Автоматизація технологічних і бізнес-процесів Volume 17, Issue 1 / 2025
http://www.atbp.ontu.edu.ua/

UDC 616-004:612.8:615.21

INVESTIGATING A TECHNOLOGY TO RESTORE SIGNAL TRANSMISSION ACROSS DEMYELINATED AXONS IN MULTIPLE SCLEROSIS: A COMPREHENSIVE REVIEW

ДОСЛІДЖЕННЯ ТЕХНОЛОГІЇ ВІДНОВЛЕННЯ ПЕРЕДАЧІ СИГНАЛУ ЧЕРЕЗ ДЕМІЄЛІНІЗОВАНІ АКСОНИ ПРИ РОЗСІЯНОМУ СКЛЕРОЗІ: КОМПЛЕКСНИЙ ОГЛЯД

AGJ Chathurika[1], B Hettige[2], FMMT Marikar[3]
[1,2] Department of Computer Engineering, Faculty of Computing, General Sir John Kotelawala Defence University, Ratmalana, Sri Lanka
[3] Staff Development Centre, General Sir John Kotelawala Defence University, Ratmalana, Sri Lanka
ORCID:
E-mail: [3]to faiz@kdu.ac.lk

DOI: 10.15673/atbp.v%vi%i.3092

Abstract. *Multiple sclerosis (MS) is a chronic autoimmune disorder characterized by the degradation of myelin, a critical component of axons in the central nervous system (CNS). This demyelination disrupts signal transmission, leading to severe neurological impairments. Despite advancements in immunomodulatory therapies, no existing treatments directly restore signal transmission across demyelinated axons. This comprehensive review explores emerging technologies designed to address this unmet need. We examine innovative approaches such as bioengineered myelin substitutes, nanotechnology-based interventions, and electrical stimulation techniques that aim to facilitate functional recovery. Additionally, advancements in stem cell therapies and pharmacological agents targeting remyelination are discussed in the context of preclinical and clinical studies. By synthesizing current research, this review highlights critical challenges, including biocompatibility, targeted delivery, and long-term efficacy, while identifying potential pathways for future innovation. The findings underscore the necessity of multidisciplinary collaboration to develop transformative therapies capable of restoring neurological function and improving quality of life for individuals with MS.*

Анотація. *Розсіяний склероз (РС) — це хронічне автоімунне захворювання, яке характеризується деградацією мієліну — критично важливого компонента аксонів у центральній нервовій системі (ЦНС). Демієлінізація порушує передачу нервових імпульсів, що призводить до серйозних неврологічних порушень. Незважаючи на досягнення в галузі імуномодулюючої терапії, на сьогодні не існує методів лікування, які б безпосередньо відновлювали передачу сигналів через демієлінізовані аксони. Цей комплексний огляд присвячений дослідженню новітніх технологій, спрямованих на подолання цієї незадоволеної медичної потреби. Розглядаються інноваційні підходи, такі як біоінженерні замінники мієліну, нанотехнологічні втручання та методи електричної стимуляції, що мають на меті сприяння функціональному відновленню. Окрім того, аналізуються досягнення у галузі терапії стовбуровими клітинами та використання фармакологічних засобів, спрямованих на ремієлінізацію, в контексті доклінічних та клінічних досліджень. На основі синтезу сучасних наукових результатів, у цьому огляді висвітлюються ключові виклики, зокрема біосумісність, цільова доставка та довготривала ефективність, а також визначаються перспективні напрямки подальших інновацій. Отримані висновки підкреслюють важливість міждисциплінарної співпраці для розробки проривних методів лікування, здатних відновити неврологічні функції та покращити якість життя людей, які страждають на РС.*

Keywords: Demyelination, Signal Transmission, Multiple Sclerosis, Remyelination, Neurorestoration
Ключові слова: Демієлінізація, Передача сигналу, Розсіяний склероз, Ремієлінізація, Нейровідновлення

Introduction

In a healthy, normal person, signal transmission along a neuron occurs via action potentials, which are rapid changes in membrane potential that travel along the axon. This process starts at the axon hillock when the membrane potential reaches a threshold (around -55 mV) due to a stimulus, causing voltage-gated sodium (Na+) channels to open. As Na+ ions rush into the neuron, the inside of the cell becomes more positive, a process called depolarization, and the membrane potential spikes to around +30 mV.

In myelinated neurons, the axon is covered by segments of myelin sheath that insulate the axon, preventing ion leakage. Between these myelinated segments are nodes of Ranvier, which are gaps where the axon membrane is exposed. The myelin sheath increases the speed and efficiency of signal transmission by allowing the action potential to travel via saltatory conduction. In saltatory conduction;

- The electrical signal moves passively through the myelinated segments, thanks to the insulation provided by the myelin.
- When the signal reaches a node of Ranvier, the high concentration of voltage-gated sodium channels allows the action potential to be regenerated. This regeneration involves a fresh influx of Na+ ions, which depolarizes the membrane at each node.

The action potential "jumps" from one node to the next, skipping over the internodal segments (the myelinated regions). This jumping, or saltatory conduction (from Latin "saltare," meaning "to jump"), significantly increases the speed of transmission—up to 100 times faster compared to continuous conduction in unmyelinated neurons.

After depolarization at each node, voltage-gated potassium (K+) channels open, allowing K+ ions to leave the cell, which brings the membrane potential back down—a process called repolarization. During repolarization, the membrane briefly becomes more negative than the resting potential (around -70 mV) in a phase called hyperpolarization, before returning to the resting state through the action of the sodium-potassium pump.

The action potential travels along the axon until it reaches the axon terminal, where it triggers the opening of voltage-gated calcium (Ca2+) channels. Calcium influx causes synaptic vesicles to fuse with the membrane, releasing neurotransmitters into the synaptic cleft. These neurotransmitters bind to receptors on the postsynaptic cell, whether it be another neuron, muscle cell, or gland, allowing the signal to be transmitted further. This entire process allows for the rapid and efficient transmission of information, necessary for all the body's activities—from muscle movements to sensory processing and thought.

Signal transmission process in a person with multiple sclerosis (MS), along with the molecular mechanisms are required to study for further analysis.

1. Myelin Damage and Axonal Demyelination

- Normal Mechanism: In a healthy neuron, myelin sheaths formed by oligodendrocytes (in the central nervous system) wrap tightly around the axon, providing insulation. The nodes of Ranvier, which are gaps between these myelin segments, are crucial for saltatory conduction.
- Molecular Mechanism in MS: In MS, immune cells (e.g., T-cells and macrophages) incorrectly recognize myelin proteins (like myelin basic protein (MBP)) as foreign. This leads to the production of inflammatory cytokines (such as TNF-α, IFN-γ, and IL-17), causing damage to the myelin and leading to demyelination. Activated macrophages engulf and degrade the myelin, exposing the axon membrane to the surrounding environment.

2. Disruption of Saltatory Conduction

- Normal Mechanism: In myelinated axons, saltatory conduction allows action potentials to "jump" from one node of Ranvier to the next, bypassing the insulated internodal segments. The voltage-gated sodium (Na+) channels at the nodes enable rapid regeneration of the action potential, which maintains its strength.
- Molecular Mechanism in MS: When myelin is damaged, saltatory conduction is disrupted. The exposed axon lacks the high concentration of voltage-gated Na+ channels found at the nodes. This results in an inability to effectively regenerate the action potential at the previously insulated segments. Additionally, redistribution of sodium channels may occur as an adaptive response, but this process takes time, and the number of newly distributed channels is often insufficient to compensate for the loss of myelin.

3. Ion Channel Dysfunction

- Normal Mechanism: In healthy neurons, Na+ channels at the nodes of Ranvier are responsible for action potential regeneration, while voltage-gated potassium (K+) channels help in repolarization.
- Molecular Mechanism in MS: In demyelinated regions, the normal clustering of sodium channels at the nodes of Ranvier is disrupted. Instead, both Na+ and potassium channels are more widely distributed along the exposed axon. The inappropriate exposure of K+ channels allow excessive K+ efflux, which can hyperpolarize the axon, making it harder for the membrance to reach the threshold potential for action potential regeneration. Additionally, the lack of adequate Na+ channel denisty in the exposed areas means the action potenital weakens or even fails entirely before reaching the next code.

4. Conduction Block and Signal Decay

- Normal Mechanism: The myelin sheath serves as an effective electrical insulator, ensuring minimal ion leakage and rapid signal transmission along the internodal regions.
- Molecular Mechanism in MS: When myelin is lost, the axon membrane is exposed to the extracellular environment, leading to increased ion leakage across the membrane. The absence of insulation means the passive conduction of the electrical signal is compromised, leading to a significant drop in membrane potential. The action potential may decay before reaching the next node of Ranvier, causing a conduction block. The neuron is often unable to effectively propagate the signal, which leads to interrupted communication between neurons.

5. Increased Energy Demand

- Normal Mechanism: In a myelinated neuron, energy consumption is minimized since action potentials only need to be regenerated at nodes, reducing the workload of sodium- potassium pumps (which restore the ionic gradient after an action potential).
- Molecular Mechanism in MS: In the demyelinated axon, action potentials propagate along the entire axon, and not just at the nodes of Ranvier. As a result, sodium-potassium pumps are recruited all along the demyelinated axonal membrane to restore the disrupted Na+/K+ gradients after depolarization. This increased activity leads to elevated ATP consumption and puts the axon under metabolic stress. The excessive energy demand can deplete the neuron's energy reserves, contributing to axonal injury.

6. Axonal Degeneration

- Normal Mechanism: In a healthy neuron, the myelin sheath helps protect the axon from mechanical and metabolic stress, ensuring its long-term integrity.
- Molecular Mechanism in MS: The loss of myelin exposes the axon to chronic stress, which can lead to calcium (Ca2+) dysregulation. The redistribution of sodium channels often leads to increased Na+ influx, which activates the sodium-calcium exchanger, resulting in excessive Ca2+ entry into the axon. Elevated intracellular Ca2+ levels activate enzymes like calpains and caspases, which cause axonal damage and degeneration. This degeneration is progressive and irreversible, contributing to the permanent disability observed in MS patients.

7. Symptoms and Functional Impairment

- Normal Mechanism: Effective myelination ensures rapid and reliable communication between the CNS and the body, allowing for normal motor, sensory, and cognitive functions.
- Molecular Mechanism in MS: The cumulative effect of demyelination, conduction blocks, ion channel dysfunction, and axonal degeneration results in a range of neurological symptoms. For instance;
  - Muscleweaknessandspasticityoccurduetoimpairedmotorneuron signalling.
  - Numbness, tingling, or sensory deficits result from failed sensory neuron communication.
  - Visionproblems,suchasopticneuritis,arisefromdemyelinationofthe optic nerve, leading to impaired visual signal transmission.
  - Cognitiveimpairmentsmaydevelopifdemyelinationaffectsbrainareas involved in memory and processing.
  - Fatigueiscommonduetotheincreasedmetabolicdemandsplacedon neurons and the inefficient conduction of nerve signals.

In a healthy individual, myelin and nodes of Ranvier enable fast, efficient signal transmission through saltatory conduction, maintaining ion homeostasis and reducing energy demands. In a person with MS, immune-mediated demyelination disrupts this process, causing signal transmission to slow, weaken, or even stop due to ion leakage, inadequate sodium channel density, and conduction blocks. The increased exposure of potassium channels leads to further difficulties in regenerating action potentials. The loss of myelin results in increased energy requirements to maintain ion gradients, contributing to metabolic stress and axon degeneration via calcium overload. Over time, these changes lead to chronic symptoms such as muscle weakness, sensory deficits, visual problems, and cognitive impairments, significantly impacting the quality of life of individuals with MS.

Neural treatment for MS

Neural Bypasses

Neuromodulation is a rapidly growing field that involves altering neural activity through direct electrical or pharmaceutical delivery. Deep brain stimulation (DBS) was FDA-approved in 1997, and early neuro-modulatory devices were one-way systems. The advent of responsive neurostimulation (RNS) for epilepsy in 2013 marked the first approval for a neural system that records, modulates, and stimulates neurons in a bi-directional manner. Other bi-directional, or 'closed-loop' systems are in development, including closed-loop DBS and ECoG[1].

A novel group of recently developed neuro-modulation devices may be better described as a neural bypass, which attempts to transmit the same neural data from one location to another in the nervous system. There are varying terminologies for this technology in the literature, including artificial cortical-muscular connection (ACMC), neural bypass, or the broader category of brain- computer interface/brain-machine interface [2, 3]. This technology has progressed from animal feasibility studies[4] to successful demonstration in humans over the last two decades[5, 6]. Most work in neural bypasses has focused on transmitting cortical information to effector muscles in cases of spinal cord injury (SCI) or stroke. However, neural bypasses also have potential for cortical-cortical, cortical-spinal, and cortical/spinal-muscular communications, or artificial autonomic neural connections. Unlike the RNS system, which provides disruptive stimulation to a new location in the nervous system, neural bypasses aim to transmit the same information from one location to another location in the nervous system.

This review aims to define neural bypasses as a topic and review active studies for how it useful for restoring signal transmission through demyelination neurons in multiple sclerosis. It will review the current state of neural bypasses as an independent or combined therapeutic modality for spinal cord pathology, stroke, and additional broader uses. Additionally, it will review the technologies currently used for neural interfacing, propose new avenues for this technology, and discuss the limitations and potential benefits of neuroplasticity to further progress the efficacy of neural bypass techniques.

Various Technological Methods

1) Recording Techniques

Neural bypass systems can perform neural recordings, process data, and deliver neurostimulation with varying spatial and temporal resolution. Methods include EEG (electrode stimulation), ECoG (electrode counting), microelectrode arrays, and single neuron recordings. EEG, which typically records on the order of 1,000,000 neurons; ECoG, which typically records on the order of 100,000 neurons; microelectrode arrays, which can record local field potentials from 10,000s of neurons or up to 100 individual neurons within 60 μm, and then single neuron recordings which have the highest spatial and temporal resolution of a single neuron [7, 8]. The Neuroport System has a 10 kHz sampling rate[9]. EEG is less invasive but has lower spatial resolution than ECoG[10]. The sensorimotor cortex is the most common site for recording. Stereo encephalography (SEEG) is an invasive electrode strategy for recording fine movement signals in humans. This strategy has potential for low operative risk in neural bypass [11]. Chronically implanted recording devices are prone to signal decay due to factors like gliosis, but multi-unit recording devices are more resistant to decay. Multi-unit recording devices have been shown to be more resistant to decay compared to chronically implanted devices[12].

2) Stimulation Methods

Stimulation methods are all typically carried out by delivering electrical impulses through electrodes. Functional electrical stimulation (FES) is a method of stimulating effector muscles with neural recordings to produce desired movements. It can be performed through implanted invasive electrodes placed in effector muscles or non-invasive electrode stickers[13]. Studies have developed non-invasive electrode sleeves capable of reproducing muscle movements with stimulation while others have implanted electrodes in effector muscles [14-16]. FES systems vary in complexity, from single electrodes to combinations of 130 electrodes with varying stimulation pulse dynamics such as frequency and amplitude[17]. Additional neural recording and stimulation devices are in development, such as Neuralink with micrometer electrode threads, Stentrode with an intravascular recording/stimulating device, flexible injectable probes, and Neural Dust with a wireless ultrasound-based nanometer recording device[18]. The best methods for invasive neural recording and stimulation remain to be determined.

3) Signal Processing Strategies

Numerous methods exist to filter noise, determine stimulation, decode, and predict neural activity. Some authors have attempted neural decoding through training sessions, while others have determined arbitrary thresholds for neural plasticity. When EEG is used in neural bypasses, recording thresholds are determined, which translate to effector stimulation, often with FES. EEG thresholds to stimulate FES are typically obtained through motor imagery, attention with sensorimotor rhythm and beta/theta oscillation ratios, or Common Spatial Patterns based on Event De/Synchronization[19-38]. Some have used steady-state visual evoked potentials (SSVEP) to trigger FES stimulation[39]. Some studies have used alpha rhythms as a deactivating signal following a stimulation event[40]. Single-cell recordings typically use cell firing rate as the threshold for stimulating FES[4]. When ECoG is used, the rate of high-gamma oscillations is selected as a threshold for effector muscle stimulation[2]. In studies with microelectrode arrays, neuronal action potential rate or average spectral high-frequency power are typically used as thresholds for stimulation of effector muscles[14]. Microelectrode arrays are often used during training sessions prior to paralysis or with simulated motor tasks to create predictive models of neuronal control of muscle activity[17], [41, 42]. However, daily calibration is required to train neural decoding algorithms, which presents a limitation for their translation to real-world environments. One possible approach is a neural network capable of decoding without daily training sessions[16]. Other decoding methods include gradient boosted trees, support vector machines, and linear methods[9, 43]. Nonlinear methods of decoding may help increase the robustness and accuracy of specific decoders[44]. As methods increase in complexity, so do their associated assumptions. Machine learning methods can organize multiple decoding models in ensembles[43], leading to positive outcomes and accurate decoding [9].

Developing devices to maximize spatial resolution, temporal resolution, and biocompatibility will be crucial for developing robust neural interfaces. Additionally, a number of unidirectional recording or stimulation devices exist that have not yet been combined into neural bypasses, including novel spinal cord stimulators or neurotransmitter sensing electrodes[45, 46]. Additionally, there is a lack of comparative analysis across studies with different methodologies to determine the most efficacious methods of achieving neural bypass.

State-of-the-art by Neural Bypass Types

1) Cortical/Spinal → Peripheral/Muscular Neural Bypasses

Neuronal bypass is a technique that pairs EEG-based recordings with peripheral stimulation, often through Functional Electrical Stimulation (FES) at the muscle level. This method has been successful in stimulating previously paralyzed muscles, allowing independent control of previously paralyzed muscles. Early studies have shown that neural EEG recordings of primary motor cortex or single neuron recordings can be used to stimulate forearm and wrist muscles in humans and primates[4], [20]. Motor imagery with EEG paired with FES has also been used to activate shoulder movements through stimulation of deltoid and supraspinatus muscles[21, 22].

Studies have utilized microelectrode arrays implanted in the motor cortex or implanted ECoG grids paired with FES to control the magnitude and time course of arm movements, including reaching and grasping [41, 42, 47]. Cortical microelectrode recordings from M1 have also been decoded to produce graded force in wrist movements, moving past binary flexion and extension movements[48]. These systems have also been combined with computer vision to produce more targeted grasping motions[31].

In patients with stroke or spinal cord injury (SCI), studies have shown improved assistive motor rehabilitation outcomes when undergoing motor training paired with an EEG-FES neuro- modulation [49-52]. For example, a partly implanted neural bypass paired with noninvasive FES could allow a paralyzed person to perform complex wrist and hand movements, as opposed to simple extension or flexion movements[6]. With the same patient, an experiment showed that clinical assessment scores could be improved over time by using a cortical implant-based neural bypass [40]. Colachis' study added another movement to the original six movements by using microelectrode array recordings paired with 130 FES electrodes to enable the patient to activate 7 different hand movements on Bouton's study[17]. Additional activities of daily living were achieved by combining FES with a neuroprosthesis enabling the participant to perform activities like writing and feeding[35]. Additionally, central pattern generators (CPG) play a role in natural rhythmic movements, such as swimming, walking, and scratching[53]. Other studies have improved lower extremity motor ability, such as coordinating dorsiflexion in patients with foot drop to improve gait [54-57]. EEG-FES neural bypasses have also been used to control abdominal muscles for improved respiration in patients with tetraplegia[39].

2) Cortical ←→ Spinal Neural Bypasses

Cortical-muscle neural bypass is the most common neural bypass in literature, but cortical- spinal connections have also shown promise for further application. Yadav's demonstration showed that rats could discriminate sensory information delivered by dorsal column stimulation (DCS), which was transmitted to the brain[58]. Further research could involve spinal cord recordings paired with brain stimulation to transmit sensory information and bypass damaged neural pathways. Cortical-spinal bypasses can be achieved through cortical recordings followed by spinal stimulation. Knudsen demonstrated that paralyzed rats could produce temporally precise hindlimb movements from information obtained via sensorimotor cortex electrodes transmitted to epidural lumbar spinal stimulation[59]. Capogrosso restored weight-bearing locomotion in a monkey using a microelectrode array paired with epidural lumbar electrodes[45]. Bonizzato proved that brain-controlled spinal cord stimulation immediately enables movements of paralyzed legs and improves recovery[60].

3) Cortex → Cortex Neural Bypasses

Cortex-to-cortex neural bypasses are a promising area for further research and assistive applications. In vitro studies have shown that two neocortical cell populations can regain bidirectional dialogue through activity-dependent bidirectional stimulation[61, 62]. However, Jackson demonstrated that an artificial connection between two motor cortex sites can facilitate a stable reorganization of motor output in freely-behaving primates[63]. This process uses an autonomously operating electronic implant recording action potentials to trigger electrical stimuli. This in vivo evidence of activity-dependent plasticity and its relation to cortical representations could pave the way for assistive neurorehabilitation after injury. Synaptic relationships can be formed across distances through Hebbian neural plasticity using artificial neural connections.

4) Peripheral → Central Neural Bypasses

Previous studies have explored stimulating the somatosensory cortex to create tactile perceptions[64, 65], but these often come from prosthetic limbs or artificial stimuli, not peripheral nervous system recordings. Devices like cochlear implants or retinal implants could be open-loop systems that collect perceptual information and deliver it to the nervous system. Future peripheral-sensory applications could involve recording from peripheral sensory organs like the retina or cochlea and delivering the stimulus to primary sensory areas to bypass damage.

5) Autonomic Neural Bypasses

Previous research has demonstrated the feasibility of thoracoscopic injection of therapeutics for neuromodulation of the sympathetic nervous system [66]. Future studies could use this technique to develop neural bypasses for conditions like SCI, palmar hyperhidrosis, and autonomic dysfunction, but no studies have yet developed neural bypass of the autonomic nervous system.

6) Inter-subject Neural Bypasses

Neural bypasses have been demonstrated between subjects, allowing neural information to be transmitted between the nervous systems[67]. This can be achieved by recording visual evoked potentials or motor imagery with EEG from one participant and then transmitting information to a separate participant using TMS to perform coordinated tasks and problem-solving[68], [69-71]. TMS is applied to the motor cortex or visual cortex to induce sensory percepts, such as phosphenes in the receiving participant [68-72]. Grau used these methods to transmit words like 'hola' and 'ciao' at 2-3 bits per minute between participants[72]. Lee used focused ultrasound to stimulate the somatosensory cortex in a participant performing a coordinated task with a second participant performing motor imagery EEG at a rate of 8 commands per minute[25]. These tasks can be performed in real-time, as shown by subjects successfully playing games like '20 Questions' or Tetris-like games with up to three participants through brain-brain interfaces[68], [71].These artificial neural connections have been developed across species, By recording motor imagery or SSVEPs with EEG, [73]. some researchers showing that humans can direct a rat through a navigation environment by stimulating intracortical electrodes in the rat[74-76] Similarly, Yoo showed that a human could control the movement of a rat's tail with 94% accuracy by using EEG paired with focused ultrasound stimulation[73]. Other authors have performed navigation tasks with cockroaches directed by SSVEP recordings from human EEG[77]. By using optogenetics in the nucleus incertus of two mice allowed them to mimic locomotion with an information transfer rate of 4 bits/second[78]. Finally, Yadav demonstrated a brain-to-spine interface where tactile and artificial sensory information could be decoded by one rat's brain and delivered to another rat's spinal cord, potentially transmitting prosthetic information between brains/spinal cords[58].

Implications for Spinal Cord Injury and Stroke

Spontaneous rhythmic activity, such as walking, has been demonstrated to be feasible in chicks with complete spinal cord injury[79]. Neural bypassing could re-establish sufficient input to aid mobility, with simple sustained gait being feasible when using a simple Poisson pattern[80]. This could have broad-reaching implications for Asia A and B spinal cord injury patients. Additionally, the modulation gain as outlined above, could aid in return of sensory function[81]. Recent work has investigated stimulation along the motor strip to aid in some returned functional capacity, with studies showing return of arm function in a cervical spinal cord injury model[13]. A recent study confirmed proof of concept in humans as well[82]. Primarily this has been focused on grasping objects and assisted typing for communication. As technology improves, transitioning into simple walking paradigms may be feasible. Combination approaches with stem cell implantation are in their infancy, but initial innovations have been promising[83].

Imaging has improved to detect damaged circuitry post neurologic injury[84], with the benefits of intervention being time-dependent to re-establish connections prior to rewiring that occur after injury, such as stroke. . Conceptually, the connections are still viable for post stroke motor and sensory deficits as well if treatment is implemented early and in a bidirectional manner[85]. Early neural interface adaptations have been useful in bypassing damaged circuitry[2], and early initiation of a neural bypass in cats restored physiologic function of the motor unit[86]. Transcranial direct current stimulation in humans has preliminarily shown benefit in aiding neurologic recovery post-stroke[87]. When combined with faciliatory robotics the effects are even more pronounced [88]. Implications for improving aphasia are also promising and is a topic of ongoing investigation [89]. and the era of non-invasive brain stimulation techniques is emerging with several reports showing early efficacy[90]. From the field of pre-clinical motor mapping, dendritic circuitry has shown robust response to stimulation efforts[91].

The Role of Neuroplasticity as Hindrance or Help

Neuroplasticity has hindered the development of neural bypasses due to the need for daily retraining and recalibration of decoding mechanisms. Humans have a unique ability to use tools, which may be based on their neural representation of objects and tool-specific motor representations in the brain[92]. Neural bypass research has primarily used existing motor representations, such as neural recordings for grasping actions, rather than developing new motor representations specific to the new neural prosthetic tool. Studies of humans with prosthetic limbs have shown neural representations specific to their prosthetic rather than biological limb, as seen when the prosthetic differs from an actual limb in form[93]. Primate amputations have also shown that the primary motor representation of body parts are plastic, as neural regions are redistributed to non-amputated fingers[94]. This neuroplasticity within neural regions has limited the advancement of neural bypasses. Future studies may aim to enhance the applicability of neural bypass solutions by developing greater neural-computer integration to utilize plasticity and develop new areas of neural representation for the new tool. Additional approaches to managing neuroplasticity include neural network decoding methods that evolve in real-time with changing neural signals or using recording thresholds as a 'neural switch' that allows neuroplasticity to self-orient signals and activate or deactivate the fixed switch.

Conclusion

Whereas open loop systems introduce or extract data from a neural system, and closed-loop systems record, modulate, and deliver new information typically to the same location, neural bypasses are a unique type of neuromodulation which aims to transmit neural data from one location in the nervous system to another. The most common method of neural bypass to date involves cranial EEG paired with FES at the level of the muscle to reproduce intended movements after neurologic injury. However, there is evidence in the literature for the development of cortical- spinal bypasses, cortical-cortical bypasses, peripheral-central bypasses, autonomic bypasses, and inter-subject bypasses . The most common disease entities in the literature are spinal cord injury, stroke, cerebral palsy, and traumatic brain injury, though neural bypasses could also aid in several additional neurologic conditions. There is a wide variety of methods and technologies used to develop neural bypasses, and more work is needed to develop high resolution recording and stimulating devices as well as comparative studies across different methodologies. A significant next step in increasing the precision of neural bypass technologies will be to mobilize recording and decoding strategies that are uninhibited by neuroplasticity.

References

1. M.ParastarfeizabadiandA.Z.Kouzani,“Advancesinclosed-loopdeepbrainstimulation devices,” J. NeuroEngineering Rehabil., vol. 14, no. 1, p. 79, Dec. 2017, doi: 10.1186/s12984- 017-0295-1.
2. K.Kato,M.Sawada,andY.Nishimura,“Bypassingstroke-damagedneuralpathwaysviaa neural interface induces targeted cortical adaptation,” Nat. Commun., vol. 10, no. 1, p. 4699, Oct. 2019, doi: 10.1038/s41467-019-12647-y.
3. C.E.Bouton,“RestoringMovementinParalysiswithaBioelectronicNeuralBypass Approach: Current State and Future Directions,” Cold Spring Harb. Perspect. Med., vol. 9, no. 11, p. a034306, Nov. 2019, doi: 10.1101/cshperspect.a034306.
4. C.T.Moritz,S.I.Perlmutter,andE.E.Fetz,“Directcontrolofparalysedmusclesbycortical neurons,” Nature, vol. 456, no. 7222, pp. 639–642, Dec. 2008, doi: 10.1038/nature07418.
5. S.Chandrasekaranetal.,“Historicalperspectives,challenges,andfuturedirectionsof implantable brain-computer interfaces for sensorimotor applications,” Bioelectron. Med., vol. 7, no. 1, p. 14, Sep. 2021, doi: 10.1186/s42234-021-00076-6.
6. C.E.Boutonetal.,“Restoringcorticalcontroloffunctionalmovementinahumanwith quadriplegia,” Nature, vol. 533, no. 7602, pp. 247–250, May 2016, doi: 10.1038/nature17435.

7. J. Du, I. H. Riedel-Kruse, J. C. Nawroth, M. L. Roukes, G. Laurent, and S. C. Masmanidis, “High-resolution three-dimensional extracellular recording of neuronal activity with microfabricated electrode arrays,” J. Neurophysiol., vol. 101, no. 3, pp. 1671–1678, Mar. 2009, doi: 10.1152/jn.90992.2008.

8. D. J. Caldwell, J. G. Ojemann, and R. P. N. Rao, “Direct Electrical Stimulation in Electrocorticographic Brain-Computer Interfaces: Enabling Technologies for Input to Cortex,” Front. Neurosci., vol. 13, p. 804, 2019, doi: 10.3389/fnins.2019.00804.

9. C.Boutonetal.,“DecodingNeuralActivityinSulcalandWhiteMatterAreasoftheBrainto Accurately Predict Individual Finger Movement and Tactile Stimuli of the Human Hand,” Front. Neurosci., vol. 15, p. 699631, 2021, doi: 10.3389/fnins.2021.699631.

10. G. Panuccio, M. Semprini, L. Natale, S. Buccelli, I. Colombi, and M. Chiappalone, “Progress in Neuroengineering for brain repair: New challenges and open issues,” Brain Neurosci. Adv., vol. 2, p. 2398212818776475, 2018, doi: 10.1177/2398212818776475.

11. C. Herff, D. J. Krusienski, and P. Kubben, “The Potential of Stereotactic-EEG for Brain- Computer Interfaces: Current Progress and Future Directions,” Front. Neurosci., vol. 14, p. 123, 2020, doi: 10.3389/fnins.2020.00123.

12. C. Bouton, “Cracking the neural code, treating paralysis and the future of bioelectronic medicine,” J. Intern. Med., vol. 282, no. 1, pp. 37–45, Jul. 2017, doi: 10.1111/joim.12610.

13. Y. Nishimura, S. I. Perlmutter, and E. E. Fetz, “Restoration of upper limb movement via artificial corticospinal and musculospinal connections in a monkey with spinal cord injury,” Front. Neural Circuits, vol. 7, p. 57, 2013, doi: 10.3389/fncir.2013.00057

14. A. B. Ajiboye et al., “Restoration of reaching and grasping movements through brain- controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration,” The Lancet, vol. 389, no. 10081, pp. 1821–1830, May 2017, doi: 10.1016/S0140-6736(17)30601-3.

15. J. Ciancibello et al., “Closed-loop neuromuscular electrical stimulation using feedforward- feedback control and textile electrodes to regulate grasp force in quadriplegia,” Bioelectron. Med., vol. 5, p. 19, 2019, doi: 10.1186/s42234-019-0034-y.

16. M. A. Schwemmer et al., “Meeting brain-computer interface user performance expectations using a deep neural network decoding framework,” Nat. Med., vol. 24, no. 11, pp. 1669– 1676, Nov. 2018, doi: 10.1038/s41591-018-0171-y.

17. S. C. Colachis et al., “Dexterous Control of Seven Functional Hand Movements Using Cortically-Controlled Transcutaneous Muscle Stimulation in a Person With Tetraplegia,” Front. Neurosci., vol. 12, p. 208, 2018, doi: 10.3389/fnins.2018.00208.

18. E. Musk and Neuralink, “An Integrated Brain-Machine Interface Platform With Thousands of Channels,” J. Med. Internet Res., vol. 21, no. 10, p. e16194, Oct. 2019, doi: 10.2196/16194.

19. T. Kim, S. Kim, and B. Lee, “Effects of Action Observational Training Plus Brain-Computer Interface-Based Functional Electrical Stimulation on Paretic Arm Motor Recovery in Patient with Stroke: A Randomized Controlled Trial,” Occup. Ther. Int., vol. 23, no. 1, pp. 39–47, Mar. 2016, doi: 10.1002/oti.1403.

20. G. Pfurtscheller, G. R. Müller, J. Pfurtscheller, H. J. Gerner, and R. Rupp, “’Thought’--control of functional electrical stimulation to restore hand grasp in a patient with tetraplegia,” Neurosci. Lett., vol. 351, no. 1, pp. 33–36, Nov. 2003, doi: 10.1016/s0304-3940(03)00947-9.

21. C. Vidaurre, C. Klauer, T. Schauer, A. Ramos-Murguialday, and K.-R. Müller, “EEG-based BCI for the linear control of an upper-limb neuroprosthesis,” Med. Eng. Phys., vol. 38, no. 11, pp. 1195–1204, Nov. 2016, doi: 10.1016/j.medengphy.2016.06.010.

22. Y.Y.Jang,T.H.Kim,andB.H.Lee,“EffectsofBrain-ComputerInterface-controlled Functional Electrical Stimulation Training on Shoulder Subluxation for Patients with Stroke: A Randomized Controlled Trial,” Occup. Ther. Int., vol. 23, no. 2, pp. 175–185, Jun. 2016, doi: 10.1002/oti.1422.

23. C. Reynolds, B. A. Osuagwu, and A. Vuckovic, “Influence of motor imagination on cortical activation during functional electrical stimulation,” Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol., vol. 126, no. 7, pp. 1360–1369, Jul. 2015, doi: 10.1016/j.clinph.2014.10.007.

24. B. C. A. Osuagwu, L. Wallace, M. Fraser, and A. Vuckovic, “Rehabilitation of hand in subacute tetraplegic patients based on brain computer interface and functional electrical stimulation: a randomised pilot study,” J. Neural Eng., vol. 13, no. 6, p. 065002, Dec. 2016, doi: 10.1088/1741-2560/13/6/065002.

25. S.-H. Lee, S. S. Kim, and B.-H. Lee, “Action observation training and brain-computer interface controlled functional electrical stimulation enhance upper extremity performance and cortical activation in patients with stroke: a randomized controlled trial,” Physiother. Theory Pract., vol. 38, no. 9, pp. 1126–1134, Sep. 2022, doi:10.1080/09593985.2020.1831114.

26. W. Lee et al., “Non-invasive transmission of sensorimotor information in humans using an EEG/focused ultrasound brain-to-brain interface,” PloS One, vol. 12, no. 6, p. e0178476,2017, doi: 10.1371/journal.pone.0178476.

27. T.-W. Kim and B.-H. Lee, “Clinical usefulness of brain-computer interface-controlledfunctional electrical stimulation for improving brain activity in children with spastic cerebral palsy: a pilot randomized controlled trial,” J. Phys. Ther. Sci., vol. 28, no. 9, pp. 2491–2494, Sep. 2016, doi: 10.1589/jpts.28.2491.

28. E. Chung, B.-H. Lee, and S. Hwang, “Therapeutic effects of brain-computer interface- controlled functional electrical stimulation training on balance and gait performance for stroke: A pilot randomized controlled trial,” Medicine (Baltimore), vol. 99, no. 51, p. e22612, Dec. 2020, doi: 10.1097/MD.0000000000022612.
29. Y. Miao et al., “BCI-Based Rehabilitation on the Stroke in Sequela Stage,” Neural Plast., vol. 2020, p. 8882764, 2020, doi: 10.1155/2020/8882764.
30. C. Marquez-Chin, A. Marquis, and M. R. Popovic, “BCI-Triggered Functional Electrical Stimulation Therapy for Upper Limb,” Eur. J. Transl. Myol., vol. 26, no. 3, p. 6222, Jun. 2016, doi: 10.4081/ejtm.2016.6222.
31. J. Likitlersuang et al., “EEG-Controlled Functional Electrical Stimulation Therapy With Automated Grasp Selection: A Proof-of-Concept Study,” Top. Spinal Cord Inj. Rehabil., vol. 24, no. 3, pp. 265–274, 2018, doi: 10.1310/sci2403-265.
32. M. Sebastián-Romagosa et al., “Brain Computer Interface Treatment for Motor Rehabilitation of Upper Extremity of Stroke Patients-A Feasibility Study,” Front. Neurosci., vol. 14, p. 591435, 2020, doi: 10.3389/fnins.2020.591435.
33. E. Chung, J.-H. Kim, D.-S. Park, and B.-H. Lee, “Effects of brain-computer interface-based functional electrical stimulation on brain activation in stroke patients: a pilot randomized controlled trial,” J. Phys. Ther. Sci., vol. 27, no. 3, pp. 559–562, Mar. 2015, doi: 10.1589/jpts.27.559.
34. I. Choi, G. H. Kwon, S. Lee, and C. S. Nam, “Functional Electrical Stimulation Controlled by Motor Imagery Brain-Computer Interface for Rehabilitation,” Brain Sci., vol. 10, no. 8, p. 512, Aug. 2020, doi: 10.3390/brainsci10080512.
35. M. Rohm et al., “Hybrid brain-computer interfaces and hybrid neuroprostheses for restoration of upper limb functions in individuals with high-level spinal cord injury,” Artif. Intell. Med., vol. 59, no. 2, pp. 133–142, Oct. 2013, doi: 10.1016/j.artmed.2013.07.004.
36. C. B. Tabernig, C. A. Lopez, L. C. Carrere, E. G. Spaich, and C. H. Ballario, “Neurorehabilitation therapy of patients with severe stroke based on functional electrical stimulation commanded by a brain computer interface,” J. Rehabil. Assist. Technol. Eng., vol. 5, p. 2055668318789280, 2018, doi: 10.1177/2055668318789280.
37. Y. Hashimoto, T. Kakui, J. Ushiba, M. Liu, K. Kamada, and T. Ota, “Portable rehabilitation system with brain-computer interface for inpatients with acute and subacute stroke: A feasibility study,” Assist. Technol. Off. J. RESNA, vol. 34, no. 4, pp. 402–410, Jul. 2022, doi: 10.1080/10400435.2020.1836067.
38. Fei Meng et al., “BCI-FES training system design and implementation for rehabilitation of stroke patients,” in 2008 IEEE International Joint Conference on Neural Networks (IEEE World Congress on Computational Intelligence), Hong Kong, China: IEEE, Jun. 2008, pp. 4103–4106. doi: 10.1109/IJCNN.2008.4634388.
39. H. Gollee, I. Volosyak, A. J. McLachlan, K. J. Hunt, and A. Gräser, “An SSVEP-based brain- computer interface for the control of functional electrical stimulation,” IEEE Trans. Biomed. Eng., vol. 57, no. 8, pp. 1847–1855, Aug. 2010, doi: 10.1109/TBME.2010.2043432.
40. M. Bockbrader et al., “Clinically Significant Gains in Skillful Grasp Coordination by an Individual With Tetraplegia Using an Implanted Brain-Computer Interface With Forearm Transcutaneous Muscle Stimulation,” Arch. Phys. Med. Rehabil., vol. 100, no. 7, pp. 1201–1217, Jul. 2019, doi: 10.1016/j.apmr.2018.07.445.
41. C. Ethier, E. R. Oby, M. J. Bauman, and L. E. Miller, “Restoration of grasp following paralysis through brain-controlled stimulation of muscles,” Nature, vol. 485, no. 7398, pp. 368–371, May 2012, doi: 10.1038/nature10987.
42. E. A. Pohlmeyer et al., “Toward the restoration of hand use to a paralyzed monkey: brain controlled functional electrical stimulation of forearm muscles,” PloS One, vol. 4, no. 6, p.e5924, Jun. 2009, doi: 10.1371/journal.pone.0005924.
43. J. I. Glaser, A. S. Benjamin, R. H. Chowdhury, M. G. Perich, L. E. Miller, and K. P. Kording, “Machine Learning for Neural Decoding,” eneuro, vol. 7, no. 4, p. ENEURO.0506-19.2020, Jul. 2020, doi: 10.1523/ENEURO.0506-19.2020.
44. C. E. Bouton and C. J. Czura, “Sensing and Decoding Neural Signals for Closed-Loop Neuromodulation and Advanced Diagnostics in Chronic Disease and Injury,” in Neuromodulation, Elsevier, 2018, pp. 1541–1549. doi: 10.1016/B978-0-12-805353-9.00131- 5.
45. M. Capogrosso et al., “A brain-spine interface alleviating gait deficits after spinal cord injury in primates,” Nature, vol. 539, no. 7628, pp. 284–288, Nov. 2016, doi: 10.1038/nature20118.
46. D. A. Zhang et al., “Carbon nanofiber electrode for neurochemical monitoring,” Mol. Neurobiol., vol. 48, no. 2, pp. 380–385, Oct. 2013, doi: 10.1007/s12035-013-8531-6.
47. A. A. Vučković, L. Wallace, and D. B. Allan, “Hybrid brain-computer interface and functional electrical stimulation for sensorimotor training in participants with tetraplegia: a proof-of- concept study,” J. Neurol. Phys. Ther. JNPT, vol. 39, no. 1, pp. 3–14, Jan. 2015, doi: 10.1097/NPT.0000000000000063.
48. D. A. Friedenberg et al., “Neuroprosthetic-enabled control of graded arm muscle contraction in a paralyzed human,” Sci. Rep., vol. 7, no. 1, p. 8386, Aug. 2017, doi: 10.1038/s41598-017-08120-9.
49. A. Biasiucci et al., “Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke,” Nat. Commun., vol. 9, no. 1, p. 2421, Jun. 2018, doi: 10.1038/s41467- 018-04673-z.
50. B. M. Young et al., “Case report: post-stroke interventional BCI rehabilitation in an individual with preexisting sensorineural disability,” Front. Neuroengineering, vol. 7, p. 18, 2014, doi: 10.3389/fneng.2014.00018.
51. N. Mrachacz-Kersting et al., “Efficient neuroplasticity induction in chronic stroke patients by an associative brain-computer interface,” J. Neurophysiol., vol. 115, no. 3, pp. 1410–1421, Mar. 2016, doi: 10.1152/jn.00918.2015.
52. M. Mukaino et al., “Efficacy of brain-computer interface-driven neuromuscular electrical stimulation for chronic paresis after stroke,” J. Rehabil. Med., vol. 46, no. 4, pp. 378–382, Apr. 2014, doi: 10.2340/16501977-1785.

53. G. Sharma et al., “Using an Artificial Neural Bypass to Restore Cortical Control of Rhythmic Movements in a Human with Quadriplegia,” Sci. Rep., vol. 6, no. 1, p. 33807, Sep. 2016, doi: 10.1038/srep33807.

54. E. Chung, S.-I. Park, Y.-Y. Jang, and B.-H. Lee, “Effects of brain-computer interface-based functional electrical stimulation on balance and gait function in patients with stroke: preliminary results,” J. Phys. Ther. Sci., vol. 27, no. 2, pp. 513–516, Feb. 2015, doi: 10.1589/jpts.27.513.

55. A. H. Do, P. T. Wang, C. E. King, A. Schombs, S. C. Cramer, and Z. Nenadic, “Brain-computer interface controlled functional electrical stimulation device for foot drop due to stroke,” in 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society, San Diego, CA: IEEE, Aug. 2012, pp. 6414–6417. doi: 10.1109/EMBC.2012.6347462

56. A.H.Do,P.T.Wang,C.E.King,A.Abiri,andZ.Nenadic,“Brain-ComputerInterface Controlled Functional Electrical Stimulation System for Ankle Movement,” J. NeuroEngineering Rehabil., vol. 8, no. 1, p. 49, 2011, doi: 10.1186/1743-0003-8-49.

57. C. M. McCrimmon, C. E. King, P. T. Wang, S. C. Cramer, Z. Nenadic, and A. H. Do, “Brain- controlled functional electrical stimulation therapy for gait rehabilitation after stroke: a safety study,” J. NeuroEngineering Rehabil., vol. 12, no. 1, p. 57, Dec. 2015, doi: 10.1186/s12984-015-0050-4.

58. A.P. Yadav, D. Li, and M. A. L. Nicolelis, “A Brain to Spine Interface for Transferring Artificial Sensory Information,” Sci. Rep., vol. 10, no. 1, p. 900, Jan. 2020, doi: 10.1038/s41598-020- 57617-3.

59. E. B. Knudsen and K. A. Moxon, “Restoration of Hindlimb Movements after Complete Spinal Cord Injury Using Brain-Controlled Functional Electrical Stimulation,” Front. Neurosci., vol. 11, p. 715, 2017, doi: 10.3389/fnins.2017.00715.

60. M. Bonizzato et al., “Brain-controlled modulation of spinal circuits improves recovery from spinal cord injury,” Nat. Commun., vol. 9, no. 1, p. 3015, Aug. 2018, doi: 10.1038/s41467- 018-05282-6.

61. S. Buccelli et al., “A Neuromorphic Prosthesis to Restore Communication in Neuronal Networks,” iScience, vol. 19, pp. 402–414, Sep. 2019, doi: 10.1016/j.isci.2019.07.046.

62. M. Chiappalone et al., “Neuromorphic-Based Neuroprostheses for Brain Rewiring: State-of- the-Art and Perspectives in Neuroengineering,” Brain Sci., vol. 12, no. 11, p. 1578, Nov. 2022, doi: 10.3390/brainsci12111578.

63. A. A. Jackson, J. Mavoori, and E. E. Fetz, “Long-term motor cortex plasticity induced by an electronic neural implant,” Nature, vol. 444, no. 7115, pp. 56–60, Nov. 2006, doi: 10.1038/nature05226.

64. S. Chandrasekaran et al., “Evoking highly focal percepts in the fingertips through targeted stimulation of sulcal regions of the brain for sensory restoration,” Brain Stimulat., vol. 14, no. 5, pp. 1184–1196, 2021, doi: 10.1016/j.brs.2021.07.009.

65. D. R. Kramer et al., “Utility and lower limits of frequency detection in surface electrode stimulation for somatosensory brain-computer interface in humans,” Neurosurg. Focus, vol. 48, no. 2, p. E2, Feb. 2020, doi: 10.3171/2019.11.FOCUS19696.

66. P. Texakalidis, M. S. Tora, T. Federici, J. J. Javidfar, and N. M. Boulis, “Thoracoscopic delivery of therapeutics in the swine sympathetic chain: Implications for future neuromodulation,” J. Clin. Neurosci. Off. J. Neurosurg. Soc. Australas., vol. 77, pp. 199–202, Jul. 2020, doi: 10.1016/j.jocn.2020.04.099.

67. C. S. Nam, Z. Traylor, M. Chen, X. Jiang, W. Feng, and P. Y. Chhatbar, “Direct Communication Between Brains: A Systematic PRISMA Review of Brain-To-Brain Interface,” Front. Neurorobotics, vol. 15, p. 656943, 2021, doi: 10.3389/fnbot.2021.656943.

68. L. Jiang, A. Stocco, D. M. Losey, J. A. Abernethy, C. S. Prat, and R. P. N. Rao, “BrainNet: A Multi-Person Brain-to-Brain Interface for Direct Collaboration Between Brains,” Sci. Rep., vol. 9, no. 1, p. 6115, Apr. 2019, doi: 10.1038/s41598-019-41895-7.

69. M. E. M. Mashat, G. Li, and D. Zhang, “Human-to-human closed-loop control based on brain-to-brain interface and muscle-to-muscle interface,” Sci. Rep., vol. 7, no. 1, p. 11001, Sep. 2017, doi: 10.1038/s41598-017-10957-z.

70. R. P. N. Rao et al., “A direct brain-to-brain interface in humans,” PloS One, vol. 9, no. 11, p. e111332, 2014, doi: 10.1371/journal.pone.0111332.

71. A.Stocco et al., “Playing 20 Questions with the Mind: Collaborative Problem Solving by Humans Using a Brain-to-Brain Interface,” PloS One, vol. 10, no. 9, p. e0137303, 2015, doi: 10.1371/journal.pone.0137303.

72. A.Grau et al., “Conscious brain-to-brain communication in humans using non-invasive technologies,” PloS One, vol. 9, no. 8, p. e105225, 2014, doi: 10.1371/journal.pone.0105225.

73. S.-S. Yoo, H. Kim, E. Filandrianos, S. J. Taghados, and S. Park, “Non-invasive brain-to-brain interface (BBI): establishing functional links between two brains,” PloS One, vol. 8, no. 4, p. e60410, 2013, doi: 10.1371/journal.pone.0060410.

74. S.Zhangetal.,“HumanMindControlofRatCyborg’sContinuousLocomotionwithWireless Brain-to-Brain Interface,” Sci. Rep., vol. 9, no. 1, p. 1321, Feb. 2019, doi: 10.1038/s41598- 018-36885-0.

75. B. Koo et al., “Manipulation of Rat Movement via Nigrostriatal Stimulation Controlled by Human Visually Evoked Potentials,” Sci. Rep., vol. 7, no. 1, p. 2340, May 2017, doi: 10.1038/s41598-017-02521-6.

76. Y.Yu,C.Qian,Z.Wu,andG.Pan,“Mind-controlledratbot:Abrain-to-brainsystem,”in2014 IEEE International Conference on Pervasive Computing and Communication Workshops (PERCOM WORKSHOPS), Budapest, Hungary: IEEE, Mar. 2014, pp. 228–231. doi: 10.1109/PerComW.2014.6815207.

77. G. Li and D. Zhang, “Brain-Computer Interface Controlled Cyborg: Establishing a Functional Information Transfer Pathway from Human Brain to Cockroach Brain,” PloS One, vol. 11, no. 3, p. e0150667, 2016, doi: 10.1371/journal.pone.0150667.
78. L. Lu, R. Wang, and M. Luo, “An optical brain-to-brain interface supports rapid information transmission for precise locomotion control,” Sci. China Life Sci., vol. 63, no. 6, pp. 875– 885, Jun. 2020, doi: 10.1007/s11427-020-1675-x.
79. M. J. O’Donovan, P. Wenner, N. Chub, J. Tabak, and J. Rinzel, “Mechanisms of spontaneous activity in the developing spinal cord and their relevance to locomotion,” Ann. N. Y. Acad. Sci., vol. 860, pp. 130–141, Nov. 1998, doi: 10.1111/j.1749-6632.1998.tb09044.x.
80. S. Kochubey, A. Semyanov, and L. Savtchenko, “Network with shunting synapses as a non- linear frequency modulator,” Neural Netw. Off. J. Int. Neural Netw. Soc., vol. 24, no. 5, pp. 407–416, Jun. 2011, doi: 10.1016/j.neunet.2011.03.005.
81. A.Ayaz and F. S. Chance, “Gain modulation of neuronal responses by subtractive and divisive mechanisms of inhibition,” J. Neurophysiol., vol. 101, no. 2, pp. 958–968, Feb. 2009, doi: 10.1152/jn.90547.2008.
82. T. Tazoe and Y. Nishimura, “[Artificial Neural Connection Restores Voluntary Motor Function After Stroke and Spinal Cord Injury],” Brain Nerve Shinkei Kenkyu No Shinpo, vol. 74, no. 9, pp. 1111–1116, Sep. 2022, doi: 10.11477/mf.1416202190.
83. T. D. Azad, A. Veeravagu, and G. K. Steinberg, “Neurorestoration after stroke,” Neurosurg. Focus, vol. 40, no. 5, p. E2, May 2016, doi: 10.3171/2016.2.FOCUS15637.
84. G. Yao et al., “Alterations of Functional Connectivity in Stroke Patients With Basal Ganglia Damage and Cognitive Impairment,” Front. Neurol., vol. 11, p. 980, 2020, doi: 10.3389/fneur.2020.00980.
85. E. E. Fetz, “Restoring motor function with bidirectional neural interfaces,” Prog. Brain Res., vol. 218, pp. 241–252, 2015, doi: 10.1016/bs.pbr.2015.01.001.
86. R. E. Burke, R. E. Fyffe, and A. K. Moschovakis, “Electrotonic architecture of cat gamma motoneurons,” J. Neurophysiol., vol. 72, no. 5, pp. 2302–2316, Nov. 1994, doi: 10.1152/jn.1994.72.5.2302.
87. G. Schlaug, V. Renga, and D. Nair, “Transcranial direct current stimulation in stroke recovery,” Arch. Neurol., vol. 65, no. 12, pp. 1571–1576, Dec. 2008, doi: 10.1001/archneur.65.12.1571.
88. K. K. Ang et al., “A Randomized Controlled Trial of EEG-Based Motor Imagery Brain- Computer Interface Robotic Rehabilitation for Stroke,” Clin. EEG Neurosci., vol. 46, no. 4, pp. 310–320, Oct. 2015, doi: 10.1177/1550059414522229.
89. X. Xie et al., “Resting-State Neural-Activity Alterations in Subacute Aphasia after Stroke,” Brain Sci., vol. 12, no. 5, p. 678, May 2022, doi: 10.3390/brainsci12050678.
90. G. Di Pino et al., “Modulation of brain plasticity in stroke: a novel model for neurorehabilitation,” Nat. Rev. Neurol., vol. 10, no. 10, pp. 597–608, Oct. 2014, doi: 10.1038/nrneurol.2014.162.
91. F. Zeldenrust and W. J. Wadman, “Modulation of spike and burst rate in a minimal neuronal circuit with feed-forward inhibition,” Neural Netw. Off. J. Int. Neural Netw. Soc., vol. 40, pp. 1–17, Apr. 2013, doi: 10.1016/j.neunet.2012.12.008.
92. L. Cardinali, C. Brozzoli, C. Urquizar, R. Salemme, A. C. Roy, and A. Farnè, “When action is not enough: tool-use reveals tactile-dependent access to Body Schema,” Neuropsychologia, vol. 49, no. 13, pp. 3750–3757, Nov. 2011, doi: 10.1016/j.neuropsychologia.2011.09.033.
93. F. M. Z. van den Heiligenberg et al., “Artificial limb representation in amputees,” Brain J. Neurol., vol. 141, no. 5, pp. 1422–1433, May 2018, doi: 10.1093/brain/awy054.
94. T. MakinandL. PlasticityLab,“PhantomLimbsandBrainPlasticityinAmputees,”inOxford Research Encyclopedia of Neuroscience, Oxford University Press, 2020. doi: 10.1093/acrefore/9780190264086.013.50.
95. J. Correale, M. Marrodan, and E. E. Benarroch, “What is the role of axonal ion channels in multiple sclerosis?,” Neurology, vol. 95, no. 3, pp. 120–123, Jul. 2020, doi: 10.1212/WNL.0000000000009754.

Отримана в редакції 12.01.2025. Прийнята до друку 03.02.2025. Received 12 January 2025. Approved 03 Februry 2025. Available in Internet 28 March 2025.