Neural functional rehabilitation: Exploring neuromuscular reconstruction technology advancements and challenges

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From the Contents

Abstract

Neural machine interface technology is a pioneering approach that aims to address the complex challenges of neurological dysfunctions and disabilities resulting from conditions such as congenital disorders, traumatic injuries, and neurological diseases. Neural machine interface technology establishes direct connections with the brain or peripheral nervous system to restore impaired motor, sensory, and cognitive functions, significantly improving patients' quality of life. This review analyzes the chronological development and integration of various neural machine interface technologies, including regenerative peripheral nerve interfaces, targeted muscle and sensory reinnervation, agonist–antagonist myoneural interfaces, and brain–machine interfaces. Recent advancements in flexible electronics and bioengineering have led to the development of more biocompatible and high-resolution electrodes, which enhance the performance and longevity of neural machine interface technology. However, significant challenges remain, such as signal interference, fibrous tissue encapsulation, and the need for precise anatomical localization and reconstruction. The integration of advanced signal processing algorithms, particularly those utilizing artificial intelligence and machine learning, has the potential to improve the accuracy and reliability of neural signal interpretation, which will make neural machine interface technologies more intuitive and effective. These technologies have broad, impactful clinical applications, ranging from motor restoration and sensory feedback in prosthetics to neurological disorder treatment and neurorehabilitation. This review suggests that multidisciplinary collaboration will play a critical role in advancing neural machine interface technologies by combining insights from biomedical engineering, clinical surgery, and neuroengineering to develop more sophisticated and reliable interfaces. By addressing existing limitations and exploring new technological frontiers, neural machine interface technologies have the potential to revolutionize neuroprosthetics and neurorehabilitation, promising enhanced mobility, independence, and quality of life for individuals with neurological impairments. By leveraging detailed anatomical knowledge and integrating cutting-edge neuroengineering principles, researchers and clinicians can push the boundaries of what is possible and create increasingly sophisticated and long-lasting prosthetic devices that provide sustained benefits for users.

Key Words: agonist–antagonist myoneural interface; biocompatibility; brain–machine interface; clinical anatomy; neural machine interface; neuroprosthetics; peripheral nerve interface; proprioception; targeted muscle reinnervation; targeted sensory reinnervation

Introduction

Advancements in the fields of biomedical engineering, neuroscience, and surgery have continuously pushed the boundaries of prosthetic technology. In particular, myoelectric prosthetic devices utilizing neural machine interfaces (NMIs) are heralded as some of the most effective solutions for amputees. These devices closely mimic the functionality of biological limbs by providing natural motor-sensory feedback (Bates et al., 2020). NMI technology represents a synthesis of innovative techniques, including neuromuscular grafting, bioelectrode implantation, signal decoding technology, and exoskeleton frameworks (Cho et al., 2023; **Figure 1**). The muscles and nerves of the limb stump are strategically reconstructed, and implanted electrodes are adept at extracting both effective nerve electrical signals and myoelectric signals. The peripheral nervous system generates the signals that power these prosthetic systems; this enables patients to operate the devices using their own nerve conduction systems, both directly and indirectly (Bergmeister et al., 2019; He et al., 2020; Wang et al., 2022; Gupta et al., 2023).

Traditional myoelectric systems employ surface electrodes to record electromyographic (EMG) signals, which indirectly activate motor commands. NMIs, on the other hand, acquire signals through direct contact with the nervous system. Neuroelectric signal decoding technologies are used to facilitate a bidirectional, intuitive control interface between the prosthesis and the residual neuromuscular control; in this way, this method enhances the interaction between the prosthetic and the user (Pan et al., 2018; Starr, 2018). Despite the considerable promise of NMI technology for the realm of human–computer interaction systems, its widespread application is impeded by some formidable challenges. The complexity of the human nervous system, together with the instability and variability of bioelectronic interfaces, are currently significant barriers limiting the scope of NM technology's clinical application (Daly and Wolpaw, 2008). In addition, the precise localization and reconstruction of clinical anatomy are crucial for engineering NMIs for clinical use. The accuracy of anatomical reconstructions significantly influences the success of these

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engineering applications, impacting patients' clinical outcomes and recovery processes. Errors in anatomical localization can result in less effective neuromuscular integration and may increase the risk of complications (Zhang et al., 2021).

The objective of this review is to demonstrate that the efficacy of diverse NMI methodologies is contingent upon the reconstruction and restoration of anatomical structures in clinical settings, thereby establishing a fundamental foundation for the technical implementation of engineering solutions. For example, in surgical contexts, NMI technology selection must take into account the individualized structural characteristics of clinical cases and the feasibility of the surgical plan. This review provides a comprehensive overview of contemporary neuroprosthetic technologies, including the regenerative peripheral nerve interface (RPNI), targeted muscle reinnervation (TMR), targeted sensory reinnervation (TSR), agonist-antagonist myoneural interface (AMI), and brain–machine interface (BMI). Each of these technologies presents unique benefits and distinct challenges, particularly in terms of their integration with existing biological systems and their long-term viability. Additionally, this review proposes a more robust integration of clinical surgery with electrical engineering. This interdisciplinary approach will be crucial for developing next-generation bionic limbs that are more integrated, functional, and responsive to user needs (**Figure 2**). By bridging the gap between theoretical research and practical clinical applications, we can enhance the adoption and effectiveness of prosthetic technologies, ultimately improving the lives of millions of individuals with disabilities (Polikov et al., 2005; Seymour et al., 2017). **Table 1** presents NMIs' classification features.

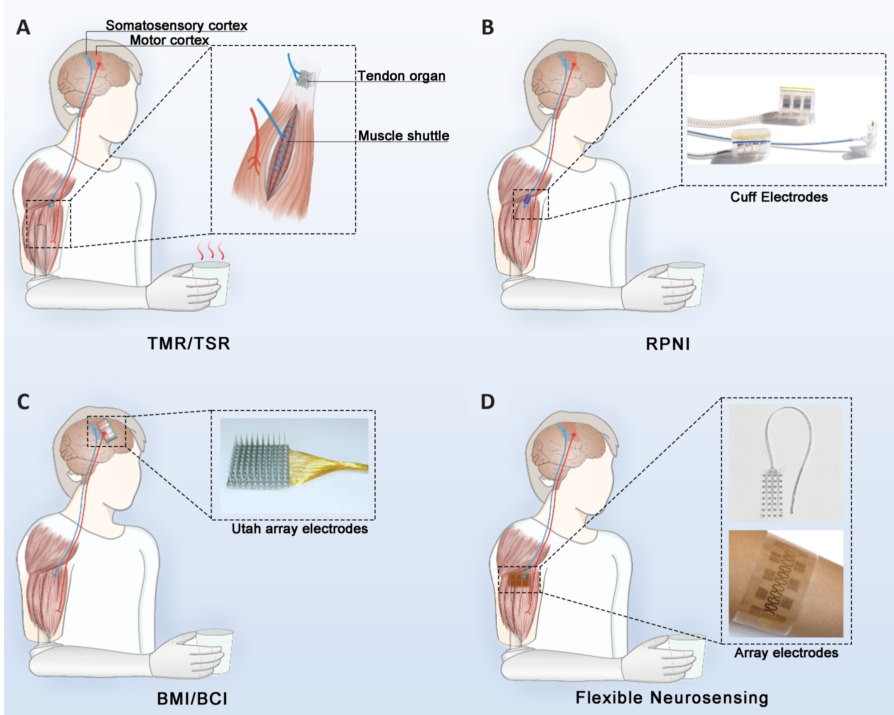

Figure 1 | **Neural functional rehabilitation.**
(A) Targeted muscle reinnervation (TMR)/targeted sensory reinnervation (TSR): The electrode array is placed on the surface skin of reinnervated muscles and sensory nerves. This technique reroutes nerves that previously controlled the lost limb to remaining muscles and sensory pathways, improving prosthetic control and sensory feedback using signals from these reinnervated muscles and nerves. (B) Regenerative peripheral nerve interface (RPNI): The cuff electrodes are applied to peripheral nerves. This interface supports nerve regeneration and interfaces with peripheral nerves to restore function after nerve injury, allowing for the restoration of motor and sensory functions (Song et al., 2018). (C) Brain–machine interface (BMI)/brain–computer interface (BCI): It highlights utah array electrodes implanted in the brain (Normann and Fernandez, 2016). These electrodes record neural activity directly from the brain to control prosthetic devices, computers, or other external systems, providing direct neural control. (D) Flexible neurosensing (Xie et al., 2022). This approach uses flexible, biocompatible sensors to monitor and interface with neural activity, allowing for long-term, comfortable neural recording and stimulation.

Search Strategy

We searched PubMed using the terms "regenerative peripheral nerve interface," "targeted muscle reinnervation," "agonist–antagonist myoneural interface," "brain–machine interface," "targeted sensory reinnervation," "neural machine interface," "myoelectric prosthesis," "neural interfaces," "motor and sensory feedback," and "biocompatibility" as keywords and then excluded irrelevant articles based on the abstracts. Findings related to neurological rehabilitation were summarized. Most of the articles (85% of all references) were published between 2014 and 2024.

Motion Control-Related Neural Machine Interface Technology

Traditional commercial prosthetics often lack sensory feedback that mimics natural human sensation, primarily relying on the movements of an amputee's remaining limb. This restricts their flexibility, speed, and ability to operate in multiple degrees of freedom (Farina and Aszmann, 2014). In contrast, myoelectric prostheses harness EMG signals to regulate the movement of prosthetic limbs, closely mimicking natural limb motion. These EMG signals are electrical impulses generated by muscle activity in the intact limb or shoulder, detected by sensors to control prosthetic movements (Khosravi et al., 2022).

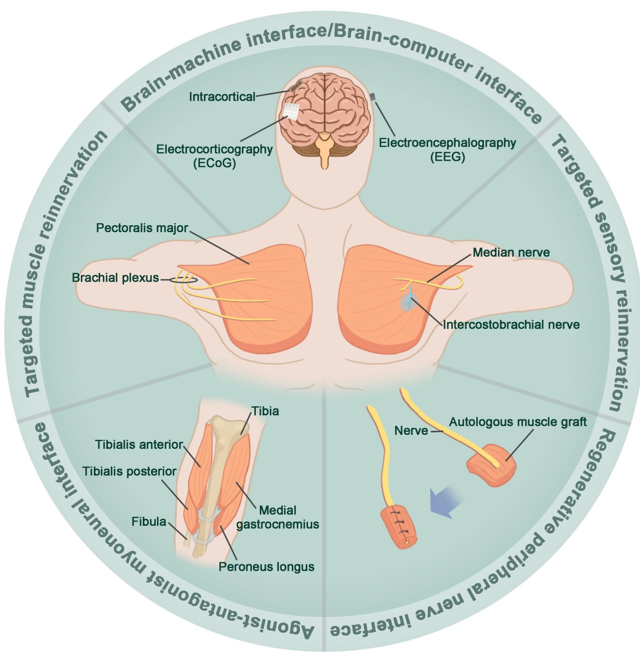

Figure 2 | **Neural machine interfaces for neuroprosthetics and neurorehabilitation.**

Most myoelectric prostheses rely on recording electrodes for control. However, challenges arise from the nonlinear correlation between the amplitude of surface EMG signals and actual muscle force, leading to unstable and unpredictable control signals. Consequently, the abandonment rate of such devices is high, with approximately 23% of adults and 32% of children with severe physical disabilities discontinuing their use long-term (Biddiss and Chau, 2007; Østlie et al., 2012). To reduce abandonment rates and enhance usability, control performance, and user satisfaction, advancements in myoelectric prosthesis technology are critical. Innovations in implanted electrode technology, sophisticated signal processing, and bone fusion techniques have led to the development of peripheral nerve interface technology. This approach uses individual peripheral nerves as channels for relaying signals between the brain and external devices, enabling bidirectional communication. Afferent nerve fibers transmit sensory information about the external environment to the central nervous system, while efferent fibers send motor commands to muscles, allowing implanted electrodes to modulate signals effectively (Dietrich et al., 2012; Dumanian et al., 2019).

Ongoing research is focusing on refining the stability and accuracy of signal interpretation to improve the integration of these devices with users' biological systems. This includes the application of advanced machine learning algorithms for better signal decoding and the development of materials that are more compatible with human tissue (Roche et al., 2014). The aim of these improvements is to provide users with a more intuitive and responsive prosthetic experience, which is expected to lead to higher adoption rates and improved quality of life for amputees. Furthermore, the future of prosthetic technology is likely to incorporate fully integrated sensory feedback systems that replicate tactile and proprioceptive sensations, providing users with a sense of touch and position that further mimics natural limb functions. Collaboration between neuroscientists, engineers, and clinicians is essential to advancing these technologies and promises to significantly transform the rehabilitation landscape for individuals with limb loss (Navarro et al., 2005; Raspopovic et al., 2014).

Table 1 | Overview of neural machine interface technology

Types	Features	Studies
Regenerative peripheral nerve interface	Facilitates nerve regeneration and restores motor and sensory function	Hooper et al., 2020; González-Prieto et al., 2024
Targeted muscle reinnervation	Enhances prosthetic control by rerouting nerves to muscles	Kuiken et al., 2007b, 2009
Targeted sensory reinnervation	Improves sensory feedback by rerouting sensory nerves	Hebert et al., 2014; Festin et al., 2024
Agonist–antagonist myoneural interface	Provides natural prosthetic control through muscle connection	Srinivasan et al., 2017; Song et al., 2022
Brain–machine interfaces/ brain–computer interfaces	Enables direct neural control of devices through brain implants	Hochberg et al., 2006, 2012

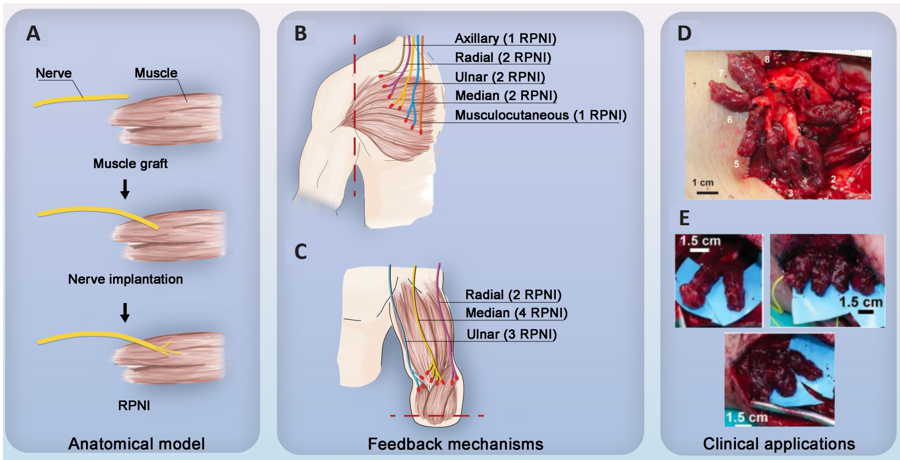

Figure 3 | RPNI model diagram and surgical case diagram.
(A) Anatomical principle model: The process of forming an RPNI begins with the removal of the neuroma bulb. The proximal end of the nerve is then enveloped with a small free muscle graft, creating the RPNI. (B) RPNI creation at the glenohumeral amputation level (P2): A total of eight RPNIs were established: two for each of the median, ulnar, and radial nerves, and one each for the musculocutaneous and axillary nerves. This arrangement facilitates the transmission of motor signals from the brain to the prosthesis and the reception of sensory feedback from the prosthesis to the brain. (C) RPNI creation at the proximal transradial amputation level (P1): A total of nine RPNIs were formed: four for the median nerve, three for the ulnar nerve, and two for the radial nerve. This setup enables effective decoding of motor signals from the muscle grafts, providing precise feedback mechanisms essential for the control of prosthetic movements. (D) Clinical applications: The surgical procedure of RPNIs, which involved in the implantation process. (E) Detailed views of muscle grafts and nerve implantation: Close-up images of the muscle grafts prepared for nerve implantation, displaying the intricacies of the grafting technique and the resulting RPNIs. Reprinted from Vu et al. (2020). RPNI: Regenerative peripheral nerve interface.

Overview of regenerative peripheral nerve interface

The RPNI is a sophisticated surgical technique, primarily aimed at controlling neural prosthetic devices, that uses free muscle autografts as physiological targets to enhance motor nerve signals (Kuiken et al., 2007b; **Figure 3A–E**). This method is particularly effective when used to alleviate pain caused by neuromas or to repair or reconstruct damaged nerves, especially when a nerve breaks or when deficits are too extensive to allow for direct connections (Urbanchek et al., 2016). RPNI utilizes grafts, such as autologous nerves or artificial nerve conduits, as bridgeheads to promote nerve regeneration. A thorough understanding of neuroanatomy is essential to performing the RPNI procedure, enabling the anatomical localization of nerve injuries. This anatomical insight is crucial for developing effective treatment strategies and surgical interventions (Guse and Ostrum, 1995). Crafting a tailored treatment plan for each patient relies on the accurate assessment of the location, size, and severity of nerve damage. RPNI also depends heavily on detailed knowledge of vascular and muscle anatomy. Understanding the vascular supply around the nerve is necessary for preventing vascular injury during the procedure and ensuring an adequate blood supply, which is vital for the survival and integration of the grafts (Talis et al., 2022). Additionally, selecting the most appropriate area for muscle grafting requires a thorough understanding of muscle anatomy. This selection is crucial for successful clinical applications of RPNI, as it ensures that the muscle grafts can support the regenerative process and effectively integrate with the nerve fibers to facilitate efficient signal transmission. By integrating these anatomical considerations, RPNI offers a robust framework for restoring functionality and reducing discomfort in patients with severe nerve damage. The procedure can significantly improve patients' quality of life, being efficacious in terms of pain management and nerve repair and enhancing the functionality and integration of neural prosthetics (Berberoglu et al., 2024).

The RPNI technique has demonstrated substantial potential in improving the quality of life for individuals with upper limb amputations (Woo et al., 2016; Kubiak et al., 2018; Ganesh Kumar and Kung, 2021). A pivotal study involving four amputees employed the method to develop an advanced bioprosthetic nerve interface that used separate muscle grafts connected to multiple nerve bundles. The approach was exemplified in the case of a 72-year-old male patient diagnosed with sarcoma on his right upper extremity, necessitating a glenohumeral amputation. During the amputation procedure, RPNIs were strategically placed to preemptively address the potential development of neuromas, a common complication that can lead to significant post-operative pain. The surgical team meticulously dissected the nerve fascicles associated with the median, ulnar, and radial nerves. This precise isolation is crucial for the detailed construction of the interfaces, ensuring that each nerve is equipped with its dedicated RPNI, as depicted in the study's (Vu et al., 2020; **Figure 3B**). These interfaces enhance the prosthesis' endurance and functionality. By connecting the nerve bundles to tailored muscle grafts, the RPNI facilitates a direct and robust conduit for nerve signals, which is essential for controlling the prosthetic limb. This setup mitigates pain from neuromas, reduces stump wear, and significantly improves the prosthesis' overall functionality and comfort

(Santosa et al., 2020). In addition, the RPNI's integration of advanced signal processing technology allows for the extraction and decoding of neural signals from the muscle grafts. These signals undergo pattern recognition to decode various grasping postures, enabling precise and responsive control of the prosthesis (Lee et al., 2024). The system's effectiveness is reflected in its high signal-to-noise ratio of 68.9, indicating that it provides the clear and reliable signal transmission necessary for accurate prosthetic movements.

Another male participant underwent a horizontal amputation to address ulnar, median, and radial nerve tumors located in the anterior elbow fossa (Vu et al., 2020). The surgical procedure involved accurately dissecting the affected nerves and then inserting nerve bundles into individual muscle grafts (**Figure 3C**). To monitor the action potential linked with the movement of the thumb at the median nerve, a thin wire implant was temporarily percutaneously inserted and placed above the grafted muscle (Kung et al., 2014). Pattern recognition of signals from these muscle grafts was used to decode four distinct grasping postures for a patient with right-hand amputation (Tenore et al., 2009). The patient underwent resection of the sensory neuroma in the distal forearm on the median, ulnar, and radial nerves, and bipolar electrodes were implanted in the muscles. The system has been in operation in this patient for 2 years, continuing to monitor the action potential associated with thumb movement at the median nerve via the thin wire. The muscle graft was used to achieve this objective by enhancing the efferent motor nerve action potential.

Peripheral nerve interface technology promises to enable precise control of neuroprostheses by recording nerve signals from the remaining limb and translating them into motion. However, many existing interfaces are subject to declining function over time, necessitating frequent readjustments. In contrast, participants in Vu et al.'s (2020) study experienced stable performance, avoiding the need for complex device tuning for over 300 days. Additionally, RPNI technology has proven effective in regulating motor function (Frost et al., 2018). By providing an implantable interface for precise fine motor control of the prosthesis, RPNI incorporates peripheral nerves into implanted myogenic grafts to stimulate nerve regeneration and neovascularization (Hu et al., 2021). This innovative approach prolongs the lifespan of upper limb prostheses and alleviates the discomfort associated with neuromas and stump wear, ultimately enhancing patients' quality of life.

RPNIs represent a cutting-edge approach in the field of NMIs that relies heavily on a thorough understanding of clinical anatomy. These interfaces utilize free muscle grafts reinnervated by residual peripheral nerves to create bioelectrical interfaces for prosthetic control. This technology depends on a comprehensive knowledge of peripheral nerve distribution and muscle anatomy. Surgeons must identify suitable nerves for reinnervation, typically those with a robust axonal count, and pair them with muscle grafts capable of generating discernible EMG signals. Detailed anatomical mapping ensures the grafts are placed where they can be adequately reinnervated and vascularized, reducing the risk of ischemia and enhancing signal fidelity. The precise suturing of nerves to muscle grafts requires meticulous dissection and an in-depth understanding of nerve fascicles, achievable only with extensive anatomical knowledge. This ensures the resulting bioelectrical interface can provide the necessary control signals for advanced prosthetic devices, thereby improving the user's ability to interact with their environment.

The best indications for RPNI technology include upper limb amputations, particularly cases in which enhancing residual limb function through the reinnervation of muscle grafts is necessary. RPNI is also ideal for patients with nerve damage characterized by extensive deficits that make direct nerve connections unsuitable, necessitating the bridging of gaps with muscle grafts. Additionally, this technology can reduce neuroma formation, making it highly beneficial for managing neuroma-related pain (Wang et al., 2023). RPNI has shown significant promise in providing the high-fidelity EMG signals necessary for the precise control of advanced prosthetic devices. Clinical applications have demonstrated its versatility across various amputation levels, offering substantial improvements in prosthetic functionality and user comfort.

Advantages and disadvantages of regenerative peripheral nerve interface

RPNI technology offers several advantages, including enhanced signal quality for precise prosthetic control, effective pain alleviation, and the promotion of nerve regeneration and neovascularization, which aids in motor function restoration. The technique has demonstrated stable long-term performance without the need for frequent adjustments, enhancing prosthetic usability. Additionally, RPNI mitigates issues such as stump wear, improving overall comfort for amputees. However, there are disadvantages to this technology. The surgical procedure is complex, requiring high surgical skill and extensive anatomical knowledge. The procedure comes with the risk of ischemia due to compromised vascularization and the risk of inadvertent nerve injury during meticulous dissection. The need for careful postoperative management adds to the complexity and cost of the procedure. Furthermore, the reliance on advanced signal processing technology increases costs and necessitates ongoing technical support (Ursu et al., 2016).

Outlook on regenerative peripheral nerve interface technology

The future of RPNI technology looks promising, with ongoing advancements expected to further improve its efficacy and accessibility. Research is focused on refining surgical techniques to reduce its complexity and enhance outcomes. Innovations in bioengineering, such as the development of more biocompatible and durable materials for grafts, are anticipated to enhance RPNIs' longevity and functionality. Additionally, advancements in signal processing algorithms and machine learning are likely to improve the precision and reliability of EMG signal interpretation, thereby enhancing prosthetic control. The integration of RPNI with other emerging technologies, such as BMI and advanced prosthetic designs, has the potential to create more seamless and intuitive control systems for amputees. Efforts to miniaturize and optimize these interfaces could make them more accessible and practical for a broader range of patients. As the understanding of peripheral nerve and muscle anatomy deepens, the precision and effectiveness of these procedures are expected to increase, reducing complications and improving patient outcomes. In conclusion, while RPNI technology currently presents some challenges, its continued evolution is poised to significantly enhance the quality of life for individuals with limb loss. By addressing current limitations and leveraging technological advancements, RPNI can offer more effective, reliable, and user-friendly solutions for neuroprosthetic control, paving the way for a new era in prosthetic technology (Adewole et al., 2016; Shahriari et al., 2020).

Motor and Sensory Feedback–Related Neural Machine Interface Technology

Despite significant progress in prosthetic technology and motor control, the lack of sensory feedback remains a critical challenge. Sensory feedback is crucial for improving motor control and reinstating a sense of embodiment, both necessary for enhancing amputees' overall function and quality of life. Without proprioception, individuals cannot identify the position of their limb in space, forcing them to rely on visual cues as their only source of feedback (Lian et al., 2024). Before the emergence of neural interfaces, non-invasive alternatives like electrotactile or vibrotactile feedback were developed to restore sensation (Wu et al., 2018; D'Anna et al., 2019; Zollo et al., 2019; Zhu et al., 2020; Sun et al., 2022). While these techniques may offer some sensory stimulation, they lack the requisite level of selectivity for clinical applications. It is, therefore, imperative to expedite the development of implantable neuroelectrode technology and the mechanism for feeding back prosthetic signals to both the neural interface and the central system (Ortiz-Catalan et al., 2014).

Targeted muscle reinnervation

TMR is an innovative surgical technique designed to enhance myoelectric prosthetic control systems by overcoming several of the limitations of traditional prostheses, such as control restricted to a single degree of freedom, lack of sensory feedback, and untreated neuropathic pain (Miller et al., 2008; Kuiken et al., 2009). TMR surgery involves replanting residual nerves from amputated limbs into target muscles with weaker innervation. This process is achieved by transecting the natural nerve close to the donor muscle and attaching it to the muscle's entry point (Bishay et al., 2024; Goodyear et al., 2024; Reid et al., 2024). Splicing the nerve into the weakly innervated target muscle transforms the muscle into multiple bioamplifiers of motor control (**Figure 4A** and **B**).

TMR reconnects the residual nerves at the amputation site to surrounding muscles, allowing the patient to control the prosthesis or artificial limb through nerve signals (Cheesborough et al., 2015; Simon et al., 2023). The clinical foundation of TMR is rooted in a comprehensive understanding of neuroanatomy and the muscular system. Before TMR surgery, the surgeon uses neurophysiological and imaging studies to determine the location and trajectory of the residual nerves and surrounding muscles at the amputation site. This process helps the surgeon select the relevant nerves for reinnervation and predict postoperative muscle control. Clinical anatomical models that frequently aid in TMR reconstruction include residual neuroanatomy and muscle anatomy. Residual nerve anatomy helps the surgeon identify targets for reinnervation through an understanding of the anatomy and trajectory of the residual nerve at the amputation site (Chen et al., 2024; Eberlin et al., 2023; Phair et al., 2024). Similarly, muscle anatomy helps the surgeon select the appropriate muscles for reinnervation through an understanding of their anatomy and trajectory (Li et al., 2023b, c). During surgery, residual nerve anastomosis is performed at the amputation site to the surrounding muscle to enable reinnervation. Through meticulous anatomical localization and reconstruction, engineering solutions can restore muscle control to prostheses or artificial limbs, thereby enhancing amputees' motor function and quality of life (Goodyear et al., 2024; Gstoettner et al., 2024).

Kuiken et al. (2007a, b, 2009, 2017) discovered that cortical reorganization is directly linked to the recovery of hand function following upper limb amputation. Their research demonstrated that the cortical sensory representation of the adjacent intact region extends into the cortical area corresponding to the amputated limb. In one notable case, the team recruited a left-hand dominant patient with bilateral shoulder disarticulation caused by an electrical shock injury (**Figure 4C**). Prior to surgery, the normal innervation of the left pectoralis major and pectoralis minor muscles was meticulously mapped. To optimize the nerve transfer, the pectoralis major muscle was divided into three distinct segments based on its segmental neurovascular anatomy. The pectoralis minor muscle was selected as the fourth target for nerve transfers. During the procedure, the myocutaneous nerve was implanted into the clavicular head of the pectoralis major muscle. The median nerve was sutured to the superior segment of the sternal head of the pectoralis major muscle, the radial nerve to the inferior segment, and the ulnar nerve to the pectoralis minor. Three months postoperatively, the patient showed significant contraction of the pectoralis muscle when attempting to flex the elbow, providing the first indication of successful reinnervation. By 5 months post surgery, the patient could voluntarily activate four different regions of the pectoralis major muscle by attempting to move his phantom arm. This finding suggested that the peripheral and central sensory pathways are still present and active even after a long period of deactivation (Kuiken et al., 2009).

Chen et al. (2013) demonstrated that a few months after targeted nerve distribution reconstruction, a new functional connection between the nerve and the target muscle can be established, restoring motor function. This reconstruction allows the nerve to re-establish a "normal" motor cortical map of the missing limb, which is associated with motor function. The TMR technique enables the reconnection of residual nerve fibers with the target muscle, restoring motor function to the amputated limb and enhancing the microenvironment for the survival of residual nerve fibers and neuronal cell bodies, leading to effective reinnervation of limb muscles (Lu et al., 2022a, b). In addition to restoring motor function, TMR has proven effective in transhumeral amputees (**Figure 4D**). For example, the median nerve was surgically transferred to the short head of the motor branch of the biceps brachii muscle to restore hand closure or forward flexion. The ulnar nerve was transferred to the residual brachioradialis muscle motor branch, providing an additional site for control of the biceps brachii muscle. The radial nerve was reinnervated to the lateral head of the motor branch of the triceps brachii, enabling the control of hand opening or extension. Furthermore, the TMR technique restores nerve reinnervation of tactile, pressure, vibration, and temperature sensations in the skin of the missing limb (Cheesborough et al., 2015). This suggests that replanting nerves into other muscles can effectively extract sensory signals, enabling bidirectional feedback for prosthetic control. By enhancing both motor and sensory reinnervation, TMR offers a comprehensive approach to improving amputees' functionality and quality of life.

TMR is particularly well-suited for individuals with upper limb amputations who require enhanced control over myoelectric prosthetic devices. It is also especially beneficial for patients experiencing neuroma-related pain and phantom limb pain and can effectively address these issues by providing new targets for nerve endings (Dumanian et al., 2019; Mioton et al., 2020; Kang et al., 2022). Additionally, TMR is advantageous for those needing multiple degrees of freedom in their prosthetic control, improving their fine motor skills and reducing reliance on visual feedback for movement. Finally, the use of this technique is also effective at restoring motor function in transhumeral and shoulder disarticulation amputations by reinnervating target muscles with residual nerves.

Advantages and disadvantages of targeted muscle reinnervation

TMR offers several significant advantages, providing substantial relief from neuroma and phantom limb pain and enhancing the control of prosthetic devices through improved EMG signal quality (Bowen et al., 2017, 2019). Additionally, TMR enables sensory feedback, improving the user's sense of embodiment and interaction with their environment. This technique allows for more intuitive prosthetic control by converting neural signals into muscle signals that the prosthetic device can detect. However, TMR also has its disadvantages. The surgical procedure is complex, requiring extensive anatomical knowledge and precise surgical skills. There is a risk of nerve damage during the procedure, and postoperative rehabilitation can be lengthy and intensive. The initial costs associated with TMR, including surgery and rehabilitation, are high, and the need for advanced prosthetic technology to interpret the enhanced signals adds to the overall expense.

The future of TMR technology is promising, with ongoing research and development focused on improving surgical techniques and outcomes. Innovations in imaging and neurophysiological mapping are expected to enhance the precision of nerve transfers, reducing the risks associated with the surgery. Advances in prosthetic technology, including the integration of machine learning algorithms and enhanced signal processing, are likely to improve the functionality and responsiveness of prosthetic limbs. Furthermore, the development of hybrid systems combining TMR with other neuroprosthetic technologies, such as RPNI and BMI, could offer more comprehensive solutions for amputees. As these technologies evolve, they are expected to become more accessible and affordable, providing advanced prosthetic solutions to a broader range of patients. The potential for bidirectional sensory feedback remains a key area of research, aiming to provide users with a more natural and integrated prosthetic experience.

Comparing targeted muscle reinnervation with regenerative peripheral nerve interfaces

Both TMR and RPNI are innovative surgical techniques designed to enhance prosthetic limb functionality by interfacing with the peripheral nervous system. TMR involves rerouting residual nerves to the remaining muscles, transforming them into bioamplifiers for motor control signals, which is particularly beneficial for performing complex upper limb movements (Tian et al., 2024). In contrast, RPNI involves grafting free muscle tissue onto the end of a severed nerve, creating a stable platform for nerve signal extraction and transmission that makes it applicable for both upper and lower limb amputations. While both techniques aim to reduce neuropathic pain and improve motor control, TMR typically involves more complex procedures with detailed neurophysiological mapping, whereas RPNI focuses on creating a reliable biological interface through muscle grafts. Choosing between TMR and RPNI will depend on the individual patient's needs, with TMR offering precise control for intricate movements and RPNI providing a simpler, direct nerve–muscle interface for effective prosthetic integration (Ohnishi et al., 2007).

Targeted sensory reinnervation

TSR is an innovative surgical procedure designed to restore sensation to amputees by rerouting residual nerves in the amputated area to connect with different sensory nerves (**Figure 5A** and **B**). This technique provides patients tactile feedback from their prosthetic limbs through newly established neural pathways (Hebert et al., 2014). TSR's success relies on a comprehensive understanding of neuroanatomy and the sensory system (Adidharma et al., 2022). Prior to surgery, neurophysiological examinations and imaging assessments are conducted to identify the location and pathways of the remaining sensory nerves at the amputation site. This enables the selection of suitable sensory nerves for reinnervation and predicts potential outcomes of postoperative sensory recovery. Clinical anatomical models, such as sensory neuroanatomy and systemic anatomy, are frequently applied in TSR reconstruction (Hebert et al., 2016).

During the surgical procedure, an anastomosis is performed between the residual nerve at the amputation site and a specifically chosen sensory nerve (Taminato et al., 2021). This precise anatomical localization and reconstruction restore sensory transmission to prosthetic or artificial limbs. The connection can be achieved through direct neuroanastomosis, where the nerve ends are sutured together, or using a nerve graft to bridge the gap between the residual and sensory nerve. The integration of advanced surgical techniques and detailed anatomical knowledge in TSR has significantly improved the quality of life for amputees. By restoring sensory feedback, TSR allows amputees to experience a more natural interaction with their prosthetic limbs, enhancing both functional outcomes and overall patient satisfaction (Cage et al., 2013). This procedure represents a major advancement in neuroprosthetics, offering a comprehensive solution to the challenge of sensory loss in amputees by rerouting residual nerves to sensory nerves in the skin, thus providing tactile feedback from the prosthetic limb. The combination of engineering technology and medical expertise in TSR has dramatically enhanced patient outcomes and quality of life. For instance, by reconnecting the median, ulnar, and radial nerves to appropriate sensory receptors, patients can regain the ability to feel touch, pressure, and temperature changes. This improves the functional use of the prosthetic limb and reduces phantom limb pain, providing a more holistic rehabilitation approach. In addition, detailed anatomical mapping ensures precise nerve connections, minimizing the risk of neuromas and enhancing the stability and longevity of the sensory feedback provided by the prosthesis (**Figure 5**).

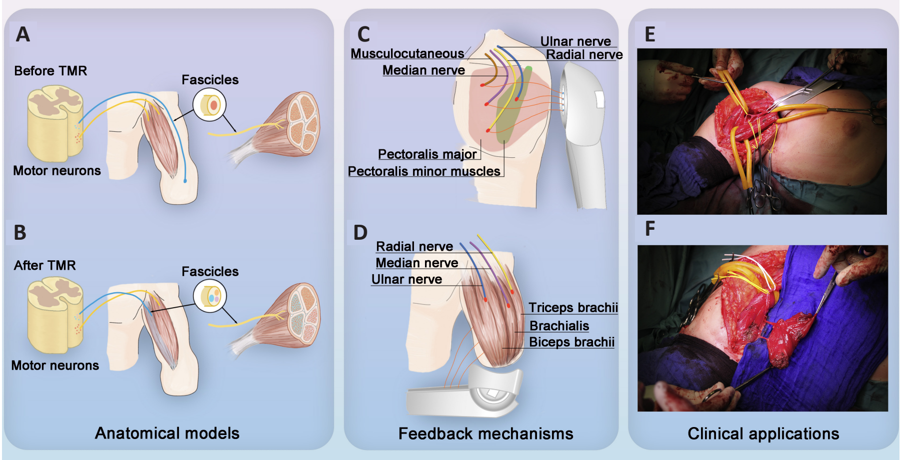

Figure 4 | TMR model diagram and surgical case diagram.
(A) Anatomical models indicating peripheral nerves typically innervate multiple muscles through different motor fascicles, with the motor neurons located in the spinal cord's motor neuron columns. Each motor neuron controls a specific number of muscle fibers, known as the muscle unit. After amputation, these motor neurons and fascicles remain intact but lose their function. (B) During TMR surgery, the amputated nerves are transferred to replace the original motor nerve of the target muscle. The donor nerve used in TMR surgery is usually a multi-fascicular nerve that contains a higher number of motor neurons. As a result, the targeted muscle receives a hyper-reinnervation from a more significant number of motor neurons, forming smaller muscle units. The individual motor fascicles may also establish fascicular territories within the muscle, potentially allowing independent contraction. Adapted from Bergmeister et al. (2017). (C) According to human anatomy, the pectoralis major muscle is divided into upper, middle and lower segments. The musculocutaneous nerve was implantead into the upper segment of the pectoralis major muscle. The median nerve was sutured to the middle segment of the pectoralis major muscle. The radial nerve was sutured to the lower segment of the pectoralis major muscle. The ulnar nerve was implanted into the pectoralis minor muscle. (D) The TMR technique applied to upper limb amputation: The illustration shows the transfer of the ulnar, radial, and median nerves to the triceps brachii, brachialis, and biceps brachii muscles, respectively, to provide new motor pathways and enhance prosthetic control. Adapted from Bergmeister et al. (2017). (E, F) Surgical diagram of TMR humeral amputation. (E) Recognition of the biceps and musculodermal nerve before nerve transfer. (F) Surgical separation of EMG signals involves separating the muscle from its point of origin, while leaving the pedicle intact. Nerve transfers are then performed to reinnervate the muscle, creating a new target signal for EMG. Reprinted from Bergmeister et al. (2021). Copyright 2021 Elsevier Inc. EMG: Electromyographic; TMR: targeted muscle reinnervation.

Challenges and advanced solutions of targeted sensory reinnervation

TSR is particularly indicated for upper limb amputees who require enhanced sensory feedback to enable better prosthetic control and a more natural interaction with their environment (Festin et al., 2024; Huang et al., 2024). Because rerouting nerves to new sensory sites can relieve pain, the procedure is especially beneficial for patients suffering from phantom limb pain (Sparling et al., 2024). TSR is also ideal for amputees needing precise control of their prosthetics, as it reestablishes sensory pathways that enable more nuanced and intuitive use of prosthetic limbs.

Despite TSR's regenerative capabilities and effectiveness in generating tactile feedback, patients have reported unsatisfactory sensory feedback post-surgery. This issue arises because the reinnervated skin, which overlays the muscles, produces additional EMG signals, complicating the extraction of the signals needed for precise control. Additionally, a significant amount of skin surface area is required for successful TSR due to the use of touch feedback tactile equipment and EMG electrodes. This presents a challenge for amputees who have limited skin surface area. Larger skin surface areas provide more contact points, enhancing the accuracy and precision of haptic feedback and ensuring optimal contact between EMG electrodes and muscles, which enables more accurate and reliable detection and recording of muscle signals (Cage et al., 2013).

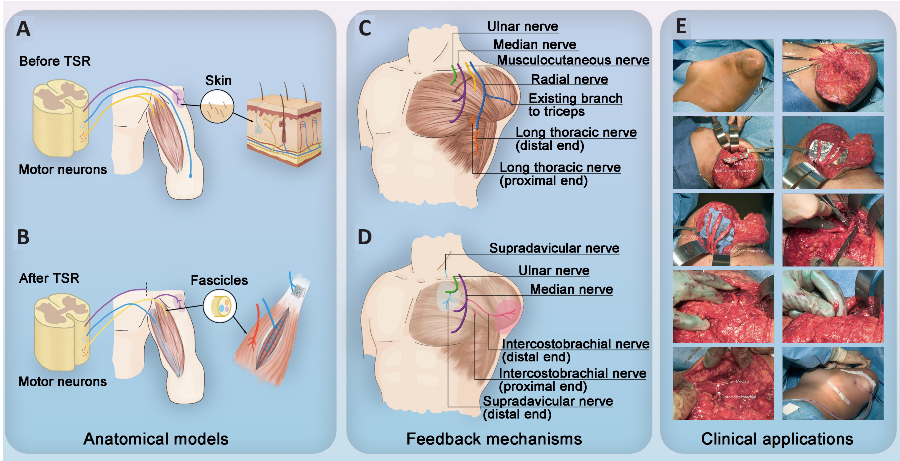

Figure 5 | A series of detailed diagrams of the TSR and TMR procedures.
(A, B) The atomic model of TSR. (A) Before TSR, the motor neurons and fascicles remain intact but lose their function after amputation. (B) After TSR, the residual nerves are connected to sensory nerves in the skin, allowing for sensory feedback from the prosthetic limb, thus rerouting the motor neurons' signals to the skin's sensory receptors. Adapted from Bergmeister et al. (2017). (C) The TMR procedure, where the musculocutaneous, ulnar, and median nerves are transferred to different sections of the pectoralis major muscle. Additionally, the long thoracic nerve, which innervates the lower three slips of the serratus anterior muscle, is divided, and its distal segment is connected to the radial nerve. This procedure allows patients to control prosthetic movements with greater precision and without relying solely on visual feedback. Clinical applications are demonstrated by two subjects who underwent TMR combined with TSR surgery and are now capable of controlling the movement of objects and cups. (D) The TSR procedure, where the supraclavicular cutaneous nerve is cut and its distal segment connected to the ulnar nerve, and similarly, the intercostobrachial cutaneous nerve is cut and coapted to the median nerve. The remaining triceps muscle is preserved, with the remnant identified using a nerve stimulator, and any fat and scar tissue over the remnant triceps muscle is excised to enhance the surface myoelectric signal. (E) The surgical procedure diagrams, which illustrate the clinical applications and outcomes of these detailed and meticulous surgical techniques, ultimately improving the sensory and motor integration of the prosthetic limb. C–F were reprinted from Kuiken et al. (2007b). TMR: Targeted muscle reinnervation; TSR: targeted sensory reinnervation.

Researchers are exploring alternative methods to enhance TSR's functionality to address these challenges. This includes developing advanced prosthetic systems that use artificial intelligence and machine learning algorithms to improve the interpretation of EMG signals (Shu et al., 2024). These systems can adapt to the user's specific patterns of movement and sensation, providing more intuitive and responsive control of the prosthetic limb. Advances in material science are also contributing to the development of more biocompatible and flexible EMG electrodes (Cheng et al., 2023; Imani et al., 2024). These electrodes, made from materials such as silicone, hydrogels, and stretchable electronics, can conform more closely to the skin and muscle tissue, improving the quality of signal acquisition and reducing the discomfort associated with rigid electrodes (Zhang et al., 2023; Harland et al., 2024). Integrating these new materials can enhance the overall user experience by providing more stable and reliable connections between the electrodes and the underlying muscle tissue. Furthermore, exploring alternative sensory feedback mechanisms, such as vibrotactile and electrotactile feedback, offers potential solutions to the limitations of current TSR techniques. These feedback mechanisms can provide more nuanced and varied sensory experiences, such as the ability to feel different textures, detect varying pressure levels, and sense temperature changes, potentially improving users' overall satisfaction with their prosthetic devices. For instance, vibrotactile feedback can simulate the sensation of vibrations corresponding to different surface textures, while electrotactile feedback can mimic the sensation of touch by delivering small electrical stimuli to the skin.

Comparing targeted muscle reinnervation with targeted sensory reinnervation

TMR and TSR are both advanced surgical techniques designed to enhance the functionality of prosthetic limbs for amputees, yet they focus on different aspects of neural interface technology. TMR's primary aim is to improve motor control by rerouting residual nerves to new muscle targets, transforming these muscles into biological amplifiers that generate clear and strong EMG signals for myoelectric prosthetic control. This technique is especially beneficial for upper limb amputees who require multiple degrees of freedom in their prosthetic movements, and it has the added advantage of reducing neuropathic pain by preventing neuroma formation. In contrast, TSR focuses on restoring sensory feedback by connecting residual nerves to new sensory nerve targets, allowing patients to perceive tactile sensations such as touch, pressure, and temperature through their prosthetic devices. This sensory feedback is crucial for improving the functional use of the prosthesis and enhancing the user's interaction with their environment. While TMR excels in providing precise control over prosthetic movements, TSR addresses the critical need for sensory feedback, which is essential for a holistic rehabilitation approach. Both techniques require complex surgical procedures and a deep understanding of neuroanatomy, but they offer complementary benefits that can significantly improve amputees' quality of life. However, each technique also presents unique challenges, such as the need for extensive skin surface area in TSR and the high surgical skill required for TMR, highlighting the necessity for continued innovation and multidisciplinary research in neuroprosthetics.

Proprioceptive Feedback–Related Neural Machine Interface Technology

Technologies like TSR provide valuable sensory input like touch and pressure yet overlook proprioception—the ability to sense limb position and movement—a critical aspect of limb function. Similarly, while TMR enhances prosthetic control precision by supplying residual EMG and neuroelectrical signals, it does not address the regulation of postural adjustments and balance maintenance, which are primarily managed by proprioceptive receptors in the joints, muscles, and tendons (Kwak et al., 2020; Mendez et al., 2020; Valle et al., 2021). Walking, for example, requires a delicate interplay of low-level and high-level cognitive control; individuals using prostheses must engage in heightened cognitive processing to achieve successful mobility (Gallone and Naish, 2022; Tran et al., 2022). Despite significant advancements in prosthetic functionality with the use of contemporary technologies, there is ample room for further development in addressing the intricate and multifaceted challenges associated with the prosthetic sense of posture and movement.

Agonist–antagonist myoneural interface

The Clites team introduced the AMI as an approach for proprioceptive reconstruction with the aim of addressing these challenges (Clites et al., 2018a; Herr and Carty, 2021). This method establishes a direct connection between two muscle tendons in a serial arrangement, where one functions as the agonist muscle and the other as the antagonist muscle. By reconstructing the fundamental muscle–tendon relationship between the agonist and antagonist, this technique can potentially restore sensory feedback and establish a mutually beneficial muscle connection. It effectively sustains the tension of the agonist muscle while preserving the intricate muscle receptor activation pattern (Srinivasan et al., 2017; Clites, 2018). AMI reconstruction relies on a thorough understanding of muscle anatomy. Surgeons must comprehend the anatomical structure and trajectory of corresponding active and opposing muscles to choose the right muscles for surgery. Following reconstruction, AMI technology can be implemented using surgical techniques. The residual muscle is reconnected to the selected antagonist muscle at the amputation site to restore muscle control (Srinivasan et al., 2021b).

Between 2016 and 2019, preclinical trials at the Massachusetts Institute of Technology used murine and caprine animal models to scientifically evaluate AMI (Clites et al., 2019). These studies showed that both native and regenerative AMI constructs cause the agonist muscle to contract in sync with the electrical activation of its motor nerve. This contraction produces a graded EMG signal in the agonist muscle and a corresponding stretch in the antagonist muscle. Additionally, the research demonstrated that AMI provides afferent neural feedback, which increases proportionally with the stretch of the antagonist muscle caused by the contraction of the linked agonist muscle. These findings suggest that AMI can convey meaningful proprioceptive feedback from a prosthetic limb by replicating the dynamics between the agonist and antagonist muscles that are essential for physiological proprioception (Chicos et al., 2024).

Clites et al. (2018b) applied the AMI technique to a 53-year-old male patient who had undergone an elective unilateral transtibial amputation (**Figure 6**). To enhance control over prosthetic gait, the patient's posterior tibialis muscle was connected to the tibialis longus muscle to regulate prosthetic internal rotation and abduction. The lateral gastrocnemius muscle was also attached to the tibialis anterior muscle to control prosthetic internal rotation and dorsiflexion. Myoelectric signals were captured from four bipolar surface electrodes to regulate prosthetic gait by way of muscle synergy. The outcomes revealed significantly improved prosthesis control compared to conventional surgery. Contraction of the agonist's muscle by standard motor efferent nerves not only activates its native contractile mechanoreceptors but also mechanically couples native intra-axial stretch fibers of the antagonist's muscle. Both mechanisms provide afferent proprioceptive signals via the sensory components of their respective innervated nerves. Subsequent activation of the antagonist muscle induces complementary stretching of the agonist muscle, enabling AMI to replicate the physiologically relevant mechanical coupling of agonist–antagonist muscles. This provides non-isometric bundle strain and feedback on the state of the agonist–antagonist muscle bundle (Herr and Carty, 2021).

Amputation entails the loss of the entire limb, including nerves, muscles, blood vessels, skin, bones, and joints (He et al., 2023). Hence, the reconstruction of limb function is contingent upon rebuilding the body's motor and superficial sensory functions. Based on the original amputation method, the AMI technique integrates nerves, muscles, and superficial pathways into a cohesive unit. This simplified surgical approach minimizes bodily impact due to muscle grafting (Srinivasan et al., 2020b). The agonist–antagonist muscle interface converts sensory input from prosthetic devices related to muscle stretch and tension into neural signals, utilizing endogenous tissue mechanoreceptors. This method also employs adaptive interface techniques and proprioceptive feedback mechanisms associated with natural neural pathways to re-establish sensory capabilities, such as movement position and vibration perception in the limb (Carty and Herr, 2021).

The AMI technique is particularly beneficial for patients undergoing transtibial or transfemoral amputations, as it can significantly improve prosthetic limb control by restoring the natural agonist–antagonist muscle relationship (Harrington et al., 2023). This method is especially advantageous for those seeking to regain a more natural gait and proprioception, which are crucial for coordinated and balanced movements. Clinical studies have demonstrated AMI's effectiveness in providing meaningful proprioceptive feedback and improving the overall functionality and integration of advanced prosthetic limbs (Slootweg, 2023).

One of the primary advantages of AMI is the restoration of proprioceptive feedback. This feedback also reduces the risk of phantom limb pain and neuromas (Srinivasan et al., 2020a, 2021a). By having more intuitive control of prosthetic devices, users can perform complex tasks without relying solely on visual cues. Additionally, AMI enhances the overall sense of embodiment and integration of the prosthetic limb, contributing to better functional outcomes and user satisfaction.

However, the procedure is complex and requires extensive anatomical knowledge and precision, risking surgical complications. Integrating AMI with prosthetic devices requires advanced signal processing and adaptive control algorithms, which can be costly and require significant computational power. Additionally, the long-term stability and maintenance of the interface can be challenging, necessitating ongoing technical support and potential revisions. The reliance on sophisticated technology may also limit its accessibility and widespread adoption.

Despite these challenges, the future of AMI technology is promising, and current research is focusing on enhancing its integration with advanced prosthetic systems. Innovations in material science, such as the development of more flexible and biocompatible electrodes, aim to improve the interface's durability and signal quality. Advances in machine learning and adaptive control algorithms are expected to refine the interpretation of proprioceptive signals, enabling more responsive and intuitive prosthetic control. Researchers are also exploring the potential of combining AMI with other neural interface technologies to create a more comprehensive and seamless sensory feedback system. These developments hold the potential to significantly enhance the quality of life of individuals with limb amputations by providing more natural and effective prosthetic solutions (Homs-Pons et al., 2024; Song et al., 2024).

Brain–Machine Interface/ Brain–Computer Interface

Neural interfaces provide direct access to electrophysiological information from the nervous system using miniature electrodes to contact neurons. This allows for the study of higher cellular resolution methods of cortical communication. BMI/brain–computer interfaces (BCIs) offer a more direct way of making contact with the brain's motor and sensory cortex (Kingwell, 2012; Balasubramanian et al., 2017; Zhang et al., 2024). Limb receptors have a special coding function that converts changes in external stimuli into afferent neural action potentials, which are then transmitted to the appropriate sensory cortex, which will process the information from the external stimulus and provide feedback (Flesher et al., 2021). The brain then sends commands from the motor cortex through motor nerves to the limbs to complete motor control. Types of BMI/BCI are classified as invasive or non-invasive. Invasive BCIs offer more accurate signals by surgically implanting electrodes, but they entail surgical risks. Non-invasive BCIs, such as EEG, provide a risk-free and painless option but may be subject to potential signal interference, compromising signal quality (Liu et al., 2023; **Figure 7**).

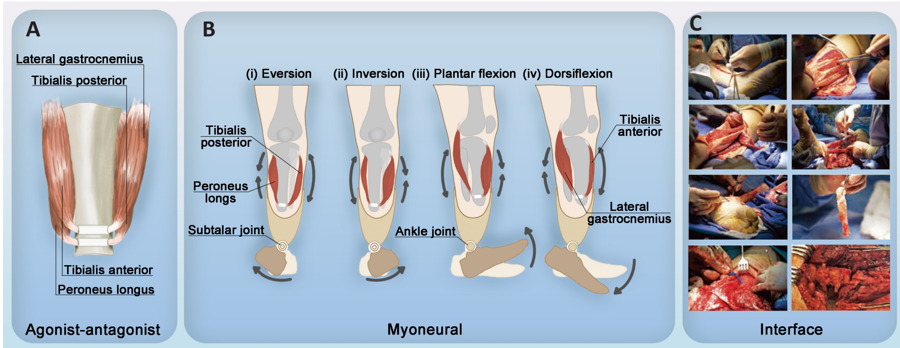

Figure 6 | AMI model diagram and surgical case diagram.
(A) Anatomical models: The tibialis posterior muscle is connected to the tibialis longus muscle, and the gastrocnemius lateralis muscle is connected to the tibialis anterior muscle, thus forming two AMI models. During primary transtibial amputation, two AMIs are surgically created. Tarsal tunnels extracted from the amputated ankle joint are securely fastened to the medial side of the tibia, serving as pulleys for the AMIs. Once the patient has been fitted with a robotic prosthesis, the proximal and distal AMIs are connected to the prosthetic ankle and subtalar joints, respectively, using myoelectric signals. Two AMIs, for controlling prosthetic subtalar and ankle joint movements, were surgically implanted in the residual limb of a patient. (B) The movements of the prosthetic subtalar and ankle joints. (i) The prosthetic subtalar joint rotates outwards (indicated by the arrow) when the peroneus longus muscle contracts, resulting in the stretching of the tibialis posterior muscle. (ii) The subtalar joint rotates inwards (indicated by the arrow) when the tibialis posterior muscle contracts, leading to the stretching of the peroneus longus muscle. (iii) The prosthetic ankle joint bends upwards (indicated by the arrow) when the tibialis anterior muscle contracts, causing the stretching of the lateral gastrocnemius muscle. (iv) The ankle joint undergoes plantar flexion (indicated by the arrow) as a result of contraction of the lateral gastrocnemius muscle, which stretches the tibialis anterior muscle. Dashed arrows represent muscle contraction and stretching. (C) Clinical applications: Surgical diagram. Reprinted from Clites et al. (2018a). AMI: Agonist-antagonist myoneural interface.

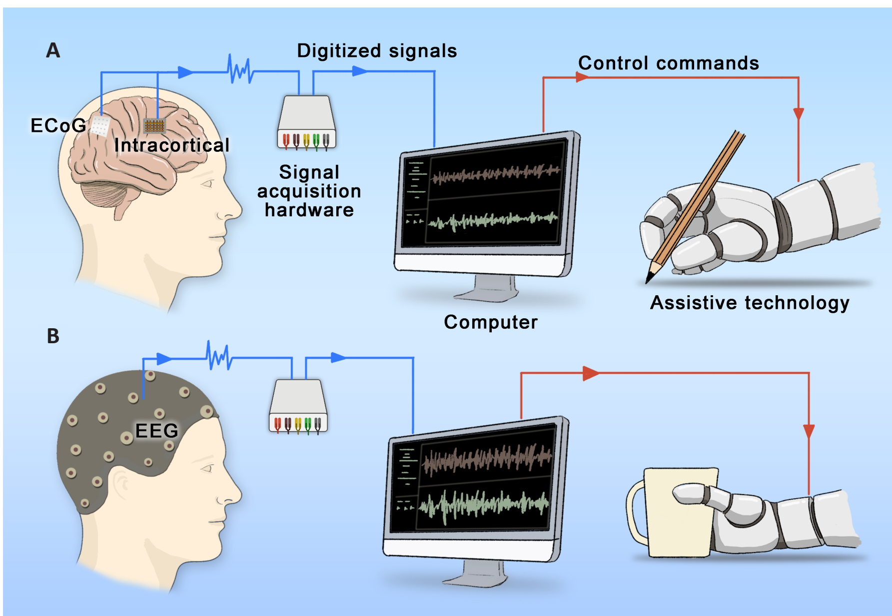

Figure 7 | An illustration of BCI systems.
(A) Invasive BCI methods: ECoG (Electrocorticography): Electrodes are placed just below the surface of the cerebral cortex to record neural signals. ECoG provides more precise signals than EEG but is relatively less invasive compared to other techniques. It is commonly used in situations where higher signal fidelity is needed without penetrating deeply into the brain tissue. Intracortical: Microelectrodes are inserted directly into the cerebral cortex to record the activity of single neurons or small groups of neurons. This is a highly invasive technique that offers extremely fine and detailed neural signals, making it ideal for precise neural studies and applications requiring detailed neuronal data. The neural signals captured through ECoG or Intracortical methods are digitized by signal acquisition hardware, processed by a computer, and used to control assistive technology, such as a robotic hand holding a pencil. (B) Non-invasive BCI methods: EEG electrodes are placed on the scalp detect brain activity. The captured signals are digitized, processed by a computer, and used to control assistive technology, such as a robotic hand holding a cup. BCI: Brain–computer interface; ECoG: electrocorticography; EEG: electroencephalography.

Invasive brain–computer interface

BCIs involve directly implanting a microelectrode array into the cerebral cortex, providing high-resolution neural recordings and robust control signals (**Figure 7A**). These microelectrode arrays can comprise hard metal electrodes or flexible high-density array electrodes. This advanced technology is particularly valuable for clinical applications. For motor restoration, invasive BCIs can significantly improve the quality of life of individuals with spinal cord injuries or limb amputations by decoding neural signals from the motor cortex to control prosthetic limbs or external devices, thereby restoring movement and independence (Moritz et al., 2008; Hochberg et al., 2012; Slutzky, 2019). In the treatment of neurological disorders such as epilepsy, invasive BCIs can monitor brain activity to predict and prevent seizures through precise neural modulation (Tabot et al., 2015; Flesher et al., 2016). In addition, these BCIs are being explored to enhance communication for patients with severe disabilities, such as those with locked-in syndrome, allowing them to interact with their environment through thought-controlled systems (Ang et al., 2010; Shanechi, 2019). The ability to directly tap into brain activity also opens new avenues for research into cognitive processes and neural disorders, potentially leading to more targeted and effective therapies. Additionally, invasive BCIs are being investigated for their potential to aid in neurorehabilitation, offering real-time feedback and training to patients recovering from strokes or other brain injuries (Selimbeyoglu and Parvizi, 2010). Emerging applications include the use of BCIs to manage chronic pain by modulating neural circuits involved in pain perception and providing sensory feedback from prosthetics, enabling users to experience touch sensations.

The surgical implantation of invasive BCIs requires meticulous planning and execution, often involving a multidisciplinary team of neurosurgeons, neurologists, and biomedical engineers. The process begins with detailed imaging studies, such as magnetic resonance imaging or computed tomography, to identify the precise location for electrode implantation. During the surgery, the patient's scalp is incised, and a small burr hole is drilled into the skull. Using advanced navigation systems, surgeons carefully insert the microelectrode array into the target brain region; for motor restoration applications, this is typically the motor cortex (Polikov et al., 2005; Seymour et al., 2017). Intraoperative monitoring is crucial to ensure accurate placement and to minimize potential damage to surrounding brain tissue. Post-operative care includes managing any immediate surgical complications and long-term monitoring of electrode function and biocompatibility.

Despite the remarkable potential of invasive BCIs, several drawbacks remain. The primary advantages of these systems include their high precision and robust control, allowing for accurate decoding of neural activity and effective modulation of brain functions. These systems enable precise interventions, which could potentially lead to significant improvements in patient outcomes for various neurological conditions. However, the implantation process carries significant surgical risks, such as infection, inflammation, and potential damage to brain tissue. Maintaining the long-term biocompatibility and stability of implanted electrodes is also challenging, with signal degradation over time being a common issue. Additionally, the cost of surgical procedures and post-operative care can be prohibitive, limiting accessibility for many patients. The use of flexible high-density array electrodes aims to mitigate some of these issues by improving biocompatibility and signal fidelity, but difficulties remain (Rashid et al., 2020). These disadvantages underscore the need for continued research and development to optimize the safety, efficacy, and accessibility of invasive BCIs. The precision and capabilities of these systems make them a powerful tool in modern neurotechnology and clinical neuroscience, but careful consideration of their limitations is essential for their successful integration into clinical practice (Saha et al., 2021).

Non-invasive brain–computer interface

Non-invasive BCIs use external devices like EEG caps to detect brain signals without the need for surgical implantation (**Figure 7B**). These BCIs are highly valuable in various clinical applications due to their safety and accessibility. For motor restoration, non-invasive BCIs enable individuals with spinal cord injuries or strokes to control external devices or robotic limbs with thought, facilitating rehabilitation and daily functioning (He et al., 2015; Forenzo et al., 2024). In treating neurological disorders such as epilepsy, non-invasive BCIs monitor brain activity to predict and manage seizures without invasive procedures (Mikołajewska and Mikołajewski, 2014). They also enhance communication for patients with severe disabilities, such as those with amyotrophic lateral sclerosis, by translating neural signals into text or speech (Zhuang et al., 2020). Additionally, non-invasive BCIs are being explored for cognitive training and neurofeedback in conditions like attention deficit hyperactivity disorder (ADHD) and depression (Khorev et al., 2024). Emerging applications include using BCIs for pain management by providing neurofeedback to help patients control pain perception and for sleep disorders by monitoring and adjusting sleep patterns through neural activity analysis (González-Zamorano et al., 2021; Demarest et al., 2024).

Although non-invasive BCIs have significant potential, several challenges hinder their widespread clinical adoption. These systems' primary advantages include their non-invasiveness, safety, and ease of use, making them accessible to a broader population without the risks associated with surgical procedures. However, they often suffer from lower signal resolution and higher noise levels compared to invasive BCIs, limiting the accuracy and reliability of the detected signals (Babiloni et al., 2000). Additionally, non-invasive BCIs provide less robust control, which may be insufficient for complex or fine motor tasks, and are more susceptible to interference from external factors. These disadvantages highlight the need for ongoing research and technological advancements to improve signal quality and control capabilities. Despite these limitations, non-invasive BCIs remain a powerful tool in neurotechnology, offering a non-invasive alternative for various clinical applications while ensuring patient safety and comfort.

The outlook for both invasive and non-invasive BCIs is highly promising, driven by ongoing technological advancements. For invasive BCIs, future improvements of the biocompatibility and durability of electrodes, along with enhanced signal processing through artificial intelligence, are expected to reduce complications and increase their clinical applications, such as in neuroprosthetics and neurological treatments. Non-invasive BCIs are set to benefit from advancements in sensor technology and machine learning, which will improve signal accuracy and robustness, making them more accessible and integrated into everyday technology for rehabilitation, mental health treatment, and human–computer interaction. These developments collectively indicate a transformative impact on healthcare and neurotechnology, with broader applications and improved patient outcomes.

Current Status and Requirements of Electrode Research and Development in Neural Machine Interface

In addition to the mentioned technologies, ongoing research is focusing on further enhancing the functionality and usability of prosthetic devices. Motor unit interfaces, for example, enable more intuitive control by directly interfacing with residual muscles, allowing users to manipulate prosthetic limbs with greater precision and naturalness. Current research in NMI focuses on enhancing the structure and performance of implantable electrodes to facilitate more intuitive and precise control of prosthetic devices. For instance, motor unit interfaces enable users to manipulate prosthetic limbs by directly interfacing with residual muscles, providing greater precision and naturalness in movement (Twardowski et al., 2019). The development of electronic skin adds tactile feedback, allowing users to perceive pressure and temperature, thus improving interaction with the environment (Wang et al., 2015; Chortos et al., 2016). Exoskeletons represent another promising avenue, offering support and assistance to individuals with mobility impairments by augmenting strength and endurance (de la Tejera et al., 2021). Additionally, advancements in bone fusion technologies have led to more secure and stable attachments between prosthetic limbs and the residual bone, reducing the risk of loosening or dislocation over time (Croft et al., 2023).

The full potential of prosthetic technology hinges on the development of long-term implantable electrode technology and sophisticated signal-processing algorithms. These innovations are crucial for ensuring reliable and precise communication between the user's nervous system and the prosthetic device (Liu et al., 2020). Additionally, research is underway to address the challenges associated with long-term implantation, such as changes in impedance and signal degradation over time. The groundbreaking work of Ortiz-Catalan et al. (2020), who successfully implanted a stand-alone robotic arm, represents a significant milestone in the field of prosthetics. Their achievement demonstrates the feasibility of establishing bidirectional communication between the user's nervous system and the prosthetic device, paving the way for more advanced and functional prosthetic solutions. The remarkable performance of the robotic arm in assisting users with various tasks underscores its potential to significantly improve quality of life for individuals with limb loss. As research and development in prosthetic technology continue to advance, it is essential to prioritize ongoing exploration and innovation. By continually pushing the boundaries of what is possible, researchers and engineers can create increasingly sophisticated and long-lasting prosthetic devices that offer enduring benefits to users. Ultimately, the goal is to empower individuals with limb loss to lead fulfilling and independent lives, with prosthetic technology playing a pivotal role in achieving this vision.

To improve the performance and longevity of neural interfaces, advancements in electrode technology are needed. Slim guidewire electrodes offer enhanced biocompatibility, but they may compromise signal acquisition due to their single-channel rigid design. Moreover, motion artifacts resulting from the mismatch between rigid electrodes and tissue modulus can introduce noise that interferes with signal processing. To address these challenges, there is a growing emphasis on developing denser and higher-resolution miniature electrodes capable of capturing more accurate neuroelectric and myoelectric signals (Kim et al., 2019; He et al., 2024). The field of flexible and stretchable electronics is rapidly evolving, offering unique advantages such as flexibility, stretchability, and adhesion, which are particularly well-suited for implantable electrical signal acquisition. Various types of electrodes, including thin-film electrodes, cuff electrodes, patch electrodes, and array electrodes, have been developed to accommodate the complex structures of muscle fibers, nerves, skin, and cortical tissue. Choi et al. (2020) developed stretchable, dynamic covalent polymers for soft, bioresorbable electronic stimulators designed to facilitate neuromuscular regeneration. These advanced materials exhibit long-term stability in biological fluids and enable high-resolution electrophysiological mapping, making them highly suitable for use in neural interfaces. The innovative design of these polymers ensures enhanced biocompatibility, mechanical resilience, and signal transduction capabilities, which are critical for successful integration into dynamic biological environments.

Yi et al. (2023) developed water-responsive supercontractile polymer films for bioelectronic interfaces, which offer enhanced biocompatibility and signal transduction capabilities. These polymer films can adapt to the dynamic environment of biological tissues, improving long-term integration and performance. Another study by Li et al. (2023a) introduced three-dimensional flexible electronics using solidified liquid metal with regulated plasticity that provide a versatile and durable solution for creating highly adaptable neural interfaces. These innovations demonstrate the potential for flexible electronics to significantly improve the functionality and reliability of NMIs by addressing critical issues such as biocompatibility, flexibility, and signal integrity. In a significant review, Song et al. (2020a) at Northwestern University highlighted advancements in bioelectronic systems that facilitate stability in biological fluids over extended periods. These systems enable multiplexed electrophysiological mapping with high spatial and temporal resolution across large areas. Notably, Song et al.'s review discusses systems that maintain stability in living animal models and have the potential to scale up to thousands of channels for human brain applications. This advancement represents a substantial step forward in neural interface technology, offering the possibility of more comprehensive and precise neural monitoring and stimulation. The stability and scalability of these bioelectronic systems pave the way for future research and clinical applications. For example, high-resolution mapping of neural activity can facilitate the development of more sophisticated brain–computer interfaces, allowing for finer control of prosthetic devices and potentially restoring more complex functions to individuals with neurological impairments.

Despite these advancements, flexible and stretchable electrodes face significant challenges, particularly regarding their long-term biocompatibility. Electrodes encapsulated by fibrous tissue during implantation can suffer from reduced performance and lifespan due to immune rejection (Valle et al., 2022). Consequently, enhancing the biocompatibility of flexible, stretchable electrodes has emerged as a critical area of focus for further research and development efforts in neural interface technology. These efforts involve several strategies. One approach is to develop biocompatible coatings that can prevent fibrous encapsulation and immune rejection. These coatings can be made from materials that mimic the properties of the extracellular matrix, promoting better integration with the surrounding tissue. Another strategy involves using advanced manufacturing techniques to create micro- and nanoscale features on the electrode surface, which can reduce the foreign body response and improve the stability of the electrode–tissue interface. Additionally, integrating bioactive molecules—such as anti-inflammatory agents or growth factors—into the electrode design can further enhance biocompatibility (Song et al., 2020b; Yang et al., 2024). These molecules can modulate the local immune response and promote tissue healing around the implantation site, extending the functional lifespan of the electrodes.

Looking to the future, the field of neural interfaces is poised for significant advancements. To eliminate the need for physical connectors, which can be a source of discomfort and infection, researchers are exploring the use of wireless technologies (Kong et al., 2024). Additionally, the integration of artificial intelligence and machine learning algorithms holds promise for improving the interpretation of neural signals and adapting the performance of prosthetic devices to the individual needs of users (Sun et al., 2023; Taha and Morren, 2024). Continuous advancements in electrode technology are crucial for improving neural interfaces. By addressing the challenges associated with biocompatibility and signal acquisition, researchers are paving the way for more reliable and durable neural interfaces. These innovations hold the potential to significantly enhance the quality of life for individuals relying on neural prosthetics and other implantable devices. As research progresses, the goal is to develop electrodes that can seamlessly integrate with the body's tissues, providing stable and precise neural communication over long periods (**Figure 8**).

Challenges and Conclusion

Neural interface technology offers promising prospects for individuals with limb motor and sensory dysfunction, with the potential to provide solutions that are more reliable than external mechanical devices. However, several challenges must first be addressed for this technology to realize its full clinical potential. One significant challenge is the potential interference of inherent neuromuscular signals with the acquisition of reconstructed neuromuscular signals. When the original anatomy is surgically altered, it is difficult to fully dissociate these signals, potentially leading to complications in signal interpretation and prosthetic control. This highlights the importance of understanding clinical anatomy, which can aid surgeons in evaluating the anatomical structure and trajectory of corresponding active and opposing muscles, thus enabling more precise surgical interventions.

In TSR procedures, for instance, a thorough understanding of sensory neuroanatomy is essential for identifying suitable targets for reinnervation. Surgeons must accurately locate and assess residual and other sensory nerves at the amputation site to facilitate successful reinnervation and restoration of sensory feedback. This requires a detailed understanding of nerve pathways, distribution patterns, and sensory receptor locations within the skin and muscles. Similarly, AMI reconstructions rely on a deep understanding of muscle anatomy to establish the desired muscle–tendon relationships. Surgeons must identify and select appropriate agonist and antagonist muscle pairs to ensure optimal function and proprioceptive feedback. Knowledge of muscle origins, insertions, innervation patterns, and functional interactions is critical for achieving successful muscle interface reconstructions.

Considerations of systemic anatomy are also essential for addressing challenges related to graft failure and postoperative care. Surgeons must navigate complex anatomical structures to isolate donor nerves, excise damaged tissues, and establish new neural pathways. A comprehensive understanding of vascular supply, tissue compatibility, and wound healing processes is crucial for ensuring successful surgical outcomes and long-term functional stability. Leveraging miniature, flexible electrode materials and high-density, multiple-channel configurations holds promise for improving nerve signal extraction and stability. Coupled with advancements in signal processing algorithms, including machine learning techniques, these innovations can enhance the accuracy and reliability of neural signal interpretation. By reducing noise and optimizing signal-to-noise ratios in real-time, these integrated approaches have the potential to overcome challenges related to signal acquisition and processing in neural interface technology. This interdisciplinary synergy between material science,

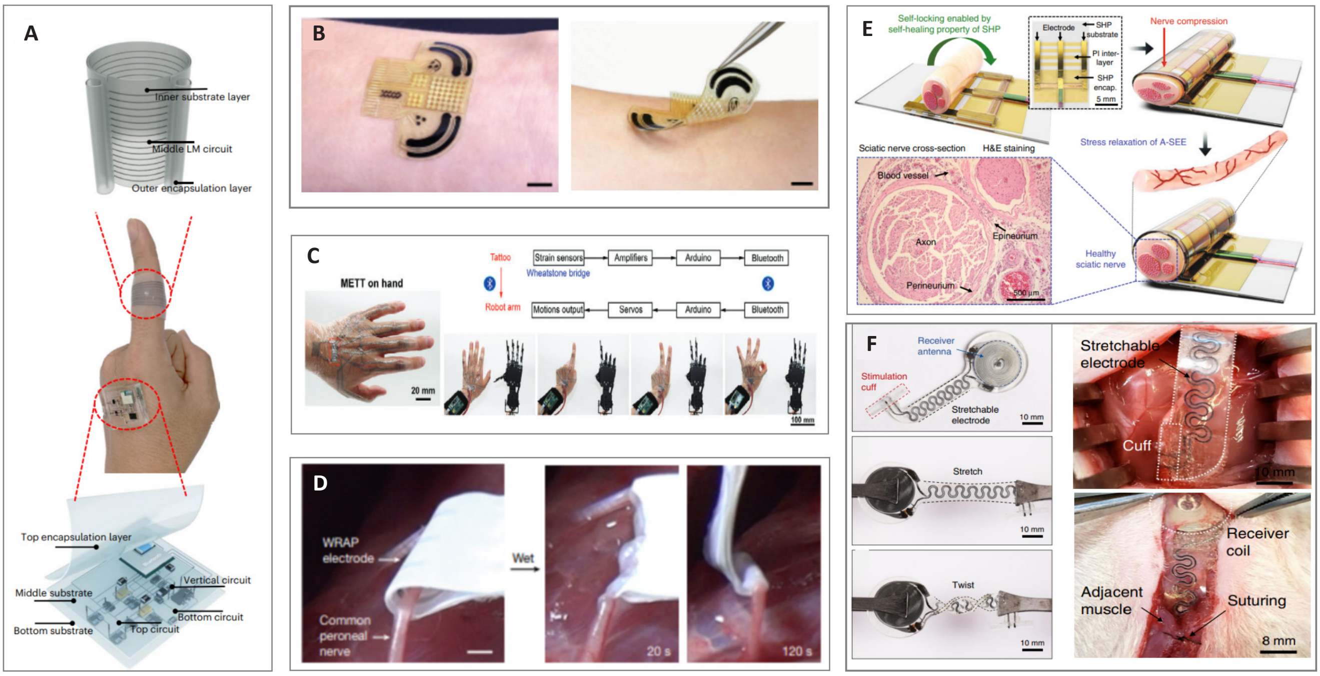

Figure 8 | Advanced electrode designs for neural interfaces.

(A) Three-dimensional flexible electronics. Reprinted from Li et al. (2023a). (B) Electronic skin. Reprinted from Xu et al. (2024). (C) Flexible wearable electrodes. Reprinted from Kong et al. (2024). (D) Water-responsive supercontractile polymer films for bioelectronic interfaces (Yi et al., 2023). (E) Adaptive self-healing electronic epineurium. Reprinted from Song et al. (2020b). (F) Absorbable electronic stimulator. Reprinted from Choi et al. (2020).

engineering, and computational neuroscience underscores the importance of collaborative efforts in advancing the field toward more effective clinical applications.

Additionally, there is a risk of graft failure during the reconstruction of anatomical relationships after donor nerve isolation and excision. This highlights the need for long-term solutions related to biocompatibility and signal stability during implantation. The use of miniature, flexible electrode materials and high-density, multiple-channel configurations could offer potential solutions to improve nerve signal extraction and stability. Furthermore, engineering efforts should address postoperative stump care, ensuring the functional stability of prosthetic systems and the development of lightweight, aesthetically pleasing exoskeleton devices. These considerations are essential for enhancing patient comfort, mobility, and overall quality of life.

Specific technologies and future prospects

Advancements in NMI technologies will continue to rely on the integration of clinical anatomy and neuroengineering. Researchers are exploring the use of wireless physiological signal acquisition methods and flexible neural tissue interface technologies to eliminate the need for physical connectors, reducing discomfort and infection risks. The development of self-healing materials promises to enhance the durability and longevity of neural interfaces. Artificial intelligence and machine learning algorithms are being integrated to improve neural signal interpretation and adapt prosthetic device performance to individual needs. These advancements could significantly enhance quality of life for individuals relying on NMIs. RPNI technology, facilitating nerve regeneration and enhancing motor control, shows promise in terms of long-term stability. Further research into optimizing muscle grafts and electrode integration could improve its efficacy and reliability. TMR and TSR techniques, which reroute nerves to muscles and new skin sites, respectively, could benefit from advancements in anatomical mapping and surgical precision. AMI technology, pairing agonist and antagonist muscles for bidirectional control, could see improvements through better anatomical mapping and more accurate sensor placement, enhancing the natural movement control of prosthetic limbs. Invasive BMIs, involving the surgical implantation of electrodes, provide high-quality signals but come with surgical risks. Future improvements could focus on developing less invasive methods that still offer high signal fidelity. Non-invasive BCIs could benefit from advancements in signal processing and machine learning algorithms to improve accuracy and usability, making them viable for a wider range of applications.

Clinical applications and future directions

The clinical applications of advanced NMIs are vast. They hold promise for improving prosthetic control, restoring sensory functions, and treating neurological disorders. For example, integrating electronic skin with prosthetic limbs can restore the sense of touch, significantly improving a user's interaction with their environment. NMIs are also being explored for the purpose of neurorehabilitation, with the aim of providing real-time feedback and training to patients recovering from strokes or other brain injuries. Ongoing research aims to address the remaining challenges, such as improving long-term biocompatibility and signal fidelity. By continually pushing the boundaries of what is possible, researchers and engineers can create increasingly sophisticated and long-lasting prosthetic devices that offer enduring benefits to users. Ultimately, the goal is to empower individuals with limb loss to lead fulfilling and independent lives, with prosthetic technology playing a pivotal role in achieving this vision.

Integration with clinical anatomy and animal models

These technologies all started out using animal models, such as rats, and then progressed to humans step by step. They have also relied on the development of anatomy understanding, ranging from the use of cadavers to today's digital humans and artificial intelligence. This progression highlights the importance of iterative testing and refinement in both basic research and clinical application. Animal models provided the initial proof of concept and safety data, which were crucial before transitioning to human trials. This stepwise approach ensured that each technology was thoroughly vetted and optimized for safety and efficacy. The integration of neuroengineering principles with clinical anatomy is essential for advancing NMI technologies. Neuroengineering provides the tools and techniques for creating sophisticated interfaces, while clinical anatomy offers the knowledge necessary for accurate and effective implementation. For instance, developing high-resolution electrode arrays for BCIs involves understanding the cortical layers and the types of neurons present, which are critical for optimizing electrode design and placement. Similarly, creating flexible and stretchable electrodes for RPNIs and TMR involves understanding the biomechanics and tissue properties of the target anatomical regions. This interdisciplinary approach ensures that NMIs are designed with a deep understanding of human physiology, leading to more effective and reliable outcomes.

Conclusion

While this review provides a comprehensive summary of the latest advances in neural interface technology, it is important to recognize certain limitations. The need to focus on key studies, incorporate the most recent literature, and adhere to article length constraints means that not all emerging trends or technological nuances could be explored in depth. Nonetheless, the insights presented here are intended to inform future research and development, highlighting the ongoing need to address the challenges and unlock the full potential of these technologies.

The progress of neural interface technology is critical for achieving more accurate nervous system control. This necessitates multidisciplinary collaboration involving biomedical engineering, surgery, and prosthetic device design fields. Addressing interface issues and developing new approaches to interacting with the peripheral nervous system are paramount. To achieve these objectives, sustained refinement of implantable technology and the development of intuitive, natural human–machine interfaces are necessary. Additional research and developmental efforts are crucial for overcoming existing limitations and establishing more efficient neural interfaces. Ultimately, these advancements hold the potential to significantly improve the lives of individuals with limb motor and sensory dysfunction, offering new opportunities for enhanced mobility and independence.

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