Convergence
A Journal for Young Researchers

ORIGINAL REVIEW

Received: 8-26-25; Accepted: 11-25-25;
Managing Editor: Jonas Katona;
Action Editor: Jonas Katona

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

Charalampos Filippou

Forum School, Nisou, Cyprus

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 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 neuroplasticity-related biomarkers and measurable indicators of cortical plasticity to guide prosthetic performance, thereby improving clinical outcomes.

Keywords: neurogenetic remodeling, cortical plasticity, sensorimotor cortex, limb loss, neuroprosthetics, brain-machine interface

1. 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), presenting 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.

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.

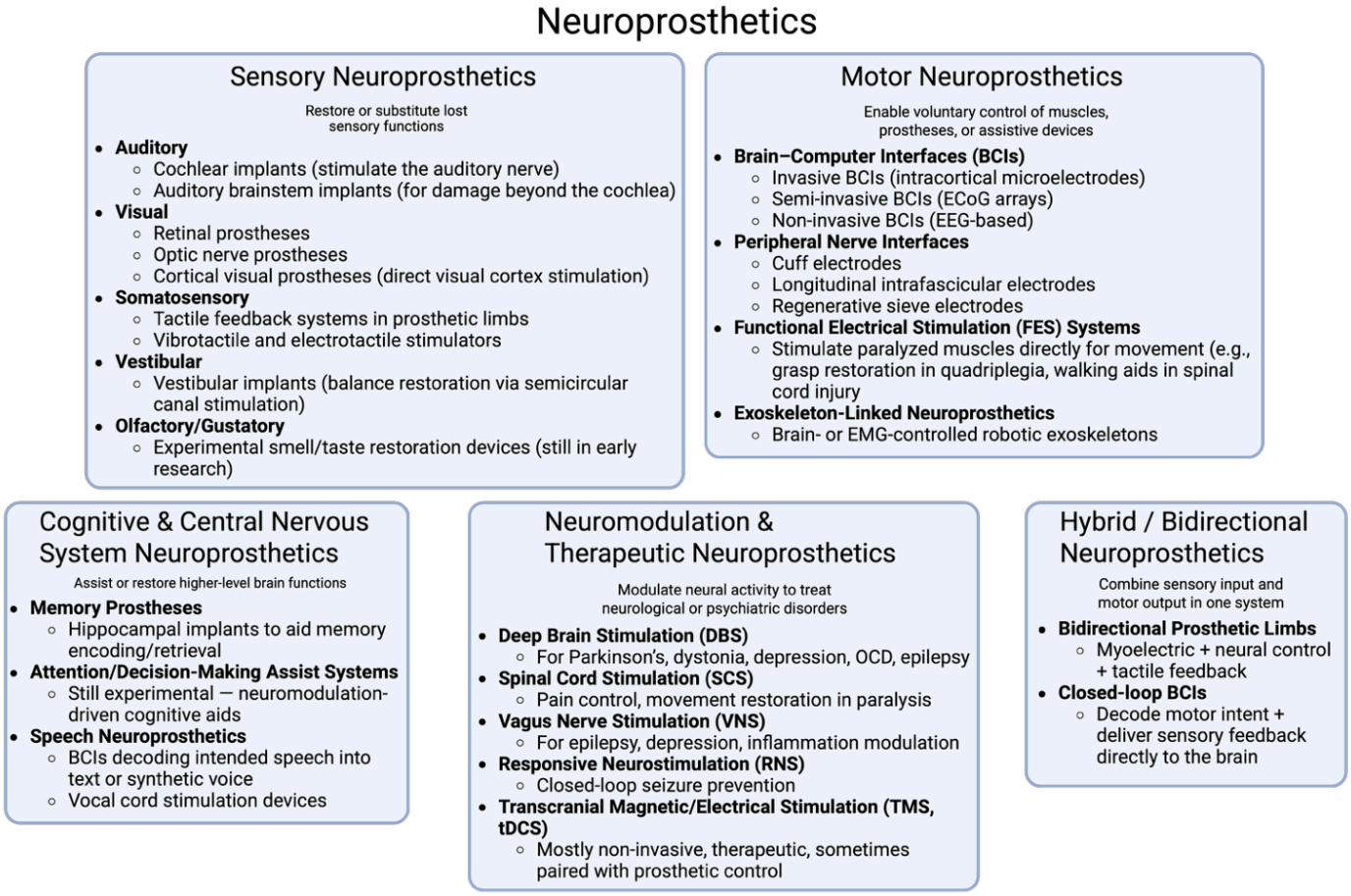

Figure 1: Summaries of the main categories of neuroprosthetics (sensory, motor, cognitive/central nervous system, neuromodulation/therapeutic, and hybrid/bidirectional) and examples of representative devices with their corresponding interface locations. This review primarily focuses on systems enabling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

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 biomarker-informed, offline personalization as a potential translational direction. We conclude by

identifying interdisciplinary priorities needed to achieve truly bidirectional, feedback-responsive neuroprosthetic systems.

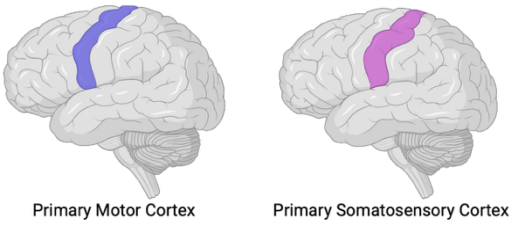

Figure 2: Locations of the primary motor (M1) and somatosensory (S1) cortices in the brain

2. Sensorimotor Cortical Remodeling After Limb Loss

2.1. 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.

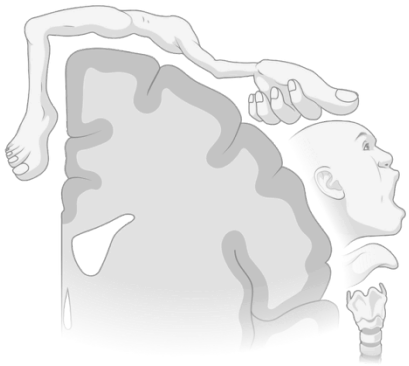

Figure 3: A representation of the motor homunculus by Penfield et al., showing the areas of the brain and their representative parts of the body.

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), the measurement of blood oxygenation level and dependent

hemodynamic mapping, and magnetoencephalography (MEG), millisecond-scale recordings of cortical magnetic fields. These, as well as transcranial magnetic stimulation (TMS), a noninvasive cortical stimulation used to probe excitability, and the 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. supports 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 supports 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)—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 the 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, an 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.

2.2. 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 creates 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.

3. 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 has 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 structures 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, 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 decreased 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.

4. Challenges in Current Neuroprosthetic Integration

4.1. 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 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.

4.2. 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 the 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.

5. Future Directions: Linking Neurogenetics with Adaptive Prosthetics

5.1. 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 molecular pathways (Carulli et al., 2011). Various studies in the general literature show evidence that plasticity-related pathways can be upregulated and enhance motor control with the use of peripheral nerve interfaces and neurostimulation. Notably, implanted electrodes delivering sensory feedback are shown to increase BDNF levels 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 on the molecular pathways that support cortical plasticity. Other studies focusing on rodent models show that naturalistic whisker use 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 neuroplasticity. This is supported by clinical observations with TMR prosthetic users exhibiting improved cortical representation of the missing limb and PLP reduction, while evidence suggests 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.

5.2. Personalized, Biomarker-Informed Design Strategies

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

Neuroplasticity varies among individuals, suggesting that different sensory feedback parameters need to be implemented among prosthetic users. Attempting to measure gene expression directly is not feasible for real-time or near-real-time control, so future approaches may rely on downstream biomarkers that reflect the influence of neurogenetic remodeling. A way to achieve this is by using machine learning models integrating electrophysiological signals (EEG, high-density EEG) and functional near-infrared spectroscopy (fNIRS) to 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 on a 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).

BDNF and other neurotrophins represent additional downstream biomarkers of plasticity. Although these are regulated by gene-expression pathways, their measurable concentrations can provide an indicator of plasticity readiness. For instance, users with high BDNF levels may need different sensory feedback intensity and frequency than people with lower BDNF levels, so adaptive algorithms could modulate stimulation to match the excitatory plasticity window (Sparling et al., 2024). 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.

5.3. 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 exon transcription, enhanced BDNF protein levels, and increased CREB phosphorylation (Fritsch et al., 2010; Podda et al., 2016). Thus, a combination of these techniques with training in prosthetics could theoretically assist cortical remapping and prosthetic adaptation.

5.4. Synthetic Biology & Gene Editing

Advancements in synthetic biology could also provide future pathways for precise neural circuit manipulation. A great example of this nature is the use of viral vectors to deliver CRISPR-Cas9 or transcriptional activators to locally enhance growth factor expression or the silencing of plasticity-inhibiting genes. Engineered cells could also serve as biosensors within peripheral nerves or even actuators by releasing neurotrophic 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.

6. 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, genomic profiles, 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 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.

7. 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 biomarker-informed approaches, including multimodal neurophysiological monitoring and longer-timescale biochemical indicators, 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.

8. References

Almeida, L. E. F., Murray, P. D., Zielke, H. R., Roby, C. D., Kingsbury, T. J., & Krueger, B. K. (2009). Autocrine activation of neuronal NMDA receptors by aspartate mediates dopamine- and cAMP-induced CREB-dependent gene transcription. *The Journal of Neuroscience*, *29*(40), 12702–12710. https://doi.org/10.1523/JNEUROSCI.1166-09.2009

Brambilla, C., Pirovano, I., Mira, R. M., Rizzo, G., Scano, A., & Mastropietro, A. (2021). Combined use of EMG and EEG techniques for neuromotor assessment in rehabilitative applications: A systematic review. *Sensors*, *21*(21), Article 7014. https://doi.org/10.3390/s21217014

Buccino, A. P., Keleş, H. O., & Omurtag, A. (2016). Hybrid EEG-fNIRS asynchronous brain-computer interface for multiple motor tasks. *PLOS ONE*, *11*(1), Article e0146610. https://doi.org/10.1371/journal.pone.0146610

Capsi-Morales, P., Piazza, C., Sjoberg, L., Catalano, M. G., Grioli, G., Bicchi, A., & Hermansson, L. M. (2023). Functional assessment of current upper limb prostheses: An integrated clinical and technological perspective. *PLOS ONE*, *18*(8), Article e0289978. https://doi.org/10.1371/journal.pone.0289978

Carulli, D., Foscarin, S., & Rossi, F. (2011). Activity-dependent plasticity and gene expression modifications in the adult CNS. *Frontiers in Molecular Neuroscience*, *4*, Article 50. https://doi.org/10.3389/fnmol.2011.00050

Chen, J., Xia, Y., Zhou, X., Vidal-Rosas, E. E., Thomas, A., Loureiro, R., Cooper, R. J., Carlson, T., & Zhao, H. (2023). fNIRS-EEG BCIs for motor rehabilitation: A review. *Bioengineering*, *10*(12), Article 1393. https://doi.org/10.3390/bioengineering10121393

Del Blanco, B., Guiretti, D., Tomasoni, R., Lopez-Cascales, M. T., Muñoz-Viana, R., Lipinski, M., Scandaglia, M., Coca, Y., Olivares, R., Valor, L. M., Herrera, E., & Barco, A. (2019). CBP and SRF co-regulate dendritic growth and synaptic maturation.

Cell Death & Differentiation, *26*(11), 2208–2222. https://doi.org/10.1038/s41418-019-0285-x

Demofonti, A., Germanotta, M., Zingaro, A., Bailo, G., Insalaco, S., Cordella, F., Aprile, I. G., & Zollo, L. (2025). Restoring somatotopic sensory feedback in lower limb amputees through noninvasive nerve stimulation. *Cyborg and Bionic Systems*, *6*, Article 0243. https://doi.org/10.34133/cbsystems.0243

Dietrich, C., Nehrdich, S., Seifert, S., Blume, K. R., Miltner, W. H. R., Hofmann, G. O., & Weiss, T. (2018). Leg prosthesis with somatosensory feedback reduces phantom limb pain and increases functionality. *Frontiers in Neurology*, 9, Article 270. https://doi.org/10.3389/fneur.2018.00270

Dijk, L. van, van Sluis, C. K., van Dijk, H. W., & Bongers, R. M. (2016). Learning an EMG controlled game: Task-specific adaptations and transfer. *PLOS ONE*, *11*(8), Article e0160817. https://doi.org/10.1371/journal.pone.0160817

Fang, C., He, B., Wang, Y., Cao, J., & Gao, S. (2020). EMG-centered multisensory based technologies for pattern recognition in rehabilitation: State of the art and challenges. *Biosensors*, *10*(8), Article 85. https://doi.org/10.3390/bios10080085

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., & Lu, B. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: Potential implications for motor learning. *Neuron*, *66*(2), 198–204. https://doi.org/10.1016/j.neuron.2010.03.035

Gunduz, M. E., Pinto, C. B., Saleh Velez, F. G., Duarte, D., Pacheco-Barrios, K., Lopes, F., & Fregni, F. (2020). Motor cortex reorganization in limb amputation: A systematic review of TMS motor mapping studies. *Frontiers in Neuroscience*, 14, Article 314. https://doi.org/10.3389/fnins.2020.00314

Hays, S. A., Rennaker, R. L., & Kilgard, M. P. (2013). Targeting plasticity with vagus nerve stimulation to treat neurological disease. *Progress in Brain Research*, 207, 275–299. https://doi.org/10.1016/B978-0-444-63327-9.00010-2

Hoellwarth, J. S., Tetsworth, K., Rozbruch, S. R., Handal, M. B., Coughlan, A., & Al Muderis, M. (2020). Osseointegration for amputees: Current implants, techniques, and future directions. *JBJS Reviews*, 8(3), Article e0043. https://doi.org/10.2106/JBJS.RVW.19.00043

Kikkert, S., Mezue, M., O'Shea, J., Henderson Slater, D., Johansen-Berg, H., Tracey, I., & Makin, T. R. (2019). Neural basis of induced phantom limb pain relief. *Annals of Neurology*, *85*(1), 59–73. https://doi.org/10.1002/ana.25371

Kim, S., Shin, D. Y., Kim, T.-K., Lee, S., Hyun, J. K., & Park, S. (2022). Enhanced recognition of amputated wrist and hand movements by deep learning method using multimodal fusion of electromyography and electroencephalography. *Sensors*, *22*(2), Article 680. https://doi.org/10.3390/s22020680

Li, R., Yang, D., Fang, F., Hong, K., Reiss, A. L., & Zhang, Y. (2022). Concurrent fNIRS and EEG for brain function investigation: A systematic, methodology-focused review. *Sensors*, *22*(15), Article 5865. https://doi.org/10.3390/s22155865

Li, X., Samuel, O. W., Zhang, X., Wang, H., Fang, P., & Li, G. (2017). A motion-classification strategy based on sEMG-EEG signal

combination for upper-limb amputees. *Journal of NeuroEngineering and Rehabilitation*, 14(1), Article 2. https://doi.org/10.1186/s12984-016-0212-z

Lorenz, E., Su, X., & Skjæret-Maroni, N. (2024). A review of combined functional neuroimaging and motion capture for motor rehabilitation. *Journal of NeuroEngineering and Rehabilitation*, 21(1), Article 3. https://doi.org/10.1186/s12984-023-01294-6

Makin, T. R., & Flor, H. (2020). Brain (re)organisation following amputation: Implications for phantom limb pain. *NeuroImage*, 218, Article 116943. https://doi.org/10.1016/j.neuroimage.2020.116943

Makin, T. R., Scholz, J., Henderson Slater, D., Johansen-Berg, H., & Tracey, I. (2015). Reassessing cortical reorganization in the primary sensorimotor cortex following arm amputation. *Brain*, 138(8), 2140–2146. https://doi.org/10.1093/brain/awv161

McDonald, C. L., Westcott-McCoy, S., Weaver, M. R., Haagsma, J. A., & Kartin, D. (2021). Global prevalence of traumatic non-fatal limb amputation. *Prosthetics and Orthotics International*, 45(2), 105–114. https://doi.org/10.1177/0309364620972258

Pereira, J., Direito, B., Lührs, M., Castelo-Branco, M., & Sousa, T. (2023). Multimodal assessment of the spatial correspondence between fNIRS and fMRI hemodynamic responses in motor tasks. *Scientific Reports*, 13, Article 2244. https://doi.org/10.1038/s41598-023-29123-9

Peters, B. R., Russo, S. A., West, J. M., Moore, A. M., & Schulz, S. A. (2020). Targeted muscle reinnervation for the management of pain in the setting of major limb amputation. *SAGE Open Medicine*, 8, Article 2050312120959180. https://doi.org/10.1177/2050312120959180

Podda, M. V., Cocco, S., Mastrodonato, A., Fusco, S., Leone, L., Barbati, S. A., Colussi, C., Ripoli, C., & Grassi, C. (2016). Anodal transcranial direct current stimulation boosts synaptic plasticity and memory in mice via epigenetic regulation of Bdnf expression. *Scientific Reports*, 6(1), Article 22180. https://doi.org/10.1038/srep22180

Resnik, L., Huang, H., Winslow, A. T., Crouch, D. L., Zhang, F., & Wolk, N. (2018). Evaluation of EMG pattern recognition for upper limb prosthesis control: A case study in comparison with direct myoelectric control. *Journal of NeuroEngineering and Rehabilitation*, 15(1), Article 23. https://doi.org/10.1186/s12984-018-0361-3

Rocamora, N., Welker, E., Pascual, M., & Soriano, E. (1996). Upregulation of BDNF mRNA expression in the barrel cortex of adult mice after sensory stimulation. *The Journal of Neuroscience*, 16(14), 4411–4419. https://doi.org/10.1523/JNEUROSCI.16-14-04411.1996

Schroeter, M. L., Kupka, T., Mildner, T., Uludağ, K., & von Cramon, D. Y. (2006). Investigating the post-stimulus undershoot of the BOLD signal—A simultaneous fMRI and fNIRS study. *NeuroImage*, 30(2), 349–358. https://doi.org/10.1016/j.neuroimage.2005.09.048

Shi, J., Wang, H., Gou, H., Chen, Y., Jia, H., Qu, Y., Wei, X. X., Fan, M., Wang, Y., Zhu, Y., & Zhu, Y. (2025). Construction of a deep-learning-based rehabilitation prediction model for lower-limb motor dysfunction after stroke using synchronous EEG-EMG and fMRI. *Frontiers in Neuroscience*, 19, Article 1616957. https://doi.org/10.3389/fnins.2025.1616957

Simões, E. L., Bramati, I., Rodrigues, E., Franzoi, A., Moll, J., Lent, R., & Tovar-Moll, F. (2012). Functional expansion of sensorimotor representation and structural reorganization of callosal connections in lower limb amputees. *The Journal of Neuroscience*, 32(9), 3211–3220. https://doi.org/10.1523/JNEUROSCI.4592-11.2012

Sparling, T., Iyer, L., Pasquina, P., & Petrus, E. (2024). Cortical reorganization after limb loss: Bridging the gap between basic science and clinical recovery. *The Journal of Neuroscience*, 44(1), Article e1051232024. https://doi.org/10.1523/JNEUROSCI.1051-23.2023

Srinivasan, S. S., Tuckute, G., Zou, J., Gutierrez-Arango, S., Song, H., Barry, R. L., & Herr, H. M. (2020). Agonist-antagonist myoneural interface amputation preserves proprioceptive sensorimotor neurophysiology in lower limbs. *Science Translational Medicine*, 12(573), Article eabc5926. https://doi.org/10.1126/scitranslmed.abc5926

Sugawara, A. T., Simis, M., Fregni, F., & Battistella, L. R. (2021). Characterisation of phantom limb pain in traumatic lower-limb amputees. *Pain Research and Management*, 2021, Article 2706731. https://doi.org/10.1155/2021/2706731

Sun, X., Dai, C., Wu, X., Han, T., Li, Q., Lu, Y., Liu, X., & Yuan, H. (2024). Current implications of EEG and fNIRS as functional neuroimaging techniques for motor recovery after stroke. *Medical Review*, 4(6), 492–509. https://doi.org/10.1515/mr-2024-0010

Tyler, D. J. (2015). Neural interfaces for somatosensory feedback: Bringing life to a prosthesis. *Current Opinion in Neurology*, 28(6), 574–581. https://doi.org/10.1097/WCO.0000000000000266

Vandermosten, M., Boets, B., Wouters, J., & Ghesquière, P. (2012). A qualitative and quantitative review of diffusion tensor imaging studies in reading and dyslexia. *Neuroscience & Biobehavioral Reviews*, 36(6), 1532–1552. https://doi.org/10.1016/j.neubiorev.2012.04.002

Wilkins, K. L., McGrath, P. J., Finley, A. G., & Katz, J. (1998). Phantom limb sensations and phantom limb pain in child and adolescent amputees. *Pain*, 78(1), 7–17. https://doi.org/10.1016/S0304-3959(98)00109-2

Wöhrle, H., Tabie, M., Kim, S. K., Kirchner, F., & Kirchner, E. A. (2017). A hybrid FPGA-based system for EEG- and EMG-based online movement prediction. *Sensors*, 17(7), Article 1552. https://doi.org/10.3390/s17071552

Yuan, B., Hu, D., Gu, S., Xiao, S., & Song, F. (2023). The global burden of traumatic amputation in 204 countries and territories. *Frontiers in Public Health*, 11, Article 1258853. https://doi.org/10.3389/fpubh.2023.1258853

Zhang, J., Zhang, Y., Wang, L., Sang, L., Li, L., Li, P., Yin, X., & Qiu, M. (2018). Brain functional connectivity plasticity within and beyond the sensorimotor network in lower-limb amputees. *Frontiers in Human Neuroscience*, 12, Article 403. https://doi.org/10.3389/fnhum.2018.00403

Acknowledgements & Mentor Contribution Statement

I would like to extend my appreciation to **Dr. Jorge Avila**, who mentored me throughout the research and writing process. He guided me in shaping the scientific direction of the paper and helped me understand how to approach an academic topic by grounding arguments in evidence from molecular neuroscience, neurophysiology, and neuroengineering. Through his feedback, he encouraged me to think critically about the relationships between neuroplasticity, cortical remodeling, and prosthetic adaptation, and his guidance greatly strengthened the analytical depth of the manuscript, ensuring the work remained rigorous, well-structured, and aligned with academic standards.

I would also like to express my appreciation to **Bre Calhoun**, who supported me throughout the refinement of the manuscript. Her assistance with organizing and evaluating the literature and thoughtful feedback helped improve the clarity and flow of the paper.

Author Biography

Charalampos Filippou is a recent high school graduate from Cyprus and is currently serving in the National Guard. He was drawn to neurogenetics after developing BionicReach, a startup focused on affordable AI-driven, 3D-printed prosthetics. His work in prosthetic design led him to explore how injury-induced brain plasticity and genetic mechanisms could inform more adaptive, biologically aligned rehabilitation technologies. His long-term goal is to integrate neuroengineering and molecular biology to develop next-generation prosthetics that better complement the body's innate regenerative and adaptive processes.

Beyond research, Filippou has distinguished himself through international competitions and academic programs. He represented Cyprus at the International Junior Science Olympiad in 2022 and earned a bronze medal at the European Olympiad of Experimental Science in 2024. He has also participated in advanced programs at Johns Hopkins University's Center for Talented Youth, the Center for Talented Youth Greece, and the Sakura Science Exchange Program in Japan. In addition, he is a medical sciences mentee in Global Talent Mentoring and a recipient of multiple national awards in biology and other scientific disciplines.

Looking ahead, he plans to study biomedical engineering to deepen his work on adaptive, user-centered prosthetic systems, with future expansion into technologies aimed at restoring neural function in neurodegenerative diseases, spinal cord injuries, and paralysis. To support this mission with clinical expertise, he intends to ultimately pursue an MD/PhD, integrating medical practice with translational research in neuroengineering and regenerative medicine.