Review

Neurological Recovery in the Aging Brain: Challenges and Emerging Therapies

DELIA-MARIA POPESCU[1], IANIS KEVYN STEFAN BOBOC[2], SIMION PATRU[1], MIHAI-CRISTIAN PAPA[1], AUREL POPA-WAGNER[3]

[1]Doctoral School, University of Medicine and Pharmacy of Craiova, Romania
[2]Department of Pharmacology, Faculty of Pharmacy, University of Medicine and Pharmacy of Craiova, Romania
[3]Experimental Research Center for Normal and Pathological Aging, University of Medicine and Pharmacy of Craiova, Romania

ABSTRACT: Restoration of neurological function after stroke, spinal cord injury and neurodegeneration remains limited by irreversible tissue loss, age-associated changes in neural plasticity and the difficulty of translating experimental repair strategies into sustained clinical benefit. This narrative review critically examines pharmacological neuroprotection, rehabilitation, cellular and extracellular-vesicle therapies, and endogenous neuronal reprogramming, with particular emphasis on ischemic stroke and the aged brain. We then evaluate brain-computer interfaces and related neuroprosthetic technologies for motor assistance, communication, rehabilitative feedback and closed-loop neuromodulation. Advances in artificial intelligence are expanding neural decoding and adaptive control, but technical feasibility must be distinguished from demonstrated clinical effectiveness. Evidence is strongest for established responsive neurostimulation in focal epilepsy and conventional deep brain stimulation in selected Parkinson's disease patients; other invasive motor, speech and brain-spine interfaces remain at earlier stages of clinical evaluation. We propose that biological interventions and neuroprosthetics may eventually provide complementary therapeutic benefits, while emphasizing that combined approaches remain largely hypothetical. Progress will require rigorous patient selection, durable device performance, validated patient-centered endpoints and assessment of functional gains beyond active device assistance.

KEYWORDS: *Biological neurorestoration, brain-computer interface, neuroprosthetics, artificial intelligence, ischemic stroke, aging; neural plasticity.*

Introduction

Restoration of neurological function following acute brain injury, spinal cord injury, or progressive neurodegeneration remains a major challenge in contemporary neuroscience.

Although substantial advances have been achieved in understanding the cellular and molecular mechanisms of neural injury and repair, the translation of these discoveries into effective restorative therapies has been considerably less successful. Ischemic stroke provides a particularly instructive example.

Despite major improvements in acute reperfusion treatment and organized stroke care, many survivors experience persistent motor, cognitive, language, and sensory impairments that substantially compromise independence and quality of life. The development of effective treatments capable of restoring lost neurological functions therefore remains an important unmet clinical need [1,2].

Over the past several decades, numerous therapeutic strategies have been investigated to limit secondary neuronal injury and enhance recovery. These include pharmacological neuroprotection, modulation of neuroinflammatory responses, physical rehabilitation, electrical and magnetic stimulation, stem-cell transplantation, extracellular-vesicle-based therapies, and interventions designed to stimulate endogenous neurogenesis or reprogram resident glial cells into neurons. Many of these approaches have produced encouraging experimental results, including reductions in infarct volume, attenuation of neuroinflammation, improved neuronal survival, and enhanced behavioral recovery. Nevertheless, the clinical translation of these findings has remained disappointing, particularly for interventions intended to produce durable structural or functional restoration after established injury [3,4,5].

Several factors contribute to this translational gap. Experimental studies frequently employ young, otherwise healthy animals, whereas human neurological disorders predominantly affect older individuals with multiple comorbidities. Aging alters cerebrovascular regulation, mitochondrial function, inflammatory signaling, blood-brain barrier integrity, synaptic plasticity, and the regenerative capacity of neural tissue. These changes influence both the initial response to injury and the subsequent capacity for

This is an open-access article distributed under the terms of a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International Public License, which permits unrestricted use, adaptation, distribution and reproduction in any medium, non-commercially, provided the new creations are licensed under identical terms as the original work and the original work is properly cited.
10.12865/CHSJ.52.03.02

repair. In addition, experimental interventions are often administered under tightly controlled conditions, within therapeutic windows that may be difficult to reproduce in clinical practice. Differences in lesion size, anatomical location, disease severity, treatment timing, and rehabilitation intensity further complicate the interpretation of clinical outcomes [6,4].

The limitations of biological neurorestoration are particularly evident when successful tissue protection or cellular replacement does not translate into the reconstruction of functional neural circuits.

Although experimental interventions may increase the number of surviving neurons, promote axonal sprouting, or generate cells expressing neuronal markers, meaningful recovery requires coordinated integration into existing networks. Newly generated neurons must establish appropriate synaptic connections, participate in physiologically relevant activity, and remain functional over extended periods. These requirements become increasingly difficult to satisfy in the chronically injured or aged nervous system.

Against this background, neuroprosthetics represents an alternative and potentially complementary therapeutic paradigm. Rather than relying exclusively on the biological reconstruction of damaged tissue, neuroprosthetic systems exploit residual neural activity to restore communication, movement, or other neurological functions. Brain-computer interfaces (BCIs) establish a direct functional relationship between neural signals and external devices or therapeutic systems, enabling preserved neural circuits to control effectors despite disruption of conventional motor pathways [7,8].

Recent advances have substantially expanded the capabilities of these technologies. Intracortical and cortical-surface interfaces have enabled increasingly sophisticated control of robotic devices and communication systems, while brain-spine interfaces have demonstrated the feasibility of reconnecting cortical motor intention with spinal stimulation to support locomotion after spinal cord injury [9,10].

Similarly, neural decoding of attempted speech has enabled rapid text generation and synthesized speech in individuals with severe paralysis [11,12].

Importantly, neuroprosthetics is entering a new developmental phase driven by artificial intelligence. Machine-learning algorithms increasingly enable the extraction of meaningful information from complex and variable neural signals, the prediction of intended movements or speech, and the adaptation of stimulation parameters to individual neurological states. The convergence of AI with high-density neural recording, advanced signal processing, and bidirectional sensorimotor feedback may substantially improve the accuracy, naturalness, and adaptability of neuroprosthetic systems.

Objective

However, the distinction between functional compensation and biological restoration remains essential. Successful operation of a neuroprosthetic device does not necessarily indicate recovery of the underlying damaged neural circuitry. Conversely, closed-loop interfaces that associate neural intention with appropriately timed sensory or motor feedback may promote activity-dependent plasticity and potentially contribute to more persistent improvements in endogenous function.

The present narrative review examines the limitations of conventional biological and experimental restorative therapies, using ischemic stroke and the aged brain as principal examples, before considering the emerging role of neuroprosthetics across major neurological disorders. Particular attention is given to the accelerating influence of AI on neural decoding, adaptive neuromodulation, and personalized rehabilitation. We propose that the future of neurological restoration may depend increasingly on the integration of biological repair strategies with AI-driven neuroprosthetic technologies capable of exploiting and reshaping surviving neural networks.

Methods

The literature considered here consists primarily of peer-reviewed studies published between 2019 and 2026, identified through PubMed, Scopus, and Google Scholar using combinations of the terms *brain-computer interface*, *neuroprosthesis*, *closed-loop neuromodulation*, and indication-specific search terms, supplemented by reference screening of relevant clinical studies and reviews. Consumer-oriented neurotechnology and purely preclinical BCI applications are considered only where they directly inform clinical translation. Accordingly, we first examine the principal BCI architectures and the neural acquisition-decoding pipeline underlying them. We then consider sensorimotor feedback and closed-loop control before critically

evaluating clinical evidence across major neurological indications.

Finally, we examine the technological, biological, clinical, economic, regulatory, and neuroethical barriers that currently separate experimental performance from routine clinical implementation and discuss emerging strategies that may facilitate the transition toward durable, individualized, and clinically scalable neuroprosthetic systems (Figure 1).

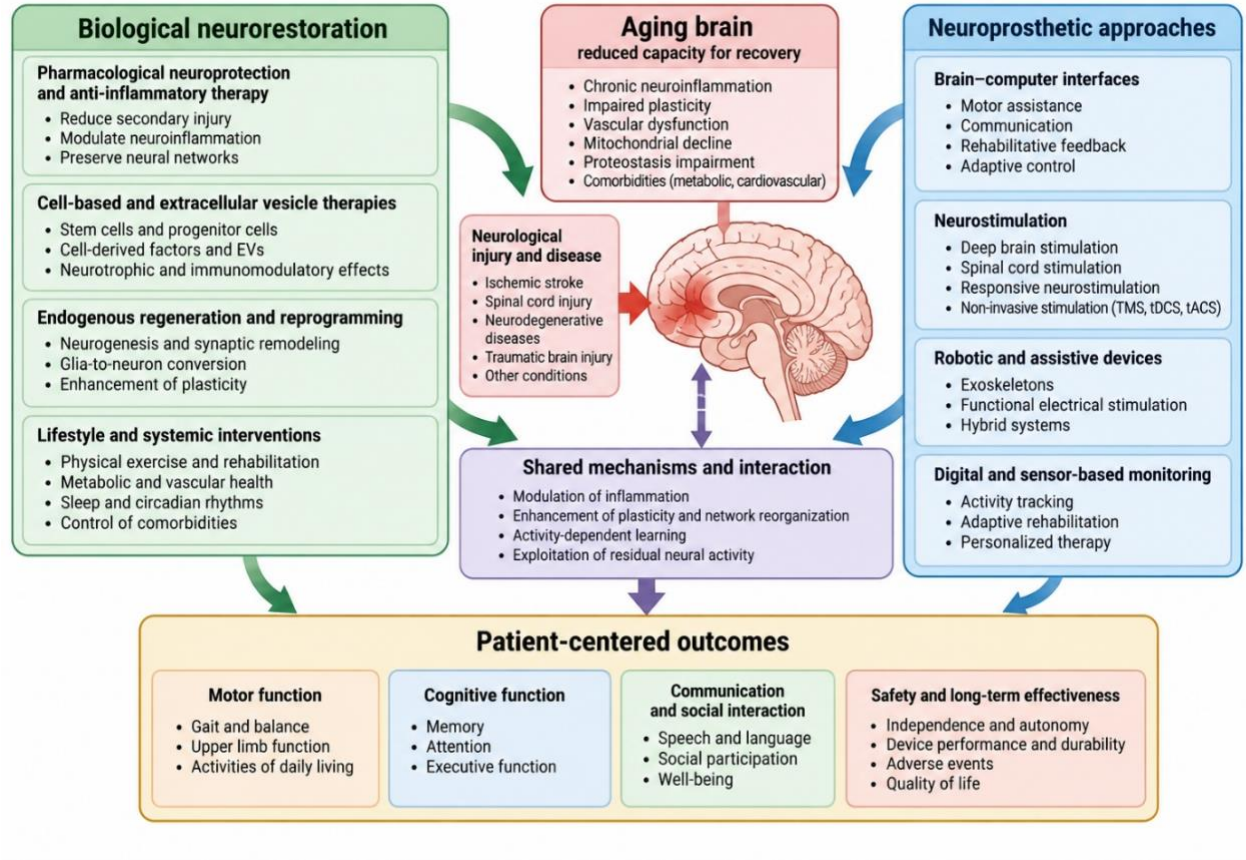


Figure 1. Biological and neuroprosthetic strategies for neurological recovery in the aging brain.

Aging-associated alterations, including chronic neuroinflammation, impaired neural plasticity, cerebrovascular dysfunction, mitochondrial decline, proteostasis impairment, and comorbidities, constrain neurological recovery following stroke, spinal cord injury, traumatic brain injury, and neurodegenerative diseases. Biological neurorestorative strategies encompass pharmacological neuroprotection, anti-inflammatory interventions, cell-based and extracellular-vesicle therapies, endogenous regeneration, and systemic interventions. Complementary neuroprosthetic approaches include brain-computer interfaces, neuromodulation, robotic assistance, and sensor-based rehabilitation. These strategies may interact through modulation of neuroinflammation, enhancement of neural plasticity, network reorganization, and activity-dependent learning. Their therapeutic effectiveness should ultimately be assessed through clinically meaningful outcomes, including motor and cognitive recovery, communication, functional independence, quality of life, and long-term safety. The proposed interactions represent a conceptual framework; synergistic therapeutic benefits and sustained device-independent neurological recovery remain to be demonstrated.

Biological and Conventional Therapeutic Strategies for Neurological Recovery: Clinical Achievements, Translational Limitations, and Unmet Needs

The distinction between acute neuroprotection and restoration of established neurological deficits

Over several decades, substantial experimental efforts have been directed toward limiting neuronal injury and promoting neurological recovery following cerebral ischemia and other central nervous system disorders. These approaches have targeted excitotoxicity, oxidative stress, mitochondrial dysfunction, neuroinflammation, apoptosis, and mechanisms of endogenous tissue repair.

Although numerous interventions have produced encouraging results in experimental models, translation into effective clinical treatments has remained challenging, particularly when the therapeutic objective is restoration of function after established structural injury.

It is important, however, to distinguish failure of experimental neuroprotective agents from the considerable clinical progress achieved in acute stroke treatment. Intravenous thrombolysis and mechanical thrombectomy have transformed the management of eligible patients with acute

10.12865/CHSJ.52.03.02

ischemic stroke by restoring cerebral perfusion and limiting the extent of irreversible injury. The DAWN and DEFUSE 3 trials further demonstrated that appropriately selected patients may benefit from endovascular treatment beyond conventional early therapeutic windows [13,14].

These advances represent major successes of translational cerebrovascular research.

Nevertheless, reperfusion treatment is not equivalent to restoration of neurological function after extensive neuronal loss. Many patients continue to experience persistent motor, cognitive, and language impairments despite successful recanalization. Furthermore, access to reperfusion therapy is restricted by time, clinical eligibility, vascular anatomy, and the availability of specialized stroke services.

The development of treatments capable of improving recovery during the subacute and chronic stages of neurological injury therefore remains an important unmet clinical need.

Pharmacological neuroprotection: lessons from experimental and clinical studies

The limited clinical translation of pharmacological neuroprotection represents one of the most extensively documented challenges in experimental stroke research. A clinical or experimental study [3] systematically evaluated 1,026 experimental treatments for acute stroke, highlighting the considerable discrepancy between promising preclinical findings and subsequent clinical outcomes.

Several compounds that demonstrated neuroprotective effects in experimental cerebral ischemia subsequently failed to produce convincing clinical benefits. The free-radical-trapping agent NXY-059 provides a particularly informative example. Initial clinical findings generated considerable interest, but the larger SAINT II trial failed to demonstrate a significant improvement in disability outcomes following acute ischemic stroke [15].

This result raised fundamental questions concerning experimental model selection, pharmacokinetics, treatment timing, and the predictive validity of preclinical endpoints.

Other pharmacological strategies have encountered similar difficulties. The FAST-MAG trial, which investigated prehospital magnesium sulfate administration, did not demonstrate improved disability outcomes despite the rationale for very early neuroprotective intervention [16].

These findings do not establish that neuroprotection is intrinsically ineffective. Rather, they indicate that the biological complexity of human stroke cannot always be adequately represented by experimental systems involving relatively homogeneous animals, standardized lesions, and tightly controlled treatment conditions.

The development of the Stroke Therapy Academic Industry Roundtable recommendations reflected increasing recognition of these methodological problems and emphasized improved experimental rigor, clinically relevant models, and more appropriate translational strategies [4].

More recent developments have also challenged an overly pessimistic interpretation of pharmacological neuroprotection. In the ESCAPE-NA1 trial, nerinetide did not significantly improve the primary clinical outcome in the overall study population, although subgroup findings generated further hypotheses concerning treatment interactions and patient selection [17].

Such results illustrate that the translational question is not simply whether a compound protects neurons experimentally, but whether it provides additional clinical benefit under specific treatment conditions.

Thus, the principal limitation of pharmacological neuroprotection is not the absence of experimentally identifiable therapeutic targets, but the difficulty of translating target modulation into reproducible, clinically meaningful neurological outcomes.

Advanced age, neuroinflammation, and the reduced capacity for neurological recovery

Advanced age is among the most important biological factors influencing the consequences of cerebral ischemia. Nevertheless, many experimental stroke studies have historically relied on young, otherwise healthy animals, creating a substantial mismatch between experimental conditions and the clinical population.

Aging is associated with alterations in cerebrovascular function, impaired neurovascular coupling, mitochondrial dysfunction, chronic low-grade inflammation, and changes in immune responsiveness. These processes influence both the severity of ischemic injury and the capacity of surviving neural networks to undergo adaptive reorganization.

Studies of cerebral ischemia in aged animals have demonstrated that the postischemic response differs substantially from that observed in young animals. In particular, aged brains may exhibit more persistent inflammatory activation, altered glial responses, and reduced effectiveness of endogenous repair mechanisms [6].

Neuroinflammation is especially relevant because its contribution to neurological injury is strongly dependent on cellular context and temporal stage. Acute inflammatory responses may participate in debris removal and tissue remodeling, whereas persistent or dysregulated inflammatory activity can interfere with synaptic function, vascular integrity, and neurological recovery.

Consequently, broad suppression of inflammatory signaling may not reproduce the benefits observed when selected pathways are modulated at specific stages of injury.

The aging brain also exhibits changes in synaptic plasticity, growth-factor signaling, and extracellular matrix composition that may restrict the reorganization of residual neural networks. These limitations are relevant not only to biological regenerative therapies but also to neurorehabilitation and activity-dependent neuroprosthetic interventions.

A clinically useful restorative strategy must therefore account for the age-dependent biological environment in which neural recovery occurs.

Physical rehabilitation and non-invasive neuromodulation: established benefits and remaining limitations

Unlike many experimental pharmacological interventions, physical and occupational rehabilitation have established roles in neurological recovery. Task-specific training, repetitive movement practice, and multidisciplinary rehabilitation can improve functional performance following stroke and other neurological injuries.

However, rehabilitation outcomes remain heterogeneous. The extent of recovery depends on lesion characteristics, residual motor pathways, cognitive function, comorbidities, treatment intensity, and the timing of intervention.

The limitations of rehabilitation are particularly evident in patients with severe paresis, who may be unable to generate sufficient voluntary movement to engage effectively in conventional motor training.

Non-invasive brain stimulation techniques, including repetitive transcranial magnetic stimulation and transcranial direct current stimulation, have been investigated as potential methods for modifying cortical excitability and enhancing rehabilitation-associated plasticity.

Although selected studies have reported beneficial effects, clinical results remain variable, and the optimal stimulation parameters, treatment schedules, and patient-selection criteria are incompletely established.

A related limitation concerns the relationship between stimulation and behavioral activity. Non-invasive stimulation delivered independently of the patient's movement intention may not consistently engage the specific neural circuits required for functional recovery.

This provides a mechanistic rationale for brain-computer interface-assisted rehabilitation, in which movement-related neural activity can be detected and coupled to temporally contingent sensory feedback, robotic assistance, or peripheral electrical stimulation.

The potential advantage of this approach is not simply the addition of another rehabilitation device, but the possibility of linking intended movement to its sensory consequences in a manner that reinforces activity-dependent neural plasticity.

Nevertheless, BCI-assisted rehabilitation must demonstrate benefits beyond those attributable to conventional training intensity, attention, or nonspecific feedback.

Stem-cell-based therapies: biological potential and the challenge of clinical efficacy

Stem-cell-based interventions have attracted considerable interest as potential treatments for neurological disorders because of their capacity to influence inflammatory responses, trophic signaling, tissue remodeling, and, under selected conditions, cellular replacement.

Experimental studies involving mesenchymal stromal cells and other cellular populations have demonstrated improvements in neurological outcomes in several models of cerebral ischemia.

However, the mechanisms underlying these effects remain complex. Many observed benefits appear to involve paracrine signaling and modulation of the host tissue environment rather than extensive differentiation of transplanted cells into functionally integrated neurons.

Clinical translation has progressed more slowly than initially anticipated.

10.12865/CHSJ.52.03.02

The MASTERS trial investigated multipotent adult progenitor cells in patients with acute ischemic stroke. Although the treatment demonstrated an acceptable safety profile, the study did not meet its primary efficacy endpoint [18].

This example illustrates the importance of distinguishing biological plausibility and clinical feasibility from demonstrated therapeutic effectiveness.

Cell-based therapies also present challenges involving product characterization, donor variability, manufacturing procedures, dose selection, treatment timing, and long-term safety.

Moreover, neurological improvement following cellular treatment does not necessarily establish neuronal replacement or restoration of damaged neural circuits.

Future investigations must therefore determine whether cell-based interventions can reproducibly improve clinically meaningful outcomes, identify the mechanisms responsible for benefit, and establish which patient populations are most likely to respond.

Extracellular vesicles and cell-free biological therapies

The recognition that many beneficial effects of mesenchymal stromal cells may be mediated through secreted factors has stimulated interest in extracellular vesicles and related cell-free therapeutic preparations.

These vesicles can transport proteins, lipids, and nucleic acids capable of influencing recipient cells and modulating inflammatory or trophic signaling.

In experimental neurological disorders, mesenchymal stromal cell-derived extracellular vesicles have been investigated for their potential to reduce inflammatory activation, support neuronal survival, and promote tissue remodeling.

Their cell-free nature may offer practical advantages over transplantation of living cells, including the possibility of more standardized storage and administration.

Nevertheless, extracellular-vesicle-based therapies remain subject to important translational limitations.

Preparations may differ substantially according to cellular origin, culture conditions, isolation methods, vesicle composition, and purification procedures. These variables can influence biological activity and complicate comparisons between experimental studies.

Additional challenges concern biodistribution, dosing, biological potency, manufacturing reproducibility, and the establishment of clinically meaningful efficacy.

Importantly, the presence of neuroprotective or anti-inflammatory effects in experimental models does not establish that vesicle-based treatment can reconstruct damaged neural networks or restore complex neurological functions.

For these reasons, extracellular-vesicle therapies should currently be considered promising investigational approaches rather than established treatments for neurological restoration

Endogenous neurogenesis and astrocyte-to-neuron reprogramming

Strategies designed to stimulate endogenous neurogenesis or convert resident glial cells into neurons represent a more direct attempt to replace lost neuronal populations.

Astrocyte-to-neuron reprogramming has generated considerable interest because resident astrocytes are abundant in injured brain tissue and may potentially provide a local source of newly generated neurons.

Experimental approaches involving transcription factors and other molecular regulators have reported the acquisition of neuronal characteristics by selected glial populations.

However, interpretation of these findings requires careful distinction between neuronal marker expression, authentic lineage conversion, electrophysiological maturation, and functional circuit integration.

The validity of lineage tracing is particularly important because apparent conversion may be confounded by unintended neuronal labeling or other technical artifacts.

Even when neuronal conversion is convincingly demonstrated, successful neurological restoration requires newly generated cells to survive, establish appropriate synaptic connections, and contribute to behaviorally relevant neural networks.

These requirements are especially difficult to fulfill in the aged injured brain, where chronic inflammation, extracellular matrix remodeling, and limited trophic support may compromise neuronal survival and integration.

Consequently, neuronal reprogramming remains an important experimental strategy, but its ability to produce durable clinical neurological recovery has not been established.

Why biological improvement does not necessarily translate into functional restoration

The therapeutic strategies discussed above share an important limitation: improvement in a selected biological endpoint does not necessarily establish restoration of complex neurological function.

Reduction of infarct volume, attenuation of inflammatory signaling, increased neuronal survival, or expression of neuronal differentiation markers may provide valuable mechanistic evidence. However, these outcomes cannot automatically be equated with recovery of coordinated movement, communication, cognition, or independent daily function.

Neurological performance emerges from distributed neural networks whose operation depends on anatomical connectivity, synaptic organization, temporal coordination, and interactions with peripheral effectors.

Consequently, preserving individual neurons or modifying the tissue environment may be insufficient when the pathways required for functional output remain severely disrupted.

This limitation is particularly relevant in advanced neurological injury, where irreversible tissue loss may restrict the capacity for endogenous reconstruction.

An additional difficulty concerns the distinction between biological repair and functional compensation. Improvements in behavioral performance may reflect adaptive use of surviving circuits without restoration of the original neural architecture.

This distinction should not diminish the clinical value of compensation. Rather, it emphasizes that meaningful neurological recovery can be achieved through mechanisms other than anatomical reconstruction.

From biological repair to neuroprosthetic functional restoration

The limitations of biological neurorestoration provide a rationale for therapeutic strategies that exploit preserved neural activity rather than relying exclusively on the regeneration of damaged tissue.

Neuroprosthetic technologies approach neurological dysfunction at the level of functional information processing.

Brain-computer interfaces can detect neural activity associated with movement intention, attempted speech, or other physiological states and translate this information into commands controlling external devices, peripheral stimulation, or adaptive neuromodulation.

This approach may permit selected functions to be restored or compensated for even when the original neural pathways remain anatomically disrupted.

The clinical achievements of motor, communication, and brain-spine interfaces demonstrate that preserved neural activity can provide a substrate for functional intervention in patients with severe neurological disability.

However, neuroprosthetics introduces its own translational challenges involving long-term interface stability, patient selection, device dependence, clinical validation, and accessibility.

Accordingly, the transition from biological neurorestoration to neuroprosthetics should not be interpreted as the replacement of one therapeutic paradigm by another.

Instead, these approaches address complementary levels of neurological dysfunction. Biological therapies seek to preserve or improve the neural substrate, whereas neuroprosthetic systems exploit surviving neural activity to restore selected functions or modify pathological network dynamics.

Artificial intelligence is increasingly important in this process because it enables more sophisticated interpretation of neural signals, adaptation to changing physiological states, and individualized control of therapeutic output.

The potential convergence of biological and AI-driven neuroprosthetic strategies may therefore provide a framework for future neurological rehabilitation, although the efficacy of such combinations remains to be demonstrated.

Neuroprosthetics as a New Paradigm for Functional Restoration

From structural repair to functional substitution

Conventional neurorestorative therapies have largely been developed around the assumption that neurological recovery requires preservation, replacement, or regeneration of damaged neural tissue. Although this approach remains biologically justified, its therapeutic effectiveness is constrained by the limited regenerative capacity of the adult central nervous system and the complexity of reconstructing distributed neural networks. Neuroprosthetics introduces a complementary strategy in which preserved neural activity is exploited to restore

10.12865/CHSJ.52.03.02

functional output without necessarily requiring anatomical reconstruction of disrupted pathways.

The central principle of neuroprosthetics is that the loss of an observable neurological function does not always imply complete loss of the neural representations underlying that function. Following spinal cord injury (SCI), for example, cortical networks responsible for movement intention may remain active despite interruption of descending motor pathways.

Similarly, individuals with amyotrophic lateral sclerosis (ALS) or severe paralysis may retain neural activity associated with attempted speech or movement even when conventional muscular output becomes severely impaired.

Brain-computer interfaces (BCIs) exploit this dissociation between neural intention and behavioral execution. By recording neural signals and translating them into commands for external devices or therapeutic systems, BCIs can establish alternative pathways for communication, movement, or environmental interaction [7,8].

This approach shifts the immediate therapeutic objective from repairing damaged neural structures to restoring the functional relationship between neural activity and the external environment.

Early demonstrations of intracortical BCI control established that individuals with severe paralysis could modulate neuronal activity to control computer cursors and robotic devices (Hochberg et al., 2006, 2012). Subsequent developments have substantially expanded these capabilities. Intracortical interfaces have enabled coordinated reaching and grasping through functional electrical stimulation of paralyzed muscles [9], while a brain-spine interface has demonstrated the feasibility of translating cortical motor intentions into patterned spinal stimulation to support walking after SCI [10].

These achievements illustrate an important distinction between biological and neuroprosthetic restoration. Whereas biological therapies attempt to recover function by modifying the damaged tissue itself, neuroprosthetic systems can restore specific activities by establishing alternative functional pathways.

Nevertheless, the resulting performance often remains dependent on continued operation of the device, and should not automatically be interpreted as evidence of permanent neurological recovery.

Assistive, rehabilitative, and therapeutic neuroprosthetics

Neuroprosthetic systems can be classified according to their principal therapeutic objective into three partially overlapping categories.

Assistive neuroprosthetics aim to compensate for lost neurological functions by translating neural activity into external commands. Applications include computer control, robotic limb movement, communication devices, synthesized speech, and environmental interaction. These systems are particularly relevant for individuals with severe paralysis or advanced motor neuron disease, in whom preserved cortical activity may provide a means of communication despite profound motor impairment.

Rehabilitative neuroprosthetics are designed not only to compensate for impaired function but also to facilitate the reorganization of surviving neural circuits. These systems typically combine neural decoding with contingent sensory feedback, functional electrical stimulation, robotics, or task-specific training. Their therapeutic rationale is based on the hypothesis that repeatedly coupling movement intention with appropriate sensory consequences may reinforce activity-dependent plasticity and improve endogenous motor function.

Following stroke, for example, EEG-based BCIs have been combined with robotic assistance or peripheral stimulation to promote motor recovery. Clinical investigations have reported improvements in selected motor outcomes, although treatment effects vary considerably across studies and the persistence of benefit remains an important question [19,20,21].

Therapeutic closed-loop neural interfaces represent a third category in which neural activity is continuously monitored to guide the delivery of electrical stimulation. Unlike assistive BCIs, these systems do not necessarily decode voluntary intentions. Instead, they detect disease-relevant physiological patterns and adapt stimulation to modify pathological network activity.

Responsive neurostimulation for drug-resistant focal epilepsy and adaptive deep brain stimulation for Parkinson's disease illustrate this approach. These technologies use recorded neural activity to inform therapeutic stimulation, although their mechanisms, clinical maturity, and regulatory status differ substantially [22,23].

These categories should not be considered mutually exclusive. An assistive device may simultaneously provide rehabilitative feedback,

while a therapeutic stimulation system may modify neural plasticity over time. The progressive convergence of these functions is likely to become increasingly important as AI-driven algorithms enable more sophisticated integration of neural sensing, behavioral feedback, and adaptive stimulation.

Preserved neural networks as therapeutic substrates

The effectiveness of neuroprosthetic technologies depends fundamentally on the availability of neural signals that retain information relevant to the intended function or pathological state.

Following neurological injury, residual networks may preserve representations of motor intention, sensory processing, language, or cognitive operations despite disruption of the pathways required for normal behavioral expression. The ability to detect and decode these representations provides the physiological foundation for neuroprosthetic intervention.

However, the organization of surviving neural networks varies considerably across neurological disorders. In SCI, cortical motor representations may remain relatively preserved despite interruption of descending pathways. Following ischemic stroke, cortical and subcortical lesions may directly damage the networks responsible for generating motor commands. In ALS, progressive neurodegeneration and changes in cortical physiology may alter the stability of signals available for decoding.

These differences have important implications for patient selection and interface design. A system that successfully decodes attempted movement in an individual with SCI may not provide equivalent performance after extensive cortical stroke. Similarly, communication BCIs developed for individuals with preserved language networks may be less effective when the underlying cortical representations are severely disrupted.

The therapeutic objective must therefore be matched to the anatomical and physiological characteristics of each disorder. This principle supports a disease-specific approach to neuroprosthetic development rather than the assumption that a single interface architecture will be equally effective across neurological conditions.

Neuroprosthetics and activity-dependent neural plasticity

An important development in neuroprosthetics is the transition from purely compensatory systems toward interfaces capable of engaging neural plasticity.

Activity-dependent plasticity is influenced by the temporal relationship between neural activity, sensory feedback, and behavioral consequences. When intended movement is repeatedly associated with appropriate peripheral stimulation or sensory input, surviving networks may undergo changes in excitability, connectivity, and functional organization.

BCI-assisted rehabilitation provides a particularly relevant example. By detecting movement-related neural activity and triggering contingent stimulation or robotic assistance, these systems can reinforce the association between cortical intention and the sensory consequences of movement.

The clinical significance of this mechanism depends on whether repeated training produces improvements that persist when the device is removed. This distinction is essential because enhanced performance during active neuroprosthetic assistance may reflect successful compensation rather than durable biological recovery.

Evidence from BCI-assisted stroke rehabilitation supports the feasibility of inducing changes in motor function and neural connectivity, but the extent to which these changes represent stable restoration of damaged networks remains incompletely established [19,21].

Future studies should therefore distinguish immediate device-dependent performance, short-term training effects, and sustained improvements in unassisted neurological function. Longitudinal neurophysiological measurements, standardized clinical outcomes, and appropriate control interventions will be necessary to establish whether neuroprosthetic training can produce durable neurobiological benefits.

Neuroprosthetics as a complement to biological therapies

Although neuroprosthetics can restore selected functions without requiring complete structural repair, its therapeutic potential should not be interpreted as evidence that biological interventions have become unnecessary.

10.12865/CHSJ.52.03.02

Biological therapies and neuroprosthetic technologies act at different, potentially complementary levels. Pharmacological and cellular interventions may modify inflammation, preserve neural tissue, support synaptic remodeling, or improve the biological environment for recovery. Neuroprosthetic systems can exploit surviving neural activity to restore functional output and provide patterned stimulation capable of engaging residual networks.

The combination of these strategies may be particularly relevant in chronic neurological disorders, where biological repair alone is insufficient to restore complex functions. For example, an intervention that improves neuronal survival or reduces chronic neuroinflammation might enhance the responsiveness of surviving circuits to BCI-assisted rehabilitation.

Conversely, appropriately timed neuroprosthetic feedback could provide activity-dependent signals that support the functional integration of newly established or remodeled connections.

Such combinations remain largely hypothetical and require direct experimental validation. Nevertheless, they provide a conceptual framework for moving beyond the traditional separation between biological neurorestoration and technological compensation.

Neural Interfaces and Decoding: Technological Foundations of Neuroprosthetics

Neural signal acquisition across the invasiveness continuum

The performance of a neuroprosthetic system depends substantially on the quality, stability, and information content of the neural signals available for decoding.

Neural acquisition technologies range from non-invasive scalp recordings to cortical-surface, endovascular, intracortical, and depth-electrode systems. These approaches differ in spatial and temporal resolution, invasiveness, surgical requirements, long-term stability, and suitability for clinical use.

Electroencephalography (EEG) remains the most widely investigated non-invasive BCI recording method. It provides millisecond-scale temporal resolution and can detect oscillatory activity associated with movement intention, attention, and sensory processing. Its principal advantages include relatively low cost, repeatability, and avoidance of neurosurgical implantation.

However, EEG signals are affected by volume conduction, limited spatial specificity, environmental noise, and artifacts associated with muscle activity and movement. These limitations constrain the amount of information that can be reliably extracted, particularly for complex multidimensional motor control or continuous speech decoding.

Functional near-infrared spectroscopy provides an alternative non-invasive approach by detecting changes in cortical hemodynamics. Although potentially useful in selected communication paradigms, its relatively slow physiological response limits applications requiring rapid control.

Electrocorticography (ECoG) records neural activity directly from the cortical surface and provides improved spatial resolution and access to high-frequency cortical activity. These characteristics make ECoG particularly attractive for speech decoding and motor neuroprosthetics, although surgical implantation is required.

Intracortical microelectrode arrays provide access to local field potentials and neuronal population activity, enabling high-dimensional decoding of intended movements and other neural representations. Their advantages have been demonstrated in robotic control, functional electrical stimulation, and communication neuroprostheses [24,9,12].

Endovascular interfaces represent an alternative approach intended to access cortical activity through electrodes implanted within cerebral blood vessels. Initial clinical feasibility studies have demonstrated the potential for long-term recording without conventional open cortical implantation, although the information content and clinical capabilities of these systems remain under investigation [25].

Depth electrodes and sensing-enabled deep brain stimulation systems are particularly relevant for neurological disorders involving pathological activity within distributed or subcortical networks.

The choice of recording modality should therefore be determined by the therapeutic objective rather than by signal resolution alone. High-dimensional motor and speech decoding may require recording technologies with substantial information content, whereas rehabilitation or adaptive neuromodulation may be feasible using less invasive approaches.

The comparative advantages, limitations, and translational roles of the principal acquisition strategies are summarized in Table 1.

Table 1. Neural acquisition strategies: comparative characteristics and translational applications.

Interface	Neural access	Information content	Principal advantage	Major limitation	Most suitable translational role
EEG	Scalp	Population-level oscillations; low spatial specificity	Non-invasive, portable, repeatable	Low SNR; artifacts; limited spatial resolution	Rehabilitation, communication, home-use BCI
fNIRS	Scalp / hemodynamic	Regional cortical activation	Portable; relatively motion tolerant	Hemodynamic delay	Rehabilitation and hybrid BCIs
ECoG	Cortical surface	Local field potentials / high-gamma activity	High temporal and spatial fidelity	Requires cranial implantation	Motor and speech neuroprostheses
Endovascular	Intracranial vessel adjacent to cortex	Local cortical field activity	Avoids open craniotomy	Vascular access and chronic-device considerations	Implanted assistive BCIs
SEEG / depth electrodes	Cortical / subcortical depth	Local field activity from distributed deep networks	Access to otherwise inaccessible structures	Invasive stereotactic implantation	Network decoding, epilepsy, adaptive stimulation
Intracortical MEA	Cortical parenchyma	Single units, multi-units, LFPs	Highest information density and decoding capability	Tissue response, signal drift, surgical risk	High-performance motor, handwriting and speech BCIs
DBS sensing electrodes	Deep nuclei	Disease-related oscillatory biomarkers	Simultaneous sensing and stimulation	Disease/target-specific; invasive	Therapeutic closed-loop BCI / aDBS

Abbreviations and notes. EEG, electroencephalography; ECoG, electrocorticography; fNIRS, functional near-infrared spectroscopy; BCI, brain-computer interface; SNR, signal-to-noise ratio.

Neural decoding and the translation of intention into functional output

Neural decoding refers to the computational transformation of recorded neural activity into estimates of intended movement, speech, cognitive state, or disease-relevant physiological activity.

A typical decoding pipeline includes signal acquisition, preprocessing, feature extraction, algorithmic interpretation, and generation of an output command. Depending on the application, this output may control a cursor, robotic device, electrical stimulator, speech synthesizer, or adaptive therapeutic system.

Early BCI systems frequently relied on linear classifiers, regression methods, and state-space models to establish relationships between neural activity and intended behavior. These approaches remain important because they can provide relatively interpretable and computationally efficient decoding.

More recently, machine-learning methods have enabled the analysis of increasingly complex neural representations. Neural networks and other nonlinear algorithms can identify relationships between distributed patterns of neural activity and behavioral variables that may be difficult to capture using conventional linear models.

However, the complexity of the decoding algorithm must be balanced against requirements for reliability, computational efficiency, interpretability, and long-term stability.

A decoder that achieves high accuracy during controlled laboratory testing may perform less effectively during independent home use, where changes in electrode characteristics, patient behavior, physiological state, and environmental conditions can alter the recorded signals.

Consequently, the development of clinically useful decoding systems requires attention not only to peak accuracy but also to robustness, calibration burden, error correction, and adaptation over time.

Neural non-stationarity and long-term interface stability

One of the major challenges facing neuroprosthetic translation is the non-stationary nature of neural recordings.

Neural signals may change over time because of physiological adaptation, disease progression, changes in electrode impedance, tissue responses to implanted devices, or alterations in the patient's cognitive and behavioral state.

These changes can reduce decoding accuracy and necessitate repeated recalibration. In experimental settings, recalibration may be performed by trained researchers or engineers. In clinical practice, however, frequent technical intervention can substantially increase patient and caregiver burden.

10.12865/CHSJ.52.03.02

Long-term stability is particularly important for individuals with progressive neurological disorders, including ALS, in whom the physiological characteristics of the neural signals may change as the disease advances.

Adaptive decoding strategies are therefore increasingly being investigated to maintain performance despite changes in neural activity. These approaches include periodic model updating, online learning, recalibration using recent neural data, and algorithms designed to generalize across recording sessions.

The development of stable, self-adapting decoders will be essential for moving neuroprosthetic technologies from supervised demonstrations toward independent long-term use.

Bidirectional interfaces and sensory feedback

Conventional BCIs primarily translate neural activity into external commands. However, natural sensorimotor behavior depends on continuous interaction between motor intention and sensory feedback.

The absence of appropriate sensory information can impair the precision, efficiency, and naturalness of neuroprosthetic control. For example, manipulation of objects normally requires feedback concerning limb position, contact, force, and movement consequences.

Bidirectional neuroprosthetic systems attempt to address this limitation by integrating neural decoding with sensory stimulation or other forms of feedback.

Feedback may be delivered through visual displays, auditory signals, haptic devices, peripheral nerve stimulation, or direct stimulation of sensory cortical regions.

These approaches can improve the user's ability to control neuroprosthetic devices and may reduce reliance on visual monitoring.

Importantly, appropriately timed feedback may also reinforce activity-dependent neural plasticity by linking motor intention with sensory consequences.

Thus, bidirectional interfaces represent a critical transition from isolated neural decoding toward integrated sensorimotor interaction.

Clinical Applications of Neuroprosthetics Across Major Neurological Disorders

The clinical relevance of neuroprosthetics extends beyond the restoration of isolated motor or communicative functions. Neural interfaces are increasingly being investigated as therapeutic platforms capable of compensating for disrupted neural pathways, supporting activity-dependent rehabilitation, and modifying pathological network activity. However, the maturity of these applications varies substantially across neurological disorders, reflecting differences in disease mechanisms, residual neural function, therapeutic objectives, and the availability of clinical evidence.

Importantly, the clinical evaluation of neuroprosthetics requires a distinction between three outcomes: immediate functional assistance provided by an active device, improvement in neurological performance through repeated training, and persistent recovery of endogenous function after neuroprosthetic assistance has been withdrawn. These outcomes are not interchangeable and should be evaluated using disease-specific endpoints.

Ischemic stroke: from biological neurorestoration to BCI-assisted rehabilitation

Ischemic stroke represents one of the most relevant neurological conditions for evaluating the transition from biological neurorestoration toward neuroprosthetic rehabilitation. Despite substantial advances in acute reperfusion treatment, many survivors experience persistent motor, language, and cognitive impairments. These deficits frequently reflect damage to distributed neural networks rather than the isolated loss of individual neuronal populations.

As discussed in Section 2, numerous pharmacological, cellular, and molecular interventions have demonstrated beneficial effects in experimental stroke models, yet relatively few have produced reproducible clinical improvements in established neurological disability. This translational gap is particularly pronounced in older patients, in whom chronic inflammation, vascular comorbidities, reduced synaptic plasticity, and limited regenerative capacity constrain recovery [3,4,6].

Neuroprosthetic rehabilitation approaches this problem differently. Rather than attempting to replace lost neurons or reconstruct damaged tissue directly, BCI-assisted therapy exploits residual cortical activity associated with movement intention to provide contingent sensory or motor feedback.

Early clinical studies demonstrated that the coupling of motor-related brain activity to robotic assistance could improve upper-limb function in selected patients with chronic stroke. A clinical or experimental study [19] reported improvements

following BCI-based training, supporting the concept that temporally coordinated neural activity and movement-related feedback may facilitate functional recovery.

Subsequent studies extended this principle by combining EEG-based BCIs with visual feedback, motor imagery, and peripheral stimulation. A clinical or experimental study [20] demonstrated the feasibility of BCI-supported motor imagery training during post-stroke rehabilitation, while A clinical or experimental study [21] reported that coupling brain activity to functional electrical stimulation could promote recovery-associated changes in motor function and neural connectivity.

A meta-analysis by A clinical or experimental study [26] provided additional support for the therapeutic potential of BCI-assisted motor rehabilitation, although the included studies differed in patient characteristics, intervention protocols, and clinical endpoints.

These findings suggest that BCI-assisted rehabilitation may be particularly valuable when residual motor-related cortical activity can be detected despite impaired voluntary movement. The therapeutic mechanism is based on the repeated association between neural intention and appropriate sensory consequences, potentially reinforcing surviving sensorimotor pathways.

Nevertheless, several limitations remain. Improvements in motor performance may result from task-specific training, compensatory strategies, increased patient engagement, or genuine neuroplastic reorganization. Distinguishing these mechanisms requires appropriately controlled clinical studies and longitudinal measurements of neural function.

Furthermore, stroke lesions differ considerably in anatomical location and extent. Patients with preserved motor cortical representations but disrupted descending pathways may respond differently from those with extensive damage to the cortical networks responsible for generating movement intention.

Artificial intelligence may improve BCI-assisted stroke rehabilitation by enabling more reliable detection of movement-related neural activity, adapting training intensity to individual performance, and integrating multiple physiological signals to estimate the patient's capacity for engagement.

AI-guided systems could potentially identify changes in cortical responsiveness during rehabilitation and modify feedback or stimulation parameters accordingly. However, whether such adaptive approaches produce superior and more persistent neurological recovery than conventional BCI protocols remains to be demonstrated.

The major clinical challenge is therefore to establish which patients benefit most, when treatment should begin, how rehabilitation should be individualized, and whether improvements persist after device-assisted training has ended.

Spinal cord injury: functional reconnection of disrupted motor pathways

Spinal cord injury provides a particularly compelling indication for neuroprosthetic intervention because neural networks responsible for movement intention may remain substantially preserved despite interruption of descending motor pathways.

Unlike extensive cortical injury, SCI frequently produces a dissociation between the generation of motor commands and their transmission to spinal motor circuits. This anatomical and physiological organization creates an opportunity to bypass damaged pathways through neural interfaces.

Early intracortical BCI studies demonstrated that individuals with tetraplegia could control robotic arms and other external devices using neuronal activity recorded from motor cortical regions [24].

A major subsequent development involved the integration of cortical decoding with functional electrical stimulation of paralyzed muscles. A clinical or experimental study [9] demonstrated that intracortical neural signals could be translated into stimulation patterns enabling coordinated reaching and grasping in an individual with chronic tetraplegia.

This approach represented an important transition from controlling external robotic effectors toward restoring movement through the patient's own musculoskeletal system.

More recently, brain-spine interfaces have extended the concept of functional bypass by linking cortical motor activity to stimulation of spinal circuits below the level of injury.

A clinical or experimental study [10] demonstrated that a fully implanted brain-spine interface could support standing and walking in an individual with chronic SCI. The system translated cortical activity associated with movement intention into stimulation commands delivered to spinal regions involved in locomotor control.

These findings provide compelling proof of concept for the functional reconnection of anatomically disconnected neural pathways.

10.12865/CHSJ.52.03.02

However, the distinction between device-dependent locomotion and biological recovery remains important. Although repeated training may contribute to improvements in residual motor function, the ability to walk while the interface is active does not necessarily establish restoration of the original descending pathways.

Artificial intelligence may accelerate the development of brain-spine interfaces by improving the interpretation of movement intention, optimizing stimulation patterns, and integrating sensory information related to posture, balance, and limb movement.

Future systems may combine cortical decoding with wearable sensors, spinal recordings, and adaptive stimulation algorithms to provide more natural and robust locomotor control.

Nevertheless, clinical translation will require substantial improvements in long-term reliability, surgical safety, usability, and accessibility. Current evidence remains concentrated in small numbers of highly selected individuals, and larger studies are needed to establish generalizability and comparative clinical effectiveness.

Amyotrophic lateral sclerosis and severe paralysis: restoring communication

Amyotrophic lateral sclerosis is a progressive neurodegenerative disorder characterized by the loss of upper and lower motor neurons, leading to increasing weakness, paralysis, and, in advanced stages, profound impairment of communication.

Although pharmacological treatments may modify aspects of disease progression, they do not reliably restore lost motor functions. For individuals who lose the ability to speak or operate conventional assistive communication devices, neuroprosthetics may provide an alternative route for expressing intended messages.

BCI-based communication systems exploit neural activity associated with attempted movement, attention, or speech. Non-invasive approaches have employed EEG signals to support letter selection and computer interaction, while implanted interfaces provide access to cortical activity with potentially greater information content.

The clinical importance of these systems extends beyond technical decoding performance. For patients with advanced paralysis, even relatively slow but reliable communication may substantially improve autonomy, participation in care decisions, and social interaction.

Long-term implantation studies have demonstrated the feasibility of using neural interfaces for communication outside conventional laboratory environments. A clinical or experimental study [27] described an implanted BCI that enabled independent communication in an individual with ALS.

More recent investigations have demonstrated increasingly sophisticated speech neuroprostheses. A clinical or experimental study [12] reported high-performance decoding of attempted speech into text, while A clinical or experimental study [11] demonstrated the reconstruction of speech and facial-avatar movements from cortical activity in a participant with severe paralysis.

These studies illustrate the rapid convergence of neural interfaces and advanced computational decoding.

Artificial intelligence is particularly important in this application because speech involves complex, rapidly changing patterns of neural activity. Modern decoding algorithms can learn relationships between neural signals and attempted phonemes, articulatory movements, or linguistic sequences.

Language models can further improve communication speed by incorporating contextual information and predicting likely sequences of words.

However, these advances introduce important ethical and technical challenges. A generative model may produce linguistically plausible output that does not accurately represent the patient's intended message. The preservation of patient agency therefore requires transparent error correction, mechanisms for confirming generated content, and safeguards against unintended communication.

Progressive neurological disease also presents challenges for long-term decoder stability. Changes in cortical physiology, fatigue, cognition, and disease severity may alter the neural signals available for interpretation.

Parkinson's disease: adaptive neuromodulation of pathological neural networks

Parkinson's disease differs fundamentally from stroke and SCI because its principal therapeutic challenge is not necessarily the interruption of a single motor pathway but the progressive dysfunction of distributed basal ganglia-thalamocortical networks.

Conventional deep brain stimulation (DBS) has become an established treatment for selected

patients with Parkinson's disease, particularly when motor fluctuations, tremor, or dyskinesias remain insufficiently controlled by pharmacological treatment.

However, conventional DBS generally delivers stimulation according to parameters programmed during clinical assessments. These parameters may not fully account for changes in symptoms, medication state, sleep, or other physiological conditions.

Adaptive DBS represents an important development toward closed-loop neuroprosthetic therapy.

In these systems, neural signals associated with pathological network activity are recorded and used to adjust stimulation delivery. Oscillatory activity within basal ganglia circuits, particularly in the beta-frequency range, has been investigated as a physiological marker relevant to motor impairment.

A clinical or experimental study [23] reported findings from a blinded randomized feasibility study comparing adaptive DBS with conventional stimulation, demonstrating the potential of individualized neural biomarkers to guide therapeutic stimulation.

The significance of adaptive DBS extends beyond Parkinson's disease. It illustrates a broader therapeutic principle in which neural interfaces continuously monitor physiological activity and modify treatment according to the patient's current neurological state.

Artificial intelligence may further advance this approach by integrating multiple neural and behavioral biomarkers rather than relying on a single electrophysiological feature.

Future systems could combine local field potentials, movement sensors, medication-related information, and other physiological measurements to estimate symptom severity and adapt stimulation.

Nevertheless, the development of increasingly autonomous therapeutic algorithms requires careful validation. Changes in neural biomarkers do not always correspond directly to clinical symptoms, and inappropriate stimulation adjustments may produce adverse effects.

It is also important to distinguish symptomatic control from disease modification. Although adaptive DBS may improve treatment delivery and reduce fluctuations in motor symptoms, current evidence does not establish that it prevents or reverses the underlying neurodegenerative process.

Thus, Parkinson's disease provides an important example of neuroprosthetics as a means of regulating dysfunctional neural networks rather than reconstructing damaged anatomical pathways.

Epilepsy: established clinical experience with responsive neurostimulation

Drug-resistant focal epilepsy represents one of the most clinically mature applications of closed-loop neural interfaces.

In contrast to assistive BCIs, which decode voluntary intentions, responsive neurostimulation systems detect electrophysiological patterns associated with epileptic activity and deliver stimulation intended to interrupt or modify pathological network dynamics.

The therapeutic rationale is based on the recognition that epileptic seizures arise from abnormal electrical activity within distributed neural networks. Continuous monitoring of these networks provides an opportunity to intervene according to detected physiological changes.

A clinical or experimental study [22] reported long-term outcomes from a prospective study of brain-responsive neurostimulation for focal epilepsy, demonstrating sustained reductions in seizure frequency over extended follow-up.

These findings provide an important example of successful clinical translation of closed-loop neurotechnology.

However, responsive neurostimulation is not equivalent to a curative biological treatment. Although substantial reductions in seizure burden may be achieved, many patients continue to experience seizures, and the underlying epileptogenic network may remain active.

The effectiveness of responsive stimulation also varies between patients, emphasizing the importance of individualized electrode placement, detection algorithms, and stimulation parameters.

Artificial intelligence may contribute to future improvements by enabling more sophisticated identification of seizure-related activity, prediction of evolving pathological states, and adaptation of therapeutic stimulation.

Nevertheless, seizure prediction remains technically and clinically challenging. Algorithms must distinguish clinically relevant pathological activity from normal physiological fluctuations while minimizing false detections and inappropriate stimulation.

The extensive longitudinal experience with responsive neurostimulation provides valuable lessons for other neuroprosthetic applications, particularly regarding chronic implantation,

10.12865/CHSJ.52.03.02

device reliability, individualized programming, and the evaluation of long-term therapeutic outcomes.

Disease-specific therapeutic objectives and translational maturity

The clinical applications described above demonstrate that neuroprosthetics does not represent a single therapeutic intervention but a family of technologies addressing fundamentally different neurological problems.

In stroke, the principal objective is frequently to enhance rehabilitation and promote recovery of residual sensorimotor function. In SCI, neural interfaces may bypass interrupted descending pathways and restore selected motor activities. In ALS and severe paralysis, communication neuroprostheses primarily provide functional compensation.

In Parkinson's disease and epilepsy, closed-loop systems modify pathological neural activity rather than replacing lost motor or communicative functions. In disorders of consciousness, neural interfaces currently have a particularly important role in detecting preserved cognitive processing, while their therapeutic potential remains uncertain.

These differences require distinct clinical endpoints.

For stroke rehabilitation, meaningful outcomes include improvements in standardized motor assessments and the persistence of unassisted functional gains. For SCI, relevant outcomes include independent mobility, upper-limb function, and performance in everyday activities. Communication neuroprostheses should be evaluated according to accuracy, speed, reliability, user satisfaction, and independent usability.

For Parkinson's disease and epilepsy, clinical outcomes should focus on symptom burden, adverse effects, quality of life, and long-term therapeutic stability.

In disorders of consciousness, diagnostic accuracy and reliable demonstration of command following must be distinguished from restoration of communication or consciousness.

The available evidence also differs substantially in maturity. Responsive neurostimulation in epilepsy and conventional DBS in Parkinson's disease have established clinical applications, whereas adaptive DBS, invasive communication BCIs, and brain-spine interfaces are at different stages of clinical development.

BCI-assisted stroke rehabilitation has accumulated controlled clinical evidence, but substantial heterogeneity remains concerning treatment protocols, patient selection, and the persistence of functional improvements.

The indication-specific objectives, available evidence, unresolved challenges, and translational maturity of these approaches are summarized in Table 2.

Table 2. Clinical applications of neuroprosthetics: therapeutic objectives, evidence and translational maturity.

Indication	Primary BCI objective	Typical interface	Functional output	Evidence achieved	Key unresolved issue	Translational maturity
Stroke	Neurorehabilitation	EEG	FES / robotics	Motor improvement in controlled trials	Specific contribution of neural contingency	Clinical trials
SCI / tetraplegia	Neural bypass / restoration	Intracortical	Robotic limb / FES / spinal stimulation	High-dimensional control; restored movement	Long-term stability and scalability	Early clinical translation
ALS / severe paralysis	Communication	ECoG / intracortical	Text / speech	High-rate communication demonstrated	Home reliability and intent fidelity	Early clinical translation
Parkinson's disease	Adaptive therapy	DBS sensing	Adaptive stimulation	Symptom-responsive stimulation	Biomarker robustness	Clinical implementation emerging
Epilepsy	Closed-loop therapy	Intracranial	Responsive stimulation	Long-term seizure reduction	Patient-specific optimization	Clinically established
Disorders of consciousness	Detection / communication	EEG / fMRI	Binary communication	Covert command following demonstrated	Diagnostic validation and therapeutic benefit	Experimental

Abbreviations and notes. BCI, brain-computer interface; DBS, deep brain stimulation; EEG, electroencephalography; FES, functional electrical stimulation; SCI, spinal cord injury. Evidence categories indicate the approximate stage of clinical development rather than regulatory approval.

Evidence maturity reflects the cited clinical literature; categories are indicative rather than regulatory classifications.

Importantly, the success of neuroprosthetics should not be measured exclusively by decoding accuracy, stimulation precision, or performance under laboratory conditions. The ultimate clinical objective is to provide reliable, meaningful, and sustainable improvements in patients' everyday lives.

Artificial intelligence may accelerate progress across these indications, but its contribution must be evaluated in relation to clinically relevant outcomes rather than computational performance alone.

The next challenge is therefore to translate these promising technological developments into safe, accessible, and durable clinical interventions (Table 2).

Translational Challenges and Clinical Implementation of Neuroprosthetic Technologies

The disease-specific evidence reviewed above illustrates both the therapeutic potential and the current limitations of neuroprosthetics.

While selected applications have progressed into established clinical practice, others remain experimental despite remarkable technological achievements.

The next phase of development will depend not only on more sophisticated neural decoding and artificial intelligence but also on resolving persistent challenges concerning chronic interface stability, biological compatibility, patient selection, clinical trial design, independent home use, regulatory approval, and equitable access.

Equally important will be determining whether neuroprosthetic interventions can move beyond device-dependent functional compensation to promote durable reorganization of surviving neural networks. These challenges are addressed below.

From experimental proof of concept to clinically meaningful neurological recovery

Recent developments in brain-computer interfaces (BCIs) have demonstrated that neural activity can be decoded and translated into increasingly sophisticated motor, communicative, and therapeutic outputs.

However, the transition from technically successful experimental demonstrations to routine clinical application remains challenging. Many of the most advanced invasive neuroprosthetic systems have been evaluated in small numbers of carefully selected participants, frequently under conditions requiring substantial engineering support. Although these studies provide compelling evidence of technological feasibility, they do not necessarily establish reproducible clinical efficacy, long-term independence, or cost-effectiveness.

This translational challenge has important parallels with the historical development of biological neurorestorative therapies. As discussed in Section 2, numerous pharmacological and cellular interventions demonstrated encouraging effects in experimental neurological disorders but failed to produce comparable clinical benefits. In both fields, an important source of difficulty is the distinction between improvement in a selected experimental endpoint and restoration of a clinically meaningful function. For neuroprosthetics, high decoding accuracy, successful control of a robotic device, or improved performance during supervised training may not adequately predict independent functional benefit in everyday life.

Clinical evaluation must therefore distinguish immediate device-dependent assistance from rehabilitation-associated improvements and persistent recovery of endogenous neurological function. These outcomes require different study designs and clinical endpoints. Assistive communication devices may provide substantial benefit without modifying the underlying neurological disorder, whereas rehabilitative BCIs should ideally demonstrate improvements that persist beyond the period of active device use.

The clinical achievements reported by A clinical or experimental study [9], A clinical or experimental study [10], A clinical or experimental study [11], and A clinical or experimental study [12] illustrate the remarkable capabilities of contemporary neuroprosthetics.

Nevertheless, their translation into broadly applicable therapies will require larger prospective investigations, standardized outcome measures, and evidence of sustained performance under realistic conditions.

Patient selection and disease-specific therapeutic windows

The clinical effectiveness of neuroprosthetic intervention depends on the anatomical and physiological characteristics of the underlying neurological disorder.

10.12865/CHSJ.52.03.02

In spinal cord injury, preserved cortical representations of movement may provide a relatively accessible substrate for decoding despite interruption of descending motor pathways. In ischemic stroke, however, cortical lesions may directly damage the networks responsible for generating motor intention, making successful decoding more dependent on lesion location and the integrity of residual circuits.

Similarly, progressive neurological disorders introduce challenges related to changing neural representations and declining physiological function.

In amyotrophic lateral sclerosis, communication neuroprostheses may remain useful despite severe motor impairment, but disease progression may influence signal quality, cognitive function, and the patient's ability to participate in calibration or training.

These differences indicate that neuroprosthetic development must be accompanied by increasingly precise patient selection.

Potential selection criteria include lesion anatomy, residual neural activity, cognitive capacity, disease stage, anticipated progression, and the feasibility of independent device use.

Advanced neuroimaging, electrophysiological assessment, and AI-assisted analysis may help identify patients with sufficient residual network integrity to benefit from specific interventions.

The concept of a therapeutic window also requires reconsideration. Biological neuroprotective therapies frequently depend on intervention during the acute phase of injury, whereas neuroprosthetic systems may remain applicable months or years after neurological damage.

However, chronic neurological injury is accompanied by progressive changes in cortical representations, muscle physiology, spinal circuitry, and compensatory behavior. Thus, the absence of a narrow acute treatment window does not imply that the timing of neuroprosthetic intervention is irrelevant.

For rehabilitative BCIs, early intervention may exploit periods of heightened plasticity, whereas later treatment may require more intensive training or different feedback strategies.

Determining the optimal timing for individual neuroprosthetic applications remains an important clinical research objective.

Clinical trial design and the need for meaningful functional endpoints

The rapid development of neuroprosthetic technologies has created challenges for conventional clinical trial methodology.

Implanted BCIs often require individualized surgical procedures, extensive calibration, and repeated technical adjustments. These characteristics complicate the use of conventional randomized controlled trial designs, particularly during early feasibility studies.

Nevertheless, the absence of large-scale randomized evidence should not be confused with evidence of clinical effectiveness. Proof-of-concept demonstrations are valuable for establishing technical feasibility and identifying safety concerns, but they cannot reliably determine comparative therapeutic benefit.

Future trials should use endpoints appropriate to the intended application. For assistive communication systems, relevant outcomes include communication accuracy, speed, independent usability, patient satisfaction, and the ability to participate in meaningful daily activities.

Motor neuroprostheses should be evaluated through standardized measures of functional independence, task completion, safety, and performance outside supervised laboratory environments.

For rehabilitative BCIs, a particularly important endpoint is the persistence of neurological improvement after device-assisted training has ended. Such studies should include appropriate control interventions and sufficiently long follow-up periods to distinguish genuine rehabilitation-associated recovery from temporary performance enhancement.

Adaptive neuromodulation systems require different endpoints, including symptom burden, stimulation-related adverse effects, quality of life, and the stability of therapeutic benefit over time.

The design of future studies should also account for clinically relevant heterogeneity, including age, sex, comorbidities, disease severity, and prior treatment exposure.

These considerations are especially important in stroke, where the historical failure of numerous experimental therapies has demonstrated the limitations of extrapolating from highly standardized models to heterogeneous clinical populations.

Future Perspectives: Convergence of Biological Neurorestoration, Artificial Intelligence, and Neuroprosthetics

Figure 1 illustrates the complementary, but not yet clinically validated, convergence of biological neurorestoration and AI-driven neuroprosthetic strategies.

Aging and neuroinflammation as determinants of neuroprosthetic responsiveness

Advanced age is likely to influence the effectiveness of neuroprosthetic rehabilitation through several interconnected mechanisms.

Aging alters synaptic plasticity, mitochondrial function, neurovascular coupling, inflammatory regulation, and the capacity of neural networks to adapt to repeated stimulation.

These changes may influence the acquisition of neuroprosthetic control and the persistence of rehabilitation-associated improvements.

In addition, chronic neuroinflammation may affect the biological response to implanted electrodes and potentially contribute to changes in recording stability.

These considerations suggest that neuroprosthetic interventions developed in young experimental animals or relatively young patients may not achieve equivalent outcomes in older populations.

This issue is particularly relevant for stroke, where advanced age is common and residual neurological function is influenced by multiple vascular and metabolic comorbidities.

Future investigations should therefore examine whether age-associated inflammatory and metabolic states predict responsiveness to BCI-assisted rehabilitation.

The identification of biological markers associated with favorable neuroprosthetic outcomes could support more individualized treatment selection.

Potential candidates include measures of systemic inflammation, vascular function, neural network integrity, and physiological responsiveness to stimulation.

However, the predictive value of these markers remains to be established, and their incorporation into clinical decision-making will require prospective validation.

A translational framework for future research

The integration of biological neurorestoration and AI-driven neuroprosthetics will require a more comprehensive experimental and clinical framework than has traditionally been employed in either field.

Preclinical investigations should incorporate aged animals and clinically relevant comorbidities whenever these factors are central to the intended patient population.

Experimental endpoints should extend beyond histological changes or short-term behavioral improvements to include measures of network function, neural plasticity, and the persistence of recovery.

Studies combining biological and neuroprosthetic interventions should determine whether the effects of the two approaches are independent, additive, or synergistic.

Clinical investigations should distinguish immediate device-dependent assistance from persistent neurological improvement and should include standardized measures of quality of life and functional independence.

AI-based systems must undergo external validation and prospective assessment to establish reliability across patients and changing physiological conditions.

Finally, the development of clinically scalable neuroprosthetics will require consideration of long-term maintenance, reimbursement, accessibility, and ethical governance from the earliest stages of translational research.

The ultimate objective should not be to maximize decoding accuracy or demonstrate increasingly complex device control in isolation, but to provide sustainable improvements in neurological function that are meaningful to patients (Figure 1).

Conclusions

Decades of experimental research have substantially advanced our understanding of the mechanisms underlying neurological injury, degeneration, and repair.

Pharmacological neuroprotection, modulation of neuroinflammation, physical rehabilitation, stem-cell-derived therapies, and cellular reprogramming have each contributed important insights into the biological processes governing neural recovery.

Nevertheless, many interventions that demonstrated encouraging effects in experimental models have failed to produce substantial and reproducible clinical benefits, particularly when the therapeutic objective involves restoration of complex neurological functions after established tissue injury.

10.12865/CHSJ.52.03.02

This translational gap is especially evident in ischemic stroke and the aged brain, where chronic inflammation, vascular comorbidities, reduced regenerative capacity, and disruption of distributed neural networks constrain the effectiveness of conventional restorative approaches.

Neuroprosthetics introduces a complementary therapeutic paradigm by exploiting preserved neural activity to restore lost functions, bypass disrupted pathways, and modulate dysfunctional circuits.

Advances in brain-computer interfaces have enabled increasingly sophisticated motor control, communication, and closed-loop neuromodulation across several major neurological disorders.

The emergence of artificial intelligence is accelerating these developments through improved neural decoding, adaptive algorithms, personalized stimulation, and increasingly naturalistic interaction between neural activity and external devices.

Nevertheless, remarkable technological achievements must be distinguished from established clinical efficacy, and device-dependent functional assistance should not automatically be interpreted as durable biological recovery.

The future of neurological restoration may increasingly depend on the convergence of biological and technological strategies. Biological interventions may improve the environment for neural survival and plasticity, while AI-driven neuroprosthetic systems may exploit residual networks and provide precisely timed activity-dependent feedback.

Their integration offers a promising framework for developing more effective and individualized approaches to neurological rehabilitation.

However, this convergence remains a research objective rather than an established therapeutic solution. Its clinical value will depend on rigorous experimental validation, carefully designed clinical trials, and demonstration of meaningful long-term functional benefits.

The central challenge for the coming decade will therefore be to determine whether AI-driven neuroprosthetics can progress beyond functional compensation toward sustained neurological recovery, either independently or through integration with biological neurorestorative therapies.

Acknowledgement

None to declare.

Author Contributions

Conceptualization: A.P.-W. and M.-C.P.; Methodology and literature review: D.-M.P., I.K.S.B., and S.P.; Literature analysis and interpretation: D.-M.P., I.K.S.B., S.P., M.-C.P., and A.P.-W.; Writing-original draft preparation: D.-M.P., M.-C.P., and A.P.-W.; Writing-review and editing: all authors; Supervision: A.P.-W. and M.-C.P.

Funding

This research received no specific funding.

Conflicts of interest

The authors declare no competing interests.

Institutional Review Board

Not applicable

Consent Statement

Not applicable

Data availability

All data presented in the manuscript are available from the authors upon request.

References

1. Feigin VL, Brainin M, Norrving B, Martins S, Sacco RL, Hacke W, Fisher M, Pandian J, Lindsay P. World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. Int J Stroke, 2022, 17(1):18-29.
2. Campbell BCV, De Silva DA, Macleod MR, Coutts SB, Schwamm LH, Davis SM, Donnan GA. Ischaemic stroke. Nat Rev Dis Primers, 2019, 5(1):70.
3. O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1,026 experimental treatments in acute stroke. Ann Neurol, 2006, 59(6):467-477.
4. Fisher M, Feuerstein G, Howells DW, Hurn PD, Kent TA, Savitz SI, Lo EH, STAIR Group. Update of the Stroke Therapy Academic Industry Roundtable preclinical recommendations. Stroke, 2009, 40(6):2244-2250.
5. Savitz SI, Yavagal D, Rappard G, Likosky W, Rutledge N, Graffagnino C, Alderazi Y, Elder JA, Chen PR, Budzik RF Jr, Tarrel R, Huang DY, Hinson JM. A phase 2 randomized, sham-controlled trial of internal carotid artery infusion of autologous bone marrow-derived ALD-401 cells in patients with recent stable ischemic stroke (RECOVER-Stroke). Circulation, 2019, 139(2):192-205.
6. Popa-Wagner A, Carmichael ST, Kokaia Z, Kessler C, Walker LC. The response of the aged brain to stroke: too much, too soon? Curr Neurovasc Res, 2007, 4(3):216-227.
7. Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM. Brain-computer interfaces for communication and control. Clin Neurophysiol, 2002, 113(6):767-791.

8. Hochberg LR, Serruya MD, Friehs GM, Mukand JA, Saleh M, Caplan AH, Branner A, Chen D, Penn RD, Donoghue JP. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature, 2006, 442(1):164-171.
9. Ajiboye AB, Willett FR, Young DR, Memberg WD, Murphy BA, Miller JP, Walter BL, Sweet JA, Hoyen HA, Keith MW, Peckham PH, Simeral JD, Donoghue JP, Hochberg LR, Kirsch RF. Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration. Lancet, 2017, 389(5):1821-1830.
10. Lorach H, Galvez A, Spagnolo V, Martel F, Karakas S, Intering N, Vat M, Faivre O, Harte C, Komi S, Ravier J, Collin T, Coquoz L, Sakr I, Baaklini E, Hernandez-Charpak SD, Dumont G, Buschman R, Buse N, Denison T, van Nes I, Asboth L, Watrin A, Struber L, Sauter-Starace F, Langar L, Auboiroux V, Carda S, Chabardes S, Aksenova T, Demesmaeker R, Charvet G, Bloch J, Courtine G. Walking naturally after spinal cord injury using a brain-spine interface. Nature, 2023, 618:126-133.
11. Metzger SL, Littlejohn KT, Silva AB, Moses DA, Seaton MP, Wang R, Dougherty ME, Liu JR, Wu P, Berger MA, Zhuravleva I, Tu-Chan A, Ganguly K, Anumanchipalli GK, Chang EF. A high-performance neuroprosthesis for speech decoding and avatar control. Nature, 2023, 620:1037-1046.
12. Willett FR, Kunz EM, Fan C, Avansino DT, Wilson GH, Choi EY, Kamdar F, Glasser MF, Hochberg LR, Druckmann S, Shenoy KV, Henderson JM. A high-performance speech neuroprosthesis. Nature, 2023, 620:1031-1036.
13. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribó M, Cognard C, Hanel RA, Sila CA, Hassan AE, Millán M, Levy EI, Mitchell P, Chen M, English JD, Shah QA, Silver FL, Pereira VM, Mehta BP, Baxter BW, Abraham MG, Cardona P, Veznedaroglu E, Hellinger FR, Feng L, Kirmani JF, Lopes DK, Jankowitz BT, Frankel MR, Costalat V, Vora NA, Yoo AJ, Malik AM, Furlan AJ, Rubiera M, Aghaebrahim A, Olivot JM, Tekle WG, Shields R, Graves T, Lewis RJ, Smith WS, Liebeskind DS, Saver JL, Jovin TG. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med, 2018, 378(1):11-21.
14. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, Sarraj A, Kasner SE, Ansari SA, Yeatts SD, Hamilton S, Mlynash M, Heit JJ, Zaharchuk G, Kim SU, Carrozzella J, Palesch YY, Demchuk AM, Bammer R, Lavori PW, Broderick JP, Lansberg MG. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med, 2018, 378(8):708-718.
15. Shuaib A, Lees KR, Lyden P, Grotta J, Davalos A, Davis SM, Diener HC, Ashwood T, Wasiewski WW, Emeribe U, SAINT II Trial Investigators. NXY-059 for the treatment of acute ischemic stroke. N Engl J Med, 2007, 357(6):562-571.
16. Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S, Conwit R, Liebeskind DS, Sung G, Kramer I, Moreau G, Goldweber R, Sanossian N. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. N Engl J Med, 2015, 372(6):528-536.
17. Hill MD, Goyal M, Menon BK, Nogueira RG, McTaggart RA, Demchuk AM, Poppe AY, Buck BH, Field TS, Dowlatshahi D, van Adel BA, Swartz RH, Shah RA, Sauvageau E, Zerna C, Ospel JM, Joshi M, Almekhlafi MA, Ryckborst KJ, Lowerison MW, Heard K, Garman D, Haussen D, Cutting SM, Coutts SB, Roy D, Rempel JL, Rohr AC, Iancu D, Sahlas DJ, Yu AXY, Devlin TG, Hanel RA, Puetz V, Silver FL, Campbell BCV, Chapot R, Teitelbaum J, Mandzia JL, Kleinig TJ, Turkel-Parrella D, Heck D, Kelly ME, Bharatha A, Bang OY. Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (ESCAPE-NA1): a multicentre, double-blind, randomised controlled trial. Lancet, 2020, 395:878-887.
18. Hess DC, Wechsler LR, Clark WM, Savitz SI, Ford GA, Chiu D, Yavagal DR, Uchino K, Liebeskind DS, Auchus AP, Sen S, Sila CA, Vest JD, Mays RW. Safety and efficacy of multipotent adult progenitor cells in acute ischaemic stroke (MASTERS): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Neurol, 2017, 16(5):360-368.
19. Ramos-Murguialday A, Broetz D, Rea M, Läer L, Yilmaz O, Brasil FL, Liberati G, Curado MR, Garcia-Cossio E, Vyziotis A, Cho W, Agostini M, Soares E, Soekadar S, Caria A, Cohen LG, Birbaumer N. Brain-machine interface in chronic stroke rehabilitation: a controlled study. Ann Neurol, 2013, 74(1):100-108.
20. Pichiorri F, Morone G, Petti M, Toppi J, Pisotta I, Molinari M, Paolucci S, Inghilleri M, Astolfi L, Cincotti F, Mattia D. Brain-computer interface boosts motor imagery practice during stroke recovery. Ann Neurol, 2015, 77(5):851-865.
21. Biasiucci A, Leeb R, Iturrate I, Perdikis S, Al-Khodairy A, Corbet T, Schnider A, Schmidlin T, Zhang H, Bassolino M, Viceic D, Vuadens P, Guggisberg AG, Millán JDR. Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke. Nat Commun, 2018, 9(1):2421.
22. Nair DR, Laxer KD, Weber PB, Murro AM, Park YD, Barkley GL, Smith BJ, Gwinn RP, Doherty MJ, Noe KH, Zimmerman RS, Bergey GK, Anderson WS, Heck C, Liu CY, Lee RW, Sadler T, Duckrow RB, Hirsch LJ, Wharen RE Jr, Tatum W, Srinivasan S, McKhann GM, Agostini MA, Alexopoulos AV, Jobst BC, Roberts DW, Salanova V, Witt TC, Cash SS, Cole AJ, Worrell GA, Lundstrom BN, Edwards JC, Halford JJ, Spencer DC, Ernst L, Skidmore CT, Sperling MR, Miller I, Geller EB, Berg MJ, Fessler AJ, Rutecki P, Goldman AM, Mizrahi EM, Gross RE, Shields DC, Schwartz TH, Labar DR, Fountain NB, Elias WJ, Olejniczak PW, Villemarette-Pittman NR, Eisenschenk S, Roper SN, Boggs JG, Courtney TA, Sun FT, Seale CG, Miller KL, Skarpaas TL, Morrell MJ, RNS System LTT Study. Nine-year prospective efficacy and safety of brain-responsive neurostimulation for focal epilepsy. Neurology, 2020, 95(9):e1244-e1256.
23. Oehrn CR, Cernera S, Hammer LH, Shcherbakova M, Yao J, Hahn A, Wang S, Ostrem JL, Little S, Starr PA. Chronic adaptive deep brain stimulation versus conventional stimulation in Parkinson's disease: a blinded randomized feasibility trial. Nat Med, 2024, 30(11):3345-3356.

24. Hochberg LR, Bacher D, Jarosiewicz B, Masse NY, Simeral JD, Vogel J, Haddadin S, Liu J, Cash SS, van der Smagt P, Donoghue JP. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature, 2012, 485:372-375.
25. Mitchell P, Lee SCM, Yoo PE, Morokoff AP, Sharma RP, Williams DL, MacIsaac C, Howard ME, Irving L, Vrljic I, Williams C, Bush S, Balabanski AH, Drummond KJ, Desmond P, Weber D, Denison T, Mathers S, O'Brien TJ, Mocco J, Grayden DB, Liebeskind DS, Opie NL, Oxley TJ, Campbell BCV. Assessment of safety of a fully implanted endovascular brain-computer interface for severe paralysis in 4 patients: the Stentrode with Thought-Controlled Digital Switch (SWITCH) study. JAMA Neurol, 2023, 80(3):270-278.
26. Cervera MA, Soekadar SR, Ushiba J, Millán JDR, Liu M, Birbaumer N, Garipelli G. Brain-computer interfaces for post-stroke motor rehabilitation: a meta-analysis. Ann Clin Transl Neurol, 2018, 5(6):651-663.
27. Vansteensel MJ, Pels EGM, Bleichner MG, Branco MP, Denison T, Freudenburg ZV, Gosselaar P, Leinders S, Ottens TH, Van Den Boom MA, Van Rijen PC, Aarnoutse EJ, Ramsey NF. Fully implanted brain-computer interface in a locked-in patient with ALS. N Engl J Med, 2016, 375(22):2060-2066.
28. Claassen J, Doyle K, Matory A, Couch C, Burger KM, Velazquez A, Okonkwo JU, King JR, Park S, Agarwal S, Roh D, Megjhani M, Eliseyev A, Connolly ES, Rohaut B. Detection of brain activation in unresponsive patients with acute brain injury. N Engl J Med, 2019, 380(26):2497-2505.
29. Bodien YG, Allanson J, Cardone P, Bonhomme A, Carmona J, Chatelle C, Chennu S, Conte M, Dehaene S, Finoia P, Heinonen G, Hersh JE, Kamau E, Lawrence PK, Lupson VC, Meydan A, Rohaut B, Sanders WR, Sitt JD, Soddu A, Valente M, Velazquez A, Voss HU, Vrosgou A, Claassen J, Edlow BL, Fins JJ, Gosseries O, Laureys S, Menon D, Naccache L, Owen AM, Pickard J, Stamatakis EA, Thibaut A, Victor JD, Giacino JT, Bagiella E, Schiff ND. Cognitive motor dissociation in disorders of consciousness. N Engl J Med, 2024, 391(7):598-608.
30. Salatino JW, Ludwig KA, Kozai TDY, Purcell EK. Glial responses to implanted electrodes in the brain. Nat Biomed Eng, 2017, 1(12):862-877.

Corresponding Author: Mihai-Cristian Papa, Doctoral School, University of Medicine and Pharmacy of Craiova, Romania, e-mail: cmidrpapa10@gmail.com