

Mechanoneural interfaces for bionic integration

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Abstract

Our expanding expertise in peripheral nerve regeneration and soft tissue reconstruction is enabling the development of novel innervated tissue constructs that can be combined with artificial interfacing technologies to facilitate control and sensation of limb prostheses. By utilizing the body's native afferent and efferent signalling pathways, these mechanoneural interfaces have demonstrated the capacity to enhance volitional prosthetic control, refer somatosensory sensation within proprioceptive and cutaneous modalities, and reduce post-amputation pain. This Review discusses the biophysical principles underpinning recent advancements in targeted reinnervation techniques, regenerative peripheral nerve interfaces and agonist–antagonist neuromuscular architectures that can be combined with artificial technologies, including implanted electrodes, magnetic interfacing and osseointegrated structures, for improved integration with upper-extremity and lower-extremity prostheses. Expanding the capacity for bidirectional information transfer between the peripheral nervous system and external assistive devices will increase the potential of prosthetic embodiment and rehabilitation.

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Key points

- A mechanoneural interface combines surgically modified soft tissue constructs, such as nerves and muscles, with artificial components to enhance peripheral neural signalling for the reconstruction of bionic limbs
- A more thorough understanding of end organ cross-innervation and regeneration dynamics may inform mechanoneural interface design
- Mechanoneural interfaces afford improved physiological efferent and afferent neural signalling that could sustain prosthetic embodiment
- Mechanoneural interface soft tissue constructs show reduced post-amputation pain and neuroma formation in clinical settings
- Next-generation mechanoneural interfaces suggest additional utility with respect to efferent prosthetic control and prosthetic somatosensation

Introduction

Sophisticated tool usage is a hallmark of humanity, and archaeological records from past millennia suggest that the practice of applying this skill toward restoring bodily form using prosthetic components began as early as 2,900 BCE¹. Although this intuitive approach to rehabilitation has persisted until the modern epoch^{2,3}, recent advances in medicine and artificial technology have enabled researchers to begin leveraging the complex interactions between these two aspects towards more integrative solutions^{4–7}. Their accelerating convergence marks the beginning of an age of bionics that are capable of facilitating sensation and fluid control of limb prostheses and other assistive devices⁸. New and exciting challenges emerge in the pursuit of fundamental physiological limits and the elusive nature of prosthetic embodiment, or the complete conscious and subconscious assimilation of an artificial limb^{9–12}.

To utilize the capabilities afforded by mechatronic devices of ever-increasing power density, computational capability and degrees of freedom towards complete rehabilitation from limb amputation^{13,14}, novel innervated soft tissue constructs have been developed that leverage advances in peripheral nerve regeneration and soft tissue reconstruction to increase the degree of restored human sensorimotor bandwidth. These surgically created soft tissue constructs are combined with artificial devices capable of sensing or stimulating to form mechanoneural interfaces (MIs) that facilitate prosthetic integration through the enhancement of efferent neural signals conveying motor commands outward from the peripheral nervous system (PNS), afferent neural signals conveying sensory information back from the external prosthesis to the central nervous system (CNS) or both. As its name suggests, an MI transduces neural commands to muscle actuation for use in efferent prosthetic control through muscle sensing or mechanical attachment, provides mechanical actuation to cause an afferent neural signal through biological mechanoreceptors, or enables both efferent and afferent modalities. For improved efferent signalling, contemporary MIs often increase the number of neuromuscular control sites along with their specificity. For improved afferent signalling, MIs typically utilize mechanoreceptors in muscle and cutaneous tissue to provide the user with somatosensory information. Additionally, free nerve-ending modalities, including chemical nociception

and thermoreception, are also available to provide auxiliary afferent signalling.

Considering the complexity of modern MIs, it may come with some surprise that a recognizable human example of an MI for efferent prosthetic control was implemented as early as 1900 (ref. 15). Originally designed by the Italian surgeon Giuliano Vanghetti and generally referred to as cineplasty, this approach to rehabilitation directly couples the body's residual musculotendinous tissue beneath the skin to cables that mechanically actuate a prosthetic joint, thus allowing for some muscular control of the prosthesis⁴. Today, cineplastic techniques are no longer popular due to issues related to skin irritation, infection, muscular fatigue and cases characterized by limited availability of natively innervated musculature^{16,17}. Despite challenges, a century of cineplastic exploration has yielded important suggestions for subsequent research in neuromuscular MIs. Contemporary efforts have continued to sharpen the resolution of MIs through computational integration with mechatronic devices^{4,7,18,19}. Looking forward, a sufficiently refined understanding of the scientific principles underpinning physiological mechanoneural transduction may even be applied towards augmenting baseline physical capability⁸.

In this Review, we discuss the development of modern MIs with increased control and sensing capabilities. These considerations are timely as the past 2 decades have borne witness to an accelerating interest in functionalizing soft tissues for improved clinical outcomes related to prosthetic control, sensory feedback and embodiment⁸. The first third of this Review outlines the importance of neural signalling for prosthetic interfacing and suggests mechanisms to enhance its quality. The subsequent section describes the capabilities and limitations of the following MI architectures most prevalently applied in clinical practice (Fig. 1): targeted muscle reinnervation (TMR) and targeted sensory reinnervation (TSR), regenerative peripheral nerve interfaces (RPNI), and the agonist–antagonist myoneural interface (AMI). The final section is dedicated to the many preclinical MI architectures currently being explored in animal models. To maintain a focused discourse on principles and applications of MIs, this Review provides only limited coverage of complementary topics, such as direct peripheral nerve interfaces, and it excludes altogether approaches pertaining to the control of mechatronics based on brain–computer interfaces.

A bionic approach to rehabilitation

The loss of a limb is objectively understood as a loss of physical ability. However, a person with amputation may additionally experience subjective disruptions to their subconscious body representation, sense of well-being and identity. Therefore, in addition to techniques that advance an artificial limb's physiological integration, researchers are simultaneously seeking methodologies to quantify the subjective outcomes of this integration to holistically address all mentioned deficiencies.

Post-amputation objectives

The human body requires a pervasive internal communications network to effectively manage its interactions with the environment. The PNS, primarily composed of long axons stemming from the brain and spinal cord of the CNS, fulfils this role through its enteric, autonomic and somatic subsystems. Of these, the somatic nervous system most acutely facilitates physical interaction by providing the CNS with afferent sensory signals through the dorsal root and conveying efferent motor commands through the ventral root of the spinal cord. Consequently, conventional limb amputation most acutely disrupts

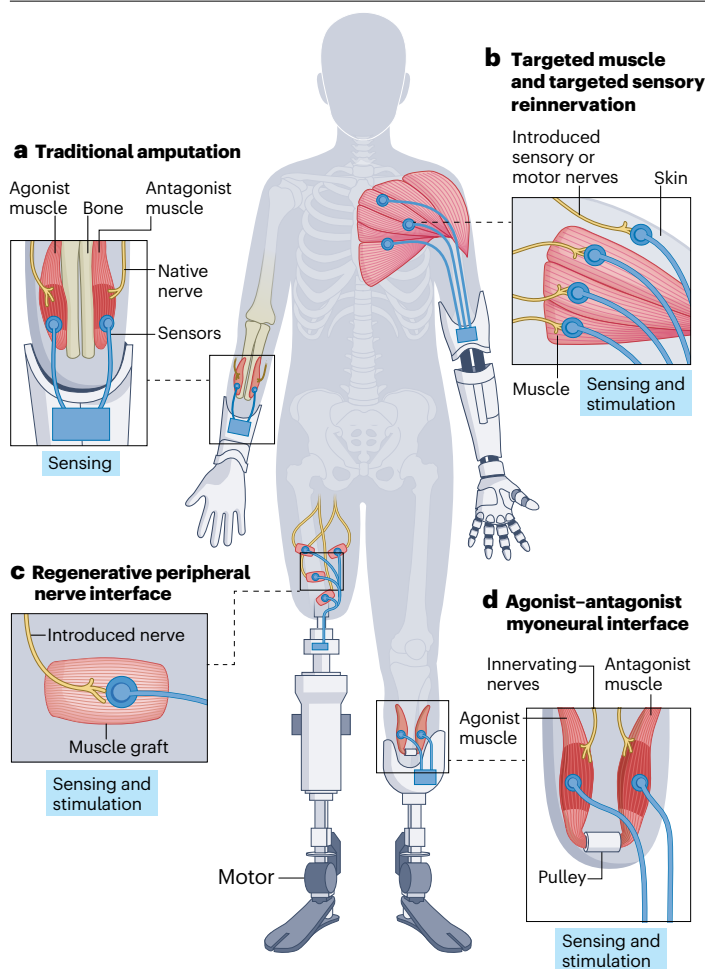


Fig. 1 | Conventional amputation and clinical mechanoneural interfaces.

a, Traditional amputation disrupts efferent and afferent signalling. Although efferent signalling may still elicit muscle contractions, muscles do not generate relevant limb dynamics, as they are surgically arranged to mitigate the risk of neuroma formation and optimally pad a prosthetic socket. Afferent proprioceptive signalling is negatively affected by the pathologically altered muscle insertion points and the loss of distal tissue, and it is further corrupted through mechanisms such as phantom limb pain. **b**, Targeted muscle reinnervation and targeted sensory reinnervation are neuromuscular and cutaneous mechanoneural interface constructs implemented in persons with amputation that are aimed at efferent control and somatosensory feedback. During targeted muscle reinnervation, non-native peripheral nerves are anastomosed (that is, surgically connected) to denervated but vascularized muscles. During targeted sensory reinnervation, sensory nerves or fascicles are directly coapted into dermal tissue or to the cutaneous nerve innervating dermal tissue. **c**, During the construction of regenerative peripheral nerve interfaces, denervated and devascularized muscle grafts are wrapped around transected motor nerves. Grafts are subsequently reinnervated over the course of many months to serve as biophysical amplifiers. **d**, The agonist–antagonist myoneural interface comprises the mechanical coupling of agonist and antagonist muscles for efferent and afferent signalling. This coupling allows for native mechanoreceptors, such as muscle spindles and Golgi tendon organs, to provide proprioceptive feedback through the mechanisms of muscle and tendon stretch, respectively.

this ability by transecting the biological pathways and structures necessary for closed-loop control of the body's extremities^{20,21}. Although somatosensory signals may still be afferently conducted along relevant dorsal root axons post-amputation, they are often corrupted through various pathological mechanisms that induce residual limb pain and phantom limb pain (PLP)^{22–24}. In the efferent direction, motor commands originating from a ventral root may still permit residual muscle contraction, but they can no longer generate joint dynamics and may only serve to stabilize the residual limb within a prosthetic socket²⁵.

The majority of research on prosthetic rehabilitation for persons with amputation has historically emphasized functionality^{26,27}. This approach focuses on decreasing prosthesis abandonment by optimizing the comfort of the socket interface, decreasing prosthesis weight and enhancing the ability of a prosthesis to fulfil the practical duties of the missing limb^{28–30}. Indeed, the scope of this research may be satisfactory for the minority of users who perceive prostheses as artificial tools and nothing more, as reported through interviews in which the distinction between artificial prosthesis and natural body is emphasized³¹. However, addressing psychosocial factors related to body representation and prosthesis adaptation using corresponding metrics of success is seen as increasingly important^{29,32}. Studies have also noted the additional desire for tactile and postural feedback when people gain experience using powered upper-extremity prostheses^{33,34}. These evolving demands suggest that the goals of

prosthetic rehabilitation may be more nuanced even if functionality remains a necessary component, especially as technology improves³⁵.

To unify these goals, researchers have begun to more evenly incorporate both functional and psychometric evaluations of interventions involving efferently controlled prosthetic devices with technologically induced afferent somatosensory feedback. A study involving two participants with transradial amputation demonstrated that biomimetic cutaneous feedback delivered through intraneural stimulation improved both functional performance and perceived naturalness of powered prosthesis use³⁶. Another study on two individuals with upper-extremity amputation found that providing both cutaneous and illusory kinesthetic feedback (that is, awareness of the position and movement of the prosthesis induced by vibrotactile stimuli) mediated by MIs improved functional performance with respect to providing cutaneous feedback alone. Furthermore, one participant reported that the presence of both feedback modalities increased the degree of prosthetic incorporation within their self-image³⁷. These studies, both published within the past 5 years, are representative of a larger trend in which experimental prosthesis researchers attempt to capture the novel subjective experiences made possible by combined efferent control and afferent feedback, while they simultaneously seek to refine the capabilities of both.

The pursuit of embodiment

The design of experimental limb prostheses is rooted in guiding principles derived from the human motor control theory established in the 20th century. These principles emphasize the simultaneous observation, generation and correction of limb dynamics in the task space by integrating afferent signals and efferent motor commands^{38,39} (Fig. 2). Within this framework, an optimal prosthetic interface allows the user to perceive all sensory modalities as they would with an intact limb, as the prosthesis concurrently generates the dynamics expected from the user's internal mental representation of their limb. The resulting perceptual experience of this idealized closed-loop control is referred to as embodiment.

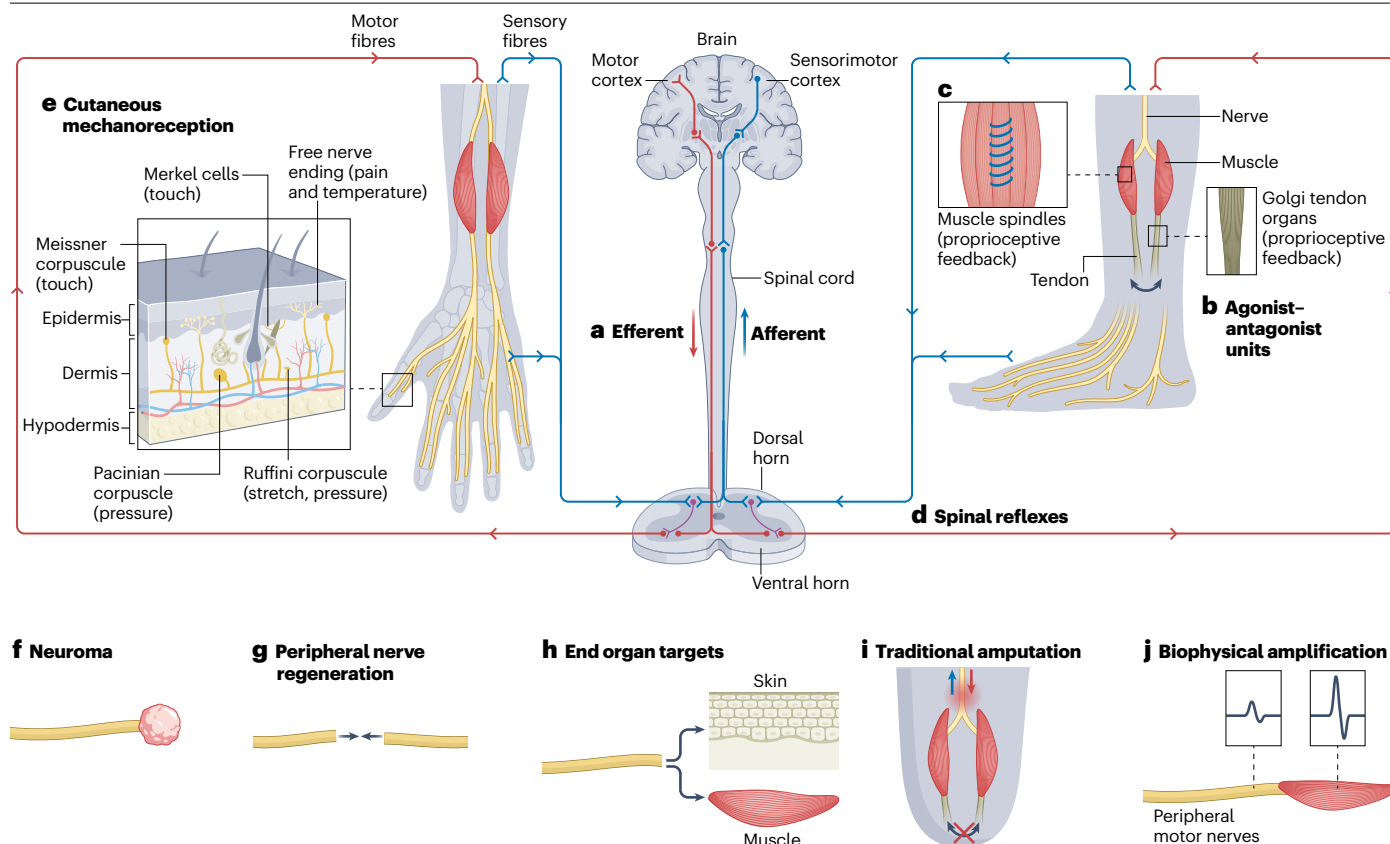


Fig. 2 | Principles of mechanoneural transduction and soft tissue reconstruction. **a**, Schematic of efferent signalling from and afferent signalling to the brain. Signals ultimately responsible for movement originate in the motor cortex and propagate impulse trains down to motor neurons located in the ventral horn of the spinal cord, before being conveyed to motor units that contract a particular muscle. **b**, Muscles in physiological agonist–antagonist pairs transfer force to the bone through tendons. Contraction of one muscle produces a corresponding stretch in its antagonist during non-isometric movements. **c**, Mechanoreceptors such as muscle spindles and Golgi tendon organs provide proprioceptive information that propagates back through the spinal cord to the sensory region of the sensorimotor cortex. **d**, Somatosensory afferents can also trigger motor neurons to amplify or suppress muscle activation through spinal reflexive circuits, without involvement of the sensorimotor cortex. Reflexes function to avoid injury or to quickly compensate for sudden dynamic

perturbations, among other purposes. **e**, Cutaneous mechanoreceptors, such as free nerve endings, Merkel cells, Pacinian corpuscles, Meissner corpuscles and Ruffini corpuscles, provide cutaneous sensory information to the cortex through the spinal cord. **f**, Neuromas form when transected nerves cannot find appropriate end organs and become entangled with non-neural soft tissue. Symptomatic neuromas generate nociceptive afferents and contribute to residual limb pain and phantom limb pain. **g**, Peripheral nerves have remarkable regenerative capabilities across lesions, so long as the distal portion remains unaffected. **h**, End organ targets for reinnervation are found in muscle and dermal tissue. **i**, Traditional amputation, with extant but pathological signal transmission through residual nerves and pathological muscle coupling (no agonist–antagonist coupling), can lead to phantom limb pain and residual limb pain. **j**, Muscles act as biophysical amplifiers that increase the magnitude of action potential spikes received from peripheral motor nerves by an order of magnitude.

The definition of prosthetic embodiment is a subject of active debate among academics and researchers focused on clinical realization. Some undertake efforts to redefine the phenomenon while, simultaneously, others evaluate the current working definition in clinical settings. Although the scope of this Review cannot encompass all opinions on embodiment, we give a concise overview of the most prominent perspectives to provide a contextual framework on motivations for bionic limb reconstruction.

Prosthetic embodiment is often conceptualized as being composed of at least two aspects, which have previously been defined as: i) ‘agency’, or the understanding that we are the initiator of the action and in control of the movement (volition); and ii) ‘ownership’, or the sense that parts of our own body belong to ourselves^{10,11}. Critically, these

studies argue that embodiment is a continuous perceptual state that is relatively agnostic to the nature of the substrates involved, whether artificial or biological. For instance, studies have demonstrated that the overall shape of a hand is crucial for fostering a sense of ownership in upper-extremity amputees⁴⁰, but skin colour and material composition of the limb itself do not hinder it^{41,42}. To underscore this idea, some academics have summarized key studies to propose alternative time-dependent and visceral principles that sustain the perception of ownership and agency, particularly in the context of the upper extremities⁴³: to facilitate ownership, sensory information should be synchronously integrated from an anatomically relevant appendage with spatial and tactile congruence^{44,45}. To facilitate agency, it is essential to establish a causal link between movement intent and the

corresponding spatial and temporal outcomes^{46–48}. As a corollary, the degree of agency is significantly reduced as a multivariate function of the magnitudes of spatial and temporal discrepancies^{47,49}.

An additional third aspect, ‘body representation’, is proposed by a different study and defined to be the “knowledge, beliefs, and experiences we have of the physical structure of our bodies, and the cognitive and neural mechanisms by which we dynamically interact with our physical bodies”¹². The authors posit that body representation can be divided into subcomponents that constitute the conscious body image and subconscious body schema. The body image encompasses the subjective experience of factors such as size, shape, structure, function and even beliefs held of the body^{50,51}. By contrast, the body schema encompasses the internalized forward and reverse models updated by somatosensory feedback that facilitate real-time control of the body and its environmental interactions⁵². To elaborate, the qualitative experience of a phantom limb is a phenomenon that can be cleanly classified under body representation, and a prosthesis that is represented within the body schema in a similar manner to an intact limb can be said to be ‘incorporated’⁵³.

Principles of mechanoneural interfaces

To minimize the gap between a bionic limb reconstruction and intact physiology, researchers now pursue a technology-assisted ‘digital nervous system’ as a means to mediate the dual nature of prosthesis function and embodiment. This term represents the physical implementation of the ideal human–prosthesis interface as a seamlessly integrated system of organic tissue and artificial components that enables computationally modulated sensing and stimulation. However, achieving technologies that enable afferent and efferent signalling at native information bandwidths, even within a single modality, remains a challenge. This Review presents a contemporary and expanding body of research that describes how MIs may operate within a digital nervous system to sustain prosthetic embodiment.

A modern MI is a surgically altered mechanoneural soft tissue construct with a synthetic interface for efferent and/or afferent signalling between the human PNS and an external prosthesis. In current practice, an MI most typically comprises surgically altered soft tissue constructs complemented by computationally modulated artificial components to facilitate biophysical amplification, selectivity and mechanoneural transduction of relevant motor and somatosensory neural signals. Biophysical amplification refers to the physiological propagation of alpha motor neuron action potential spikes into motor unit action potentials of greater amplitude. Selectivity is defined here as a measure of the ability to distinguish independent neural or biophysical signals that contain efferent or afferent information. Mechanoneural transduction is the forward and reverse conversion between neural action potentials and mechanical force. In a more limited manner, mechanoreception relates only to the elicitation of unidirectional afferent neural action potentials from input mechanical energy.

In this Review, we will provide examples of MIs that enable neuromuscular or neurocutaneous interfaces between the PNS and a prosthesis to highlight a major movement in prosthetic interfacing that contrasts against traditional techniques with lower functionality. Because the definition of an MI contains subtleties, examples and non-examples are presented here to appropriately frame the subsequent discussion on prosthetic architectures. A conventional residual limb produced from myodesis and myoplasty^{54,55} (that is, the surgical attachment of muscle to bone and of muscle to muscle, respectively) does not constitute an MI, because there is no physical

connection between biophysical motor units, sensory end organs, free nerve endings and artificial components. Similarly, a conventional osseointegrated, that is, bone-anchored, implant for prosthetic attachment should not be considered an MI. Although hard tissues and soft tissues are surgically altered for integration with an external prosthesis, there are (by design) no soft tissues that provide somatosensory feedback from the prosthesis, other than the unaltered proximal joint capsules⁵⁶. Hence, it is more descriptive to refer to osseointegration as a purely mechanical interface. By contrast, a surface electrode that facilitates prosthetic integration by providing myoneural control through electromyography (EMG) or by eliciting muscle contraction through functional electrical stimulation⁵⁷ (FES) can be classified as part of an MI, as long as the electrode is integrated with amputation musculature of any given architecture. By contrast, any direct nerve interface through an electrode array does not meet the requirements to be considered an MI, because soft tissue end organs and free nerve endings are neither utilized to provide afferent feedback upon electrical stimulation nor involved in the reading of efferent neural impulses. This exclusion is true despite demonstrated computational control and sensation of prosthetic limbs using direct nerve interfaces^{58–60}. Free nerve endings operating as chemical nociceptors or thermoreceptors may be considered as part of an MI out of convenience due to their concurrent polymodal functionality that includes mechanoreception⁶¹. Given these comparisons, it is clear that the definition of an MI does not consider the effectiveness or complexity of any particular technique for prosthetic integration, but it instead specifies that information is transferable to or from modified neuromuscular and neurocutaneous soft tissues for the purpose of prosthetic integration.

Efferent and afferent signalling modalities

MIs can be classified based on their efferent and afferent functional modalities. An MI with efferent control is able to directly actuate a prosthesis as an effort source, indirectly actuate a prosthesis by providing reference signals for mechatronic control or potentially operate under both modalities. When operating as an effort source, as in cineplastic techniques, efferent MIs activate motor units in which alpha motor neuron action potential spikes elicit actin and myosin cross-bridge interactions, resulting in a muscle force that is propagated through a mechanical transmission to the prosthesis. When operating as a reference signal source, motor units are activated in the same manner, but instead of directly transmitting force to the prosthesis, measurements of resultant muscle state are used to inform a mechatronic controller responsible for prosthetic actuation. Candidate state signals include correlates of muscle activation measurements using for example EMG and physiological measurements, such as fascicle length⁶². Mechanoneural transduction and the corresponding biophysical amplification involving the motor units within neuromuscular soft tissues occurs whether an efferent MI operates as an effort source or a reference signal source.

An MI with afferent capabilities provides somatosensory feedback through mechanoreception, a phenomenon fundamental to the execution of organismal biomechanics. Two classes of mechanoreceptive afferents present as most relevant to the realization of movement: cutaneous and proprioceptive (Fig. 2). Broadly, cutaneous mechanoreceptive afferents convey sensations related to interfacial contact with the environment. These perceived sensations include, but are not limited to, touch, pressure, roughness and skin stretch⁶³ (Fig. 2e). Proprioceptive afferents convey sensations of internal bodily state

that also provide indirect information about external environmental forces – muscle spindles convey muscle fascicle length and velocity, and Golgi tendon organs convey tendon and ligament force (Fig. 2c). Other proprioceptive afferents such as those from joint capsules also contribute towards perception of bodily movement, but their importance for proprioception is understood to be lower than that of muscle spindles and Golgi tendons⁶⁴. Most typically, an MI capable of cutaneous feedback possesses cutaneous sensory nerves and cutaneous end organs, and an MI capable of proprioceptive feedback possesses neuromuscular tissues (which may also be used for efferent control).

The roles of cutaneous and proprioceptive feedback have been ascertained in humans primarily through studies on their absence or disruption. In the upper extremities, it is believed that cutaneous feedback facilitates discrimination of contact points, texture, slippage and gross shape^{65–67}. Proprioceptive feedback is thought to contribute to hand and finger positioning in support of efficient reaching⁶⁸ and to augment discrimination of specific shape, weight and impedance^{69,70}. The absence of either modality has been shown to diminish performance in functional tasks, suggesting that both cutaneous and proprioceptive feedback are necessary for the restoration of physiological performance^{71–73}. In the lower extremities, plantar cutaneous feedback (that is, from the sole of the foot) plays a crucial role in adapting stance posture and recognizing ground contact events during gait^{74–77}, and proprioceptive feedback is essential for maintaining gait stability and for responding to terrain irregularities⁷⁸. Both modalities of feedback serve as input into spinal reflexive circuits that sustain the rhythmic bipedal gait cycle under a wide range of dynamic perturbations⁷⁹.

Native innervation and reinnervation

Modern MIs depend on soft tissue constructs that are surgically assembled with special consideration given to their spatial, vascularization and innervation constraints. Although successful implementation of all three aspects determines a construct's post-operative viability, it can be argued that the quality of innervation is the parameter that most strongly determines its functional efficacy. Bearing this in mind, MIs can also be divided into two types based on their innervation: native and regenerative⁸. Native MIs retain the original efferent and afferent nerve-to-muscle fibre or nerve-to-end organ innervations, preserving all motor and somatosensory pathways. However, in scenarios in which these native pathways no longer exist, perhaps due to traumatic loss of soft tissues or a previous surgery, a regenerative MI can be pursued, in which a transected nerve is introduced into the target tissue containing denervated muscle fibres or end organs to attempt to restore functionality through axonal reinnervation.

Mammalian peripheral axons possess a remarkable capacity to regenerate free nerve endings and regenerate into denervated targets through biomolecular mechanisms, such as the upregulation of neurotrophic factors and the formation of bands of Büngner from specialized Schwann cells that provide directional guidance^{80,81}. In most cases, following PNS injury, there is a tendency for the majority of proximal motor axons to eventually reinnervate motor pathways, a phenomenon known as preferential motor reinnervation, which is hypothesized by several studies to be the result of collateral axonal pruning^{82–84}. Another perspective presented by the same authors claims that, in addition to preferential motor reinnervation, sensory axons exhibit a preference for sensory pathways and their specificity is further preserved in that they preferentially target proprioceptors or cutaneous mechanoreceptors, depending on their origin⁸⁵. However, these preferences are rather weak, and the authors note that the magnitude of specificity is low for

all the reinnervations they observed in rodent models: only 53.88% for motor neurons, 60.44% for proprioceptors and 60.97% for cutaneous mechanoreceptors. In practical terms, an increased proportion of misdirected axons results in decreased functional recovery following peripheral nerve injury⁸⁶. Considered together, these findings indicate the need for enhanced comprehension and refinement of peripheral nerve regeneration processes to reduce end organ cross-innervation and improve signalling quality.

Functional advantages

The creation of an MI emphasizes specialized qualities that improve upon long-standing approaches to amputation. Care is taken to optimize the health of the soft tissue construct and the utility of artificial components for subsequent integration with prosthetic devices.

Suppression of post-amputation pain. Although transected and crushed nerves naturally attempt to reinnervate nearby end organs, regenerating axons may also become entangled within non-neural soft tissue to create bulbous formations known as neuromas⁸⁷. This outcome is more likely when appropriate regenerative targets are not available⁸¹. Regenerative MIs leverage the tendency of transected nerves to reinnervate denervated sensory end organs, such as those located in the dermis and muscle fascicles, to preclude neuroma formation^{88–91}. It is hypothesized that symptomatic neuromas are responsible for irrelevant nociceptive afferents (that is, signals without a meaningful origin that are interpreted as pain by the CNS), which significantly contribute to PLP in a number of limb amputation cases⁹². However, not all neuromas contribute to PLP or residual limb pain (pain with perceived spatial origins within the amputated residuum), and physical indicators of neuroma swelling are not significantly associated with the presence of either type of post-amputation pain^{93,94}. Additionally, although sensory and mixed nerves (that is, nerves containing both sensory and motor fibres) may form symptomatic neuromas, at least one group of surgeons has not observed their formation in proximal aspects of transected motor nerves⁸⁹. Nonetheless, given the unpredictable potential of any particular neuroma to contribute to pathological nociceptive sensitization, researchers emphasize that reducing the overall formation of neuromas is functionally equivalent to reducing the prevalence of symptomatic neuromas and corresponding post-amputation pain⁹⁴.

Of note, regenerative soft tissue constructs can have a protective role against nociceptive afferents and CNS sensitization, without having a corresponding role as MIs for prosthetic function⁹⁵. Through the provision of end organs as targets for transected axons, a regenerative construct confers an innate physiological advantage over conventional amputation procedures in which nerves are simply sectioned and allowed to retract into the residuum to potentially form neuromas^{54,55}.

Elicitation of afferents. MIs offer a more long-term approach to referring somatosensory sensation than direct nerve stimulation. Regarding the direct nerve stimulation family of techniques, it is well understood how patterns of electrical stimulation through high-density intrafascicular arrays and nerve cuffs can encode cutaneous information corresponding to touch and pressure^{96,97}. Promisingly, several studies have shown that increases in the degree of biomimicry of these electrical stimulation patterns correlate with relative improvements in both closed-loop prosthetic control and tactile sensation quality^{36,98,99}. However, these techniques are limited by selectivity and longevity issues, and prolonged stimulation can

fatigue the sensory nerves such that stimulation-induced depression of neuronal excitability^{100,101} must be imperfectly compensated by non-biomimetic computational control strategies¹⁰². Furthermore, attempts to elicit both homologous (matching the quality of original sensation)¹⁰³ and somatotopic (perceived as originating from the correct region)¹⁰³ proprioceptive sensations through direct peripheral nerve stimulation have generally yielded varied results and often lack a full assessment of function: at least four upper-extremity studies were able to elicit homologous proprioceptive perception within the phantom hand, but they did not investigate their use as feedback modalities during functional tasks^{59,104–106}. Of the studies that do investigate proprioceptive feedback in functional tasks, one resorted to conveying finger position to individuals through nonhomologous and non-somatotopic sensations referred to the transradial residuum or lower palm⁶⁰. Another approach conveyed knee position to individuals through non-somatotopic sensations referred to perceived muscular contraction of the phantom gastrocnemius (that is, a calf muscle)¹⁰⁷. Finally, at least one study was indeed able to elicit time-variant proprioceptive sensations to improve object discrimination in a prosthetic control task within a single individual⁵⁸.

In contrast to direct nerve stimulation, MIs allow the elicitation of afferent somatosensory action potentials through biophysical processes triggered by the mechanical deformation of free nerve endings and sensory end organs with known functionality. Although target organ reinnervation remains imprecise due to sensory nerve-to-sensory end organ cross-innervation, there is evidence that suggests that afferent signalling that is sufficient for prosthetic feedback is restored by regenerative MIs⁸⁹. Consequently, artefacts and side effects typically associated with electrical nerve stimulation, such as stimulation-induced depression of neuronal excitability, can be mitigated or avoided completely using both native and regenerative MIs. In the case of regenerative cutaneous MIs in humans, cutaneous tissues reinnervated by transected upper-extremity nerves have been demonstrated to provide persons with amputation with somatotopic tactile sensations of the corresponding phantom hand upon simple physical touch^{37,96,108–110}. In these studies, the somatotopic quality of the phantom sensations was shown to be preserved despite the spatial arrangement of reinnervated cutaneous tissues in the body. In the case of neuromuscular MIs, both native and regenerative types have been demonstrated to provide varying degrees of proprioception through mechanical deformation: within the upper extremities, regenerative neuromuscular MIs were able to convey homologous and somatotopic perception of phantom hand movements when subjected to vibrotactile induction of illusory proprioception^{37,111} and when subjected to electrical stimulation¹¹². Within the lower extremities, native neuromuscular MI constructs arranged in agonist–antagonist pairs have been shown to preserve proprioceptive sensorimotor neurophysiology and relative sensations of phantom limb movement correlated with the antagonist muscle stretch, even without FES or external means of mechanical deformation^{7,113–116}. These studies provide evidence suggesting that MIs currently offer enhanced and potentially more reliable channels for somatosensory feedback than direct peripheral nerve stimulation approaches.

Amplification and selectivity of efferents. PNS-based control of prostheses requires the measurement of signals that contain latent information on motor intent, and, in this respect, neuromuscular MIs confer advantages over direct nerve interfaces in terms of efferent signal amplification and resultant signal selectivity. Unlike their

demonstrated utility in providing somatosensory feedback¹¹⁷, the ability of peripheral nerve interfaces to effectively provide electroneurograms for the purposes of efferent prosthetic control is less documented, with only a small number of individuals having used them in such a manner^{59,118}. Instead, EMG signals developed from the downstream biochemical repolarization of contracting muscle fibres, although not strictly neural signals, dominate as the most prevalent signals used for prosthetic control¹¹⁹. The reasons for this disparity are suggested by studies that discuss the practical advantages of recording EMG signals over electroneurograms¹²⁰: on the one hand, the fact that muscles are larger than their innervating nerves leads to fewer constraints on electrode size, resulting in implanted EMG electrodes and wires exhibiting lower failure rates than miniaturized intra-fascicular arrays, which are more vulnerable to corrosion and mechanical damage^{121–123}. On the other hand, muscle tissue also exhibits lower sensitivity to mechanical trauma than neural tissue, thereby mitigating issues similar to those encountered by neural tissue, such as endoneurial fibrosis (that is, scarring within the nerve) and nerve fibre loss^{124–126}. In addition, implanted muscle electrodes experience reduced source–signal crosstalk in comparison with nerve electrode arrays, which operate within a densely populated environment of both efferent and afferent neural signalling^{57,127}. Finally, the raw amplitude of EMG signals measured from subcutaneous electrodes is at least an order of magnitude larger than that of electroneurograms, typically peaking at several mV as opposed to 100 μ V, respectively^{6,19,128}.

Validating the aforementioned advantages in regenerative MIs, at least two studies have demonstrated the long-term stability and strength of EMG signals measured from electrodes chronically implanted into regenerative neuromuscular MI constructs^{129,130}. Surgeons have even demonstrated the ability to perform fascicular splits of a transected mixed nerve to create several MI constructs, with each of them serving as an efferent control site with its own channel of information^{19,131}. Moreover, surgeons have the flexibility to optimize the anatomical positioning of each regenerative neuromuscular MI within the range of its innervating fascicles, taking into account any artificial interfacing components, to maximize signal specificity and accessibility.

Mechanoneural interfaces

The MIs detailed in Table 1 have been successfully applied in clinical settings, and their outcomes have been studied in populations of persons with amputation. We examine these interfaces placing emphasis on the properties of their soft-tissue architectures, mechanism of action, demonstrated efficacy and limitations in the context of prosthetic integration.

Targeted reinnervation techniques

Envisioned as a means to improve the control of myoelectric prostheses, TMR is a surgical architecture in which non-native residual nerves are anastomosed to locally denervated, but natively vascularized, muscle tissue¹⁸ (Fig. 1b). In this way, the original functionality of native musculature is locally relinquished in exchange for biophysical amplification of the introduced nerve's efferent spikes. In practice, efferent neural pathways responsible for the movement of joints lost to amputation can be restored to generate EMG signals localized at specific TMR sites. Moreover, the construction of TMR sites offers a certain degree of flexibility, allowing the placement of the regenerative MIs at locations outside the socket¹⁸ (that is, chest in the case of upper-extremity amputations). This increased accessibility can be particularly advantageous

Table 1 | Summary of mechanoneural interfaces

Interfaces	Target tissue	Nerve type	Amputation level	Demonstrated control	Reported clinical benefits	Reported outcomes	Refs.
				Demonstrated sensation			
MIs in clinical use							
TMR	Denervated, vascularized muscle	Non-native motor or mixed nerve	Shoulder disarticulation, transhumeral, transradial, hip disarticulation, transfemoral and transtibial	Intuitive prosthetic control Kinesthetic illusions	Reduced neuroma formation, reduced PLP, improved prosthetic control, adaptation and ownership, and reduced visual fixation to the prosthesis	Number of patients>100 Reported reinnervation success rate>90%	5,8,18,37, 88,111,131, 133–138, 140–142, 145–148, 150,151
TSR	Denervated, vascularized dermal target region	Non-native cutaneous nerve	Shoulder disarticulation, transhumeral, transtibial and transfemoral	N/A All cutaneous sensations were identified, some inaccurate with reported tingling, variable somatotopic representation	Improved adaptation and ownership	Number of patients>10 Reported reinnervation success rate: N/A	108,109, 133,152, 153,199
RPNI	Denervated, devascularized muscle graft	Non-native motor or mixed nerve	Transhumeral, glenohumeral, transradial, transfemoral and transtibial	Intuitive prosthetic control Verbal descriptions of proprioceptive, cutaneous sensations	Reduced neuroma formation, reduced PLP and improved prosthetic control	Number of patients>200 Reported reinnervation success rate: N/A	6,112,135, 180,181
Native AMI	Native innervated and vascularized muscle (mechanical agonist–antagonist coupling)	Native mixed nerve	Transtibial and transfemoral	Intuitive, reflexive, prosthetic control Coupled force proprioception	Reduced PLP, physiological functional neuroimaging and improved prosthetic control	Number of patients>30 Reported reinnervation success rate: N/A	7,113–116, 159,162, 167,200
MIs in the preclinical stage							
Muscle cuff RPNI	Denervated, vascularized muscle graft wrapped around the nerve	Native intact motor nerve	N/A	Increased EMG SNR compared with ENG, indicating signal amplification N/A	N/A	N/A	169–171
Composite RPNI	Denervated, vascularized muscle graft and free dermal graft	Non-native mixed nerve	N/A	Increased EMG SNR compared with ENG Evoked potentials upon dermal electrical and mechanical stimulation	N/A	N/A	172,173
Sensory RPNI	Denervated, devascularized muscle graft	Non-native sensory nerve	Transradial	N/A Evoked potentials upon RPNI stimulation	Reduced symptomatic neuromas and PLP	Number of patients: 2 Reported reinnervation success rate: N/A	112,135,182
Superficial RPNI	Denervated, devascularized muscle graft placed superficially under the skin	Non-native mixed nerve	N/A	Robust CMAPs obtained using superficial electrodes N/A	N/A	N/A	173
Dermal sensory interface	Free dermal graft	Non-native cutaneous nerve	N/A	N/A Evoked potentials upon dermal electrical and mechanical stimulation, and pressure, vibration, heating, cooling and nociceptive stimuli	N/A	N/A	174–176
VDMT	Denervated, vascularized muscle	Non-native mixed nerve	Transradial and transhumeral	Increased CMAPs compared with RPNIs N/A	Reduced neuroma formation, PLP symptoms alleviation, reduced fibrosis and reabsorption compared with RPNI	Number of patients<10 Reported reinnervation success rate: N/A	177–179

Table 1 (continued) | Summary of mechanoneural interfaces

Interfaces	Target tissue	Nerve type	Amputation level	Demonstrated control	Reported clinical benefits	Reported outcomes	Refs.
				Demonstrated sensation			
MIs in the preclinical stage (continued)							
Regenerative AMI	Reinnervated muscle construct	Non-native mixed nerve	N/A	Graded EMG	N/A	N/A	159,160,163
				Graded afferent ENG due to coupled motion			
CMI	Muscle-actuated skin flap	Innervated muscle actuator, native cutaneous nerve (skin flap)	N/A	N/A	N/A	N/A	159,183,184
				Graded contact and vibratory afferents upon electrical stimulation of muscle actuator (strain or oscillatory vibration on skin flap)			

AMI, agonist–antagonist myoneural interface; CMAP, compound muscle action potential; CMI, cutaneous mechanoneural interface; EMG, electromyography; ENG, electroneurography; MI, mechanoneural interface; N/A, not applicable; PLP, phantom limb pain; RPNI, regenerative peripheral nerve interface; SNR, signal-to-noise ratio; TMR, targeted muscle reinnervation; TSR, targeted sensory reinnervation; VDMT, vascularized denervated muscle target.

for prostheses that depend on socket interfaces for mechanical attachment. In contrast to myoelectric methods for prosthetic control with conventionally amputated musculature, TMR enhances the precision of efferent control signals by selectively amplifying only those that are closely associated with the desired motor intent^{5,132}. TMR also reduces signal diffusion as subcutaneous fat superior to the reinnervation sites is removed during surgery¹⁸. These advantages facilitate a reduction in the required number of channels for prosthetic control tasks, even when the MI is formed from TMR constructs paired with generic wet surface electrodes¹³³.

TMR has been implemented at levels ranging from shoulder disarticulation to transradial amputation in unilateral and bilateral upper-extremity cases^{18,131,133,134}, as well as in hip disarticulation, transtibial and transfemoral cases^{135–138}. In one of the first upper-extremity cases to be provided with TMR, a patient with unilateral transhumeral amputation, simultaneous prosthetic control of hand, wrist and elbow degrees of freedom was achieved 7 months after surgical intervention¹³³. In one of the first lower-extremity cases, a patient with transfemoral amputation operating an EMG-controlled prosthetic knee–ankle device demonstrated improved ambulation (the ability to walk without assistance) over level ground, slopes and stairs when providing efferent signals sourced from TMR sites compared with providing signals sourced from natively innervated residual knee muscles¹³². To date, more than 100 patients have received TMR at various amputation levels, and several have demonstrated more efficient task completion and a generally more intuitive level of prosthetic control within laboratory settings than patients with conventional amputations^{5,8,139}. Beyond laboratory settings, patients who have undergone TMR have been fitted with commercial upper-limb prostheses to evaluate EMG pattern recognition control in home trials^{140–142}. Studies have also shown that TMR significantly improves upper-extremity functional outcomes with the use of patients' existing prescribed devices^{142–144}. Clinically, the reinnervation rate of TMR procedures for proximal upper-extremity amputations has been reported to be over 90%^{145,146}, and multiple studies have produced substantial evidence that TMR reduces the formation of symptomatic neuromas and the prevalence of PLP over a range of amputation levels^{89,139,147–149}.

In parallel, TSR was discovered by chance when it was observed that afferent somatosensory nerve fibres reinnervated the dermis beyond a target muscle section after a TMR procedure¹⁸ (Fig. 1b).

This phenomenon was later determined to be enabled by accidental dermal denervation during the portion of the surgery involving subcutaneous fat removal. Although this original form of TSR provides temperature, pain, cutaneous and some proprioceptive sensations to individuals with amputation, it is characterized by variable and simultaneously elicited native and referred cutaneous sensations¹⁰⁸. Two other TSR configurations have been investigated in people, which increase somatosensory specificity. The first variation featuring end-to-side reinnervation was investigated in 2006 in the first patient to receive a deliberate TSR procedure¹³³. During the operation, the distal end of the transected supraclavicular cutaneous nerve was coapted to the side of the ulnar nerve, and the distal end of the intercostobrachial cutaneous nerve was coapted to the side of the median nerve. The patient with the upper-extremity prosthesis reported initial perception of sensory reinnervation three months following surgery. The patient was able to perceive all modalities of cutaneous sensation somatotopically referred to varying areas of the phantom thumb, index, ring, middle and little fingers upon mechanical stimulation of their anterior chest skin. However, the patient reported persistent tingling instead of normal pressure in response to touch, and sensations were discontinuously mapped from contiguous chest skin to different areas of the phantom digits and palm. Improving upon the TSR procedure, a second variation involves end-to-end reinnervation in which sensory fascicles are first intra-operatively identified in a mixed nerve using somatosensory-evoked potentials, selectively transected and subsequently coapted to the end of another transected nerve that innervates a cutaneous region. The remainder of the mixed nerve is directed to the motor branch of a target muscle for TMR. In a case study involving a patient with transhumeral amputation, this variation produced discrete digital sensory mappings of the median and ulnar nerves into mutually exclusive upper-extremity cutaneous regions topologically distinct from both corresponding TMR sites¹⁰⁹. The patient demonstrated mechanically induced tactile perception referred to their phantom digits along with prosthetic control of a sensorized gripper in object manipulation and discrimination tasks. Subsequent studies have produced sensory maps for patients with TSR at various amputation levels^{108,110,150,151}. Lower-extremity TSR has also been implemented in which a modified prosthesis system actuates the innervated skin area to provide sensation from the missing foot¹⁵².

Targeted reinnervation has been demonstrated to facilitate improved degrees of prosthetic embodiment. In an experiment modelled after the rubber hand illusion (an experiment in which the combination of touch and visual stimuli is utilized to induce a sensation in the individual that a rubber hand model is part of their own body), homologous and somatotopic cutaneous feedback provided by mechanically palpating TSR sites increased both qualitative and quantitative embodiment of a sensorized prosthetic hand in two individuals with transhumeral amputation¹⁵³. More recent experiments have demonstrated that TMR sites can convey homologous and somatotopic perception of phantom hand movement when subjected to vibrotactile induction of illusory proprioception, a phenomenon described as kinesthesia from muscle-based TSR¹¹¹. Individuals with upper-extremity TMR and TSR demonstrated reduced visual fixation to the prosthetic hand along with improved measures of prosthetic functional performance, adaptation and ownership, when provided with both cutaneous and kinesthetic feedback, as opposed to cutaneous feedback only³⁷. This result demonstrates the possibility of additional modular utility and improved degree of embodiment following the introduction of new artificial components to established MI constructs.

However, targeted reinnervation architectures must respect fundamental practical limitations stemming from the nature of their implementation. For instance, end organs within muscles and dermis must be denervated (with denervated sensory or mixed nerves themselves requiring management for prophylactic neuroma prevention) before introducing the coapting nerve, as healthy and natively innervated end organs do not release the proper trophic factors that facilitate axonal regeneration⁸¹. This reliance on existing native neuromuscular tissue, in addition to the fact that existing functionality must be exchanged for other motor and sensory pathways, limits the number of independent degrees of freedom that can be created^{19,131}. In addition, TMR requires careful execution to prevent the construct to fail or be diminished in functionality due to excessive donor nerve redundancy, kinking, donor–recipient nerve size mismatch, superficial placement of the nerve coaptation, inappropriate target selection or incomplete target-muscle denervation^{37,111,138,145,153}. Furthermore, although evidence of perception of digital position mediated by TSR-induced cutaneous stretch¹⁰⁸, cutaneous proprioception¹⁵³ and illusory kinesthetic sensations^{37,111} has been reported in patients with targeted reinnervation architectures, a vivid sensation of joint musculotendinous proprioception and torque (that is, rotational force) feedback has yet to be reported. Finally, although lower-extremity TMR has resulted in improved prosthetic controllability¹³², it has yet to be shown whether the reflexive aspects of gait can be fully recapitulated using these architectures.

Regenerative peripheral nerve interface

To address some of the limitations of the TMR paradigm, one study demonstrated an early version of the RPNI in 2001, which was followed by the initial human implementation reported in 2012 refs. [154,155](#). RPNIs are small muscle grafts that are reinnervated by sensory, motor or mixed nerves. To create an RPNI, the surgeon first excises healthy muscle tissue in the order of several cubic centimetres from the body or amputated limb as an autologous, denervated muscle graft. The muscle graft is subsequently wrapped and coapted around the end of a transected nerve before reimplantation into the body. During the following 3 to 4 months of recovery, the nerve reinnervates the muscle graft.

The use of small muscle grafts is key to the advantages of the RPNI strategy. The creation of an RPNI does not sacrifice significant motor function even when the tissue is taken from intact, natively innervated

muscles^{19,90}. This contrasts with TMR, which repurposes large portions of healthy, biomechanically redundant musculature previously used to perform another function. In addition, using a muscle graft permits the placement of RPNI architecture at any location deemed appropriate by the surgeon. This modularity mitigates limitations related to the length of the residual peripheral nerves (especially in lower-extremity amputations, in which it is difficult to find functional tissue available to be repurposed)⁸, allows optimal placement of the RPNI for electrode interfacing and raises the practical limit on the number of neuromuscular interfaces that the surgeon can create.

When used for efferent prosthetic control, RPNIs reinnervated by motor or mixed nerves may provide more intuitive and enhanced control over prosthetic devices, with greater long-term stability, than direct-to-nerve interfaces¹⁹. Electrodes implanted alongside RPNIs have been shown to provide an order of magnitude increase in signal-to-noise ratio (SNR) through EMG acquisition compared with intraneural electrodes recording electroneurograms, and, unlike intraneural electrodes, they have been shown to be stable for years in humans^{19,130}. Because RPNIs allow greater flexibility over the positioning of the constructs, they could in theory allow for a larger number of nerve–muscle pairs than TMR in some procedures, potentially facilitating control over a proportionally larger number of prosthetic degrees of freedom¹⁹. RPNIs have been implemented at the transhumeral, glenohumeral, transradial, transfemoral and transtibial levels, with the procedure having been performed in a total of more than 200 patients^{19,156}. Clinically, patients who have received RPNIs also experience substantially lower rates of PLP and residual limb pain than patients who have received conventional surgical attempts at mitigating neuroma formation¹³⁵.

Although the body does weakly revascularize the muscle graft of an RPNI, RPNIs have also received criticism for being prone to atrophy and resorption¹⁵⁷, in turn reducing the SNR available for prosthetic control. Additionally, muscle graft size is physically limited by the high surface area-to-volume ratio required for successful revascularization¹⁵⁸. Furthermore, without implanted electrodes for EMG recording, the application of RPNIs in clinical prosthetic control experiments is typically performed with the insertion of percutaneous fine wire electrodes. This is a painful procedure that can cause individual dropout and represents a limitation of the technology used to interface with RPNI constructs¹⁹. Finally, it remains to be determined whether any patients who exercise prosthetic control using RPNIs have demonstrated increased measures of prosthetic embodiment.

Agonist–antagonist myoneural interface

The AMI is an MI whose soft tissue construct consists of the surgical coaptation of physiologically paired agonist and antagonist muscles to enable bidirectional efferent prosthetic control with afferent proprioceptive signalling^{7,113,159–164}. By preserving natural mechanical coupling at the interface between both muscles, mechanoreceptors such as spindle fibres and Golgi tendon organs are stretched to provide relevant proprioceptive feedback, when forces are generated by contraction of either muscle in the pair. As the soft tissue architecture of the AMI primarily specifies a mechanical configuration agnostic to the nature of its individual agonist and antagonist muscles, it can be composed using both natively innervated and vascularized muscles, referred to as a native AMI, and reinnervated muscle tissue, referred to as a regenerative AMI. Preclinical studies in animal models demonstrated the elicitation of antagonist muscle stretch and a corresponding antagonist afferent electroneurography signal in response to stimulation-induced contraction of the agonist muscle in both the

native^{161,164} and regenerative AMI^{160,163}. Critically, the magnitude of the response was positively graded with increasing muscle stretch, suggesting physiological proprioceptive signalling.

Early investigations of the AMI's mechanical structure yielded a theoretical basis for determining desired joint position, impedance and torque signals for prosthetic control applications¹⁶⁵. As a result, in the case of lower-extremity AMIs, one or more AMI pairs are implemented in the residuum for each intended prosthetic degree of freedom to be controlled¹⁵⁹. The first two AMI pairs for ankle and subtalar control were implemented in a person with transtibial amputation by coapting the distal ends of natively innervated and vascularized residual muscles: tibialis anterior to lateral gastrocnemius and peroneus longus to tibialis posterior^{7,113}. By utilizing surface EMG recorded from all four relevant muscles, this individual was able to demonstrate independent control of ankle and subtalar degrees of freedom within an ankle-foot prosthesis. The individual could also reflexively position the prosthesis in free space to navigate obstacles and stairs in a more physiological manner than four individuals controlling the prosthesis with conventional transtibial amputation⁷. In a demonstration of the potential of the AMI to convey environmental interaction dynamics for proprioceptive closed-loop torque control, FES of the individual's residual tibialis anterior muscle in proportion to the displacement of an underlying force-resistive foot pedal allowed them to more precisely control the plantarflexion torque generated, thus enabling them to flex their foot in a controlled manner⁷. In a separate study, another individual with transtibial amputation possessing two AMI pairs was able to demonstrate modulation of prosthetic plantarflexion torque and adaptive energetic work loops during stance while walking over level ground at various speeds¹⁶⁶.

In population studies conducted to characterize the AMI, individuals with AMI constructs have demonstrated reduced pain, enhanced phantom joint range of motion, increased muscle fascicle strain, preserved motor control and increased physiological functional neuroimaging compared with individuals with conventional amputations^{114–116,167}. In a study including 15 patients with transtibial AMI constructs, patients with AMI constructs reported less pain than patients with conventional amputation, as well as a significant reduction in pain compared with their pre-operative baseline¹⁶⁷. In a pair of studies including 15 and seven patients with transtibial AMI constructs, respectively^{115,167}, persons with AMI constructs demonstrated improved phantom ankle and subtalar joint controllability in free space with respect to persons with conventional amputation, as the former were able to produce more selective efferent control signals, greater precision of movement and greater perceived range of motion^{115,167}. This improvement can be mechanistically explained by the positive correlation between residual limb agonist–antagonist muscle strains and sensorimotor responses, which suggests that the degree of preserved agonist–antagonist muscle strain is the neuromechanical determinant of person-specific preservation of motor control and proprioception¹¹⁵. In a functional neuroimaging study on activity in brain areas associated with proprioception, 12 patients with AMI constructs demonstrated activity at levels similar to those of persons in the control without amputation during movements in free space. This is in contrast to persons with conventional amputations, whose activation in the mentioned brain areas was significantly reduced¹¹⁴. The AMI architecture has also been implemented in three patients at the transfemoral level by coapting the biceps femoris to the rectus femoris and constructing native transtibial AMI pairs in the transfemoral compartment¹¹⁶. These patients have demonstrated significant measures of preserved function and perception of distal phantom joints.

With regard to structural limitations related to the AMI architecture, any proprioceptive feedback methodology that requires the use of an AMI muscle as an actuator, such as in an FES-based approach, is unable to homologously represent all environmental interactions. This is because closed-loop control of the antagonist muscle to refer forces to the agonist results in the user experiencing a contraction in the artificially stimulated antagonist superimposed with a physiological stretch response in the agonist. The described sensation is in direct contrast to intact limbs that can experience external forces, for example, those caused by ground reaction forces and inertia, as a pure physiological stretch of musculotendinous tissue without an induced contraction in the agonist muscle¹⁶⁸. A second limitation of the AMI is that its construct can only approximate physiological muscle redundancy and spatial configurations: its mechanical transmission defined at surgery may not capture the nonlinear state-dependent leverage and biarticular nature of muscles in physiological limbs. Regarding implementation, the AMI architecture in proximal transradial amputations may require careful surgical planning around volumetric and pathing constraints to successfully construct the multiple agonist–antagonist couplings responsible for wrist and hand motions³⁷. Finally, no scientific assessments of the AMI's influence on prosthetic embodiment have been reported yet.

Preclinical mechanoneural interfaces

Although the MIs discussed thus far have demonstrated notable clinical benefits and achievements in prosthetic integration, it is the research conducted in animal models that provides a glimpse into future development. In this section, we present preclinical approaches of novel architectures that utilize principles of peripheral nerve regeneration and soft-tissue reconstruction to overcome existing limitations of clinical MIs (Table 1). Many of these aim for multimodal functionality in addition to physiological cutaneous and proprioceptive feedback (Fig. 3). For the purpose of this Review, an MI is deemed preclinical if it has not been implemented in humans or the available clinical data are limited and have yet to be reproduced in a larger population.

Muscle cuff RPNI

The muscle cuff RPNI (MC-RPNI; Fig. 3a) aims to enhance the efferent recording capabilities of intact, natively innervating, peripheral nerves. Unlike an RPNI construct, the MC-RPNI construct comprises a circumferentially wrapped autologous muscle graft around an intact nerve. Over time, the muscle graft becomes revascularized and stabilizes, providing denervated muscle fibres and proprioceptive end organs for the nerve to sprout into and reinnervate¹⁶⁹. By selectively amplifying anatomically known efferents, the MC-RPNI is hypothesized to benefit applications related to exoskeleton control for a variety of pre-existing conditions related to pathology of the neural–muscular junction or muscle damage itself. For example, the MC-RPNI could be an effective treatment option for muscle-based conditions resulting from trauma, muscular dystrophy, inflammatory myopathies and myasthenia gravis. In initial rodent studies, the MC-RPNI demonstrated a 10–20 times higher SNR of efferent motor signals measured as an EMG signal from the muscle graft instead of their associated electroneurogram¹⁶⁹. No loss of distal muscle function was observed, as the force generated by the rodents' distal MC-RPNI extensor digitorum longus muscle was comparable with that of the unaltered ipsilateral muscle. Another study showed signal amplification up to 100 times greater than the corresponding recorded electroneurogram¹⁷⁰. In a third study, the MC-RPNI demonstrated a 50-fold signal amplification during volitional behaviour¹⁷¹.

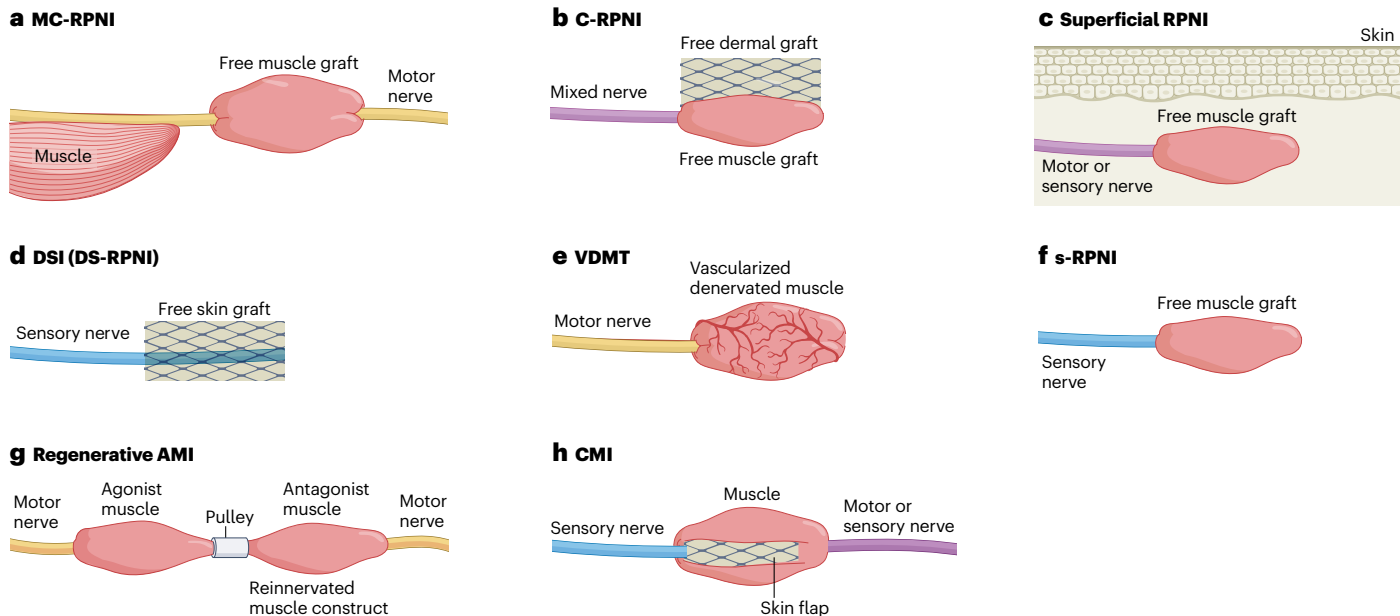


Fig. 3 | Soft tissue architectures of preclinical mechanoneural interfaces. **a**, A muscle cuff regenerative peripheral nerve interface (MC-RPNI) comprises a denervated and devascularized muscle graft (free muscle graft) wrapped circumferentially around an intact nerve to enhance efferent recordings. **b**, A composite regenerative peripheral nerve interface (C-RPNI) uses muscle and dermal grafts secured around a transected mixed nerve to achieve simultaneous afferent cutaneous and efferent motor capabilities. **c**, Superficial regenerative peripheral nerve interfaces (RPNIs) are placed close to the skin surface to facilitate transcutaneous mechanoreception and transcutaneous efferent recording. **d**, A dermal sensory interface (DSI), also known as a dermal sensory peripheral regenerative peripheral nerve interface (DS-RPNI), consists of a peripheral sensory

nerve that reinnervates a dermal graft for cutaneous feedback. **e**, A vascularized denervated muscle target (VDMT) comprises a denervated but natively vascularized muscle and reinnervating nerve. **f**, A sensory regenerative peripheral nerve interface (s-RPNI) uses a sensory nerve to reinnervate a denervated, devascularized muscle graft for sensory feedback. **g**, The regenerative agonist–antagonist myoneural interface (regenerative AMI) comprises two coapted, reinnervated muscle grafts or vascularized denervated muscles to facilitate simultaneous efferent motor control and afferent proprioceptive feedback. **h**, The cutaneous mechanoneural interface (CMI) comprises an innervated skin flap coupled with a circumferential free muscle graft in a cuff configuration for cutaneous feedback.

Composite RPNI

At present, clinical MIs typically exhibit mutually exclusive afferent cutaneous or efferent motor ability due to the different sources of soft tissue required for cutaneous end organs and motor units. The composite RPNI (C-RPNI; Fig. 3b) aims to overcome this limitation by enabling simultaneous afferent cutaneous and efferent motor capabilities using a single mixed peripheral nerve¹⁷². The C-RPNI construct involves the use of dermal and muscle grafts secured around a transected mixed sensorimotor nerve with the goal of preferentially reinnervating motor fibres in the muscle graft and sensory fibres in the dermal graft. In rodent models, the SNR of EMG signals recorded from the muscle graft component was found to be 30–50 times as large as the SNR of simultaneously recorded electroneurograms. Both reinnervated motor units and reinnervated end organs were observed to be correctly located in the appropriate grafts of the C-RPNI construct¹⁷².

Although the C-RPNI appears to be as effective as other RPNI varieties in amplifying efferent motor signals, its capabilities in regard to afferent sensory elicitation are less well characterized. Compound sensory nerve action potentials produced from the mechanical and electrical stimulation of the C-RPNI's dermal component have been quantified, but they remain unqualified, as rodents cannot indicate the type or degree of sensations elicited¹⁷². In another rodent study, superficially placed RPNI (superficial RPNI; Fig. 3c) and C-RPNI constructs were investigated to overcome limited efferent signal and afferent sensory

transmission stemming from issues accessing deeply placed tissues¹⁷³. Within the study, all superficial RPNI and C-RPNI constructs demonstrated regeneration, revascularization and reinnervation, when placed beneath the skin with subcutaneous fat removed to reduce the distance between superficial electrodes and constructs. Selective EMG signals were readily obtained from both using superficial electrodes, and visible contractions were observed through the overlying skin. Dermal portions of the C-RPNIs exhibited distinct and reproducible signal patterns at the proximal nerve in response to various physical and thermal stimuli. To enable future functional applications in humans, it will be crucial to verify the feasibility of incorporating feedback hardware that can independently actuate the dermal and muscle grafts without eliciting mixed, nonhomologous sensations.

Dermal sensory interface

The dermal sensory interface, also known as the dermal sensory RPNI (DS-RPNI), aims to integrate cutaneous end organs with a peripheral sensory nerve^{174,175}. The DS-RPNI construct offers the potential for a wide variety of modality-matched sensations and decreased post-amputation pain by preventing symptomatic neuroma formation through the use of a reinnervated dermal graft. The utilization of free dermal grafts offers enhanced modularity for cutaneous feedback by removing the need to remain pedicled (attached to the donor site). Studies conducted on rodent models have demonstrated successful

revascularization and reinnervation of DS-RPNIs with minimal scar tissue formation, enabling graded afferent signalling akin to that of full-thickness skin in response to mechanical indentation and electrical stimulation^{174,175}. Another rodent study revealed that compound sensory nerve action potentials generated from various stimuli, such as pressure, vibration, heating, cooling and nociception, were comparable with or even greater than those observed in the negative control group lacking end organ targets for reinnervation, suggesting that functional reinnervation increases cutaneous afferents compared with direct stimulation of the nerve end¹⁷⁶. To utilize the DS-RPNI as an MI in humans, an actuator for the dermal site, such as a robotic palpator, might be used for functional feedback.

Vascularized denervated muscle targets

As an alternative to RPNI constructs, vascularized denervated muscle targets (VDMTs; Fig. 3e) may be constructed in which a portion of a muscle is denervated, but not devascularized, to serve as a regenerative target for a reinnervating nerve^{177,178}. Because VDMTs maintain vascularity, they can be made larger than the muscle grafts commonly used in RPNIs to yield increased SNR values. This flexibility also implies that careful sizing of VDMTs may avoid complications related to mismatched donor–recipient nerve sizing, such as those encountered in TMR¹⁷⁸. In a rodent study, elicited compound muscle action potentials were found to be greater in a VDMT group than in an RPNI group, when stimulating the proximal nerve 100 days after surgery¹⁵⁷. Additionally, reduced muscle fibrosis and reabsorption were observed in the VDMT group compared with the RPNI group, as measured by muscle bulk and collagen. In a recent preliminary human study, nine patients underwent upper-extremity VDMT surgery for neuroma prevention. After a short-term evaluation, 83% of those patients reported experiencing either no PLP or an alleviation of PLP symptoms¹⁷⁹. It is important to mention that this was a heterogeneous study with a small cohort of patients; further validation with objective measurements in a longitudinal study is required to assess the benefits of this architecture.

Maintaining native vascularization, despite its benefits, imposes unique constraints on VDMTs. The number of potential VDMTs relies on the quantity of locally available tissue and the ability of the surgeon to separate tissue without disrupting the vascular leash. Furthermore, the position and orientation of each VDMT are restricted by the length of its vascular leash, necessitating careful treatment to prevent physical harm and mechanical interference from sliding surfaces¹⁷⁸.

Sensory RPNI

Apart from the ongoing research on utilizing RPNIs for prosthetic control and pain reduction^{180,181}, current studies are also exploring the potential of RPNIs to deliver afferent somatosensory feedback. In a sensory RPNI (Fig. 3f), a reinnervating sensory nerve is intended to provide relevant cutaneous or proprioceptive feedback upon electrical stimulation of the innervated muscle graft through indwelling electrodes¹⁸². An initial investigational study of the RPNI as a sensory interface documented verbal descriptions from two patients to characterize the type and quality of experienced feedback from two and three sensory RPNIs, respectively, over 6 and 14 months following surgery, respectively¹¹². The study showed meaningful, repeatable cutaneous and proprioceptive sensations, suggesting that the sensory RPNI is a promising strategy for providing afferent feedback in prosthetic control¹¹². However, further research is required to quantitatively assess and compare the elicited sensations with direct-to-nerve interfaces¹¹².

Regenerative AMI

The regenerative AMI (Fig. 3g) architecture consists of the coaptation and reinnervation of two devascularized muscle grafts or two vascularized muscles with known efferent and afferent capabilities in a manner that restores agonist–antagonist neuromuscular dynamics¹⁶⁰. In rodent models, a regenerative AMI has been constructed using muscle grafts taken from the extensor digitorum longus that are subsequently reinnervated by transected tibial and common peroneal nerves of mixed nature¹⁶⁰. Similar to native AMIs, these grafts exhibited graded afferent electroneurograms from the antagonist muscle's nerve upon induced contraction of the agonist through stimulation of its own innervating nerve. The magnitude of the response was positively graded with increasing muscle stretch, but the response disappeared after transection of the coaptation point, suggesting that the observed signals were not caused by stimulation artefacts.

Considering the unusually small final size of the reinnervated muscle grafts in rats (a 52% reduction compared with the size at creation)¹⁶⁰, it is unclear whether similarly scaled reinnervated muscle grafts in humans will produce proprioceptive afferents of sufficient magnitude and quality to convey relevant graded sensations from volitional contractions. Similarly, it is unknown whether the regenerative AMI composed from devascularized muscle grafts is capable of activating critical spinal reflexive circuits for gait from the afferents produced. However, a recent discovery demonstrated that preserving only 20–26% of agonist–antagonist muscle strain within the residuum compared with a biologically intact limb is effective in preserving natural motor control in persons with an AMI amputation¹¹⁵. This result suggests that achieving even modest agonist–antagonist dynamics may still be clinically relevant.

Cutaneous mechanoneural interface

The cutaneous mechanoneural interface (CMI; Fig. 3h) utilizes both muscle and dermal tissues to enhance the specificity of cutaneous feedback. The CMI construct comprises a skin flap mechanically coupled to a muscle actuator^{159,183,184}. By artificially stimulating the muscle actuator, strain or oscillatory vibrations are mechanically transferred to the skin flap. The native dermal mechanoreceptors then transduce corresponding afferent signals to the CNS. Prior to implantation within the amputation site, the skin flap is epithelialized and reinnervated by a sensory nerve that originally innervated the desired skin region. The muscle actuator can be constructed from either a vascularized muscle target or a non-vascularized muscle graft. The actuator can be innervated with its native nerve or reinnervated with a non-essential motor or cutaneous nerve for maintenance of muscle size and contractility¹⁸⁵. In a rodent study, a CMI construct consisting of a circumferential muscle actuator in a cuff architecture successfully produced four distinct levels of graded contact and eight different vibratory afferent responses¹⁸³. Graded afferent responses characteristic of both slowly adapting and rapidly adapting receptors (those that relay information about ongoing stimuli and changing stimuli, respectively) were observed. Histological analysis revealed reinnervation of both the muscle and skin grafts, along with healthy mechanical adhesion at the interface. Additionally, Merkel cells and Meissner corpuscles were identified at the dermal–epidermal interface¹⁸³. However, the qualitative perception of cutaneous sensations by potential users remains unknown.

Outlook

MIIs provide novel ports to facilitate communication between the body's neural circuits and the external world's dynamics (Fig. 4).

Although MIs have demonstrated early utility for prosthetic integration and post-amputation pain reduction, there is still much to discover. In terms of nerve regeneration, it is unknown how to finely control the specificity of end organ reinnervation in humans to characterize varying degrees of mixed reinnervation on motor control and somatosensation. Regarding cutaneous sensation, natively innervated cutaneous MIs have yet to be characterized at even the preclinical level. It is feasible that selectively portioned and positioned dermal grafts that retain their native innervation, perhaps from the electively amputated fingertips or foot sole, may be more conducive for conveying vital cutaneous sensations during prosthetic manipulation and gait¹⁵⁹. Additionally, the utilization of nociception and thermoreception for closed-loop prosthetic control remains unexplored. These represent only a few directions for future studies.

Along with the soft-tissue constructs of an MI, it is of equal importance to design the artificial interfacing topologies necessary to enable their signalling. For the purposes of efferent motor control, the majority of existing directly controllable prosthetic systems use EMG to obtain an estimate of motor intent based on the electrochemical propagation of muscle activation^{30,186}. Limitations when using surface electrodes have been extensively documented, including

crosstalk from different muscles, signal variability due to shifts in electrode impedance caused by motion artefacts and sweat, and the need for extensive position calibration and fatigue compensation, among others¹⁸⁷. Some of these limitations are mitigated by using percutaneous electrodes or implanted electrodes readily accessible through osseointegrated implants that bypass the need for a socket¹⁸⁸. However, alternative approaches that obtain a direct measurement of muscle state, including novel techniques, such as muscle-implanted target tracking^{62,159,162,184,189,190} and wearable ultrasound^{191,192}, may yield signals corresponding to motor intent through accurate observations of fascicular length and velocity.

Methods of providing afferent sensation also require improvement, particularly when muscle tissue is critically involved in the feedback pathway. Although classical FES is a well-established technique, its poor specificity¹⁹³ and high rate of muscle fatigue¹⁹⁴ provide reason to further study potential muscle stimulation techniques involving optogenetics¹⁹⁴ and afferent feedback modalities, such as magnetically induced proprioception¹⁹⁵. These approaches, although promising, still require further validation with respect to immunogenicity and viability in larger animal models, before translation to humans¹⁹⁶. On the topic of clinical availability, a number of advanced prostheses

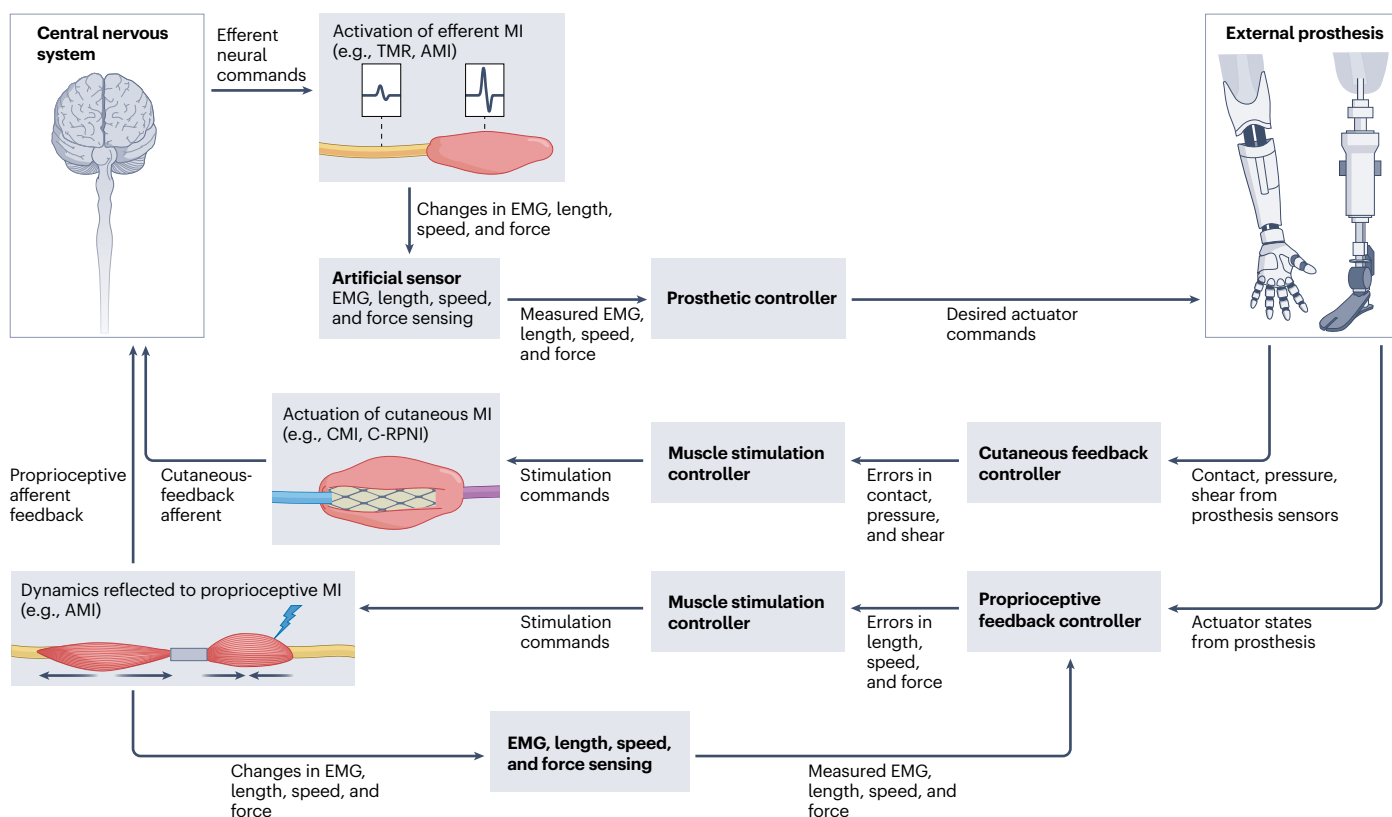


Fig. 4 | Mechanoneural interfaces in a closed-loop prosthetic architecture. The central nervous system sends a motor command to an efferent mechanoneural interface, such as a targeted muscle reinnervation (TMR) and/or an agonist–antagonist myoneural interface (AMI), producing muscular activity that is detected by artificial sensors. The corresponding digital signals are then conveyed to a prosthetic controller that computationally modulates the prosthetic joints based upon a biophysical model that transforms measured mechanoneural interface (MI) state to desired actuator dynamics. From sensors embedded in the instrumented

prosthesis, environmental stimuli, such as contact or pressure, can be transformed into digital signals that are used to stimulate a cutaneous MI, such as the cutaneous mechanoneural interface (CMI) or the composite regenerative peripheral nerve interface (C-RPNI), for afferent feedback to the central nervous system. In parallel, prosthesis state signals, such as joint angle and velocity, can be used to tightly actuate a construct such as the AMI to convey proprioceptive feedback to the central nervous system in a closed-loop manner. EMG, electromyography.

Box 1

Translational considerations

There is a lack of theoretical understanding of the relationship between restored physiological function after limb amputation and its corresponding influence on embodiment. Although experiments involving mechanoneural interfaces (MIs) that investigated the influence of neural perception on prosthetic dexterity suggest a positive correlation between signalling bandwidth and functional outcomes³⁷, greater detail is required to formulate a bionic information theory that can unify measures of bidirectional MI signalling with corresponding progress towards all aspects of embodiment. Future investigators may wish to characterize efferent and afferent MIs through measurements of physiological state and afferent firing rate during prosthetic control tasks. With additional quantification of task performance using metrics based on information theory, such as Fitts's Law (that is, the speed–accuracy trade-off) and standardized embodiment questionnaires, investigators would be able to make initial progress toward predicting prosthetic function and embodiment outcomes based upon the biophysics of MIs and their neural signalling bandwidths.

This desire for a unified bionic information theory is accentuated by accelerating developments in the use of MIs with commercially available prostheses. In 2014, direct humeral attachment through osseointegration enabled a multi-channel conduit for recording and stimulating both nerves and MIs for use with a commercial myoelectric hand¹⁸⁸. In 2017, the implementation of targeted muscle reinnervation in persons with transhumeral amputation was reported to elicit significant gains in functional performance using commercial myoelectric upper-extremity prostheses¹⁴⁰. It is increasingly apparent that both researchers and medical personnel should be able to compare amputation architectures directly to advise patients on the most effective care, given their specific physiology and the technology available to them. In the future, the translation of preclinical tools, such as muscle-implanted target tracking for efferent control^{62,159,162,184,189,190} and optogenetic stimulation for afferent feedback¹⁹⁴, will also need to be considered under the same framework to determine whether a revisional procedure to upgrade MIs can provide worthwhile benefits related to function and embodiment.

have been developed in the past years, but there are no lower-extremity prostheses capable of recording MI signals for long-term studies outside the lab. This dearth may be explained by the fact that people with lower-extremity amputation do not rely on volitional control signals as much as people with upper-extremity prostheses, due to the cyclic nature of gait that lends itself better to intrinsic control techniques¹⁹⁷. This may explain a gap in research motivation resulting in the reduced prevalence of lower extremity-targeted reinnervation and RPNI cases relative to upper-extremity cases. Furthermore, it is prudent to note that there are no commercially available prostheses at any amputation level capable of simultaneously recording and stimulating MIs, underscoring a tremendous translational opportunity in the coming years.

The creation of soft tissue constructs combining multiple different MI architectures can provide advantages unavailable from a single architecture alone⁸. For instance, mixed implementation is easily justifiable whenever natively innervated soft tissues have limited availability, in which case regenerative constructs may be formed from remaining resources to augment efferent or afferent bandwidth. In practice, native AMI constructs for efferent prosthetic control have been created in a transtibial residuum alongside RPNI constructs for neuroma prevention, while retaining the potential to use the latter as MIs in future control applications¹¹³. In a case of transhumeral amputation, both TMR and RPNI MIs were created simultaneously, and long-term measurements of EMG SNR from both types suggest the potential for independent finger control¹²⁹. Given these examples, the MIs discussed may be more appropriately considered as tools with complementary utility, as opposed to competing interventions.

By increasing their proficiency in constructing MIs, researchers can gain greater authority over human motor control and perception (Box 1). Looking ahead, focused endeavours towards the realization of a comprehensive digital nervous system may yield sufficient scientific understanding to pave the way for breakthroughs including: i) the development of compact assemblies comprising artificial components that can independently provide cutaneous signals, such as pressure, pain and temperature; ii) MIs designed to increase closed-loop control bandwidth beyond innate physiological levels; iii) multiple simultaneous methods of energy transfer, such as through light, sound and magnetic fields; and iv) selective reinnervation of biofabricated end organs for specific functionality¹⁹⁸. Attaining such a heightened degree of control over peripheral neural signalling would facilitate further exploration into the possibilities of prosthetic embodiment and rehabilitation.

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Author contributions

T.S. and G.H. researched data, contributed to content discussion, wrote the manuscript and contributed equally. C.T. researched data, contributed to content discussion and wrote the manuscript. H.H. contributed to content discussion and wrote the manuscript. All authors reviewed and approved the final manuscript.

Competing interests

H.H. holds patents on AMI and CMI mechanoneural interfacing technologies. The remaining authors declare no competing interests.

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