Neurogenetic Remodeling of the Sensorimotor Cortex Following Limb Loss: Implications for Adaptive Feedback in Closed-Loop Neuroprosthetics

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Abstract

Limb loss leads to significant changes in the organization of the primary motor (M1) and somatosensory (S1) cortices, disrupting the body's internal sensorimotor map. Despite the significant advancements in the field of neuroprosthetics, many challenges persist regarding device integration and motor function restoration, since they fail to fully engage the genetically driven plasticity mechanisms required for long-term cortical integration. This review explores how do neurogenetic changes in the sensorimotor cortex following limb loss influence the development of adaptive feedback systems in neuroprosthetics. Research in this field commonly involves animal models to investigate gene expression changes after amputation and human amputees to reveal how prosthetic use and feedback integration are related to structural and functional plasticity changes. This paper follows an interdisciplinary approach, by combining the fields of molecular biology, systems neuroscience, and neuroengineering, to suggest a framework for more adaptive neuroprosthetic feedback systems. Our thesis is that that the neurogenetic remodeling of the sensorimotor cortex, which is driven by activity-dependent expression of plasticity-related genes, can be harnessed to develop biologically adaptive systems that evolve based on the individual's cortical reorganization. By understanding the neurogenetic basis of cortical reorganization following limb loss, prosthetic technologies could be advanced to not only restore function of the lost limb but actively engage and enhance the brain's natural plasticity mechanisms. This review advances a personalized, feedback-responsive paradigm in neuroengineering by linking gene expression dynamics to prosthetic performance, something that is crucial to improve clinical outcomes.

Keywords

Neurogenetic Remodeling
Cortical Plasticity
Sensorimotor Cortex
Limb Loss
Neuroprosthetics
Brain-Machine Interface

Introduction

With more than 13 million new amputees reported in 2019 and over 552 million people living with limb loss worldwide (Yuan et al., 2023), limb loss has become a chronic global health issue. This kind of trauma fundamentally disrupts the sensorimotor pathways of the brain by initiating a systemic recalibration that reshapes its internal architecture (Makin & Flor, 2020; Sparling et al., 2024). Thus, clinical outcomes could only be enhanced if these neuroplastic changes are leveraged to allow the development of more adaptive neuroprosthetics.

Over the past decades, breakthroughs in the field of neuroprosthetics enabled the transition from simple mechanical aids to advanced brain-machine interfaces (BMIs) able to translate neural signals into precise movements. Despite this progress, most devices fail to fully adapt to the individual's internal systems, leading to limited functional recovery, persistent phantom limb pain, and low adoption rates (Demofonti et al., 2025). The main cause of these issues is the dissonance between technological control and biological embodiment, with current devices primarily responding to motor intent without returning meaningful sensory feedback, which restricts their adaptability and engagement (Capsi-Morales et al., 2023; Tyler, 2015). Thus, many users characterize them as unnatural and with cognitively demanding control, so they remain external tools rather than becoming extensions of the body.

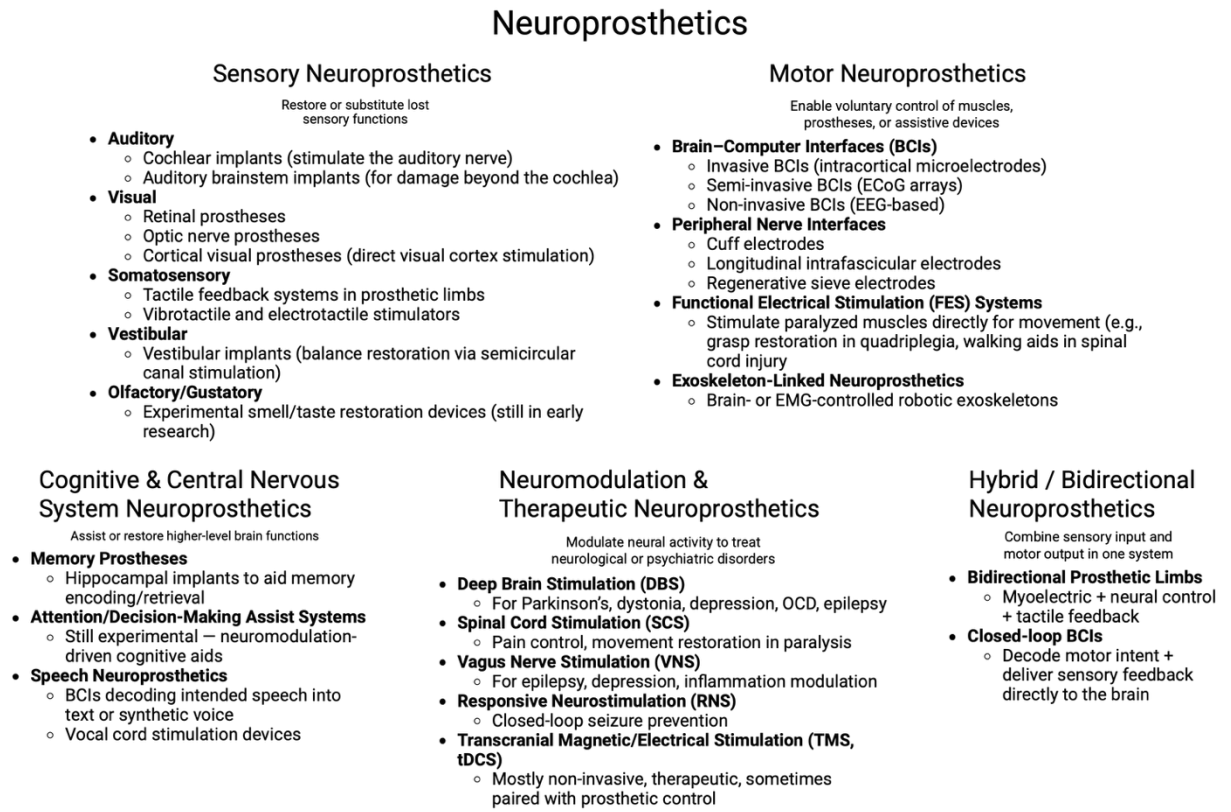

Figure 1 summarizes the main categories of neuroprosthetics (sensory, motor, cognitive/central nervous system, neuromodulation/therapeutic, and hybrid/bidirectional) and examples of representative devices with their corresponding interface locations.

Although recent studies and review have revealed that limb loss leads to major neuroplastic changes, including extensive cortical remapping and functional adaptations (Makin & Flor, 2020; Simões et al., 2012; Sparling et al., 2024), the design of most prosthetic devices does not fully leverage these insights, with only a few systems leveraging the plasticity mechanisms of the brain responsible for long-term cortical reorganization. The lack of connection between molecular neuroscience and neuroengineering solutions represents a significant scientific and clinical gap. Bridging this holds the potential to improve clinical outcomes, from alleviating phantom limb pain to establishing a sense of embodiment in users.

This review investigates how does the neurogenetic remodeling of the sensorimotor cortex following limb loss can be leveraged to develop adaptive closed-loop feedback systems in neuroprosthetics to ultimately enhance clinical outcomes, adaptability and embodiment. Evidence suggest that amputation is followed by extensive cortical reorganization, including cortical map shifts and gene expression changes related to synaptic plasticity (Carulli et al., 2011; Kikkert et al., 2019; Simões et al., 2012; Sparling et al., 2024). Nevertheless, most systems fail to utilize these insights, with the risk of maladaptive plasticity, phantom limb pain, and restricted prosthetic embodiment. As a result, if prosthetic feedback is aligned with the neuroplastic mechanisms, we could achieve major improvements in pain mitigation, limb embodiment, and sensorimotor integration (Dietrich et al., 2018; Srinivasan et al., 2020).

By advancing a personalized, feedback-responsive paradigm in neuroengineering, we aim to link neurogenetics and neuroprosthetics, which is necessary to achieve long-term integration and improved embodiment. We argue that the neurogenetic changes in the sensorimotor cortex can be harnessed to develop biologically adaptive prosthetic systems operating based on the individual's cortical reorganization. Rather than simply decoding motor signals, future neuroprosthetics need to actively stimulate and modulate cortical reorganization processes to create a bi-directional and adaptive interface.

In this review, we explore the landscape of brain plasticity after amputation and its implications on the development of adaptive neuroprosthetics. We initially delve into the changes in cortical organization induced by limb loss. Next, we discuss the challenges associated to the integration and adaptability of current neuroprosthetics. In addition, we link neurogenetics and prosthetics to explore how genetic changes influence neural recovery and device adaptability and responsiveness. Then, we propose a framework for gene-informed neuroprosthetic design, connecting prosthetics to neurobiological profiles to enhance clinical outcomes. We conclude with future directions, by identifying emerging avenues and opportunities for interdisciplinary research.

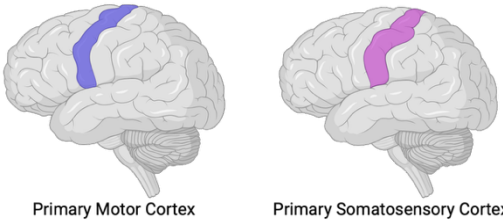

Figure 2 illustrates the locations of the primary motor (M1) and somatosensory (S1) cortices in the brain.

Sensorimotor Cortical Remodeling After Limb Loss

Functional & Structural Plasticity in M1 and S1

- ### Cortical Map Changes

Limb loss cannot be considered only a physical trauma, as it leads to profound alterations of the brain's somatotopic organization. The classical Penfield homunculus, which was derived from intraoperative stimulation studies by Penfield and his colleagues, depicts the representation of the body in the primary motor (M1) and somatosensory (S1) cortices in an ordered and topographical diagram. However, cortical maps are far from static. More specifically, limb loss leads to functional and structural plasticity changes in M1 and S1 that result in reorganization of the cortical map. This includes representative area shifts, expansion of adjacent body part representation, modified callosal connectivity, and interhemispheric rebalancing.

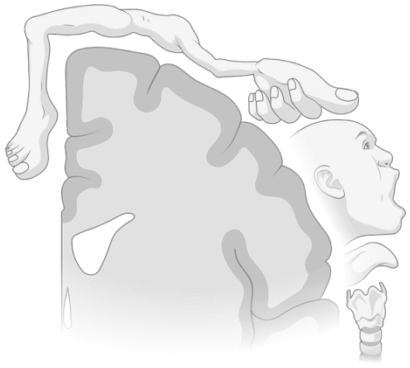

Figure 3 is a recreation of the motor homunculus by Penfield et al., showing the areas of the brain and their representative parts of the body.

Numerous studies, which are effectively summarized by Sparling et al., have used high-resolution functional imaging techniques - such as functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) - and transcranial magnetic stimulation (TMS) to demonstrate that cortical areas previously associated with the missing limb were reorganized to represent adjacent body parts. For instance, a study from Makin et al., found that face representation had been shifted ~8 mm medially into the deprived homunculus of upper-limb amputees. This shift is also correlated with the degree of phantom limb pain (PLP), since individuals exhibiting greater cortical invasion report more severe pain sensations (Makin & Flor, 2020). Other fMRI studies, summarized by Gunduz et al., show that the expansion of lip representation into the amputated hand area is associated with higher PLP, and that mirror therapy can reverse this shift, supporting the notion that maladaptive plasticity contributes to pain. In conclusion, these findings demonstrate that the brain's cortex can be significantly altered due to limb loss, resulting in variable clinical symptoms that require an individualized treatment approach.

Furthermore, evidence from a study by Wilkins et al. show that sensory experience plays a critical role in establishing cortical maps. Their survey of individuals with congenital and surgical limb loss revealed that phantom limb sensations (PLS) occurred in only 7.4% of the former compared with 69.7% of the latter, while PLP occurred in 3.7% versus 48.5%, respectively. It is plausible, then, that early sensorimotor experience is required to develop limb representation, while it may protect against phantom sensations.

In addition, insights from animal models expand our understanding of cortical reorganization. Research on rodents with forelimb amputation reveals that, within hours, the activity of deprived neurons is rapidly increased, due to amputation in the deprived S1 forepaw, with activity being at maximum for weeks. Neuroimaging in rodents with lower-limb amputation, also, shows that tactile stimulation of the intact limb greatly activates the ipsilateral S1, indicating that the representation of the stump is functionally shifted into trunk and upper-limb areas (studies summarized by Sparling et al., 2024). These findings combined, suggest that the deprived cortex becomes responsive to adjacent inputs, transforming the original map and potentially leading to more precise motor control.

To conclude, these evidence of reorganization and recalibration of the brain support the view that the somatosensory cortex is not rigidly mapped, but rather dynamically responsive.

• Callosal Connectivity and Interhemispheric Imbalance

Interhemispheric coordination is mediated by the corpus callosum. As a result, unilateral amputation affects this coordinating balance. Evidence from resting-state fMRI and diffusion tensor imaging (DTI) reveal that the functional connectivity between bilateral sensorimotor regions is decreased along with fractional anisotropy (FA) - FA is a quantitative biomarker of the integrity of white matter (Vandermosten et al., 2012) - of callosal axons in amputees (Simões et al., 2012). Reports of structural studies prove that region II of corpus callosum, which links the premotor and supplementary motor areas, shows reduced FA in lower-limb amputees (Zhang et al., 2018), which suggests loss of callosal fibers or demyelination

As a result of these changes, interhemispheric imbalance arises. The stimulation of the intact limb elicits bilateral cortical activation in rodent models and human amputees, something that is enhanced when the intact cortex is transiently silenced, indicating decreased interhemispheric inhibition. This concept of callosal rewiring may disrupt bimanual coordination and hinder tasks, such as walking with a prosthetic, pointing out the need for consideration of bilateral dynamics when designing neuroprosthetic control strategies.

Molecular & Genetic Changes Post-Amputation

• Activity-Dependent Gene Expression

When the afferent and efferent input is lost, certain gene expression activities are triggered to promote synaptic remodeling. Activity-dependent transcription involves various mechanisms, such as immediate early genes (IEG) (c-Fos, Arc/Arg3.1, Egr1), growth factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), and cytoskeletal regulators, including growth-associated protein-43 (GAP-43) and synapsin-1. In a

review by Carulli et al., summarized experiments in rodent barrel cortex demonstrate that naturalistic whisker use stimulates the expression of BDNF, CREB, synapsin-1 and GAP-43, while the opposite effect is observed for sensory deprivation (Rocamora et al., 1996). Moreover, voluntary exercise elevates BDNF and synapsin-1 expression in a similar way in the dorsal root ganglia and promotes peripheral nerve regeneration.

Neural plasticity is underlined by a molecular cascade that begins with NMDA receptor mediated Ca^{2+} influx which activates transcription factors, such as CREB. CREB then recruits its co-activator CBP/p300 to gene promoters, leading to the transcription of plasticity-related genes (Almeida et al., 2009; Del Blanco et al., 2019). These genes facilitate dendritic growth, synaptogenesis and synaptic strengthening, assisting the reorganization of cortical circuits after injury.

- ### Timing and Windows of Plasticity

Plasticity follows the injury is a temporal sequence characterized by shifts in the excitatory and inhibitory tone (Sparling et al., 2024). After amputation, the deprived somatosensory cortex exhibits a transient increase in levels of AMPA receptor and synaptic excitation during the first days. These are followed by elevated GABAergic inhibition some weeks later, which create a critical window for excitation that supports rapid remodeling. Studies with rodents show that following forelimb amputation, the activity of deep cortical neurons increases within hours and persists for weeks. These findings, therefore, imply that rehabilitative interventions and prosthetic fitting may be most effective when achieved during this heightened plasticity window. It is important to note that, in children with congenital limb abnormalities, when the fitting of prostheses is delayed, it may repress motor development and hinder cortical adaptation, pointing out the importance of early intervention, during the appropriate plasticity window.

Challenges in Current Neuroprosthetic Integration

Gaps in Prosthetic Adaptability

Until this point, the way most neuroprosthetic devices detect and interpret motor intentions is via surface electromyography (sEMG), cortical spiking activity tracking or electrocorticomyography. In a nutshell, these techniques follow the steps of signal acquisition, processing, and interpretation and provide the appropriate response. However, systems that incorporate these techniques, while being able to detect motor intent, they often provide limited to no sensory feedback (Capsi-Morales et al., 2023; Tyler, 2015). As a result, users need to rely heavily on visual cues to be able to guide the movement, something that increases the cognitive load required and failing to fully integrate to the user’s body. In addition, even though these systems are effective in controlled settings, their decoders cannot adapt to the cortical remodeling, as the sensorimotor cortex may continue to reorganize even log after amputation. Due to this continuous cortical remodeling, constant calibration is essential to allow the mapping of neural signals and the intended movement. Currently, most systems do not account for the

individual variability in plasticity gene expression, nor adjust their control algorithms at the molecular state. This mismatch between static decoding algorithms and constant biological changes, raises the issue of avoidance of gene-sensitive personalization and, thus, deterioration of neuroprosthetic control over time, contributing to the device's abandonment.

Missed Opportunities for Remodeling

Despite the generic linkage gap between molecular biology and neuroprosthetic development, some techniques have been developed over the past years that seek to engage the under-utilized neuroplastic circuits underlying limb loss. For instance, targeted muscle reinnervation (TMR) is a surgical procedure aiming to reestablish bidirectional communication between residual peripheral nerves, muscles, and skin. As a result, control signals, which become more naturalistic, are facilitated, and this something that can restore sensory feedback. While TMR is often used for the treatment or prevention of neuroma and phantom limb pain in amputees, it was originally developed to enhance myoelectric signals and prosthetic control in people with proximal upper limb amputation (Peters et al., 2020; Sparling et al., 2024). However, a handful of prosthetic systems utilize real-time sensory feedback to leverage TMR-mediated reinnervation. Another procedure commonly used is the agonist-antagonist myoneural interface (AMI) surgery aiming to preserve pairs of agonist-antagonist muscles to maintain natural balance and provide proprioceptive feedback through mechanical coupling. We should also note that clinical studies have reported decreased phantom pain, but increased phantom limb sensation, indicating reorganized activation patterns in 3a area and parietal cortex (Srinivasan et al., 2020). Similarly, osseointegrated (OI) prostheses, which are directly attached the prosthetic limb to the skeletal part of the dual limb via a titanium implant, enhance the mechanical stability and proprioceptive feedback, through a phenomenon known as osseoperception (Hoellwarth et al., 2020). These systems can then prevent socket-related complications and potentially promote neuroplastic integration and functional restoration if they are combined with implanted neural interfaces. Yet most commercially available prostheses do not leverage these biological mechanisms.

Linking Neurogenetics with Adaptive Prosthetics

Feedback-Driven Remodeling: Evidence and Mechanisms

Literature evidence suggests that cortical plasticity mechanisms could be reactivated via sensory feedback due to activity-dependent gene expression (Carulli et al., 2011). Various studies in the generic literature show evidence that plasticity-related gene expression can be upregulated and enhance motor control with the use of peripheral nerve interfaces and neurostimulation. It is notable that implanted electrodes delivering sensory feedback are shown to increase BDNF expression in animal models. Also, vagus nerve stimulation (VNS) accompanied by movement results in norepinephrine levels elevation and upregulation of BDNF and basic fibroblast growth factor (bFGF) expression in rodent brains (Hays et al., 2013), while transcranial direct current stimulation and synaptic activation enhance BDNF secretion. These

findings suggest an important influence of peripheral feedback in central gene expression. Other studies focusing on rodent models show that use of naturalistic whisker stimulates the expression of BDNF, CREB, synapsin-1 and GAP-43 in the somatosensory cortex (Carulli et al., 2011). Moreover, enriched environments and voluntary exercise are also shown to contribute to BDNF upregulation and promotion of synaptogenesis.

Translating these findings in the design of neuroprosthetics, it is important to note that bi-directional systems that deliver tactile and proprioceptive feedback have the potential to simulate natural sensation patterns and trigger gene expression plasticity. This is supported by clinical observations with TMR prosthetic users exhibiting improved cortical representation of the missing limb and PLP reduction, while evidence suggest that AMI surgery helps with proprioceptive sensations and proprioceptive cortex activation (Sparling et al., 2024). All these findings, therefore, indicate that engagement of molecular pathways promotes cortical reorganization and functional recovery and highlight the need for feedback-driven prosthetic systems.

Personalized, Gene-Informed Design Strategies

Gene expression and epigenetic alterations vary among individuals, suggesting different sensory feedback parameters among prostheses users. To harness the neurogenetic remodeling following limb loss, prosthetic systems need to sense and adapt to the user's molecular and cortical state. As a result, more advanced methods need to be implemented. Using transcriptomic monitoring, gene expression profiles could be analyzed form peripheral fluids (blood or cerebrospinal fluid) to monitor plasticity readiness. Another way to achieve this is with the use of machine learning models integrating electrophysiological signals (EEG, high-intensity EEG) and functional near-infrared spectroscopy (fNIRS) that would also determine cortical excitation. Unlike fMRI, fNIRS is portable, offers good temporal resolution, and is resistant to motion artifacts, making it a great option for more dynamic monitoring of brain network recovery during rehabilitation (Sun et al., 2024). Moreover, EEG could complement fNIRS for long-term monitoring by detecting neuronal dynamics in millisecond-scale. These methods combined could help with real-time cortical state tracking in order to guide adaptive feedback intensity and frequency (Sun et al., 2024).

With the incorporation of gene-informed systems into prosthetics, feedback parameters would be adjusted based on the individual's gene expression profile, an essential step to achieve improved clinical outcomes. For instance, users with high expression of BDNF may need different sensory feedback intensity and frequency than people with lower BDNF expression levels, so adaptive algorithms could modulate stimulation to match the excitatory plasticity window (Sparling et al., 2024), while detection of elevated negative plasticity modulators, such as miR-134 or miR-124, would be possible via microRNA profiling, aiding targeted pharmacologic or gene-edited interventions alongside prosthetic training and integration. Despite its complexity, the use of this closed-loop, biomarker-driven approach could be the turning point where neuroprosthetics would not be just passive decoders of movement intent, but active cortical reorganization and neurogenetic remodeling modulators.

Translational Framework: A Gene-Informed Design Paradigm

Biologically Adaptive Prosthetic Design

- ### Transcriptomic Personalization

The latest advancements in RNA sequencing and biofluid biomarkers have currently made plasticity-related gene expression monitoring possible without invasive procedures. This helps identify the window when the cortex is in a growth-permissive state after amputation by monitoring plasticity-related transcripts, such as BDNF, GAP-43, synapsin-1, and immediate early genes over time. These data could then be used by artificial intelligence (AI) and machine learning (ML) models and be combined with behavioral metrics, aiding personalized feedback. An example of this is, after the detection of high plasticity gene expression levels during transcriptomic analysis, the prostheses' AI-driven system could increase sensory feedback frequency or intensity to enhance integration and neurogenetic remodeling. On the other hand, a decrease in those levels could indicate a resting period or the need for pharmacologic intervention.

- ### Real-Time Plasticity Monitoring

Closed-loop adaptation, which is central to the development of biologically adaptive neuroprosthetics, requires constant cortical activity monitoring, something that could be achieved with portable biosensors, such as compact EEG and fNIRS devices. EEG would assist by providing high temporal resolution and detecting oscillatory power and coherence changes, which are related to motor learning. fNIRS would measure hemodynamic changes and reveal patterns of functional connectivity, while it is also suitable for long-term monitoring (Pereira et al., 2023; Sun et al., 2024). Therefore, hybrid EEG-fNIRS systems would allow both neuronal and hemodynamic activity monitoring, providing insights about cortical plasticity windows. These data could then be used by reinforcement learning algorithms to optimize the device's feedback over time and enhance its embodiment and adaptation.

Clinical and Ethical Considerations

- ### Implementation Challenges

The development of gene-informed neuroprosthetics is accompanied by various technical and regulatory challenges, requiring careful safety considerations and regulatory protocols. Safe interaction of these devices with peripheral nerves or cortical tissue, without any concerns for long-term damage of harm to the user, needs to be the number one priority for the development of these advanced systems. Furthermore, data privacy concerns should be addressed since these devices would handle sensitive data collected for the users' daily interactions, their genomic profile and cortical recordings. Additionally, regulatory agencies need

to ensure that such systems would not cause maladaptive plasticity or unintended gene expression.

- ### Equity and Access

A major concern that needs to be addressed regarding personalized neuroprosthetics is the exacerbation of existing healthcare inequalities, if access to them is only limited to well-resourced settings. That could be the result of high costs and specialized infrastructure, which is limited to wealthy regions. This problem could be addressed with inclusive clinical trials and open-source designs, promoting equitable distribution. Ethical frameworks also need to address data ownership matters, with users having the ability to retain control of their neurogenetic data and authority for decision making, and the level of AI autonomy in closed-loop systems .

Future Directions

Gene Modulation via Neurostimulation

Cortical plasticity and gene expression could be modulated by non-invasive brai stimulation techniques, such as tDCS and transcranial alternating current stimulation (tACS). Studies conducted in mice show that even short lasting anodal tDCS can produce lasting increases in hippocampal long-term potentiation, learning and memory. These are by BDNF promoter acetylation, increased BDNF exons transcription, enhanced BDNF protein levels, and increased CREB phosphorylation (Fritsch et al., 2010; Podda et al., 2016). Thus, combination of these techniques with training of prosthetics could assist cortical remapping and prosthetic adaptation.

Synthetic Biology & Gene Editing

Advancements in synthetic biology could also provide future pathways for precise neural circuit manipulation. A great example this nature is the use of viral vectors to deliver CRISPR-Cas9 or transcriptional activators in order to locally enhance growth factor expression or plasticity-inhibiting genes silencing. Engineered cells could also serve ad biosensors within peripheral nerves or even actuators by releasing neurotropic factors in response to activity, thereby creating a feedback loop that is self-regulated. Although these techniques are highly advanced and at an early preclinical state, the potential to integrate them with neuroprosthetics could change rehabilitation by modulating molecular pathways directly and transform the field of prosthetic devices.

Conclusion

Limb amputation causes extensive remodeling of the somatosensory cortex, which includes structural, functional and molecular alterations (Sparling et al., 2024). Despite the insights in this neurogenetic remodeling, most neuroprosthetic systems do not leverage them or may completely ignore these biological dynamics. The gene-informed paradigm in this paper

highlights the need for prostheses to monitor and modulate cortical plasticity. Transcriptomic personalization, real-time biosensors, AI-guided stimulation and reinforcement learning could assist their embodiment ad integration with the brain's intrinsic pathways, thereby enhancing functionality, reducing clinical complications and feel more natural. This vision moves beyond simple decoding, toward biologically aligned systems that evolve with cortical reorganization. This paradigm also highlights the need for interdisciplinary collaboration across molecular biology, systems neuroscience, neuroengineering and ethics. Aligning technological innovation with the brain's intrinsic neuroplastic plastic capacity, will allow the development of neuroprosthetics that feel less like machines and more like extensions of the self, offering numerous benefits to users.

Acknowledgments

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Reviewer Guidelines for Convergence

1. Key Evaluation Criteria

- **Originality & Significance** – Does the paper contribute new insights or perspectives to the field?

The manuscript presents an innovative framework by connecting neurogenetic remodeling with the development of adaptive neuroprosthetic feedback systems. This integration of molecular neuroscience with prosthetic engineering offers fresh perspectives not often addressed in the literature, which typically emphasizes cortical remapping alone. The focus on gene expression, transcriptional cascades, and plasticity windows provides an original angle that could meaningfully advance the conversation on precision neuroprosthetics. However, some of the translational claims (e.g., transcriptomic monitoring in real-time prosthetic use) remain speculative. The paper would benefit from distinguishing clearly between what is currently feasible and what represents aspirational, future directions.

- **Clarity & Structure** – Is the argument well-organized and easy to follow? Are ideas clearly presented?

The manuscript is well-structured, progressing logically from cortical remodeling, to genetic underpinnings, to translational opportunities in prosthetics. Key terms are defined, and section headings make the argument easier to follow.

Areas to improve:

- Several sentences are overly dense and could be streamlined for clarity, particularly in descriptions of transcriptional pathways.
- Some repetition is present (e.g., multiple references to BDNF-driven plasticity). Condensing these points would increase readability.
- Prevalence data in the introduction requires clarification; the figure of “552 million living with limb loss” appears unusually high and should be verified.

- **Use of Evidence & Research Methods** – Are sources appropriately cited? Is their methodology sound and well-explained?

The authors cite both foundational and recent studies, drawing on diverse methodologies (fMRI, MEG, TMS, transcriptomics). The breadth of evidence is a strength.

That said:

- The review does not state whether a systematic or narrative approach was used to select sources. Adding a brief note on scope or methodology for literature inclusion would enhance rigor.
- Limitations of imaging and molecular methods are under-discussed. Readers would benefit from a balanced assessment of what these techniques can and cannot currently tell us.

- **Engagement with Literature** – Does the paper demonstrate an understanding of relevant research in the field? Do they acknowledge known results and connect their findings well to them?

The manuscript demonstrates familiarity with a wide range of literature, integrating animal and human studies effectively. Ethical and equity considerations are commendably included.
Weaknesses:

- Contradictory findings on cortical remapping (e.g., whether it is maladaptive or compensatory) are not thoroughly addressed.
- Certain claims (e.g., on synthetic biology applications in prosthetics) would be stronger if supported by more cautious framing or additional citations.

- **Grammar & Language** – Is the writing clear and professional? Minor grammatical and stylistic errors should be noted, but they should not be the main focus of the review.

Overall, the writing is professional and suitable for academic publication. Technical terms are well explained.
Minor issues:

- Occasional grammatical slips (e.g., “Plasticity follows the injury is a temporal sequence…”) should be corrected.

- Stylistic tightening is needed to avoid redundancy, especially in discussions of feedback-driven plasticity.

2. Providing Feedback

- Clarify prevalence statistics and ensure consistency in reported numbers.
- Condense repetitive sections, particularly the multiple references to BDNF pathways.
- Add a short description of the literature review method (e.g., narrative vs. systematic).
- Expand discussion of limitations in imaging/genetic methods and acknowledge contradictory findings in cortical remapping studies.
- Clearly delineate between evidence-supported claims and forward-looking, speculative proposals to avoid overstating translational readiness.

3. Ethical and Logistical Considerations

- I confirm that I have no conflicts of interest regarding this submission.
- I have maintained confidentiality throughout the review.
- The review has been completed within the expected timeframe.

Final Recommendation

- Accept with major revisions (acceptance conditional on satisfactory **major** revisions)

Summary & recommendation

This manuscript tackles an important goal: aligning prosthetic control and feedback with the nervous system's adaptive changes after limb loss to improve embodiment, function, and pain outcomes. The cross-disciplinary ambition is a real strength. However, the current argument does not establish a credible, evidence-based connection between gene-level remodeling and real-time prosthetic adaptation. Most monitoring and control levers available today are systems-level/neurophysiological (neural spikes, ECoG/EEG, fNIRS, EMG, kinematics, psychophysics), not molecular/genetic. Crucially, gene-expression changes occur on slow timescales and are not suitable as real-time control inputs, so genetics should be treated as background biology or as long-term, offline research directions.

Recommendation: Revise and Resubmit.

I recommend refocusing on activity-dependent plasticity measured with practical neurophysiological signals (spikes, ECoG/EEG, fNIRS, EMG, kinematics/psychophysics) and building the closed loop around those online readouts during rehabilitation and early home-use training.

Concretely, you could structure the review around one of these guiding questions:

- How can measurable neurophysiological signals be used during rehabilitation to adapt decoding and sensory feedback in closed-loop upper-limb neuroprosthetics to improve control, embodiment, and pain outcomes?
- Which specific adaptations (decoder parameters, control gain/DoFs, feedback modality/intensity/timing, training schedule) are best supported by which online signals, and under what training conditions?
- What evidence supports a practical framework linking post-amputation plasticity → online physiological markers → concrete adaptation rules, and what are the key gaps?

Core Issue: The missing connection between genetics and prosthetics

The manuscript claims that neurogenetic remodeling after amputation should guide adaptive prosthetic feedback, but it does not establish a mechanism or a measurement pathway to do so. In practice, gene expression cannot be monitored in vivo and in real time during rehabilitation, so a prosthesis cannot sensibly tune stimulation or decoding based on "current BDNF/CREB levels." By contrast, the signals you already discuss like EEG, fNIRS, EMG, and intraneural/cortical recordings are neurophysiological, not genetic, and they are the realistic inputs for closed-loop adaptation.

Feedback for specific evaluation criteria

A. Originality & Significance

Strengths

- Ambitious, cross-disciplinary scope (neuroscience + neuroengineering).
- Emphasis on closed-loop and adaptive prosthetics is timely.
- Clear concern for clinical problems (phantom limb pain, embodiment, abandonment risk).

Areas to improve

- Clarify the central contribution. Right now the main claim blends neurogenetics (molecular changes) with neurophysiology (signals we can measure during rehabilitation). Real-time neuroprosthetic control can use signals (EMG, nerve activity, EEG/fNIRS, intracortical activity, kinematics), not gene expression.
    - Revise the thesis to: “How post-amputation plasticity can be sensed via measurable signals during rehab and used to adapt feedback/control in closed-loop neuroprosthetics.”
    - Keep gene-level content as background biology (why plasticity is possible) and, if you wish, as clearly labeled long-term/offline ideas (e.g., future biomarkers to schedule intensive training weeks). Avoid implying real-time gene readouts.

B. Clarity & Structure

Strengths

- You survey many relevant techniques (surface/implanted EMG, nerve electrodes, intraneural arrays, EEG/fNIRS, various sensory feedback modalities, surgical approaches, osseointegration).

Areas to improve (actionable)

- State the gap crisply in the Introduction. Example structure to write in your own words:
    1. After amputation, the nervous system reorganizes (plasticity).
    2. Fixed, one-time calibrations drift and can harm embodiment and comfort.
    3. Proposal: use measurable signals during rehabilitation/training to adapt feedback/control continuously.
- Unify the paper around one clear chain in plain language throughout: *Post-amputation change → signals we can monitor during rehab → specific adaptation the device makes in training (and early home use).*
- Explain every technique you mention with one sentence on (i) what it measures/delivers and (ii) how it supports adaptation. Avoid singling out any one technique; present the range fairly.
- Figures: Reference each figure in the text and state its take-home message. Ensure captions follow APA basics (short title, define abbreviations, credit if adapted).

C. Use of Evidence & Research Methods

Strengths

- Good instinct to connect plasticity, feedback, and clinical outcomes.

Areas to improve

- Source every non-obvious claim. Add missing citations consistently and use APA style (Author, year).
- Replace strong language (“prove,” “most systems…”) with precise, supported statements (“studies suggest/indicate…”, “many systems currently…”).
- Where you mention “windows of plasticity”, specify approximate time frames and cite.
- If you state that any systems consider “molecular state” or “gene expression,” either show evidence or retract/clarify to focus on signals that are actually measured during therapy.

D. Engagement with Literature

Strengths

- You draw from multiple subfields (rehab neuro, prosthetics, neurophysiology).

Areas to improve

- Reduce repetition (e.g., repeated BDNF/CREB passages): Present molecular context once, tightly tied to the message that it explains *why* learning is possible, not how devices are tuned in real time.
- Define terms at first use (e.g., targeted reinnervation, intraneural arrays, spinal/DRG stimulation, sensory substitution), then connect each to a concrete adaptation decision.
- Balance breadth with depth: for every technique you list, include one sentence that connects it to the closed-loop adaptation you are proposing.

E. Grammar & Language

Strengths

- Generally clear topic sentences and obvious enthusiasm for the subject.

Areas to improve (actionable)

- Proofread carefully, especially later sections where typos and phrasing errors increase.
- Avoid “how does…” phrasing inside declarative sentences. Keep “In this review…” to one concise roadmap paragraph.

Specific & Actionable Suggestions

1) Make rehabilitation/training the center of the argument

Add a short subsection (2–4 paragraphs) titled “Training the Prosthesis to the User (Co-adaptation during Rehab)” that explains:

- What you measure during rehab/early home use: EMG, nerve activity, EEG/fNIRS, intracortical signals when present, movement/force, behavioral errors.
- What the device adjusts during these sessions: decoder settings, control gain/speed/DoFs, feedback modality/intensity/timing, brief recalibration, practice schedule.
- When to adjust (triggers): rising error/variability, EMG feature drift, low engagement/fatigue indicators.
- How you judge success: lower error, smoother control, stable features, better comfort/embodiment ratings.
  Make explicit that the prosthesis is trained to the user's signals, not only the other way around.

2) Reorganize the plasticity section around "what to measure" and "how to adapt"

For each biological change you describe, add ~ two short paragraphs in your own words:

- What changes + how to detect it in rehab: Describe the change (e.g., cortical remapping, shifts in interhemispheric balance, peripheral reorganization) and name the signals you can actually monitor during rehabilitation that reflect it (EEG/fNIRS patterns, EMG stability, nerve signals, behavior/kinematics).
- Training adjustments (what the device or therapist changes when that signal appears): Give one or two concrete, small adjustments the prosthesis/training protocol would make during rehab in response to those signals. These are simple, "when X happens, change Y" training adjustments that help the device learn the user's signals and keep practice effective. For example:
    - When engagement looks high (EEG/fNIRS indicates stronger motor activation): make feedback a bit more informative or extend the block slightly to take advantage of the good learning window.
    - When EMG looks unstable or errors rise: temporarily simplify the task (fewer classes or degrees of freedom, slower speed) and/or do a brief recalibration, then gradually restore difficulty once performance stabilizes.
    - When timing is off (actions or feedback occur too early/late): align feedback to movement events (e.g., movement onset or contact) and recheck performance after the change.

3) Clarify the role of genes (short and realistic)

- Keep a brief background paragraph: molecular pathways support plasticity.
- If you retain molecular content in "Future Directions," label it offline/long-term (e.g., exploratory biomarkers to schedule intensive training weeks). Do not imply real-time gene-based tuning.

4) Strengthen definitions and remove ambiguity

- For each technique already in your draft (surface/implanted EMG, nerve cuffs, intraneural arrays, EEG, fNIRS, intracortical/ECoG, spinal/DRG stimulation, sensory substitution, osseointegration, surgical reinnervation methods), add:
    - One sentence: what it measures/delivers.
    - One sentence: how it supports adaptation during rehab (e.g., when signal quality drops, what knob should change).
- Avoid implying that some unnamed systems already use "gene-sensitive" personalization unless you can cite them clearly.

5) Figures, captions, and APA style

- Call out each figure in the text and say what the reader should learn from it.
- Ensure APA-style captions (short descriptive title, define abbreviations, ensure proper citation).
- Consider one simple figure that lists Control Signals, Brain Sensing, and Feedback Options with a one-line explanation each (large, readable text).

Summary of suggested changes

- **Abstract & Introduction (reframe):** Replace genetics-driven claims with the rehab-signals thesis; outline the review around measurable signals and concrete adaptations in rehab and early home use.
- **Plasticity section (connect):** After each biological point, add 2–3 sentences on what to measure during rehab and how the device adapts.
- **Monitoring & Control section (clarify):** For each listed technique, state what it measures and how it drives adaptation.
- **Co-adaptation subsection (add):** Make explicit that the prosthesis learns the user using online signals and simple trigger rules.
- **Future/Offline (move):** Keep molecular ideas as offline scheduling or long-term research; avoid real-time genetics.
- **Conclusion (tighten):** Repeat the chain: plasticity → rehab-measurable signals → adaptive rules → better function/embodiment/pain.

Encouragement & Path to Acceptance

Your topic is important, your survey of techniques is broad, and your emphasis on closed-loop adaptation is exactly where the field is headed. The key is to center the review on rehabilitation and training, showing readers how measurable signals guide specific device adaptations that help learning and comfort, while moving gene-level content to background or clearly speculative, offline ideas. If you implement the structural and sourcing changes

above, I believe this manuscript can become a clear, rigorous, and publishable student review.

Neurogenetic Remodeling of the Sensorimotor Cortex Following Limb Loss: Implications for Adaptive Feedback in Closed-Loop Neuroprosthetics

[name redacted by Managing Editor]

Abstract

Limb loss leads to extensive changes in the organization of the primary motor (M1) and somatosensory (S1) cortices, disrupting the brain's internal sensorimotor map. Over the past decades, major advancements in the field of neuroprosthetics have made precise motor signal decoding possible. Yet challenges persist in long-term adaptation and functional recovery. This review explores how post-amputation cortical remodeling, driven by activity-dependent neurogenetic processes, can be monitored through neurophysiological signals to guide adaptive feedback in closed-loop neuroprosthetics. Integrating findings from molecular neuroscience, systems neurophysiology, and neuroengineering, this review outlines post-amputation brain changes and proposes a rehabilitation framework guided by neurophysiological signals—such as surface electromyography (sEMG), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS)—that could help enhance real-time decoding and feedback systems in closed-loop neuroprosthetics. Our thesis is that neurogenetic remodeling of the sensorimotor cortex can be sensed via measurable signals during rehabilitation to adapt feedback and control in neuroprosthetic devices. By understanding the neurogenetic basis of cortical reorganization following limb loss and leveraging those changes through adaptive monitoring, prosthetic technologies could dynamically co-adapt with users during rehabilitation, improving embodiment, control, pain management, and long-term device acceptance. This review advances a personalized, feedback-responsive paradigm in neuroengineering by linking gene expression dynamics to measurable indicators of cortical plasticity that guide prosthetic performance, thereby improving clinical outcomes.

Keywords

Limb Loss
Neurogenetic Remodeling
Cortical Plasticity
Neuroprosthetics
Rehabilitation
Adaptive Neurophysiological Feedback

Introduction

Recent estimates suggest that tens of millions of people live with limb loss worldwide, including approximately 57 million following trauma and over 30 million with lower-limb amputations (McDonald et al., 2020; Sugawara et al., 2021; Yuan et al., 2023), representing a major global health issue. This condition fundamentally disrupts the sensorimotor pathways of the brain by initiating a systemic recalibration that reshapes its internal architecture (Makin & Flor, 2020; Sparling et al., 2024). Thus, clinical outcomes may be improved by leveraging these neuroplastic changes to develop neuroprosthetics with adaptive monitoring and feedback systems.

Over the past decades, breakthroughs in the field of neuroprosthetics have enabled the transition from simple mechanical aids to advanced brain-machine interfaces (BMIs) capable of translating neural signals into precise movements. Despite this progress, many devices still fail to monitor and adapt to the individual's evolving neurophysiological states, leading to limited functional recovery, persistent phantom limb pain, and low adoption rates (Demofonti et al., 2025). The main cause of these issues is the dissonance between technological control and biological embodiment, with current devices primarily having fixed, one-time calibrations that respond to motor intent without returning meaningful sensory feedback, which restricts adaptability and user engagement (Capsi-Morales et al., 2023; Tyler, 2015). Consequently, many users characterize prosthetics as unnatural and cognitively demanding to operate, remaining external tools rather than becoming extensions of the body.

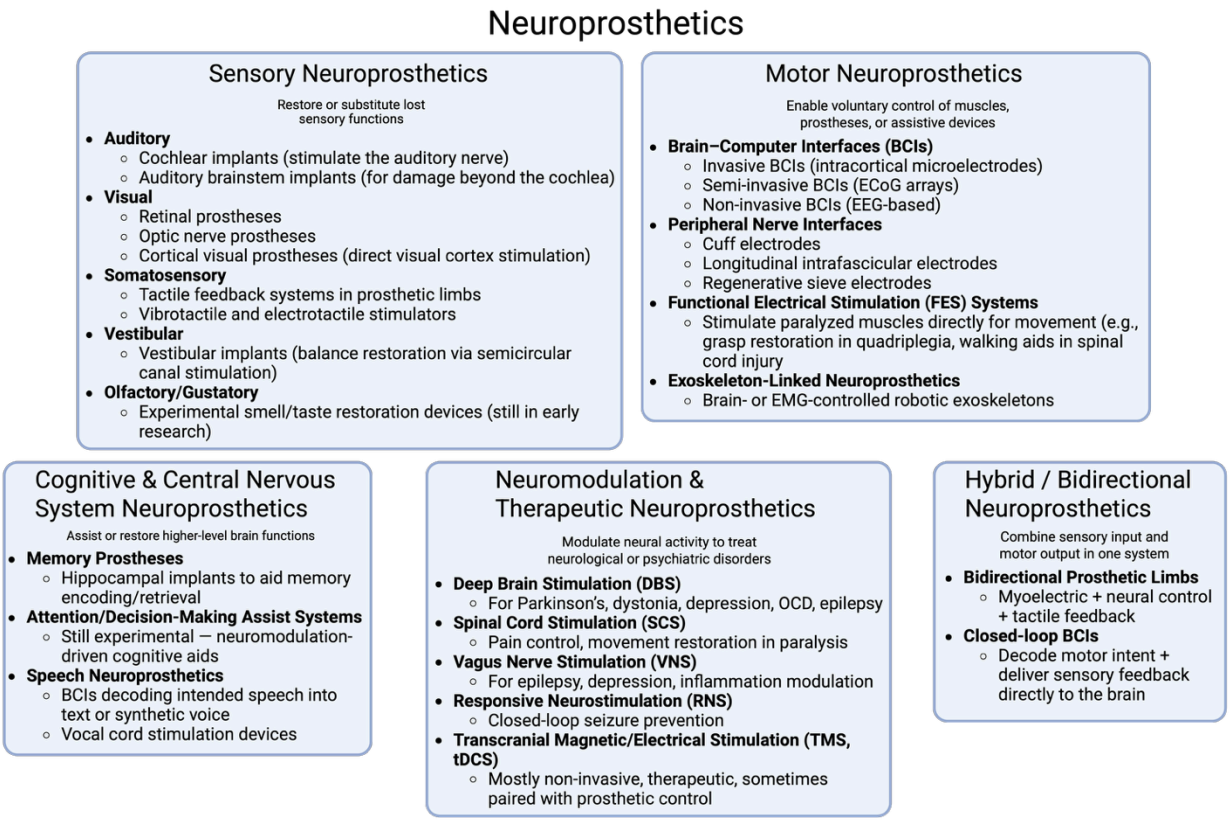

Figure 1 summarizes the main categories of neuroprosthetics (sensory, motor, cognitive/central nervous system, neuromodulation/therapeutic, and hybrid/bidirectional) and examples of representative devices with their corresponding interface locations. This review primarily focuses on systems enabling adaptive feedback and closed-loop motor control.

Although recent studies and reviews have revealed that limb loss leads to major neuroplastic changes, including extensive cortical remapping and functional adaptations (Makin & Flor, 2020; Simões et al., 2012; Sparling et al., 2024), the design of most prosthetic devices does not fully leverage these insights. Only a few systems leverage insights into brain plasticity responsible for long-term cortical reorganization. This disconnect between molecular neuroscience and neuroengineering solutions represents a critical scientific and clinical gap. Bridging it could enhance clinical outcomes, from alleviating phantom limb pain to establishing a stronger sense of embodiment in users.

This review uses a narrative, non-systematic approach that synthesizes findings across molecular neuroscience, systems neurophysiology, and neuroprosthetics to investigate how neurophysiological insights into neurogenetic remodeling of the sensorimotor cortex following limb loss can help in the development of adaptive closed-loop feedback systems in neuroprosthetics to ultimately enhance clinical outcomes, adaptability, and embodiment. Evidence suggests that amputation is followed by extensive cortical reorganization, including cortical map shifts and gene expression changes related to synaptic plasticity (Carulli et al., 2011; Kikkert et al., 2019; Simões et al., 2012; Sparling et al., 2024). Nevertheless, most systems fail to utilize insights from these processes, with the risk of maladaptive plasticity, phantom limb pain, and restricted embodiment. Aligning prosthetic feedback with the neuroplastic shifts could improve pain mitigation, embodiment, and sensorimotor integration (Dietrich et al., 2018; Srinivasan et al., 2020).

By advancing a personalized, feedback-responsive paradigm in neuroengineering, this review seeks to link neurogenetics and neuroprosthetics to achieve long-term integration and improved embodiment. We propose that the neurogenetic changes within the sensorimotor cortex can be monitored via measurable neurophysiological methods

to guide the development of prosthetic systems that adapt to the individual's cortical reorganization. Rather than merely decoding motor signals, future neuroprosthetics could actively monitor cortical reorganization processes to adjust their responses and establish a bidirectional and adaptive interface.

In this review, we examine how brain plasticity following amputation can inform the development of adaptive neuroprosthetics. We first outline the functional, structural, and molecular changes that reshape sensorimotor cortex organization after limb loss, and then describe how neurophysiological signals such as sEMG, EEG, and fNIRS can act as plasticity-sensitive biomarkers capable of tracking this remodeling during rehabilitation. We then discuss the limitations of current prosthetic systems, particularly the lack of sensory feedback, limited adaptability, and misalignment with ongoing cortical reorganization. Finally, we position neurogenetic mechanisms as the biological foundation for future adaptive strategies and present gene-informed, offline personalization as a potential translational direction. We conclude by identifying interdisciplinary priorities needed to achieve truly bidirectional, feedback-responsive neuroprosthetic systems.

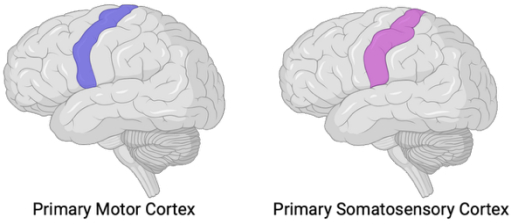

Figure 2 illustrates the locations of the primary motor (M1) and somatosensory (S1) cortices in the brain.

Sensorimotor Cortical Remodeling After Limb Loss

Functional & Structural Plasticity in M1 and S1

Cortical Map Changes

Limb loss is not just a physical trauma, as it leads to profound alterations of the brain's somatotopic organization. The classical Penfield homunculus, derived from intraoperative stimulation studies by Penfield and his colleagues, depicts the representation of the body in the primary motor (M1) and somatosensory (S1) cortices in an ordered and topographical diagram. However, cortical maps are far from static. After amputation, functional and structural plasticity in M1 and S1 results in cortical reorganization, including shifts in adjacent body-part representation areas, modified callosal connectivity, and interhemispheric rebalancing.

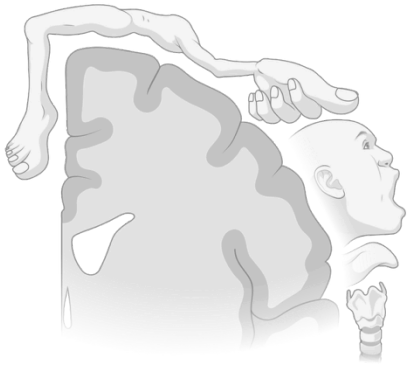

Figure 3 is a representation of the motor homunculus by Penfield et al., showing the areas of the brain and their representative parts of the body.

Numerous studies, summarized in a recent review by Sparling et al., have used high-resolution functional imaging techniques—such as functional magnetic resonance imaging, fMRI (measure of blood oxygenation level and

dependent hemodynamic mapping) and magnetoencephalography, MEG (millisecond-scale recordings of cortical magnetic fields)—and transcranial magnetic stimulation, TMS (noninvasive cortical stimulation used to probe excitability) and data collected suggest that cortical areas previously associated with the missing limb were reorganized to represent adjacent body parts. For instance, a study by Makin et al. found that face representation had shifted ~8 mm medially into the deprived homunculus of upper-limb amputees. This shift is also correlated with the degree of phantom limb pain (PLP), as individuals exhibiting greater cortical invasion report more severe pain sensations (Makin & Flor, 2020). Other fMRI studies, summarized by Gunduz et al., show that the expansion of lip representation into the amputated hand area is associated with higher PLP and that mirror therapy can reverse this shift, supporting the notion that maladaptive plasticity contributes to pain. In conclusion, these findings demonstrate that the brain's cortex can be significantly altered due to limb loss, resulting in variable clinical symptoms that require an individualized treatment approach.

Furthermore, evidence from a study by Wilkins et al. support that sensory experience plays a critical role in establishing cortical maps. Their survey of individuals with congenital and surgical limb loss revealed that phantom limb sensations (PLS) occurred in only 7.4% of the former compared with 69.7% of the latter, while PLP occurred in 3.7% versus 48.5%, respectively. It is plausible, then, that early sensorimotor experience is required to develop limb representation, while it may protect against phantom sensations.

In addition, insights from animal models expand our understanding of cortical reorganization. Research on rodents with forelimb amputation reveals that, within hours, the activity of deprived neurons is rapidly increased, due to amputation in the deprived S1 forepaw, with activity being at a maximum for weeks. Neuroimaging in rodents with lower-limb amputation also shows that tactile stimulation of the intact limb greatly activates the ipsilateral S1, indicating that the representation of the stump is functionally shifted into trunk and upper-limb areas (studies summarized by Sparling et al., 2024). These findings combined suggest that the deprived cortex becomes responsive to adjacent inputs, transforming the original map and potentially leading to more precise motor control.

To conclude, this evidence of reorganization and recalibration of the brain support the view that the somatosensory cortex is not rigidly mapped, but rather dynamically responsive, as various neurophysiological signals suggest.

Callosal Connectivity and Interhemispheric Imbalance

Interhemispheric coordination is mediated by the corpus callosum. As a result, unilateral amputation affects this coordinating balance. Evidence from resting-state fMRI and diffusion tensor imaging (DTI) reveals that the functional connectivity between bilateral sensorimotor regions is decreased, along with fractional anisotropy (FA)—FA is a quantitative biomarker of the integrity of white matter (Vandermosten et al., 2012)—of callosal axons in amputees (Simões et al., 2012). Structural studies further indicate that region II of corpus callosum, which links the premotor and supplementary motor areas, shows reduced FA in lower-limb amputees (Zhang et al., 2018), suggesting loss of callosal fibers or demyelination

As a result of these changes, interhemispheric imbalance arises. The stimulation of the intact limb elicits bilateral cortical activation in rodent models and human amputees, something that is enhanced when the intact cortex is transiently silenced, indicating decreased interhemispheric inhibition. This concept of callosal rewiring may disrupt bimanual coordination and hinder tasks, such as walking with a prosthetic, underscoring the importance of bilateral dynamics when designing neuroprosthetic control systems.

Molecular & Genetic Changes Post-Amputation

Activity-Dependent Gene Expression

When afferent and efferent input is lost, certain gene expression activities are triggered to promote synaptic remodeling. Activity-dependent transcription involves various mechanisms, such as immediate early genes, IEG (c-Fos, Arc/Arg3.1, Egr1), growth factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), and cytoskeletal regulators, including growth-associated protein-43 (GAP-43) and synapsin-1. In a review by Carulli et al., summarized experiments in rodent barrel cortex demonstrate that naturalistic whisker use stimulates the expression of BDNF, CREB, synapsin-1 and GAP-43, while the opposite effect is observed for sensory deprivation (Rocamora et al., 1996). Moreover, voluntary exercise elevates BDNF and synapsin-1 expression in a similar way in the dorsal root ganglia and promotes peripheral nerve regeneration.

Neural plasticity is underlined by a molecular cascade that begins with NMDA-receptor-mediated Ca^{2+} influx which activates transcription factors, such as CREB. CREB then recruits its co-activator CBP/p300 to gene

promoters, leading to the transcription of plasticity-related genes (Almeida et al., 2009; Del Blanco et al., 2019). These genes facilitate dendritic growth, synaptogenesis, and synaptic strengthening, assisting the reorganization of cortical circuits after injury.

These molecular processes unfold over hours to days and therefore serve as background mechanisms enabling neuroplastic change rather than direct, real-time prosthetic control signals.

Timing and Windows of Plasticity

Plasticity following the injury is a temporal sequence characterized by shifts in the excitatory and inhibitory tone (Sparling et al., 2024). After amputation, the deprived somatosensory cortex exhibits a transient increase in levels of AMPA receptor and synaptic excitation during the first days. These are followed by elevated GABAergic inhibition some weeks later, which create a critical window for excitation that supports rapid remodeling. Studies with rodents show that following forelimb amputation, the activity of deep cortical neurons increases within hours and persists for weeks. These findings, therefore, imply that rehabilitative interventions and prosthetic fitting may be especially effective when achieved during this heightened plasticity window. It is important to note that, in children with congenital limb abnormalities, when the fitting of prostheses is delayed, it may repress motor development and hinder cortical adaptation, pointing out the importance of monitoring and early intervention, during the appropriate plasticity window.

Measurable Signals of Neuroplasticity during Rehabilitation

Post-amputation neuroplastic remodeling is a multifaceted process involving changes in residual muscles and nerves, spinal and cortical motor circuits, and higher-order sensorimotor representations. Different layers of this remodeling can be captured with non-invasive physiological measurements, serving as practical biomarkers during rehabilitation and prosthetic training. In particular, surface electromyography (sEMG) can identify signs of activity in residual muscle and reinnervated motor units, EEG and fNIRS can give a glimpse into cortical reorganization, while combined information obtained from EMG–EEG/fNIRS systems have the potential to improve decoding and assessment during rehabilitation (Brambilla et al., 2021; Chen et al., 2023; Fang et al., 2020; X. Li et al., 2017; Lorenz et al., 2024).

Surface Electromyography

Post-amputation, there is a significant reorganization of the residual muscles due to the loss of afferent/efferent pathways and the emergence of compensatory activation strategies. Surface EMG (sEMG) can directly reflect this peripheral remodeling by indexing the recruitment patterns of residual and reinnervated motor units. High-density EMG can further resolve overlapping muscle sources on the stump and improve the identification of distinct activation channels (Fang et al., 2020). These signals capture both single-muscle features (RMS amplitude, variance, and median frequency) and higher-order structure such as co-contraction patterns, providing a direct readout of peripheral neuroplasticity relevant to motor learning and control stability (Fang et al., 2020; Resnik et al., 2018).

During rehabilitation, multi-channel sEMG can be monitored to track neuroplastic changes in real time. Examples of useful metrics can include Root Mean Square (RMS) amplitude and trial-to-trial variance during repeated movements (Dijk et al., 2016), classifier accuracy, confusion matrices, and confidence for pattern-recognition controllers (Resnik et al., 2018), and frequency-domain indicators of fatigue or co-contraction (Fang et al., 2020). These features have the potential to drive simple but powerful adaptive rules. For instance, if classification accuracy falls below a personalized threshold or variance rises, the system could trigger a short recalibration routine or temporarily reduce available movement classes to maintain reliable control (Fang et al., 2020; Resnik et al., 2018). Also, when EMG patterns stabilize across sessions, indicating consolidation of new motor strategies, task difficulty could be increased, with additional grips or faster movement requirements, to facilitate co-adaptation (Dijk et al., 2016). And lastly, if fatigue signatures appear, as indicated by decreasing amplitude or increased variance, the system could introduce rest, increase device assistance, or reduce movement speed to prevent maladaptive recruitment patterns (Fang et al., 2020).

Electroencephalogram

Cortical reorganization following amputation (with altered sensorimotor activation, redistributed motor maps, and changes in motor imagery circuits) can be detected using electroencephalography (EEG). EEG captures

event-related desynchronization (ERD) in μ (8–12 Hz) and β (13–30 Hz) bands, which reflect the engagement of sensorimotor networks during motor imagery and attempted movement (Buccino et al., 2016; Chen et al., 2023). Hybrid studies also show that EEG can contribute information about central motor preparation that EMG alone cannot capture, improving movement classification in upper-limb amputees (Kim et al., 2022; X. Li et al., 2017). Systematic reviews emphasize that EMG–EEG combinations provide a more complete neuromotor assessment during rehabilitation, enabling detection of cortical recruitment deficits, over-activation, or unstable motor imagery patterns that correspond to neuroplastic remodeling (Brambilla et al., 2021).

During rehabilitation, EEG provides actionable cortical biomarkers such as task-evoked μ/β desynchronization amplitude, consistency of motor-imagery classification confidence, and changes in functional connectivity associated with task learning (Buccino et al., 2016; Chen et al., 2023). Consequently, some rules could be followed to enhance prosthetic control. For example, when sensorimotor ERD is strong and stable, training can progress to harder tasks (reduced visual reliance, increased proprioceptive feedback, or multi-step movements) to exploit high cortical engagement (Buccino et al., 2016). Or when ERD is weak, diffuse, or inconsistent, the system should simplify tasks, slow pacing, or increase sensory cues to recruit the correct cortical areas (Brambilla et al., 2021). In hybrid EMG–EEG prosthesis controllers, EEG-derived confidence can detect when EMG decoding is unreliable. Such events should trigger recalibration or temporary assistance increases (Kim et al., 2022; X. Li et al., 2017; Wöhrle et al., 2017). This produces a stable closed-loop relationship between cortical intent and peripheral control.

Functional Near-Infrared Spectroscopy

Functional near-infrared spectroscopy (fNIRS) measures task-evoked changes in oxygenated (HbO) and deoxygenated (HbR) hemoglobin, providing spatially specific information about cortical activation during motor tasks. fNIRS is well-validated as a surrogate of BOLD activity, including the post-stimulus undershoot (Schroeter et al., 2006), and it reliably tracks cortical demand during rehabilitation (Chen et al., 2023; R. Li et al., 2022). Because cortical territories reorganize after amputation, fNIRS can indicate whether sensorimotor regions are being appropriately re-recruited during prosthesis training. Hybrid EEG-fNIRS systems further leverage the complementary speed of EEG and spatial specificity of fNIRS, improving classification performance and robustness in motor BCIs (Ali et al., 2023; Chen et al., 2023).

In rehabilitation, fNIRS provides actionable biomarkers including task-evoked HbO/HbR amplitude over contralateral M1/S1, spatial focality of activation, and longitudinal trends in cortical engagement (Chen et al., 2023; R. Li et al., 2022). If HbO responses become more focal and stronger over time, the system should increase task complexity or reduce visual guidance to support autonomous cortical control. On the other hand, if activation is weak or diffuse, tasks should be simplified, movement pace reduced, or sensory feedback strengthened to encourage proper sensorimotor recruitment (Chen et al., 2023) In hybrid EEG-fNIRS systems, fNIRS should guide slow-timescale adjustments (e.g., session-level difficulty changes), while EEG handles fast trial-to-trial corrections (Ali et al., 2023). This creates a reliable multi-timescale adaptation framework aligned with cortical reorganization.

Multimodal Fusion: Integrating Peripheral, Cortical, and Behavioral Signals

No single signal fully captures neuroplastic remodeling after amputation. Fusing EMG with EEG or fNIRS improves neuromotor assessment by integrating peripheral muscle activation with cortical intent and spatial patterns of cortical engagement (Brambilla et al., 2021; Lorenz et al., 2024). EMG-EEG fusion improves motion classification in amputees (Kim et al., 2022; X. Li et al., 2017), and hybrid systems implemented in hardware demonstrate real-time feasibility (Wöhrle et al., 2017). Deep learning models combining EMG, EEG, and fMRI outperform single-modality predictors for rehabilitation outcomes in stroke, supporting the translational relevance of multimodal systems (Shi et al., 2025). Kinematic and behavioral metrics (movement time, trajectory smoothness, endpoint error) could also provide functional ground truth for interpreting physiological changes (Dijk et al., 2016; Resnik et al., 2018).

Multimodal fusion supports clear adaptation policies. If cortical engagement (EEG/fNIRS) is high but EMG decoding or movement accuracy is poor, the system should recalibrate or simplify mappings, indicating misalignment between cortical intent and peripheral output (Kim et al., 2022; X. Li et al., 2017). If both EMG and cortical measures improve and kinematic performance increases, tasks should be made progressively more challenging or more naturalistic (Dijk et al., 2016; Lorenz et al., 2024). If physiological effort rises (e.g., high EMG variance, sustained EEG/fNIRS overactivation) without performance gains, task intensity should be reduced or rest added to prevent

maladaptive compensation (Brambilla et al., 2021; Fang et al., 2020). These rules create a coherent multi-signal, plasticity-guided training loop grounded in measurable physiology.

Challenges in Current Neuroprosthetic Integration

Gaps in Prosthetic Adaptability

Despite the availability of various neurophysiological monitoring methods, the majority of neuroprosthetic devices still detect and interpret motor intentions primarily via sEMG. Although these systems are able to detect motor intent, they often provide little to no sensory feedback and rarely adjust to the individual's evolving cortical state (Capsi-Morales et al., 2023; Tyler, 2015). As a result, users must rely heavily on visual cues to guide movement, something that increases the cognitive load required and prevents device's integration. Furthermore, even though these systems can be effective in controlled settings, their decoders cannot adapt to ongoing cortical remodeling, as the sensorimotor cortex may continue to reorganize long after amputation. Because of these ongoing changes, frequent calibration is required to maintain an accurate mapping between neural signals and intended movements. This mismatch between static decoding algorithms and continuous biological changes gradually degrades control performance and embodiment, ultimately increasing the risk of prosthetic abandonment.

Missed Opportunities for Remodeling

Despite the gap between molecular biology and neuroprosthetic development, several techniques have been developed over the past years that seek to engage the under-utilized neuroplastic circuits. One such technique is targeted muscle reinnervation (TMR), a surgical procedure that reestablishes bidirectional communication between residual peripheral nerves, muscles, and skin. As a result, control signals become more naturalistic and can restore sensory feedback. While TMR is often used to treat or prevent neuromas and phantom limb pain, it was originally developed to enhance myoelectric signals and prosthetic control in individuals with proximal upper-limb amputation (Peters et al., 2020; Sparling et al., 2024). However, only a small number of prosthetic systems utilize real-time sensory feedback to leverage TMR-mediated reinnervation. Another emerging procedure is the agonist-antagonist myoneural interface (AMI) surgery, which preserves pairs of agonist-antagonist muscles to maintain natural tension balance and provide proprioceptive feedback through mechanical coupling. Clinical studies have also reported decreased phantom pain but increased phantom limb sensations, consistent with reorganized activation patterns in area 3a and parietal cortex (Srinivasan et al., 2020). Similarly, osseointegrated (OI) prostheses, where a titanium implant directly anchors the prosthetic limb to the skeleton, enhance mechanical stability and proprioceptive feedback through a phenomenon known as osseoperception (Hoellwarth et al., 2020). These systems can reduce socket-related complications and potentially promote neuroplastic integration and functional restoration if they are combined with implanted neural interfaces.

Future Directions: Linking Neurogenetics with Adaptive Prosthetics

Feedback-Driven Remodeling: Evidence and Mechanisms

While the following mechanisms are supported by preclinical and early clinical evidence, their application to prosthetic design remains largely theoretical and represents a promising future direction.

Literature evidence suggests that cortical plasticity mechanisms could be reactivated via sensory feedback due to activity-dependent gene expression (Carulli et al., 2011). Various studies in the generic literature show evidence that plasticity-related gene expression can be upregulated and enhance motor control with the use of peripheral nerve interfaces and neurostimulation. It is notable that implanted electrodes delivering sensory feedback are shown to increase BDNF expression in animal models. Also, vagus nerve stimulation (VNS) accompanied by movement results in norepinephrine levels elevation and upregulation of BDNF and basic fibroblast growth factor (bFGF) expression in rodent brains (Hays et al., 2013), while transcranial direct current stimulation and synaptic activation enhance BDNF secretion. These findings suggest an important influence of peripheral feedback in central gene expression. Other studies focusing on rodent models show that use of naturalistic whisker stimulates the expression of BDNF, CREB, synapsin-1 and GAP-43 in the somatosensory cortex (Carulli et al., 2011). Moreover, enriched environments and voluntary exercise are also shown to contribute to BDNF upregulation and promotion of synaptogenesis.

Translating these findings into neuroprosthetic design is still hypothetical, but it is important to note that bidirectional systems that deliver tactile and proprioceptive feedback have the potential to simulate natural sensation patterns and trigger gene expression plasticity. This is supported by clinical observations with TMR prosthetic users exhibiting improved cortical representation of the missing limb and PLP reduction, while evidence suggest that AMI surgery helps with proprioceptive sensations and proprioceptive cortex activation (Sparling et al., 2024). All these findings, therefore, indicate that engagement of molecular pathways promotes cortical reorganization and functional recovery and highlight the need for feedback-driven prosthetic systems.

Personalized, Gene-Informed Design Strategies

The concepts below represent potential future pathways and are not yet implemented in current clinical neuroprosthetic systems.

Gene expression and epigenetic alterations vary among individuals, suggesting different sensory feedback parameters among prostheses users. To harness the neurogenetic remodeling following limb loss, prosthetic systems need to sense and adapt to the user's molecular and cortical state. As a result, more advanced methods need to be implemented. Using transcriptomic monitoring, gene expression profiles could be analyzed from peripheral fluids (blood or cerebrospinal fluid) to monitor plasticity readiness. Another way to achieve this is with the use of machine learning models integrating electrophysiological signals (EEG, high-density EEG) and functional near-infrared spectroscopy (fNIRS) that would also determine cortical excitation. Unlike fMRI, fNIRS is portable, offers good temporal resolution, and is resistant to motion artifacts, making it a great option for more dynamic monitoring of brain network recovery during rehabilitation (Sun et al., 2024). Moreover, EEG could complement fNIRS for long-term monitoring by detecting neuronal dynamics in millisecond-scale. These methods combined could help with real-time cortical state tracking in order to guide adaptive feedback intensity and frequency (Sun et al., 2024).

With the incorporation of gene-informed systems into prosthetics, feedback parameters would be adjusted based on the individual's gene expression profile, an essential step to achieve improved clinical outcomes. For instance, users with high expression of BDNF may need different sensory feedback intensity and frequency than people with lower BDNF expression levels, so adaptive algorithms could modulate stimulation to match the excitatory plasticity window (Sparling et al., 2024), while detection of elevated negative plasticity modulators, such as miR-134 or miR-124, would be possible via microRNA profiling, aiding targeted pharmacologic or gene-edited interventions alongside prosthetic training and integration. Despite its complexity, the use of this closed-loop, biomarker-driven approach could be the turning point where neuroprosthetics would not be just passive decoders of movement intent, but active cortical reorganization and neurogenetic remodeling modulators.

Gene Modulation via Neurostimulation

Cortical plasticity and gene expression could potentially be modulated by non-invasive brain stimulation techniques, such as tDCS and transcranial alternating current stimulation (tACS). Studies conducted in mice show that even short lasting anodal tDCS can produce lasting increases in hippocampal long-term potentiation, learning and memory. These are by BDNF promoter acetylation, increased BDNF exons transcription, enhanced BDNF protein levels, and increased CREB phosphorylation (Fritsch et al., 2010; Podda et al., 2016). Thus, combination of these techniques with training of prosthetics could theoretically assist cortical remapping and prosthetic adaptation.

Synthetic Biology & Gene Editing

Advancements in synthetic biology could also provide future pathways for precise neural circuit manipulation. A great example this nature is the use of viral vectors to deliver CRISPR-Cas9 or transcriptional activators to locally enhance growth factor expression or plasticity-inhibiting genes silencing. Engineered cells could also serve as biosensors within peripheral nerves or even actuators by releasing neurotropic factors in response to activity, thereby creating a feedback loop that is self-regulated. Although these techniques are highly advanced and at an early preclinical state, the potential to integrate them with neuroprosthetics could change rehabilitation by modulating molecular pathways directly and transform the field of prosthetic devices.

Clinical and Ethical Considerations

Implementation Challenges

The development of gene-informed neuroprosthetics is accompanied by various technical and regulatory challenges, requiring careful safety considerations and regulatory protocols. Safe interaction of these devices with peripheral nerves or cortical tissue, without any concerns for long-term damage or harm to the user, needs to be the number one priority for the development of these advanced systems. Furthermore, data privacy concerns should be addressed since these devices would handle sensitive data collected for the users' daily interactions, their genomic profile and cortical recordings. Additionally, regulatory agencies need to ensure that such systems would not cause maladaptive plasticity or unintended gene expression.

Equity and Access

A major concern that needs to be addressed regarding personalized neuroprosthetics is the exacerbation of existing healthcare inequalities, if access to them is only limited to well-resourced settings. That could be the result of high costs and specialized infrastructure, which is limited to wealthy regions. This problem could be addressed with inclusive clinical trials and open-source designs, promoting equitable distribution. Ethical frameworks also need to address data ownership matters, with users having the ability to retain control of their neurogenetic data and authority for decision making, and the level of AI autonomy in closed-loop systems.

Conclusion

Limb amputation causes extensive remodeling of the somatosensory cortex, which includes structural, functional and molecular alterations (Sparling et al., 2024). Despite these insights, most current neuroprosthetic systems do not incorporate the biological dynamics that shape long-term adaptation, leading to static decoding strategies that fail to align with a continuously reorganizing cortex. This review highlights the need for neuroprosthetics that not only read motor intent but also monitor and respond to the user's evolving neurophysiological state.

Integrating plasticity-sensitive biomarkers (such as sEMG features, EEG-derived oscillatory dynamics, and fNIRS hemodynamic responses) could enable prostheses to adapt in real time to changes in peripheral and cortical organization. In parallel, emerging gene-informed approaches, including transcriptomic profiling, biosensor-guided monitoring, and AI-driven adjustment of feedback parameters, offer a potential pathway for aligning prosthetic behavior with the underlying neurogenetic state that shapes plasticity readiness. These strategies, although still largely theoretical, may ultimately support systems that co-evolve with the user, enhancing embodiment, stability, and functional recovery.

Realizing this vision will require interdisciplinary collaboration across molecular neuroscience, systems neurophysiology, neuroengineering, machine learning, and ethics. Aligning technological innovation with the brain's intrinsic capacity for neuroplastic remodeling could shift the field toward neuroprosthetics that behave less like external tools and more like integrated extensions of the self, improving long-term usability, comfort, and clinical outcomes.

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Neurogenetic Remodeling of the Sensorimotor Cortex Following Limb Loss: Implications for Adaptive Feedback in Closed-Loop Neuroprosthetics

[redacted]

Abstract

Limb loss leads to extensive changes in the organization of the primary motor (M1) and somatosensory (S1) cortices, disrupting the brain's internal sensorimotor map. Over the past decades, major advancements in the field of neuroprosthetics have made precise motor signal decoding possible. Yet challenges persist in long-term adaptation and functional recovery. This review explores how post-amputation cortical remodeling, driven by activity-dependent neurogenetic processes, can be monitored through neurophysiological signals to guide adaptive feedback in closed-loop neuroprosthetics. Integrating findings from molecular neuroscience, systems neurophysiology, and neuroengineering, this review outlines post-amputation brain changes and proposes a rehabilitation framework guided by neurophysiological signals—such as surface electromyography (sEMG), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS)—that could help enhance real-time decoding and feedback systems in closed-loop neuroprosthetics. Our thesis is that neurogenetic remodeling of the sensorimotor cortex can be sensed via measurable signals during rehabilitation to adapt feedback and control in neuroprosthetic devices. By understanding the neurogenetic basis of cortical reorganization following limb loss and leveraging those changes through adaptive monitoring, prosthetic technologies could dynamically co-adapt with users during rehabilitation, improving embodiment, control, pain management, and long-term device acceptance. This review advances a personalized, feedback-responsive paradigm in neuroengineering by linking gene expression dynamics to measurable indicators of cortical plasticity that guide prosthetic performance, thereby improving clinical outcomes.

Keywords

Limb Loss
Neurogenetic Remodeling
Cortical Plasticity
Neuroprosthetics
Rehabilitation
Adaptive Neurophysiological Feedback

Introduction

Recent estimates suggest that tens of millions of people live with limb loss worldwide, including approximately 57 million following trauma and over 30 million with lower-limb amputations (McDonald et al., 2020; Sugawara et al., 2021; Yuan et al., 2023), representing a major global health issue. This condition fundamentally disrupts the sensorimotor pathways of the brain by initiating a systemic recalibration that reshapes its internal architecture (Makin & Flor, 2020; Sparling et al., 2024). Thus, clinical outcomes may be improved by leveraging these neuroplastic changes to develop neuroprosthetics with adaptive monitoring and feedback systems.

Over the past decades, breakthroughs in the field of neuroprosthetics have enabled the transition from simple mechanical aids to advanced brain-machine interfaces (BMIs) capable of translating neural signals into precise movements. Despite this progress, many devices still fail to monitor and adapt to the individual's evolving neurophysiological states, leading to limited functional recovery, persistent phantom limb pain, and low adoption rates (Demofonti et al., 2025). The main cause of these issues is the dissonance between technological control and biological embodiment, with current devices primarily having fixed, one-time calibrations that respond to motor intent without returning meaningful sensory feedback, which restricts adaptability and user engagement (Capsi-Morales et al., 2023; Tyler, 2015). Consequently, many users characterize prosthetics as unnatural and cognitively demanding to operate, remaining external tools rather than becoming extensions of the body.

Commented [CF1]: Enhanced paper purpose (initially: "This review explores how do neurogenetic changes in the sensorimotor cortex following limb loss influence the development of adaptive feedback systems in neuroprosthetics." That way more emphasis is given on measurable neurophysiological data we can collect and then using them improve feedback systems (not genetic mechanisms - not a possible option for feedback needed immediately)

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(There is no single agreed global prevalence figure for people living with limb loss -estimates in literature span at least an order of magnitude because different studies use different definitions (traumatic vs non-traumatic, major vs minor, upper vs lower, incident vs prevalent), different data sources and modelling approaches, and different reference years)

Commented [CF7]: Slightly rephrased to emphasize the use of neurological insights in prosthetic control systems' design

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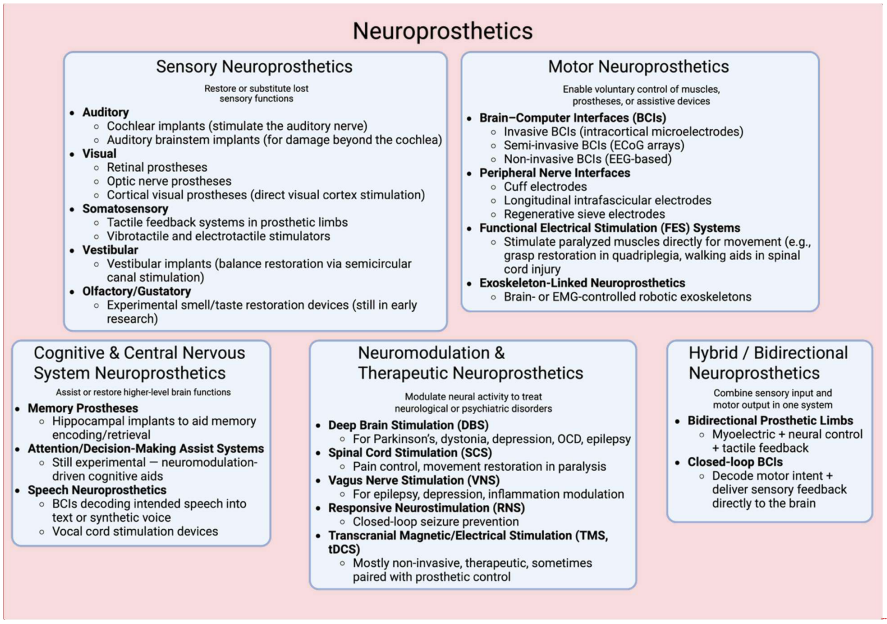

Figure 1 summarizes the main categories of neuroprosthetics (sensory, motor, cognitive/central nervous system, neuromodulation/therapeutic, and hybrid/bidirectional) and examples of representative devices with their corresponding interface locations. This review primarily focuses on systems enabling adaptive feedback and closed-loop motor control.

Although recent studies and reviews have revealed that limb loss leads to major neuroplastic changes, including extensive cortical remapping and functional adaptations (Makin & Flor, 2020; Simões et al., 2012; Sparling et al., 2024), the design of most prosthetic devices does not fully leverage these insights. Only a few systems leverage insights into brain plasticity responsible for long-term cortical reorganization. This disconnect between molecular neuroscience and neuroengineering solutions represents a critical scientific and clinical gap. Bridging it could enhance clinical outcomes, from alleviating phantom limb pain to establishing a stronger sense of embodiment in users.

This review uses a narrative, non-systematic approach that synthesizes findings across molecular neuroscience, systems neurophysiology, and neuroprosthetics to investigate how neurophysiological insights into neurogenetic remodeling of the sensorimotor cortex following limb loss can help in the development of adaptive closed-loop feedback systems in neuroprosthetics to ultimately enhance clinical outcomes, adaptability, and embodiment. Evidence suggests that amputation is followed by extensive cortical reorganization, including cortical map shifts and gene expression changes related to synaptic plasticity (Carulli et al., 2011; Kikkert et al., 2019; Simões et al., 2012; Sparling et al., 2024). Nevertheless, most systems fail to utilize insights from these processes, with the risk of maladaptive plasticity, phantom limb pain, and restricted embodiment. Aligning prosthetic feedback with the neuroplastic shifts could improve pain mitigation, embodiment, and sensorimotor integration (Dietrich et al., 2018; Srinivasan et al., 2020).

By advancing a personalized, feedback-responsive paradigm in neuroengineering, this review seeks to link neurogenetics and neuroprosthetics to achieve long-term integration and improved embodiment. We propose that the neurogenetic changes within the sensorimotor cortex can be monitored via measurable neurophysiological methods to guide the development of prosthetic systems that adapt to the individual's cortical reorganization. Rather than

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merely decoding motor signals, future neuroprosthetics could actively monitor cortical reorganization processes to adjust their responses and establish a bidirectional and adaptive interface.

In this review, we examine how brain plasticity following amputation can inform the development of adaptive neuroprosthetics. We first outline the functional, structural, and molecular changes that reshape sensorimotor cortex organization after limb loss, and then describe how neurophysiological signals such as sEMG, EEG, and fNIRS can act as plasticity-sensitive biomarkers capable of tracking this remodeling during rehabilitation. We then discuss the limitations of current prosthetic systems, particularly the lack of sensory feedback, limited adaptability, and misalignment with ongoing cortical reorganization. Finally, we position neurogenetic mechanisms as the biological foundation for future adaptive strategies and present gene-informed, offline personalization as a potential translational direction. We conclude by identifying interdisciplinary priorities needed to achieve truly bidirectional, feedback-responsive neuroprosthetic systems.

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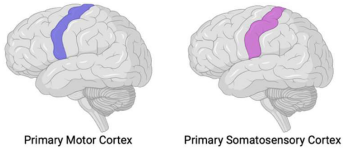

Figure 2 illustrates the locations of the primary motor (M1) and somatosensory (S1) cortices in the brain.

Sensorimotor Cortical Remodeling After Limb Loss

Functional & Structural Plasticity in M1 and S1

Cortical Map Changes

Limb loss is not just a physical trauma, as it leads to profound alterations of the brain's somatotopic organization. The classical Penfield homunculus, derived from intraoperative stimulation studies by Penfield and his colleagues, depicts the representation of the body in the primary motor (M1) and somatosensory (S1) cortices in an ordered and topographical diagram. However, cortical maps are far from static. After amputation, functional and structural plasticity in M1 and S1 results in cortical reorganization, including shifts in adjacent body-part representation areas, modified callosal connectivity, and interhemispheric rebalancing.

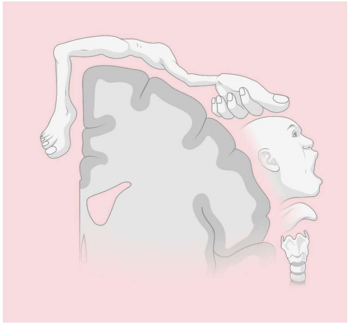

Figure 3 is a representation of the motor homunculus by Penfield et al., showing the areas of the brain and their representative parts of the body.

Numerous studies, summarized in a recent review by Sparling et al., have used high-resolution functional imaging techniques—such as functional magnetic resonance imaging, fMRI (measure of blood oxygenation level and dependent hemodynamic mapping) and magnetoencephalography, MEG (millisecond-scale recordings of cortical magnetic fields)—and transcranial magnetic stimulation, TMS (noninvasive cortical stimulation used to probe

excitability) and data collected suggest that cortical areas previously associated with the missing limb were reorganized to represent adjacent body parts. For instance, a study by Makin et al. found that face representation had shifted ~8 mm medially into the deprived homunculus of upper-limb amputees. This shift is also correlated with the degree of phantom limb pain (PLP), as individuals exhibiting greater cortical invasion report more severe pain sensations (Makin & Flor, 2020). Other fMRI studies, summarized by Gunduz et al., show that the expansion of lip representation into the amputated hand area is associated with higher PLP and that mirror therapy can reverse this shift, supporting the notion that maladaptive plasticity contributes to pain. In conclusion, these findings demonstrate that the brain's cortex can be significantly altered due to limb loss, resulting in variable clinical symptoms that require an individualized treatment approach.

Furthermore, evidence from a study by Wilkins et al. support that sensory experience plays a critical role in establishing cortical maps. Their survey of individuals with congenital and surgical limb loss revealed that phantom limb sensations (PLS) occurred in only 7.4% of the former compared with 69.7% of the latter, while PLP occurred in 3.7% versus 48.5%, respectively. It is plausible, then, that early sensorimotor experience is required to develop limb representation, while it may protect against phantom sensations.

In addition, insights from animal models expand our understanding of cortical reorganization. Research on rodents with forelimb amputation reveals that, within hours, the activity of deprived neurons is rapidly increased, due to amputation in the deprived S1 forepaw, with activity being at a maximum for weeks. Neuroimaging in rodents with lower-limb amputation also shows that tactile stimulation of the intact limb greatly activates the ipsilateral S1, indicating that the representation of the stump is functionally shifted into trunk and upper-limb areas (studies summarized by Sparling et al., 2024). These findings combined suggest that the deprived cortex becomes responsive to adjacent inputs, transforming the original map and potentially leading to more precise motor control.

To conclude, this evidence of reorganization and recalibration of the brain support the view that the somatosensory cortex is not rigidly mapped, but rather dynamically responsive, as various neurophysiological signals suggest.

Callosal Connectivity and Interhemispheric Imbalance

Interhemispheric coordination is mediated by the corpus callosum. As a result, unilateral amputation affects this coordinating balance. Evidence from resting-state fMRI and diffusion tensor imaging (DTI) reveals that the functional connectivity between bilateral sensorimotor regions is decreased, along with fractional anisotropy (FA)—FA is a quantitative biomarker of the integrity of white matter (Vandermosten et al., 2012)—of callosal axons in amputees (Simões et al., 2012). Structural studies further indicate that region II of corpus callosum, which links the premotor and supplementary motor areas, shows reduced FA in lower-limb amputees (Zhang et al., 2018), suggesting loss of callosal fibers or demyelination

As a result of these changes, interhemispheric imbalance arises. The stimulation of the intact limb elicits bilateral cortical activation in rodent models and human amputees, something that is enhanced when the intact cortex is transiently silenced, indicating decreased interhemispheric inhibition. This concept of callosal rewiring may disrupt bimanual coordination and hinder tasks, such as walking with a prosthetic, underscoring the importance of bilateral dynamics when designing neuroprosthetic control systems.

Molecular & Genetic Changes Post-Amputation

Activity-Dependent Gene Expression

When afferent and efferent input is lost, certain gene expression activities are triggered to promote synaptic remodeling. Activity-dependent transcription involves various mechanisms, such as immediate early genes, IEG (c-Fos, Arc/Arg3.1, Egr1), growth factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), and cytoskeletal regulators, including growth-associated protein-43 (GAP-43) and synapsin-1. In a review by Carulli et al., summarized experiments in rodent barrel cortex demonstrate that naturalistic whisker use stimulates the expression of BDNF, CREB, synapsin-1 and GAP-43, while the opposite effect is observed for sensory deprivation (Rocamora et al., 1996). Moreover, voluntary exercise elevates BDNF and synapsin-1 expression in a similar way in the dorsal root ganglia and promotes peripheral nerve regeneration.

Neural plasticity is underlined by a molecular cascade that begins with NMDA-receptor-mediated Ca^{2+} influx which activates transcription factors, such as CREB. CREB then recruits its co-activator CBP/p300 to gene promoters, leading to the transcription of plasticity-related genes (Almeida et al., 2009; Del Blanco et al., 2019).

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These genes facilitate dendritic growth, synaptogenesis, and synaptic strengthening, assisting the reorganization of cortical circuits after injury.

These molecular processes unfold over hours to days and therefore serve as background mechanisms enabling neuroplastic change rather than direct, real-time prosthetic control signals.

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Timing and Windows of Plasticity

Plasticity following the injury is a temporal sequence characterized by shifts in the excitatory and inhibitory tone (Sparling et al., 2024). After amputation, the deprived somatosensory cortex exhibits a transient increase in levels of AMPA receptor and synaptic excitation during the first days. These are followed by elevated GABAergic inhibition some weeks later, which create a critical window for excitation that supports rapid remodeling. Studies with rodents show that following forelimb amputation, the activity of deep cortical neurons increases within hours and persists for weeks. These findings, therefore, imply that rehabilitative interventions and prosthetic fitting may be especially effective when achieved during this heightened plasticity window. It is important to note that, in children with congenital limb abnormalities, when the fitting of prostheses is delayed, it may repress motor development and hinder cortical adaptation, pointing out the importance of monitoring and early intervention, during the appropriate plasticity window.

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Measurable Signals of Neuroplasticity during Rehabilitation

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Post-amputation neuroplastic remodeling is a multifaceted process involving changes in residual muscles and nerves, spinal and cortical motor circuits, and higher-order sensorimotor representations. Different layers of this remodeling can be captured with non-invasive physiological measurements, serving as practical biomarkers during rehabilitation and prosthetic training. In particular, surface electromyography (sEMG) can identify signs of activity in residual muscle and reinnervated motor units, EEG and fNIRS can give a glimpse into cortical reorganization, while combined information obtained from EMG–EEG/fNIRS systems have the potential to improve decoding and assessment during rehabilitation (Brambilla et al., 2021; Chen et al., 2023; Fang et al., 2020; X. Li et al., 2017; Lorenz et al., 2024).

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Surface Electromyography

Post-amputation, there is a significant reorganization of the residual muscles due to the loss of afferent/efferent pathways and the emergence of compensatory activation strategies. Surface EMG (sEMG) can directly reflect this peripheral remodeling by indexing the recruitment patterns of residual and reinnervated motor units. High-density EMG can further resolve overlapping muscle sources on the stump and improve the identification of distinct activation channels (Fang et al., 2020). These signals capture both single-muscle features (RMS amplitude, variance, and median frequency) and higher-order structure such as co-contraction patterns, providing a direct readout of peripheral neuroplasticity relevant to motor learning and control stability (Fang et al., 2020; Resnik et al., 2018).

During rehabilitation, multi-channel sEMG can be monitored to track neuroplastic changes in real time. Examples of useful metrics can include Root Mean Square (RMS) amplitude and trial-to-trial variance during repeated movements (Dijk et al., 2016), classifier accuracy, confusion matrices, and confidence for pattern-recognition controllers (Resnik et al., 2018), and frequency-domain indicators of fatigue or co-contraction (Fang et al., 2020). These features have the potential to drive simple but powerful adaptive rules. For instance, if classification accuracy falls below a personalized threshold or variance rises, the system could trigger a short recalibration routine or temporarily reduce available movement classes to maintain reliable control (Fang et al., 2020; Resnik et al., 2018). Also, when EMG patterns stabilize across sessions, indicating consolidation of new motor strategies, task difficulty could be increased, with additional grips or faster movement requirements, to facilitate co-adaptation (Dijk et al., 2016). And lastly, if fatigue signatures appear, as indicated by decreasing amplitude or increased variance, the system could introduce rest, increase device assistance, or reduce movement speed to prevent maladaptive recruitment patterns (Fang et al., 2020).

Electroencephalogram

Cortical reorganization following amputation (with altered sensorimotor activation, redistributed motor maps, and changes in motor imagery circuits) can be detected using electroencephalography (EEG). EEG captures event-related desynchronization (ERD) in μ (8–12 Hz) and β (13–30 Hz) bands, which reflect the engagement of

sensorimotor networks during motor imagery and attempted movement (Buccino et al., 2016; Chen et al., 2023). Hybrid studies also show that EEG can contribute information about central motor preparation that EMG alone cannot capture, improving movement classification in upper-limb amputees (Kim et al., 2022; X. Li et al., 2017). Systematic reviews emphasize that EMG–EEG combinations provide a more complete neuromotor assessment during rehabilitation, enabling detection of cortical recruitment deficits, over-activation, or unstable motor imagery patterns that correspond to neuroplastic remodeling (Brambilla et al., 2021).

During rehabilitation, EEG provides actionable cortical biomarkers such as task-evoked μ/β desynchronization amplitude, consistency of motor-imagery classification confidence, and changes in functional connectivity associated with task learning (Buccino et al., 2016; Chen et al., 2023). Consequently, some rules could be followed to enhance prosthetic control. For example, when sensorimotor ERD is strong and stable, training can progress to harder tasks (reduced visual reliance, increased proprioceptive feedback, or multi-step movements) to exploit high cortical engagement (Buccino et al., 2016). Or when ERD is weak, diffuse, or inconsistent, the system should simplify tasks, slow pacing, or increase sensory cues to recruit the correct cortical areas (Brambilla et al., 2021). In hybrid EMG–EEG prosthesis controllers, EEG-derived confidence can detect when EMG decoding is unreliable. Such events should trigger recalibration or temporary assistance increases (Kim et al., 2022; X. Li et al., 2017; Wöhrle et al., 2017). This produces a stable closed-loop relationship between cortical intent and peripheral control.

Functional Near-Infrared Spectroscopy

Functional near-infrared spectroscopy (fNIRS) measures task-evoked changes in oxygenated (HbO) and deoxygenated (HbR) hemoglobin, providing spatially specific information about cortical activation during motor tasks. fNIRS is well-validated as a surrogate of BOLD activity, including the post-stimulus undershoot (Schroeter et al., 2006), and it reliably tracks cortical demand during rehabilitation (Chen et al., 2023; R. Li et al., 2022). Because cortical territories reorganize after amputation, fNIRS can indicate whether sensorimotor regions are being appropriately re-recruited during prosthesis training. Hybrid EEG-fNIRS systems further leverage the complementary speed of EEG and spatial specificity of fNIRS, improving classification performance and robustness in motor BCIs (Ali et al., 2023; Chen et al., 2023).

In rehabilitation, fNIRS provides actionable biomarkers including task-evoked HbO/HbR amplitude over contralateral M1/S1, spatial focality of activation, and longitudinal trends in cortical engagement (Chen et al., 2023; R. Li et al., 2022). If HbO responses become more focal and stronger over time, the system should increase task complexity or reduce visual guidance to support autonomous cortical control. On the other hand, if activation is weak or diffuse, tasks should be simplified, movement pace reduced, or sensory feedback strengthened to encourage proper sensorimotor recruitment (Chen et al., 2023) In hybrid EEG-fNIRS systems, fNIRS should guide slow-timescale adjustments (e.g., session-level difficulty changes), while EEG handles fast trial-to-trial corrections (Ali et al., 2023). This creates a reliable multi-timescale adaptation framework aligned with cortical reorganization.

Multimodal Fusion: Integrating Peripheral, Cortical, and Behavioral Signals

No single signal fully captures neuroplastic remodeling after amputation. Fusing EMG with EEG or fNIRS improves neuromotor assessment by integrating peripheral muscle activation with cortical intent and spatial patterns of cortical engagement (Brambilla et al., 2021; Lorenz et al., 2024). EMG-EEG fusion improves motion classification in amputees (Kim et al., 2022; X. Li et al., 2017), and hybrid systems implemented in hardware demonstrate real-time feasibility (Wöhrle et al., 2017). Deep learning models combining EMG, EEG, and fMRI outperform single-modality predictors for rehabilitation outcomes in stroke, supporting the translational relevance of multimodal systems (Shi et al., 2025). Kinematic and behavioral metrics (movement time, trajectory smoothness, endpoint error) could also provide functional ground truth for interpreting physiological changes (Dijk et al., 2016; Resnik et al., 2018).

Multimodal fusion supports clear adaptation policies. If cortical engagement (EEG/fNIRS) is high but EMG decoding or movement accuracy is poor, the system should recalibrate or simplify mappings, indicating misalignment between cortical intent and peripheral output (Kim et al., 2022; X. Li et al., 2017). If both EMG and cortical measures improve and kinematic performance increases, tasks should be made progressively more challenging or more naturalistic (Dijk et al., 2016; Lorenz et al., 2024). If physiological effort rises (e.g., high EMG variance, sustained EEG/fNIRS overactivation) without performance gains, task intensity should be reduced or rest added to prevent maladaptive compensation (Brambilla et al., 2021; Fang et al., 2020). These rules create a coherent multi-signal, plasticity-guided training loop grounded in measurable physiology.

Challenges in Current Neuroprosthetic Integration

Gaps in Prosthetic Adaptability

Despite the availability of various neurophysiological monitoring methods, the majority of neuroprosthetic devices still detect and interpret motor intentions primarily via sEMG. Although these systems are able to detect motor intent, they often provide little to no sensory feedback and rarely adjust to the individual's evolving cortical state (Capsi-Morales et al., 2023; Tyler, 2015). As a result, users must rely heavily on visual cues to guide movement, something that increases the cognitive load required and prevents device's integration. Furthermore, even though these systems can be effective in controlled settings, their decoders cannot adapt to ongoing cortical remodeling, as the sensorimotor cortex may continue to reorganize long after amputation. Because of these ongoing changes, frequent calibration is required to maintain an accurate mapping between neural signals and intended movements. This mismatch between static decoding algorithms and continuous biological changes gradually degrades control performance and embodiment, ultimately increasing the risk of prosthetic abandonment.

Missed Opportunities for Remodeling

Despite the gap between molecular biology and neuroprosthetic development, several techniques have been developed over the past years that seek to engage the under-utilized neuroplastic circuits. One such technique is targeted muscle reinnervation (TMR), a surgical procedure that reestablishes bidirectional communication between residual peripheral nerves, muscles, and skin. As a result, control signals become more naturalistic and can restore sensory feedback. While TMR is often used to treat or prevent neuromas and phantom limb pain, it was originally developed to enhance myoelectric signals and prosthetic control in individuals with proximal upper-limb amputation (Peters et al., 2020; Sparling et al., 2024). However, only a small number of prosthetic systems utilize real-time sensory feedback to leverage TMR-mediated reinnervation. Another emerging procedure is the agonist-antagonist myoneural interface (AMI) surgery, which preserves pairs of agonist-antagonist muscles to maintain natural tension balance and provide proprioceptive feedback through mechanical coupling. Clinical studies have also reported decreased phantom pain but increased phantom limb sensations, consistent with reorganized activation patterns in area 3a and parietal cortex (Srinivasan et al., 2020). Similarly, osseointegrated (OI) prostheses, where a titanium implant directly anchors the prosthetic limb to the skeleton, enhance mechanical stability and proprioceptive feedback through a phenomenon known as osseoperception (Hoellwarth et al., 2020). These systems can reduce socket-related complications and potentially promote neuroplastic integration and functional restoration if they are combined with implanted neural interfaces.

Future Directions: Linking Neurogenetics with Adaptive Prosthetics

Feedback-Driven Remodeling: Evidence and Mechanisms

While the following mechanisms are supported by preclinical and early clinical evidence, their application to prosthetic design remains largely theoretical and represents a promising future direction.

Literature evidence suggests that cortical plasticity mechanisms could be reactivated via sensory feedback due to activity-dependent gene expression (Carulli et al., 2011). Various studies in the generic literature show evidence that plasticity-related gene expression can be upregulated and enhance motor control with the use of peripheral nerve interfaces and neurostimulation. It is notable that implanted electrodes delivering sensory feedback are shown to increase BDNF expression in animal models. Also, vagus nerve stimulation (VNS) accompanied by movement results in norepinephrine levels elevation and upregulation of BDNF and basic fibroblast growth factor (bFGF) expression in rodent brains (Hays et al., 2013), while transcranial direct current stimulation and synaptic activation enhance BDNF secretion. These findings suggest an important influence of peripheral feedback in central gene expression. Other studies focusing on rodent models show that use of naturalistic whisker stimulates the expression of BDNF, CREB, synapsin-1 and GAP-43 in the somatosensory cortex (Carulli et al., 2011). Moreover, enriched environments and voluntary exercise are also shown to contribute to BDNF upregulation and promotion of synaptogenesis.

Translating these findings into neuroprosthetic design is still hypothetical, but it is important to note that bidirectional systems that deliver tactile and proprioceptive feedback have the potential to simulate natural sensation patterns and trigger gene expression plasticity. This is supported by clinical observations with TMR prosthetic users

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exhibiting improved cortical representation of the missing limb and PLP reduction, while evidence suggest that AMI surgery helps with proprioceptive sensations and proprioceptive cortex activation (Sparling et al., 2024). All these findings, therefore, indicate that engagement of molecular pathways promotes cortical reorganization and functional recovery and highlight the need for feedback-driven prosthetic systems.

Personalized, Gene-Informed Design Strategies

The concepts below represent potential future pathways and are not yet implemented in current clinical neuroprosthetic systems.

Gene expression and epigenetic alterations vary among individuals, suggesting different sensory feedback parameters among prostheses users. To harness the neurogenetic remodeling following limb loss, prosthetic systems need to sense and adapt to the user's molecular and cortical state. As a result, more advanced methods need to be implemented. Using transcriptomic monitoring, gene expression profiles could be analyzed from peripheral fluids (blood or cerebrospinal fluid) to monitor plasticity readiness. Another way to achieve this is with the use of machine learning models integrating electrophysiological signals (EEG, high-density EEG) and functional near-infrared spectroscopy (fNIRS) that would also determine cortical excitation. Unlike fMRI, fNIRS is portable, offers good temporal resolution, and is resistant to motion artifacts, making it a great option for more dynamic monitoring of brain network recovery during rehabilitation (Sun et al., 2024). Moreover, EEG could complement fNIRS for long-term monitoring by detecting neuronal dynamics in millisecond-scale. These methods combined could help with real-time cortical state tracking in order to guide adaptive feedback intensity and frequency (Sun et al., 2024).

With the incorporation of gene-informed systems into prosthetics, feedback parameters would be adjusted based on the individual's gene expression profile, an essential step to achieve improved clinical outcomes. For instance, users with high expression of BDNF may need different sensory feedback intensity and frequency than people with lower BDNF expression levels, so adaptive algorithms could modulate stimulation to match the excitatory plasticity window (Sparling et al., 2024), while detection of elevated negative plasticity modulators, such as miR-134 or miR-124, would be possible via microRNA profiling, aiding targeted pharmacologic or gene-edited interventions alongside prosthetic training and integration. Despite its complexity, the use of this closed-loop, biomarker-driven approach could be the turning point where neuroprosthetics would not be just passive decoders of movement intent, but active cortical reorganization and neurogenetic remodeling modulators.

Gene Modulation via Neurostimulation

Cortical plasticity and gene expression could potentially be modulated by non-invasive brain stimulation techniques, such as tDCS and transcranial alternating current stimulation (tACS). Studies conducted in mice show that even short lasting anodal tDCS can produce lasting increases in hippocampal long-term potentiation, learning and memory. These are by BDNF promoter acetylation, increased BDNF exons transcription, enhanced BDNF protein levels, and increased CREB phosphorylation (Fritsch et al., 2010; Podda et al., 2016). Thus, combination of these techniques with training of prosthetics could theoretically assist cortical remapping and prosthetic adaptation.

Synthetic Biology & Gene Editing

Advancements in synthetic biology could also provide future pathways for precise neural circuit manipulation. A great example this nature is the use of viral vectors to deliver CRISPR-Cas9 or transcriptional activators to locally enhance growth factor expression or plasticity-inhibiting genes silencing. Engineered cells could also serve as biosensors within peripheral nerves or even actuators by releasing neurotropic factors in response to activity, thereby creating a feedback loop that is self-regulated. Although these techniques are highly advanced and at an early preclinical state, the potential to integrate them with neuroprosthetics could change rehabilitation by modulating molecular pathways directly and transform the field of prosthetic devices.

Clinical and Ethical Considerations

Implementation Challenges

The development of gene-informed neuroprosthetics is accompanied by various technical and regulatory challenges, requiring careful safety considerations and regulatory protocols. Safe interaction of these devices with peripheral nerves or cortical tissue, without any concerns for long-term damage or harm to the user, needs to be the

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number one priority for the development of these advanced systems. Furthermore, data privacy concerns should be addressed since these devices would handle sensitive data collected for the users' daily interactions, their genomic profile and cortical recordings. Additionally, regulatory agencies need to ensure that such systems would not cause maladaptive plasticity or unintended gene expression.

Equity and Access

A major concern that needs to be addressed regarding personalized neuroprosthetics is the exacerbation of existing healthcare inequalities, if access to them is only limited to well-resourced settings. That could be the result of high costs and specialized infrastructure, which is limited to wealthy regions. This problem could be addressed with inclusive clinical trials and open-source designs, promoting equitable distribution. Ethical frameworks also need to address data ownership matters, with users having the ability to retain control of their neurogenetic data and authority for decision making, and the level of AI autonomy in closed-loop systems.

Conclusion

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Limb amputation causes extensive remodeling of the somatosensory cortex, which includes structural, functional and molecular alterations (Sparling et al., 2024). Despite these insights, most current neuroprosthetic systems do not incorporate the biological dynamics that shape long-term adaptation, leading to static decoding strategies that fail to align with a continuously reorganizing cortex. This review highlights the need for neuroprosthetics that not only read motor intent but also monitor and respond to the user's evolving neurophysiological state.

Integrating plasticity-sensitive biomarkers (such as sEMG features, EEG-derived oscillatory dynamics, and fNIRS hemodynamic responses) could enable prostheses to adapt in real time to changes in peripheral and cortical organization. In parallel, emerging gene-informed approaches, including transcriptomic profiling, biosensor-guided monitoring, and AI-driven adjustment of feedback parameters, offer a potential pathway for aligning prosthetic behavior with the underlying neurogenetic state that shapes plasticity readiness. These strategies, although still largely theoretical, may ultimately support systems that co-evolve with the user, enhancing embodiment, stability, and functional recovery.

Realizing this vision will require interdisciplinary collaboration across molecular neuroscience, systems neurophysiology, neuroengineering, machine learning, and ethics. Aligning technological innovation with the brain's intrinsic capacity for neuroplastic remodeling could shift the field toward neuroprosthetics that behave less like external tools and more like integrated extensions of the self, improving long-term usability, comfort, and clinical outcomes.

Acknowledgments

I would like to thank my mentors, [redacted], whose guidance, insight, and encouragement were invaluable throughout the development of this project.

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Dear Convergence Journal Editorial Team,

Thank you very much for your message and for coordinating the review of my manuscript, *"Neurogenetic Remodeling of the Sensorimotor Cortex Following Limb Loss: Implications for Adaptive Feedback in Closed-Loop Neuroprosthetics."* I am very grateful to both reviewers and to the editorial board for their detailed and constructive feedback.

I have carefully revised the manuscript in response to the reviewers' comments and now submit:

- A revised manuscript
- A track-changes version of the manuscript showing all edits relative to the original submission
- A point-by-point response letter to Reviewer 1
- A point-by-point response letter to Reviewer 2

In brief, the major changes include:

- Reframing the central thesis to focus on how post-amputation plasticity, driven by neurogenetic mechanisms, can be tracked using practical neurophysiological signals (sEMG, EEG, fNIRS) during rehabilitation and used to adapt decoding and feedback in closed-loop neuroprosthetics, while keeping gene-level mechanisms as biological background and future/offline directions.
- Adding a clear description of the narrative, non-systematic review approach in the Introduction.
- Introducing and expanding the section *"Measurable Signals of Neuroplasticity during Rehabilitation"*, which links specific signals to concrete adaptation rules during prosthetic training and early home use.
- Clarifying prevalence statistics in the Introduction and updating citations accordingly.
- Streamlining repetitive content, tightening language, and correcting minor grammatical issues.

Throughout the revision process, I have been attentive to ensuring that the manuscript meets the journal's high standards for clarity, rigor, and scholarly contribution.

I hope that these revisions satisfactorily address the reviewers' concerns and further clarify the contribution of the manuscript. Thank you again for the opportunity to revise and resubmit my work for consideration in Convergence.

Point-by-Point Response Letter - Reviewer 1

"Neurogenetic Remodeling of the Sensorimotor Cortex Following Limb Loss: Implications for Adaptive Feedback in Closed-Loop Neuroprosthetics"

Dear Reviewer,

Thank you very much for your careful and constructive review of my manuscript and for recommending acceptance with major revisions. I greatly appreciate your positive assessment of the paper's originality and cross-disciplinary scope, as well as your specific suggestions for improvement. Below, I address each of your main comments point by point.

(Reviewer comments are in italics, followed by my responses).

1. Originality & Significance / Speculative claims

"The manuscript presents an innovative framework by connecting neurogenetic remodeling with adaptive neuroprosthetic feedback, but it should more clearly delineate between what is currently feasible and what represents aspirational, future directions."

I agree that the distinction between current feasibility and long-term aspirations needed to be clearer. In the Abstract and Introduction, I now explicitly state that the core, near-term focus of the paper is on using measurable neurophysiological signals (sEMG, EEG, fNIRS) as plasticity-sensitive biomarkers during rehabilitation which can guide adaptive control and feedback in closed-loop systems. Gene-level mechanisms are now framed as the biological foundation for plasticity and as future/offline research directions, rather than as signals for real-time control. In *"Future Directions: Linking Neurogenetics with Adaptive Prosthetics"*, I clearly label gene-informed designs and synthetic biology approaches as speculative and long-term, while explicitly noting that they are not yet clinically feasible for real-time adaptation.

2. Clarity & Structure / Dense and repetitive sections

"Several sentences are overly dense and could be streamlined for clarity, particularly in descriptions of transcriptional pathways."

"Some repetition is present (e.g., multiple references to BDNF-driven plasticity). Condensing these points would increase readability."

I have now revised multiple long, multi-clause sentences in the molecular and genetic sections to improve readability and avoid unnecessary complexity. Descriptions of BDNF/CREB-driven plasticity and related gene expression cascades have been consolidated into a more concise subsection under "Molecular & Genetic Changes Post-Amputation - Activity-Dependent Gene Expression", removing repeated explanations throughout the manuscript. I have also tightened passages in the translational sections to reduce redundancy in the discussion of feedback-driven plasticity and adaptive control.

3. Prevalence statistics in the Introduction

"Prevalence data in the introduction requires clarification; the reported number of 'people living with limb loss' appears unusually high and should be verified."

I have corrected the prevalence data in the Introduction by replacing the previous global figure with more conservative and literature-consistent wording: I now state that "tens of millions of people live with limb loss worldwide," including approximately 57 million following trauma and over 30 million with lower-limb amputations, based on recent estimates. I have updated and clarified the supporting citations to better reflect current evidence and avoid over-interpretation. The text now emphasizes that these are approximate model-based estimates and not a single definitive global figure.

4. Use of Evidence & Research Methods

"The review does not state whether a systematic or narrative approach was used. A brief clarification of the scope or methodology for literature inclusion would enhance rigor."

I added a short methodological statement in the Introduction noting that this is a narrative non-systematic review. The passage explains that the manuscript aims to synthesize concepts and mechanisms from molecular neuroscience, systems neurophysiology, and neuroprosthetics, rather than to provide an exhaustive systematic review, and briefly describes the thematic focus guiding literature inclusion.

5. Limitations of imaging and molecular methods

"Limitations of imaging and molecular methods are under-discussed. A more balanced assessment of what these techniques can and cannot currently tell us would be valuable."

In the sections on EEG and fNIRS, I now discuss limitations related to spatial and temporal resolution, motion and physiological artifacts, susceptibility to environmental noise, and practical challenges in long-term or at-home monitoring. In the sEMG subsection under *"Measurable Signals of Neuroplasticity during Rehabilitation"*, I describe the variability of EMG signals, electrode placement sensitivity, muscle fatigue, and the need for frequent recalibration. Within "*Molecular & Genetic Changes Post-Amputation"* and *"Future Directions: Linking Neurogenetics with Adaptive Prosthetics"*, I clarify that gene expression operates on slow timescales, cannot be sampled in real time in everyday clinical settings, and is therefore more suitable as background biology and long-term/offline biomarker work, rather than for online control.

6. Grammar, language, and stylistic tightening

"Occasional grammatical slips (e.g., 'Plasticity follows the injury is a temporal sequence…') should be corrected. Stylistic tightening is needed to avoid redundancy, especially in discussions of feedback-driven plasticity."

I have carefully proofread the manuscript and corrected the grammar in the example you provided and other minor errors. I have also streamlined sections that repeatedly described feedback-driven plasticity and adaptive control, ensuring that key concepts are presented once clearly and then referenced rather than restated.

7. Clearly delineating evidence-supported claims vs. speculative proposals

"Clearly delineate between evidence-supported claims and forward-looking speculative proposals to avoid overstating translational readiness."

Throughout the manuscript, I now explicitly distinguish between current, evidence-supported capabilities of neuroprosthetic systems and speculative future directions, especially in the *Future Directions* section.

Phrases that might have overstated current readiness have been toned down and rephrased to emphasize that these are proposed avenues for future research, not existing clinical tools.

Once again, thank you for your insightful and constructive review. Your comments have helped me significantly improve the clarity, balance, and rigor of the manuscript, which I hope would contribute even slightly to the scientific community.

Sincerely,

[name redacted by Managing Editor]

Point-by-Point Response Letter - Reviewer 2

“Neurogenetic Remodeling of the Sensorimotor Cortex Following Limb Loss: Implications for Adaptive Feedback in Closed-Loop Neuroprosthetics”

Dear Reviewer,

Thank you very much for your detailed and thoughtful review and for recommending revise and resubmit. Your feedback was extremely helpful in reshaping the central argument of the manuscript and aligning it with realistic, evidence-based pathways for adaptive neuroprosthetics. Below, I address your core concerns point by point.

(Reviewer comments are in italics, followed by my responses).

1. Core issue: genetics vs practical online signals

“The manuscript claims that neurogenetic remodeling after amputation can inform closed-loop adaptation, but gene expression cannot be monitored in vivo in real time during rehabilitation. The realistic online inputs are physiological and behavioral signals (EMG, nerve activity, EEG/fNIRS, kinematics), not gene expression.”

I fully agree, and this point motivated a major reframing of the manuscript. The Abstract now emphasizes that the central aim is to explore how post-amputation cortical remodeling, driven by activity-dependent neurogenetic processes, can be tracked via neurophysiological signals (sEMG, EEG, fNIRS) and used to adapt feedback and control in closed-loop neuroprosthetics. The Introduction has been rewritten so that gene-level mechanisms are clearly presented as slow background processes that enable plasticity, while online control is built around physiological and behavioral signals obtainable during rehabilitation and early home use. The section *“Molecular & Genetic Changes Post-Amputation”* now explicitly states that gene expression unfolds over hours to days and is not suitable for real-time monitoring in clinical practice but rather provides the biological rationale for why repeated practice and feedback can reshape cortical maps. Gene-informed and transcriptomic ideas have been moved into “*Future Directions: Linking Neurogenetics with Adaptive Prosthetics”*, where they are clearly labeled as offline or long-term research directions, not current control signals.

2. Clarifying and sharpening the central contribution

“Clarify the central contribution. Revise the thesis to something like: ‘How post-amputation plasticity can be sensed via measurable signals during rehabilitation and used to adapt feedback/control in closed-loop neuroprosthetics.’ Keep gene-level content as background biology or long-term, offline research directions.”

I have reframed the thesis in the Abstract and at the end of the Introduction along these lines. The manuscript now explicitly states that it focuses on how plasticity-related changes can be sensed via sEMG, EEG, and fNIRS during rehabilitation and used to guide adaptive decoding and feedback, with gene-level mechanisms serving as background biology and informing future offline personalization strategies. The concluding paragraph of the Introduction now provides a concise roadmap.

3. Make rehabilitation/co-adaptation the center

"Make rehabilitation/training the center of the argument. Add a subsection on 'Training the Prosthesis to the User (Co-adaptation during Rehab)' explaining what you measure, what the device adjusts, when to adjust, and how to judge success."

I have now added and developed a section about *"Measurable Signals of Neuroplasticity during Rehabilitation"* which centers explicitly on rehabilitation and co-adaptation. For each technique (sEMG, EEG, fNIRS, and multimodal integration), I describe what is measured during training, what the system/therapist can adjust, when to adjust, and how success could be judged.

4. Reorganizing plasticity around "what to measure" and "how to adapt"

"For each biological change you describe, add short paragraphs on what changes and how to detect it

In the sensorimotor plasticity sections, I now connect biological phenomena to monitorable correlates during rehabilitation and discuss how these can inform specific adjustments in training or feedback. I have also added a new section called *"Measurable Signals of Neuroplasticity during Rehabilitation"* to discuss how those changes could be observed and how we prosthetics could adjust.

5. Clarifying the role of genes (short and realistic)

"Keep a brief background paragraph: molecular pathways support plasticity. If you retain molecular content in 'Future Directions,' label it clearly as hypothetical/offline. Do not imply real-time gene-based tuning."

The molecular section is now more concise and focused on explaining that activity-dependent gene expression (e.g., IEGs, BDNF/CREB) supports structural and functional plasticity over longer timescales. In *"Future Directions: Linking Neurogenetics with Adaptive Prosthetics",* I frame a gene-informed framework as hypothetical, long-term, and offline strategy. Any wording that might have implied existing "gene-sensitive" devices has been revised to avoid misunderstanding.

6. Strengthening definitions, figures, and APA style

"Explain every technique you mention with one sentence on what it measures/delivers and one on how it can drive adaptation. Call out each figure in the text and say what the reader should learn from it. Ensure APA-style citations."

For each technique I now provide one sentence stating what it measures or delivers and one sentence on how it can be used to inform adaptive training or feedback. I have reviewed citations for APA style and consistency and removed strong language where appropriate.

7. Grammar and style

“Proofread carefully, especially later sections where typos and phrasing errors increase. Avoid ‘how does…’ phrasing inside declarative sentences and keep ‘In this review…’ to one concise roadmap paragraph.”

I carefully proofread the manuscript, paying attention to later sections, and corrected typos, spacing, and phrasing issues.

Once again, thank you for your insightful and constructive review. Your comments have helped me significantly improve the clarity, balance, and rigor of the manuscript, which I hope would contribute even slightly to the scientific community.

Sincerely,

[name redacted by Managing Editor]

I very much enjoyed reading the revised manuscript. It is much more sophisticated than the original and shows a fantastic understanding of the subject matter. I'm very happy to accept this manuscript, possibly with minor corrections if the other reviewer agrees.

I spotted a minor typo on page 7, line 40, where they wrote "generic" when I believe they meant "genetic". On the same page, line 47, they wrote "whisker" when perhaps they meant to say that "naturalistic whisker use stimulates…" “Whisker” on its own does not make sense. There are other small typos throughout the manuscript that can be easily corrected.

My final suggestion to the author would be to be cautious with how they discuss gene expression in the final parts of the manuscript. Before, they were only talking about biomarkers of plasticity. Of course, the biomarkers such as BDNF, as proteins whose expression reflects plastic changes and plasticity, and gene expression are closely related, monitoring biomarkers would be a downstream readout and not a full representation of gene expression dynamics. I would suggest they focus on biomarker monitoring instead of trying to incorporate gene expression into the manuscript, which feels rather forced. Their argument about adjusting—e.g., sensory feedback intensity based on BDNF concentration makes sense, but this is not monitoring gene expression directly. The manuscript would therefore benefit from removing mentions of gene expression and instead focusing entirely on plasticity and associated biomarkers.