulation (FES; in clinical use since the 1960s–1990s) restores task-level functions (e.g., foot-drop correction, grasp) and confers physiological benefits despite fatigue-limited endurance; AEs are usually local (skin irritation, muscle soreness) with low serious-event rates for implanted systems [30]. Next-generation peripheral nerve interfaces enable bidirectional control and sensory feedback; human studies demonstrate stable, naturalistic tactile percepts over months–years with improved manipulation, indicating an active innovation frontier rather than a plateau [31].

In conclusion, noninvasive modalities (TENS, neural mobilization, acupuncture) offer symptom relief with excellent safety; exoskeletons restore function at the activity level; surgery (especially processed allografts) improves anatomic continuity with gap - and context - dependent outcomes; FES provides functional gains; and invasive neural interfaces are rapidly advancing toward finer, more durable bidirectional control. Most modalities, such as TENS, neural mobilization, and grafting, reached their main innovation plateau between the 1980s and 2010s, while neural interfaces remain under active development

5 A prospective implanted device

As part of this review, we summarize a representative example of an implantable bypass concept, illustrating how current research trends may converge toward future therapeutic solutions. While current therapeutic strategies for PNIs offer a range of solutions, from pharmacological treatments to advanced surgical interventions, many of these approaches focus primarily on symptom management or partial restoration of function. These treatments often fall short of fully restoring the complex functions of the peripheral nervous system, particularly in cases of severe or chronic injury. As such, there is a growing need for alternative approaches that not only address the symptoms but also offer more comprehensive, long-term solutions for nerve regeneration and functional recovery.

In this context, a fully implantable device is proposed as a possible solution. The proposed system acts as a functional bypass, restoring information flow across the impaired peripheral pathway [32]. By capturing neural activity on one side of the lesion, interpreting it externally thanks data analysis, and reinjecting a physiologically meaningful command on the other side. This innovative approach seeks to bridge the gap between damaged neural circuits and restore vital functions.

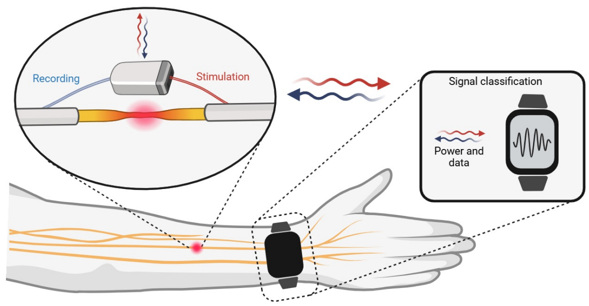


Fig. 5. Representative implantable bypass concept (illustrative example).

An example of a potential solution is illustrated in Fig. 5. The implant consists of non-penetrating, multi-contact nerve cuffs placed both proximally and distally to the lesion [3]. These cuffs gently encircle the nerve, ensuring long-term mechanical stability and a low-trauma interface for both sensing and stimulation [33].

Proximally, the cuff records neural activity associated with voluntary movements (efferent flow) or sensory signals traveling toward the brain (afferent flow). Distally, a similar cuff provides targeted electrical stimulation (neuromodulation) to recruit the appropriate nerve fibers, while ensuring safety by controlling factors such as current density, pulse width, and duty cycle. The system uses a low-power, bidirectional telemetry link to connect the implant to an external processing unit, which handles computationally demanding tasks, minimizing heat dissipation and reducing the implant size [3].

The system works as follows [3]: The proximal cuff detects weak neural signals, typically in the range of 10-50 µV, which are often masked by noise from surrounding muscle activity and environmental interference. Given the small signal size, low-impedance electrodes are required for proper signal acquisition. These signals are processed through analog and digital filtering, reject interference, and suppress common-mode artifacts, such as motion and stimulation after-potentials.

The measured signals are characterized by a low signal-to-noise ratio of around 2 dB and a wide frequency band from 500 Hz and 7 kHz with a energy peak at about 2 kHz, ensuring minimal overlap with other biological signals. Due to the complexity and variability of the signal, the external processor performs signal analysis using advanced techniques as shown in [3,34,35].

Achieving near real-time classification is essential to ensure physiological responses remain natural, which makes feature extraction from ENG signals a critical step. Three main approaches dominate the literature: spike detection, which isolates action potentials but requires high signal quality [34]; window-based feature extraction, which characterizes activity in short temporal windows and is more robust to noisy signals [35]; and hybrid kernel methods, which combine local spike information with global activity patterns [3]. The latter, often implemented with convolutional or recurrent neural networks, has shown the best balance between accuracy and robustness.

After the residual neural signal has been classified — i.e., once the intended movement direction has been identified — the system generates a stimulation pattern that respects the natural timing and spatial selectivity of neural activity, ensuring that only the appropriate fibers are activated. The system enforces charge balance, monitors current compliance, and checks electrode impedance to detect unsafe conditions, using watchdog logic to silence output in case of uncertainty or anomalies [32,36,38].

For sensory restoration, the process is reversed: the distal cuff senses sensory events (e.g., touch or proprioception), the external processor interprets them, and the proximal cuff delivers the appropriate afferent stimulation to replace the lost sensory input. Since both acquisition and stimulation occur at each site, crosstalk between recording and stimulation can arise; to mitigate this, blanking circuits are commonly implemented to suppress stimulation artifacts during signal acquisition [32,36].

To minimize latency between user intention (decoded motor command), its execution through stimulation, and the resulting sensory feedback (to give the sensation of the moviment), computation-heavy tasks are offloaded to a support external unit. This enables more sophisticated algorithms and remote updates without increasing the implant's complexity [37].

Comparable approaches have been demonstrated in recent literature. For instance, the SenseBack system provides a fully implantable 32-channel bidirectional interface for peripheral nerves, demonstrated in preclinical studies [36]. In humans, closed-loop sensory feedback via intraneural electrodes in human subjects has restored naturalistic sensations and improved function with lower-limb prostheses [38]. Together, these technologies outline the translational trajectory toward functional bypass systems capable of restoring bidirectional communication after nerve injury [32].

This proposed system represents a promising alternative to current therapies, offering a more comprehensive approach to treating peripheral nerve injuries. By bypassing the impaired pathways and restoring functional information flow, it not only addresses immediate symptoms but also facilitates long-term functional recovery. The integration of advanced computational processing, minimal invasiveness, and wireless communication underscores its potential to significantly enhance patient outcomes and reduce the overall burden on healthcare systems.

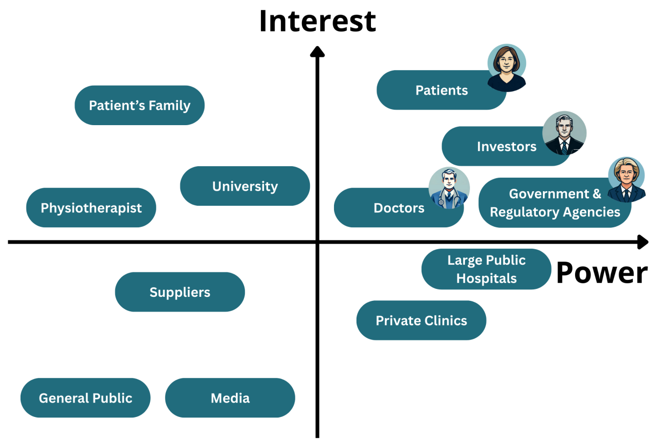


Fig. 6. Stakeholder ecosystem: Power Interest Matrix of Johnson & Scholes.

6 Conclusions

In summary, this review has outlined the multifaceted impact of PNIs and provided a structured overview of existing diagnostic and therapeutic solutions. By integrating evidence from clinical, engineering, and socioeconomic perspectives, it identifies current limitations and emerging opportunities for innovation. To move from promising therapeutic concepts to real-world impact, PNIs must be addressed not only at the technical and clinical level but also through coordinated engagement of the wider healthcare ecosystem. After outlining the dual burden of PNIs, the continuum of current care options, and the potential of a novel implantable bypass system, it becomes clear that long-term success will ultimately depend on the alignment of diverse stakeholders, each with each with varying degrees of interest and influence [39], as illustrated in Fig. 6.

Patients and caregivers are the primary beneficiaries and risk-bearers: they balance potential functional recovery and quality-of-life gains against surgical burden, device maintenance, and the psychological demands of a hybrid implanted–external system. Clinicians oversee indication, implantation, programming, and follow-up, so they require clear workflows and seamless integration with existing practice. Hospital administrators and ethics committees evaluate operational fit, liability, and governance. Payers and health-technology assessment bodies prioritize cost-effectiveness, equity of access, and evidence quality. Regulators assess safety, performance, and benefit–risk across pre- and post-market phases. Manufacturers and suppliers must ensure product quality, resilient supply chains, and field serviceability. Standards organizations and cybersecurity experts promote interoperability and secure communication. Researchers depend on ethically governed data and updatable algorithms, while public agencies, advocacy groups, and investors shape diffusion through funding, education, and transparency. Effective adoption hinges on alignment around a shared value proposition: meaningful, measurable restoration of function delivered safely and sustainably.

The analysis of stakeholders highlights that technical innovation alone is insufficient: lasting impact requires coordinated action across patients, clinicians, institutions, payers, and regulators. PNIs remain a major unmet need, and investing in solutions that are safe, effective, and economically sustainable is essential. The proposed implantable bypass exemplifies this potential, but its translation will depend on rigorous validation and early integration into healthcare systems. Addressing peripheral nerve injuries requires more than incremental progress: only sustained investment in translational solutions that unite engineering, medicine, and policy will deliver therapies capable of restoring autonomy and reducing the long-term burden on society. Future research should build upon those investigations through interdisciplinary collaboration and validation of the most promising approaches in real-world clinical contexts.

Acknowledgment We thank Alta Scuola Politecnica for the educational and financial support, and professors Maurizio Magarini and Paolo Motto Ros for their mentorship. Thanks also to all the students who helped us for their invaluable contribution and collaboration throughout our work.

References

1. A. Coviello *et al.* (2024, September). Emerging peripheral nerve injuries recovery: advanced nerve-cuff electrode model interface for implantable devices. In 2024 Global Conference on Wireless and Optical Technologies (GCWOT) (pp. 1-7). IEEE.
2. Koeppen A H (2004). Wallerian degeneration: history and clinical significance. Journal of the neurological sciences, 220(1), 115-117.
3. A. Coviello *et al.*. Artificial neural networks-based real-time classification of eng signals for implanted nerve interfaces. IEEE Journal on Selected Areas in Communications, 42(8), 2080-2095.
4. M. Zaidman *et al.*. Epidemiology of peripheral nerve and brachial plexus injuries in a trauma population. Can J Surg. 2024 Jun 26;67(3):E261-E268. doi: 10.1503/cjs.002424. PMID: 38925857; PMCID: PMC11230667.
5. EW. de Heer *et al.*. The association of depression and anxiety with pain: a study from NESDA. PLoS One. 2014 Oct 15;9(10):e106907. doi: 10.1371/journal.pone.0106907. Erratum in: PLoS One. 2014;9(12):e115077. PMID: 25330004; PMCID: PMC4198088.
6. K. D. Bergmeister, L. Große-Hartlage, S. C. Daeschler, *et al.*, "Acute and long-term costs of 268 peripheral nerve injuries in the upper extremity," *PLOS ONE*, vol. 15, no. 4, e0229530, 2020. doi:10.1371/journal.pone.0229530.
7. S. Chandrasekaran *et al.*. Case study: persistent recovery of hand movement and tactile sensation in peripheral nerve injury using targeted transcutaneous spinal cord stimulation. Front Neurosci. 2023 Jul 17;17:1210544. doi: 10.3389/fnins.2023.1210544. PMID: 37529233; PMCID: PMC10390294.

8. Magnéli M, Axenhus M (2024) Epidemiology and regional variance of traumatic peripheral nerve injuries in Sweden: A 15-year observational study. PLOS ONE 19(10): e0310988. https://doi.org/10.1371/journal.pone.0310988
9. Erlangsen A, Stenager E, Conwell Y, *et al.*. Association Between Neurological Disorders and Death by Suicide in Denmark. JAMA. 2020;323(5):444–454. doi:10.1001/jama.2019.21834
10. Y. Adu *et al.*. Psychology of nerve injury, repair, and recovery: a systematic review. Front Rehabil Sci. 2024 Nov 6;5:1421704. doi: 10.3389/fresc.2024.1421704. PMID: 39568638; PMCID: PMC11576464.
11. ZA. Landers *et al.*. The Psychological Impact of Adult Traumatic Brachial Plexus Injury. J Hand Surg Am. 2018 Oct;43(10):950.e1-950.e6. doi: 10.1016/j.jhsa.2018.02.019. Epub 2018 Apr 17. PMID: 29678427.
12. J. Ultee *et al.*. "Early posttraumatic psychological stress following peripheral nerve injury: a prospective study," *J. Plast. Reconstr. Aesthet. Surg.*, vol. 66, no. 10, pp. 1316–1321, Oct. 2013, doi: 10.1016/j.bjps.2013.05.017.
13. S. M. Yannascoli *et al.*. "A population-based assessment of depression and anxiety in patients with brachial plexus injuries," *J. Hand Surg. Am.*, vol. 43, no. 12, pp. 1136.e1–1136.e9, Dec. 2018, doi: 10.1016/j.jhsa.2018.03.056.
14. S. Jia *et al.*, "Determinants of anxiety and depression in patients with cubital tunnel syndrome," *BMC Psychiatry*, vol. 20, article 540, 2020, doi: 10.1186/s12888-020-02934-0.
15. W. M. Padovano, J. Dengler, M. M. Patterson, *et al.*, "Incidence of Nerve Injury After Extremity Trauma in the United States," *Hand (N Y)*, vol. 17, no. 4, pp. 615–623, 2022. doi:10.1177/1558944720963895.
16. C. J. Dy *et al.*, "Direct cost of surgically treated adult traumatic brachial plexus injuries," *J Hand Surg Global Online*, vol. 2, no. 2, pp. 77–79, 2020. doi:10.1016/j.jhsg.2019.12.001.
17. A. S. Gabrielli *et al.*, "The Direct and Indirect Costs to Society of Carpal Tunnel Release," *Hand (N Y)*, vol. 15, no. 2, pp. NP1–NP5, 2020 (Epub 2018). doi:10.1177/1558944718810855.
18. J. M. Felder and I. Ducic, "Cross-sectional evaluation of the economic burden on patients seeking surgical treatment for chronic nerve injuries," *Annals of Plastic Surgery*, vol. 88, no. 5, pp. 485–490, 2022. doi:10.1097/SAP.0000000000002924.
19. T. S. Hong *et al.*, "Indirect Cost of Traumatic Brachial Plexus Injuries in the United States," *Journal of Bone and Joint Surgery (Am.)*, vol. 101, no. 16, e80, 2019. doi:10.2106/JBJS.18.00658.
20. C. E. de Putter, R. W. Selles, S. Polinder, *et al.*, "Economic impact of hand and wrist injuries: health-care costs and productivity costs in a population-based study," *Journal of Bone and Joint Surgery (Am.)*, vol. 94, no. 9, e56, 2012. doi:10.2106/JBJS.K.00561.
21. S. Bolandghamat *et al.*, "Recent Findings on the Effects of Pharmacological Agents on the Nerve Regeneration after Peripheral Nerve Injury," *Curr. Neuropharmacol.*, vol. 18, no. 11, pp. 1154–1163, 2020. DOI: 10.2174/1570159X18666200507084024.
22. F. Millesi, D. J. Daniels, C. Radtke *et al.*, "Localized tacrolimus therapy: innovations in peripheral nerve regeneration through advanced drug delivery systems," *Expert Rev. Neurother.*, vol. 15, no. 10, pp. 743–748, 2024. DOI: 10.1080/20415990.2024.2392481.
23. C. G. T. Vance *et al.*, "Using TENS for Pain Control: Update on the State of the Evidence," *Medicina*, vol. 58, no. 10, Art. 1332, Oct. 2022. DOI: 10.3390/medicina58101332.

24. J. V. Bittencourt *et al.*, “Neural mobilisation effects in nerve function and nerve structure of patients with peripheral neuropathic pain: A systematic review with meta-analysis,” *PLoS ONE*, vol. 19, no. 11, Art. e0313025, Nov. 2024. DOI: 10.1371/journal.pone.0313025.
25. D. Rodriguez-Sanz *et al.*, “Effectiveness of median nerve neural mobilization versus oral ibuprofen in subjects with cervicobrachial pain: a randomized clinical trial,” *Arch. Med. Sci.*, vol. 14, no. 4, pp. 871–879, 2018. DOI: 10.5114/aoms.2017.70328.
26. L. Wang and L.-M. Wang, “Perspective on acupuncture treatment for diabetic peripheral neuropathy,” *Medicine (Baltimore)*, vol. 104, no. 23, Art. e42646, Jun. 2025. DOI: 10.1097/MD.0000000000042646.
27. G. Buncke, “Peripheral nerve allograft: how innovation has changed surgical practice,” *Plast. Aesthet. Res.*, vol. 9, p. 38, May 2022. DOI: 10.20517/2347-9264.2022.08.
28. J. Liu *et al.*, “Efficacy and safety of acupuncture for painful diabetic neuropathy: a systematic review and meta-analysis,” *Front. Neurol.*, vol. 15, Art. 1402458, Jun. 2024. DOI: 10.3389/fneur.2024.1402458.
29. Á. Gil-Agudo *et al.*, “Exoskeleton-based training improves walking independence in incomplete spinal cord injury patients: results from a randomized controlled trial,” *J. NeuroEngineering Rehabil.*, vol. 20, Art. 36, Mar. 2023. DOI: 10.1186/s12984-023-01158-z.
30. M. S. Harkema *et al.*, “Physiologic effects of electrical stimulation for rehabilitation and regeneration after spinal cord injury,” *J. Neurotrauma*, vol. 25, no. 2, pp. 201–210, 2008. DOI: 10.1089/neu.2007.0487.
31. J. M. Graczyk *et al.*, “A neural interface provides long-term stable natural touch perception,” *Sci. Transl. Med.*, vol. 10, no. 439, Art. eaao3252, Oct. 2018. DOI: 10.1126/scitranslmed.aao3252.
32. Denison T, Morrell M J (2022). Neuromodulation in 2035: the neurology future forecasting series. Neurology, 98(2), 65-72.
33. E. H. Rijnbeek *et al.*. Update on peripheral nerve electrodes for closed-loop neuroprosthetics. Frontiers in neuroscience, 12, 350.
34. Koh R G *et al.* (2020). Selective peripheral nerve recordings from nerve cuff electrodes using convolutional neural networks. Journal of Neural Engineering, 17(1), 016042.
35. Brunton E *et al.* (2017, May). Identification of sensory information in mixed nerves using multi-channel cuff electrodes for closed loop neural prostheses. In 2017 8th International IEEE/EMBS Conference on Neural Engineering (NER) (pp. 391-394). IEEE.
36. Williams, Ian *et al.* ”SenseBack-an implantable system for bidirectional neural interfacing.” IEEE Transactions on Biomedical Circuits and Systems 14.5 (2020): 1079-1087.
37. A. Coviello *et al.* (2023, October). Comparison of data compression methods for implanted real-time peripheral nervous system. In 2023 IEEE International Conference on Metrology for eXtended Reality, Artificial Intelligence and Neural Engineering (MetroXRAINE) (pp. 110-115). IEEE.
38. Petrini, Francesco Maria, *et al.* ”Enhancing functional abilities and cognitive integration of the lower limb prosthesis.” Science translational medicine 11.512 (2019): eaav8939.
39. H. D. J. Hogg, *et al.* (2023). Stakeholder Perspectives of Clinical Artificial Intelligence Implementation: A Qualitative Systematic Review. PLOS Digital Health, 2(4).