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Peripheral neurostimulation for encoding artificial somatosensations

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Abstract

The direct neural stimulation of peripheral or central nervous systems has been shown as an effective tool to treat neurological conditions. The electrical activation of the nervous sensory pathway can be adopted to restore the artificial sense of touch and proprioception in people suffering from sensory-motor disorders. The modulation of the neural stimulation parameters has a direct effect on the electrically induced sensations, both when targeting the somatosensory cortex and the peripheral somatic nerves. The properties of the artificial sensations perceived, as their location, quality and intensity are strongly dependent on the direct modulation of pulse width, amplitude and frequency of the neural stimulation. Different sensory encoding schemes have been tested in patients showing distinct effects and outcomes according to their impact on the neural activation. Here, I reported the most adopted neural stimulation strategies to artificially encode somatosensation into the peripheral nervous system. The real-time implementation of these strategies in bionic devices is crucial to exploit the artificial sensory feedback in prosthetics. Thus, neural stimulation becomes a tool to directly communicate with the human nervous system. Given the importance of adding artificial sensory information to neuroprosthetic devices to improve their control and functionality, the choice of an optimal neural stimulation paradigm could increase the impact of prosthetic devices on the quality of life of people with sensorimotor disabilities.

KEYWORDS
neural interface, neuromodulation, neuroprosthesis, peripheral nerve stimulation, sensory feedback, somatosensation

1 | INTRODUCTION

The loss of a limb is a dramatic event that substantially affects a person's quality of life (Meyer, 2003). Only considering lower-limb amputees in Europe, 3.18 million people have an amputated limb, and each year 295,000 undergo amputation (Kozak & Owings, 1998). According to World Health Organization, these numbers are forecasted to double by 2050(Ziegler-Graham et al., 2008). Poor prosthesis controllability, excessive prosthesis weight, lack of sensory feedback and inadequate embodiment are among the reasons for rejection of available commercial prostheses (Wijk & Carlsson, 2015). Because of the lack of feedback, prosthetic users do not perceive the prosthesis as a part of their own body (Blanke, 2012; Makin et al., 2017), which increases the cognitive effort when using the device itself, affecting its acceptability (Blanke, 2012; Ehrsson et al., 2008; Tsakiris & Haggard, 2005). These facts cause a confidence reduction of the subject in the prosthesis use, because they have to rely on limited residual haptic sensations (e.g., stump–socket interactions) or to continuously inspect the prosthetic device (less natural control).

To this aim, novel neurotechnologies have been recently developed to improve prosthesis performance in terms of sensory-motor functions and the quality of life of people with amputation (Bensmaia et al., 2020; Farina et al., 2021; Raspopovic et al., 2021). Reestablishing the connection between the brain and the body after an injury or a neurological disease is a fascinating but extremely difficult challenge to solve. Restoring the limb capabilities with a controllable and sensitized artificial device requires the combination of several disciplines as neurosurgery, neural, electrical and mechanical engineering, neurology, rehabilitation therapy, prosthetics and psychology (Valle, 2019). Pivotal challenges guiding the development of the new generations of prosthetic devices consisting of (1) *the mechanical interface*, to solve the problem of how to effectively and safely connect the artificial device and the residual human body (i.e., leg or skeleton) (Ortiz-Catalan et al., 2014; Ortiz-Catalan, Mastinu, Sassu, et al., 2020); (2) the *neural interface*, that is how to connect the brain to the device in order to actively control the device movements (Hargrove et al., 2013, 2015) and simultaneously feel sensations coming directly from it (Clites et al., 2018; Petrini, Bumbasirevic, Valle, et al., 2019; Petrini, Valle, Bumbasirevic, et al., 2019; Petrusic et al., 2022); (3) *the dynamic interface*, meaning build prosthetic devices that move exactly as human natural limbs (Valle, Saliji, et al., 2021), which relates to muscles like actuators and power supplies; and (4) *the multisensory interface*, meaning prosthetic devices that are felt like natural limbs, that is, optimally integrated with the residual senses and fully incorporated by the users (Makin et al., 2017; Risso et al., 2019; Risso et al., 2022; Risso & Valle, 2022).

Currently available technology can only partially support patients with amputation in their motor and sensory capabilities. As a consequence to better link the biological and the artificial systems, future challenges require to design: (1) *neural interfaces* (e.g., implantable electrodes connecting the human nervous systems with the prosthetic device) that remain stable, functional and selective over time. These biocompatible electrodes allow to record and stimulate the nerve fibers (Navarro et al., 2005; Stieglitz, 2020) creating a physical bridge between the brain and the robotic device; (2) *neural decoding/encoding* strategies (Bensmaia, 2015; Cracchiolo et al., 2020; Cracchiolo et al., 2021; Farina et al., 2017; Graczyk et al., 2016; Valle, Petrini, et al., 2018) that guarantee a bidirectional communication with the brain in order to restore the natural sensory-motor loop allowing a complete integration of the artificial limb in the user's body schema.

To tackle this difficult challenge, innovative neuroprosthetic devices exploiting implantable neural interfaces and direct peripheral nerve stimulation demonstrated the capability to restore the bidirectional flow of sensory-motor information from and to the brain (Charkhkar et al., 2018; George et al., 2019; Ortiz-Catalan, Mastinu, Sassu, et al., 2020; Overstreet et al., 2019; Petrini, Bumbasirevic, Valle, et al., 2019; Petrini, Valle, Strauss, et al., 2019; Tan et al., 2014; Zollo et al., 2019). In particular, thanks to the peripheral neural stimulation (PNS) of the somatic nerves (e.g., median, ulnar, radial, tibial and peroneal nerves) is possible to restore sensations in upper- and lower-limb amputees creating a closed-loop neuroprosthesis able to establish a unique communication between human and robotic devices (Figure 1).

The neural interface electrode has long been the limiting technological component for achieving a successful interface to the nervous system. Several previously conducted studies in animal models allowed to identify the optimal design and material of the neural interface. Indeed extraneural cuff electrodes are reliable and robust and imply a reduced invasiveness, but suffer from a limited selectivity (Tarler & Mortimer, 2004) and capability of recording neural signals. With cuff electrodes, it is possible to detect the compound activity of the nerve, and they have been used to switch on or off the contraction of muscle groups (Jensen et al., 2001). Thus, for improving selectivity, intraneural electrodes to be inserted longitudinally (Longitudinal Intrafascicular Multichannel Electrode [LIFE]; Kundu et al., 2014) or transversally (Utah Slanted Electrode Array [USEA] and Transversal Intrafascicular Multichannel Electrode [TIME]; Boretius et al., 2010) into the peripheral nerve have been developed and tested in animals (Badia, Boretius, Andreu, et al., 2011; Christensen et al., 2014; Wurth et al., 2017). On the other hand, USEA (Branner et al., 2001; Branner & Normann, 2000) is micromachined multineedle arrays made of silicon structures, originally developed as a neural interface for the brain, but modified for application in the peripheral nerve (Davis et al., 2016). USEAs are rigid silicon structures that record from the tips of the needles, transversally inserted in the nerve, where can induce damage in chronic implants (Christensen et al., 2016). In contrast, LIFEs and TIMEs are flexible

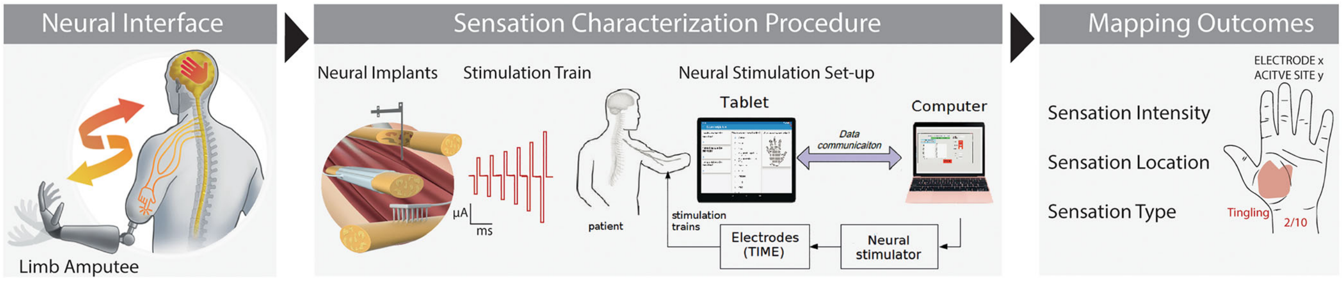

FIGURE 1 Neurostimulation for sensory feedback restoration in amputees. Sensory feedback restoration systems for both upper- and lower-limb amputees require (1) the surgical implant of electrodes in the peripheral nerves, (2) the sensation characterization to obtain the personalized optimal parameters (adapted from Valle, Iberite, et al., 2021) and (3) the implementation of stimulation parameters into paradigms able to provide meaningful tactile sensations to the user.

polymer structures inserted in the nerve and thus better suited for the longitudinal stretch motion of the nerve during limb movement (Badia, Boretius, Pascual-Font, et al., 2011; Lago et al., 2007; Lawrence et al., 2004).

Considering able-bodied individuals, interactions with objects are critically dependent on signals from the hand that convey information about the objects and our interactions with them. Without these signals, our ability to interact with objects is severely compromised, as visual signals are poor substitutes for their tactile counterparts (Augurelle et al., 2003; Johansson & Flanagan, 2009). Furthermore, somatosensation is critical to our embodiment, the feeling that our bodies are part of us (Makin et al., 2017; Risso & Valle, 2022). Indeed, deafferentation of a body part leads to its disembodiment, and the real or perceived afferentation of an artificial limb can lead to its embodiment (Botvinick & Cohen, 1998; Preatoni et al., 2021; Risso et al., 2022; Rognini et al., 2019). Finally, touch plays a critical role in affective communication. We touch the people we love and seek to be touched by them (McGlone et al., 2014). Unfortunately, because the neural stimulation policy adopted to restore touch is still rudimental and unable to replicate all the complex features of the natural neural communication (Bensmaia, 2015; Saal & Bensmaia, 2015), this neurotechnological intervention has still space for relevant improvements. Indeed, the resulting prosthetic dexterity is improved compared with conventional prosthetic devices but still far from that of natural hands in able-bodied individuals.

2 | ELECTRICAL NEUROSTIMULATION AS A TOOL TO RESTORE TOUCH SENSATIONS

The neural stimulation of peripheral nerves using implantable electrodes has shown the ability to selectively activate afferents fibers previously innervating the missing limb eliciting multiple sensation *locations* referred directly on the phantom limb (i.e., *somatotopic sensations*) (Charkhkar et al., 2018; Davis et al., 2016; Dhillon & Horch, 2005; Overstreet et al., 2019; Petrini, Valle, Bumbasirevic, et al., 2019; Strauss et al., 2019; Tan et al., 2015). Indeed, even after several years from the amputation event, the cortical map of the limb is still present and functional (Reilly et al., 2006; Schady et al., 1994). The cortical excitability in response to neural stimulation was recently measured through the phantom somatosensory-evoked potentials (Granata et al., 2018; Granata et al., 2020). Therefore, stimulating from an electrode active site (AS) with a pulse width, amplitude and frequency above the perceptual threshold, it is possible to activate the sensory afferents and then evoke a clear sensation.

Importantly, the *intensity* of the electrically evoked sensations is related to the stimulation parameters used. It is well known that, because of the physical effects of the neural stimulation on the nervous fibers, modulation of the injected charge or stimulation frequency led to a modulation of the perceived sensation intensity (Dhillon & Horch, 2005; Graczyk et al., 2016; Valle, Petrini, et al., 2018). Indeed, an increase in injected charge increases the number of fibers activated (i.e., recruited) while an increase in stimulation frequency forces the fibers afferents to spike at a higher rate. Recruitment and firing activity are the underlying mechanisms responsible for the perceived intensity. In fact, these behaviours are in accordance with the physiology of tactile afferents according to rate code (the intensity of a stimulus is proportional to the firing rate of the fibre) and population code (the intensity of a stimulus is proportional to the number of fibers that are activated) (Muniak et al., 2007; Raspopovic et al., 2017; Saal & Bensmaia, 2014). Combinations or variations of those strategies are adopted to convey to the brain more sophisticated touch features (Weber et al., 2013).

When electrically stimulating the nerve, the *type* of evoked sensation depends on the type of the activated fibers (Macefield et al., 1990; Ochoa & Torebjörk, 1983). There are four types of tactile fibers, which are normally connected to four different mechanoreceptors in the glabrous skin. Intraneural stimulation of fast-adapting (FA) fibers I and II afferents usually elicit a perception of intermittent tapping/flutter (Torebjörk et al., 1987). Complementarily, slowly adapting (SA) types I and II respond to sustained deformations of the skin. In particular, SAI encodes static or low-frequency changes of tissue deformation and evokes sensations of sustained pressure with microstimulation (Torebjörk et al., 1987). SAII encodes for skin stretches and when stimulated, generally, elicits a large diffuse pressure (Watkins et al., 2022). Moreover, very recent studies have also shown that the adopted stimulation patterns (so the strategy used to activate these sensory afferents) are strongly connected with the naturalness of the evoked sensation (Saal & Bensmaia, 2015; Valle, Mazzoni, et al., 2018).

2.1 | Somatosensory feedback for neuroprostheses

When designing an artificial sense, the aim is to develop a technology able to restore effectively and functionally as many features as possible of the missing sense. The touch is of pivotal importance, also considering its intended use in combination with an actuated sensitized prosthesis. The design of a somatosensory neuroprosthesis requires as the first step the definition of the neurostimulation parameters to adopt for evoking a reliable, specific and exploitable artificial sensory feedback (i.e., sensation characterization procedure; Valle, Iberite, et al., 2021) (Figure 1). This mapping procedure is mostly performed by an expert (e.g., clinician or bioengineer), and because it depends also by the number of ASs of the implanted electrode, it can have a long duration. For example, the implant of intraneural electrodes (e.g., TIME; Čvančara et al., 2019) requires four TIMEs for a total of 56 ASs available for the direct nerve stimulation (Petrini, Valle, Bumbasirevic, et al., 2019; Petrini, Valle, Strauss, et al., 2019). Each AS must be tested individually, and the stimulation parameters are unknown a priori. It means that the expert needs to explore the multidimensional space of parameters utilizing his/her expertise to find the optimal combination of stimulation frequency, pulse width and pulse amplitude to evoke the artificial sensation. Interestingly, to solve this practical issue, innovative methods, based on artificial intelligence models, have been considered for helping the calibration of such neurostimulating devices (Brocker et al., 2017; Kumaravelu et al., 2020; Laferriere et al., 2020; Tafazoli et al., 2020).

After having identified the personalized stimulation parameters for the user, the sensory feedback should be designed to perfectly match the experienced physical stimulus in terms of time, space, type and intensity. The neuroprosthetic device has to artificially replicate the natural sensory experience.

First, the sensation has to be perceived without any delay by the user (*real-time feedback*). This will guarantee a direct link between the visual and the tactile experience allowing for the embodiment of the prosthetic device (Risso et al., 2022). Real-time feedback is also particularly important for motor control and its integration into the residual sensory-motor loop (Clemente et al., 2019; Schiefer et al., 2016; Valle, D'Anna, et al., 2020). A recent study reported that stimulation-induced sensation could be delayed up to $111 + 62$ ms without the delay being reliably detected by the user (Christie et al., 2019). This short time should include the sensing (detecting the pressure event on the prosthetic digits), the encoding (convert the artificial readouts of the sensors in neurostimulation commands), the delivering (send the command to the neurostimulator and inject the current) and the perceiving (the user processes the artificial signal, generating the perception).

Second, the location of the perceived sensations has to be specific and directly associated with the physical body–environment interaction (*somatotopic feedback*). The spatial match between the stimulus and the perception maximizes ease of use and acceptance of the device (Makin et al., 2017; Valle, D'Anna, et al., 2020), preventing the amputee from spending long periods of training to get confident with it. In cognitive neurosciences, seminal studies on the intersensory discrepancy stated that spatial congruence between the multisensory cues (in this case vision and touch) is a fundamental feature for perceptual integration to happen (Welch & Warren, 1980). The direct neural stimulation delivered from different ASs elicits multiple spots on the phantom limb. The perceived locations of sensations are thus determined by the idiosyncratic position of the stimulating electrode in the nerve and are difficult to modify or control (Ortiz-Catalan, Mastinu, Greenspon, & Bensmaia, 2020). The evoked sensations are then directly associated with sensors placed on the same areas on the prosthetic hand or foot.

Furthermore, the ideal sensory feedback restoration device should also elicit sensations of the same quality as those perceived by the intact limb (i.e., tactile and proprioceptive sensations). This feature is defined as homology (*homologous feedback*). This property is related to the type of prosthetic sensors adopted and also to the type of

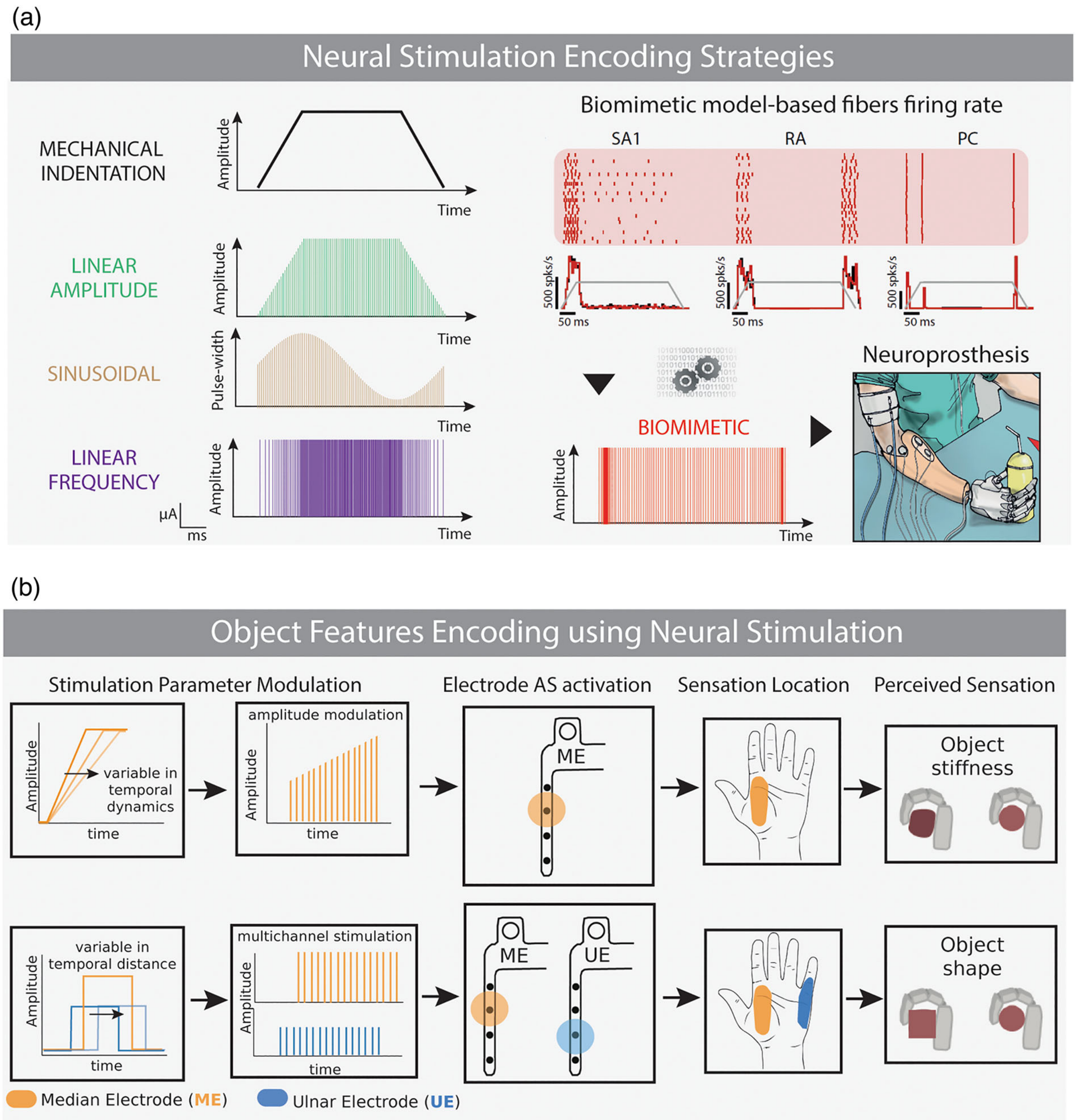

FIGURE 2 Encoding somatosensation through neural stimulation. (a) Different neural stimulation encoding strategies for sensory feedback restoration. The modulation of multiple stimulation parameters has been proposed to encode mechanical stimuli applied on the prosthesis. Classical approaches are adopting the modulation of a single stimulation parameter as linear neuromodulation of the amplitude or frequency (adapted from Valle, Mazzoni, et al., 2018). (b) Two encoding schemes to provide the user with information regarding the shape or compliance of the grasped object. The variations of intradigit temporal dynamics or interdigits temporal distance have been proposed as possible approaches to encode these object properties (adapted from Valle, Strauss, et al., 2020).

sensations achievable through neurostimulation. During the mapping phase, the expert technician identifies the ASs eliciting a sensation in a specific phantom location (correspondent to the sensor location) with a type more similar as possible to a natural pressure, avoiding painful and uncomfortable sensations.

Importantly, the artificial sensory feedback has to convey information of applied force. This feature is pivotal for interacting with the external environment and for smooth motor control (Johansson & Flanagan, 2009; Johansson & Westling, 1984). For this reason, the prosthetic user has to be able to exploit the dynamic tactile information induced by neural stimulation, that is, triggered by the sensors of the sensitized prosthesis, to adaptively modulate grasping force, thus closing the user-prosthesis loop (*modulated feedback*). The ASs were used to deliver electrical stimuli to the peripheral nerves that were traditionally proportional to the readouts of artificial sensors in the hand prosthesis (D'Anna et al., 2019; Raspopovic et al., 2014; Tan et al., 2014; Valle, Petrini, et al., 2018).

The modulation of the spatiotemporal parameters of the neural stimulation allows to also encode some aspects of more complex features related to the external stimulus, such as its texture (Mazzoni et al., 2020; Oddo et al., 2016), stiffness (Schiefer et al., 2018; Valle, Strauss, et al., 2020) (Figure 2b) or shape (Raspopovic et al., 2014; Valle, Petrini, et al., 2018). It has been achieved exploiting the intradigit temporal dynamics and interdigit temporal distance of the neural stimulation. The modulation of the individual parameters of a single-channel stimulation or the specific activation of multiple channels in time elicit artificial sensations that could be intuitively interpretable to object properties. Indeed, how the sensation intensity varies over time or which digit is in contact with the object give us information about the configuration of the hand and so, indirectly, of the grasped object (e.g., stereognosis). These studies are still preliminary, because the code for conveying this information via neuromodulation is quite simple and artificial (not bio-inspired).

Considering all the above-mentioned features, the somatosensory neuroprosthesis equipped with such artificial feedback would be able to restore, in real-time, realistic, homologous and somatotopic sensations exploitable for object discrimination and fine grasping force regulation (in upper-limb amputees) or walking (in lower-limb amputees).

2.2 | Standard neurostimulation strategies for neuroprosthetic applications

The algorithm responsible for converting the sensors' readings in neurostimulation commands in the neuroprosthesis is called the *encoding function* (Figure 3). This function is fundamental to correctly conveying the characteristics of the experienced event to the brain. In the touch sense, this conversion is achieved by the cutaneous receptors (e.g., mechanoreceptors) (Johansson & Flanagan, 2009) that are able to convert any spatiotemporal deformation of the skin into electrical signals easily interpretable by the brain (Saal & Bensmaia, 2014). The brain uses tactile afferent information related to the time course, magnitude, direction and spatial distribution of contact forces, the shapes of contacted surfaces and the friction between contacted surfaces and the skin for interacting with the external world.

In the neuroprosthetic applications, the encoding functions are used to modulate the injected charge (pulse width or pulse amplitude) (Ortiz-Catalan et al., 2014; Petrini, Valle, Strauss, et al., 2019; Raspopovic et al., 2014; Tan et al., 2014) or pulse frequency (Davis et al., 2016; Dhillon & Horch, 2005; Horch et al., 2011) of the delivered neurostimulation train according to the prosthetic sensor values (Figure 2a). This mapping generally

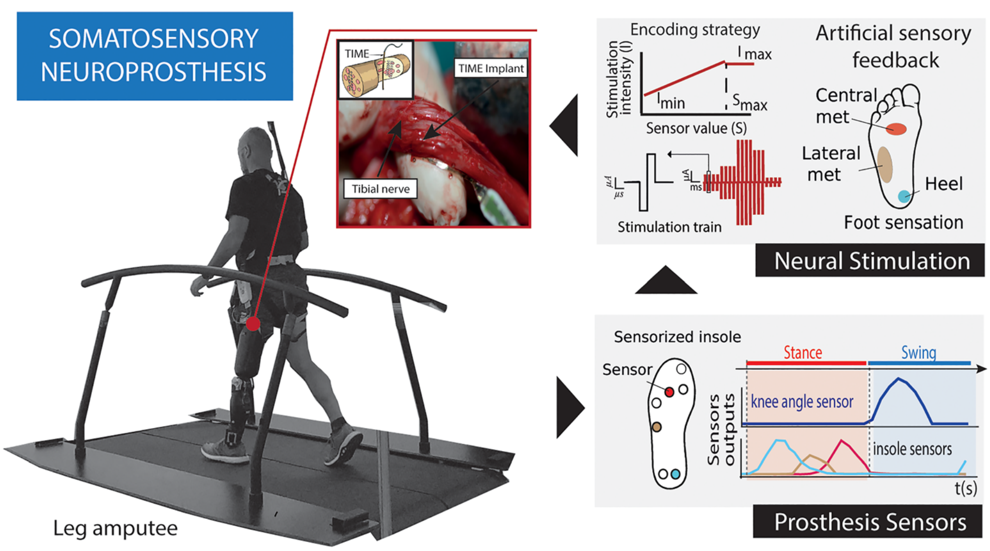

FIGURE 3 Neurostimulation on somatosensory neuroprostheses. The sensorized prosthesis is used to capture pressure information related to the body–environment interaction. The sensors are acquired and converted in real-time in neurostimulation parameters exploiting purposely designed encoding functions. The neurostimulation is delivered, through the neural implants, to the peripheral nervous system. Finally, the artificial sensation travels up to the brain, and it is interpreted by the user to improve the prosthesis control (sensory-motor integration).

follows a linear and proportional relationship with the sensor values (Katic et al., 2022) (e.g., the higher the value of the pressure measured by the sensor is, the higher the stimulation charge will be). Indeed, the intensity of the perceived sensation is proportionally associated with the stimulation charge and frequency (the higher the injected charge is, the higher the perceived sensation intensity will be) (Dhillon & Horch, 2005; Graczyk et al., 2016; Valle, Petrini, et al., 2018). Moreover, a linear encoder based on frequency or charge neuromodulation is easier implementable in real-time systems using wearable sensors on a prosthetic device.

Notably, although the encoding approach is quite simple, the linear encodings implemented in neuroprosthetic devices have shown to be easily interpretable by the user and to provide multiple benefits if added to prostheses (Raspopovic et al., 2021). Even though these techniques are functionally useful, the perceived naturalness and the richness of the electrically evoked sensations is often rated as very low by the patients (Valle, Petrini, et al., 2018).

Interestingly, Tan et al. (2014) have shown promising results in improving the sensation quality using sinusoidal modulation of the stimulation pulse width. Unfortunately, these findings have not been replicated by other research groups yet. Indeed Ortiz-Catalan et al. (2019) have evaluated the effect of sinusoidal modulations on the quality of perceived sensations. Three subjects with above-elbow amputation were implanted with cuff electrodes and stimulated with different patterned stimulations. The results showed that the quality remained largely perceived as artificial despite employing patterned modulation. Thus, the sensory transformation from paresthesia to natural qualia seems to require more than patterned and sinusoidal neurostimulations.

2.3 | Biomimicry as fundamental feature for neurostimulation design

In the neuroprosthetic field, the scheme of neural stimulation is mostly not defined by the nerve's natural coding or neuromorphic models (Saal & Bensmaia, 2015), causing the evoked sensations to be mostly described as vibration, tingling, paresthesia or electricity by users. In fact, the natural touch coding and the relationship between biological sensors and neural activity are more complex than the sole intensity coding. In the recent past, in silico models emulating the touch receptors and processing have been proposed as the bases to design stimulation strategies mimicking the natural touch coding (i.e., biomimetic stimulation). The theory of adopting more biomimetic and bio-inspired patterns of stimulation assumes that replicating the natural firing patterns would lead to more natural sensations. Indeed, the aim is to electrically induce a natural pattern of fibers activation inside the nerve, such as the one generated by the cutaneous receptors in the case of healthy touch systems. Thus, this artificial biomimetic neural activation will be processed as a natural activation, allowing for more intuitive and natural sensory information for the brain.

To this aim, efforts to sensitize bionic hands for amputees by electrical stimulation of the nerves have shown that sensory feedback that mimics natural tactile signals (so-called *biomimetic sensory feedback*) evokes more natural and more intuitive sensations that better support interactions with objects than does non-biomimetic feedback (George et al., 2019; Valle, Mazzoni, et al., 2018). Indeed, the subjects exhibited improved manual dexterity or object discriminability with the biomimetic artificial touch. In Valle, Mazzoni, et al. (2018), the patient showed an increased embodiment of the prosthesis, feeling the prosthesis as part of her body rather than an external object to a greater extent.

A relevant barrier for the currently used stimulation approaches is that neural stimulation induces highly synchronized neural firing, where each recruited afferents fires simultaneously (Saal & Bensmaia, 2015; Tyler, 2015). This is due to the physical limitation of electrical stimulation that does not guarantee a selective activation of specific groups of nervous fibers. Indeed, biologically occurring neural activity usually follows a much more desynchronized pattern with a firing frequency modelled as a Poisson point process (Johnson & Hsiao, 1992). Interestingly with the modulation of multiple stimulation parameters, Formento et al. (2020) proposed a novel stimulation scheme (i.e., BioS) designed to desynchronize the neural activity induced by electrical stimulation (validated in silico and in vitro), potentially allowing future biomimetic encoding strategies to replicate natural patterns of activity with even higher fidelity.

Notably, the previous studies have compared somatosensory stimulation often in a two-alternative forced choice task asking to the user how natural did this feel. But that is much different than being exposed to several different stimuli at once while performing activities of daily living, as would be often experienced by a prosthetic user. In these conditions, the electrically evoked sensations might even take advantage of the noisy neural processing involved in neural encoding allowing a more natural perception. Unfortunately, totally objective biomarkers of the perceived naturalness (e.g., fMRI signals) were not be acquired yet.

Nevertheless, biomimicry could become the fundamental feature for designing the next generation of brain-machine interfaces and neuroprostheses able to directly communicate with the brain, successfully encoding natural neural information using artificial electrical stimulation.

3 | CONCLUSION AND FUTURE DIRECTIONS

In this review, key mechanisms through which PNS facilitates sensory feedback and its efficacy on prosthesis performance have been presented. Thanks to this implantable technology, it is possible to create a link between the brain and the robotic limb. The stimulation parameters for an optimal and selective sensory feedback useful for the user have to be defined in a personalized manner through a sensation characterization procedure. Moreover, it is crucial that PNS guarantees artificial sensory feedback that is real time, somatotopic, homologous and intensity modulated. Linear and simple sensory encoding strategies allow to provide the user with sensory information functionally useful but not perceived as fully natural. Thanks to the novel neural interfaces and the neurostimulation techniques, it is now possible to go beyond the current limits. Indeed, there is compelling evidence suggesting that the biomimetic approach is essential for restoring a natural, rich and somatotopic sensory feedback and that acting on these signals through assistive technologies can augment the sensory-motor, multisensory integration and embodiment of the prosthesis in amputees.

Although important advances have been shown in the field, the artificial experience of somatosensation is still far from the natural one, and for this reason, its beneficial impact is still limited. Indeed, somatosensation is strongly connected to the sense of proprioception (Proske & Gandevia, 2012) (both force sense, motion sense and skin stretch), the thermal sensations (Melzack et al., 1962) and pain sensations (Melzack & Wall, 1965) that are extremely difficult to elicit or impossible to control with the current status of the somatosensory neurotechnology (D'Anna et al., 2019; Katic et al., 2021). More effort should be focus of developing novel interfaces with thousands of channels (Musk & Neuralink, 2019; Steinmetz et al., 2021) for a better communication and, in parallel, novel algorithms for a more selective and effective neural activation (Formento et al., 2020; Raspopovic et al., 2017; Valle, Mazzoni, et al., 2018).

Interestingly, different types of prosthetic devices have been tested in combination to the neural feedback provided via direct nerve stimulation both in upper-limb (Prensilia Azzurra IH2 [Petrini, Valle, Strauss, et al., 2019], Luke's Arm DEKA [George et al., 2019] and Ottobock hands [patients' standard prosthetic hand; Tan et al., 2014]) and in lower-limb amputees (RheoKneeXC Ossur [Petrini, Bumbasirevic, Valle, et al., 2019], energy-storage-and-return and active prostheses [Christie et al., 2020] and prototype ankle-foot prosthesis with powered ankle and subtalar joints [Clites et al., 2018]). In all these scenarios, the use of a prosthetic device with neural feedback has shown an advantage for the user; however, further tests are necessary to understand if the benefit would still be provided exploiting a more simplified prosthesis (e.g., hook and body-powered prosthesis).

Furthermore, the design of closed-loop neuroprostheses requires not only a real-time configuration but also a symbiotic link between the motor and the sensory loops. Indeed, we move our hands to interact with the environment in a different way according to the type of tactile feature we want to extract from the object (Lederman & Klatzky, 1987). Both the kinematics and the motor signals would be modulated according to the adopted grasping strategy. For this reason, it is of pivotal importance to put efforts in the development of more sophisticated and biomimetic control strategies sharing information with the sensory loop.

Although the benefits provided by the adoption of these neuroprosthetic devices can strongly impact the patients' quality of life, the effects are highly dependent on the implant stability, mainly related to the biointegration of electrodes in the human body over time (Grill et al., 2009). Indeed, stable and reliable sensory feedback must be guaranteed to the prosthetic users. The chronic use of these technologies is still limited and only few studies have shown a detailed analysis of the biointegration in human bodies considering both the biological reactions, the stability of the evoked sensations and the integrity of the implanted device.

These challenges are also relevant when, instead of targeting the nerves, the electrical stimulation is applied directly to the spinal cord (Chandrasekaran et al., 2020) or even to the somatosensory cortex (Tabot et al., 2013). Indeed, the application of intracortical microstimulation (ICMS) to the human cortex has been shown to evoke stable and nearly natural tactile sensations experienced at specific locations on the (otherwise insensate) hand (Flesher et al., 2016, 2021; Salas et al., 2018). However, the resulting dexterity is still not comparable with the natural one, due to problems very similar to those highlighted for the PNS (e.g., low quality, poor selectivity and limited controllability).

The use of implantable neuroprosthetic devices with patients with sensory-motor deficits is now increasing; however, more attention should be paid to the needs of the end-user (user-centred development). Indeed, to date, development has focused on clinical outcomes and functionality in the labs rather than the impact on subjective experience or the needs of daily living. Surely, this is a fundamental step for these neurotechnologies, but their evaluation requires a multifaceted approach that includes the patient's needs. It will ensure faster adoption.

All the present research is showing that evident functional benefits are provided by the restoration of the sensory information in a new generation of bionic hands. Neural stimulation through implantable electrodes represents a promising solution for future limb prostheses.

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CONFLICT OF INTEREST

The author declares no actual or potential conflict of interest.

AUTHOR CONTRIBUTION

G.V. wrote the paper and prepared the figures.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The author declares that the data supporting the findings of this study are available within the article.

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