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Symposium

Clinical Applications and Future Translation of Somatosensory Neuroprostheses

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Somatosensory neuroprostheses restore, replace, or enhance tactile and proprioceptive feedback for people with sensory impairments due to neurological disorders or injury. Somatosensory neuroprostheses typically couple sensor inputs from a wearable device, prosthesis, robotic device, or virtual reality system with electrical stimulation applied to the somatosensory nervous system via noninvasive or implanted interfaces. While prior research has mainly focused on technology development and proof-of-concept studies, recent acceleration of clinical studies in this area demonstrates the translational potential of somatosensory neuroprosthetic systems. In this review, we provide an overview of neurostimulation approaches currently undergoing human testing and summarize recent clinical findings on the perceptual, functional, and psychological impact of somatosensory neuroprostheses. We also cover current work toward the development of advanced stimulation paradigms to produce more natural and informative sensory feedback. Finally, we provide our perspective on the remaining challenges that need to be addressed prior to translation of somatosensory neuroprostheses.

Introduction

Somatosensory feedback is imperative for successful and efficient control of our body's movements and for performing activities of daily living (ADLs; Saudabayev et al., 2018). In the hand, touch provides information about object contact during reach-to-grasp movements (Johansson and Flanagan, 2009; Clemente et al., 2016) and is important for the efficient regulation of grip forces during hand grasp (Johansson et al., 1992; Augurelle et al., 2003; Johansson and Flanagan, 2009) and for object identification (Klatzky et al., 1985; Lederman and Klatzky, 1990). Even with a fully intact sensorimotor system, cutaneous anesthesia that eliminates the sense of touch results in excessively high and imbalanced grasp forces, drastically impairing object grasp and manipulation performance (Jenmalm and Johansson, 1997; Augurelle et al., 2003; Monzée et al., 2003; Nowak et al., 2004). Effective grasping and manipulation of objects is imperative for performance of activities necessary for independence. In the lower limb, somatosensory feedback from foot sole mechanoreceptors and limb proprioceptors is important for determining the timing of foot–ground contact, maintaining balance and posture, and walking over uneven terrain or surfaces (Perry et al., 2000; Roll et al., 2002).

Touch is also essential for forming and maintaining social bonds and for interpersonal communication. Caregiving touch in early childhood is necessary for normal growth and development (Field, 2010; Gallace and Spence, 2010), and touch can improve mood and reduce stress for adults (Field, 2010). Touch is also important for communicating emotions between family and friends (Hertenstein et al., 2009; Hauser et al., 2019; McIntyre et al., 2019). Crucially, touch serves a protective function. Touch and other forms of somatosensation, such as pain, signal when the body is damaged or is at risk for damage and trigger action to avoid the injurious stimuli and thereby maintain health (Gentsch et al., 2016; Walters and Williams, 2019). This avoidance of aversive stimuli is especially important for people who have compromised immune systems or poor wound healing and are at risk of serious medical complications from infection and sepsis if an injury does occur (Soden et al., 2000; Rappl, 2008).

Millions of people around the world are living with impaired sensation due to limb amputation, spinal cord injury (SCI), nerve injury, neuropathies, stroke, and other neuromuscular disorders

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(Ziegler-graham et al., 2008; B. B. Lee et al., 2013). In these conditions, part of or all of the sensory neural pathway is damaged or removed, resulting in loss of sensory perception and/or limitations in sensory processing and sensorimotor integration. In addition, ∼30% of the adult population worldwide has chronic pain (Elzahaf et al., 2012). The inability to feel tactile or proprioceptive sensations affects motor functions, as this feedback is crucial for dexterous, coordinated movement and multisensory integration (Sainburg et al., 1993; Ghez et al., 2001; Vastano et al., 2022). Psychologically, the loss of sensation can contribute to feelings of isolation, depression, and anxiety (Crossman, 1996), as patients may struggle with the loss of independence and changes in body image leading to increased depersonalization (Lenggenhager et al., 2012). Because of the lack of feedback, users do not perceive the prosthesis as a part of their own body, which increases the cognitive effort when using the device itself (i.e., low embodiment), affecting its acceptability (Makin et al., 2017). Thus, development and translation of sensory neuroprostheses is needed to restore, replace, or enhance somatosensory function in people with sensory impairments.

While considerable effort over many decades has been directed toward developing assistive technologies and neuroprosthetic devices to restore motor function to people with neurological injuries, somatosensory neuroprostheses are emerging as an important area of research and translational activity. Somatosensory neuroprostheses provide touch and/or proprioceptive information to users via electrical stimulation of the nervous system. To convey real-time feedback about interactions with the external environment, neurostimulation is modulated based on inputs from one or more sensors placed on the user's body, a prosthetic limb, a robotic limb, or a virtual limb, depending on the clinical application (Fig. 1). Here, we provide a review of sensory neurostimulation approaches currently under development or undergoing clinical studies and discuss the relative benefits, tradeoffs, and future translation for these new and emerging somatosensory neuroprosthetic technologies. We begin with an overview of neural interfacing approaches and discuss new stimulation paradigms and techniques that may enhance the performance of these systems. We then summarize the benefits of restored sensation on patient clinical outcomes and discuss barriers and progress toward future translation of somatosensory neuroprosthetic technology.

Interfacing with the Somatosensory Pathway

Somatosensory pathway

Somatosensation consists of touch, proprioception, temperature sensation, and pain. Tactile information is detected by a variety of mechanoreceptors in the skin—Merkel's disks, Meissner's corpuscles, Ruffini endings, Pacinian corpuscles, and free nerve endings on hair follicles—and each is tuned to respond to specific kinds of mechanical stimuli (Johansson and Flanagan, 2009). Proprioceptive information is detected by muscle spindles within the muscles, Golgi tendon organs in the tendons, and free nerve endings in the joints (Proske and Gandevia, 2012). Proprioceptive and tactile signals travel from these peripheral mechanoreceptors through peripheral nerves primarily via Aa and Aβ fibers, respectively, with cell bodies in the dorsal root ganglion (DRG) before entering the spinal cord (Gardner et al., 2013; Fig. 2). The axons travel through the dorsal column medial lemniscal (DCML) pathway in the spinal cord before synapsing in the *Fasciculus gracilis* (lower body) and the *Fasciculus cuneatus* (upper body) of the medulla. The second-order neurons connect to the ventral posterolateral (VPL) nucleus of the thalamus. The third-order neurons project to the primary somatosensory cortex, specifically Brodmann's areas 3a (proprioceptive) and 3b (tactile; Abraira and Ginty, 2013; Baker et al., 2018; Delhaye et al., 2018; S. Y. Bensmaia et al., 2023). Areas 3a and 3b are densely connected to areas 2 (tactile and proprioceptive) and 1 (tactile) for higher-level somatosensory processing; they also connect to area 4 (primary motor cortex), area 6, and others for sensorimotor integration (Gardner and Kandel, 2013; S. Y. Bensmaia and Yau, 2011; Abraira and Ginty, 2013; Baker et al., 2018; S. Y. Bensmaia et al., 2023). Pain and temperature information is primarily carried via Aδ and unmyelinated C-fibers and travel via the spinothalamic tract in the spinal cord (Gardner et al., 2013). Cortically, pain and thermal information is represented in the insular cortex (Björnsdotter et al., 2009).

Somatosensory neural interfaces

Somatosensory neuroprostheses can interface at multiple locations along the somatosensory pathway. These locations include the skin's surface (Pfeiffer, 1968; Tashiro and Higashiyama, 1981; Geng et al., 2012; S. Y. Bensmaia et al., 2023; Ng et al., 2020; Mesias et al., 2023), peripheral nerves (Anani et al., 1977; Dhillon and Horch, 2005; Clark et al., 2014; Ortiz-Catalan et al., 2014; Raspopovic et al., 2014; D. W. Tan et al., 2014; Graczyk et al., 2016; Christie et al., 2017; Freeberg et al., 2017; Ackerley et al., 2018; Valle et al., 2018b; Page et al., 2021), dorsal root ganglia (Fisher et al., 2014; Ayers et al., 2016; Nanivadekar et al., 2020), spinal cord (D. Tan et al., 2016; Chandrasekaran et al., 2020; Nanivadekar et al., 2023), brainstem (Sritharan et al., 2016), thalamus (Ohara et al., 2004; E. Heming et al., 2010; E. A. Heming et al., 2011; Schmid et al., 2016; Swan et al., 2018), and cortex (Boldrey and Penfield, 1937; Ojemann and Silbergeld, 1995; Johnson et al., 2013; Flesher et al., 2016, 2021; Hiremath et al., 2017; Armenta Salas et al., 2018; B. Lee et al., 2018; Fifer et al., 2022; C. L. Hughes et al., 2022; Greenspon et al., 2023a; Fig. 2). The majority of these interface locations have been studied in humans, except for the DRG (Fisher et al., 2014; Ayers et al., 2016; Nanivadekar et al., 2020) and brainstem (Sritharan et al., 2016), which have been studied in nonhuman primates (NHPs) and other preclinical models.

Electrical stimulation can be applied noninvasively via surface electrodes placed on the skin (Pfeiffer, 1968; Tashiro and Higashiyama, 1981; Geng et al., 2012; Ng et al., 2020; Mesias et al., 2023; Fig. 2). Mechanoreceptors in the skin can also be activated by mechanical indenters, vibrators, edges, bars, dots, rotating drums with various textures, and many other stimulators (Burgess et al., 1983; Cohen and Vierck, 1993; S. Y. Bensmaia and Hollins, 2003; S. Bensmaïa et al., 2005; S. Y. Bensmaïa et al., 2006; Pei et al., 2009; Weber et al., 2013; Callier et al., 2019).

Multiple types of peripheral nerve interfaces have been developed and tested for their ability to produce sensation in humans (Fig. 2). Some of these interfaces wrap around the outside of the nerve (i.e., "extraneural" electrodes), such as spiral cuff electrodes (Ortiz-Catalan et al., 2014; D. W. Tan et al., 2014; Graczyk et al., 2016; Christie et al., 2017; Ackerley et al., 2018) and flat interface nerve electrodes (FINE; D. W. Tan et al., 2014; Freeberg et al., 2017). Other types of peripheral interfaces penetrate the nerve (i.e., "intraneural" electrodes), such as transverse intrafascicular multichannel electrodes (TIME; Raspopovic et al., 2014; Valle et al., 2018b), longitudinal intrafascicular electrodes (LIFE; Dhillon and Horch, 2005; Overstreet et al., 2019), fine wire electrodes (Anani et al., 1977), and slanted Utah microelectrode arrays (Clark et al., 2014; Page et al., 2021).

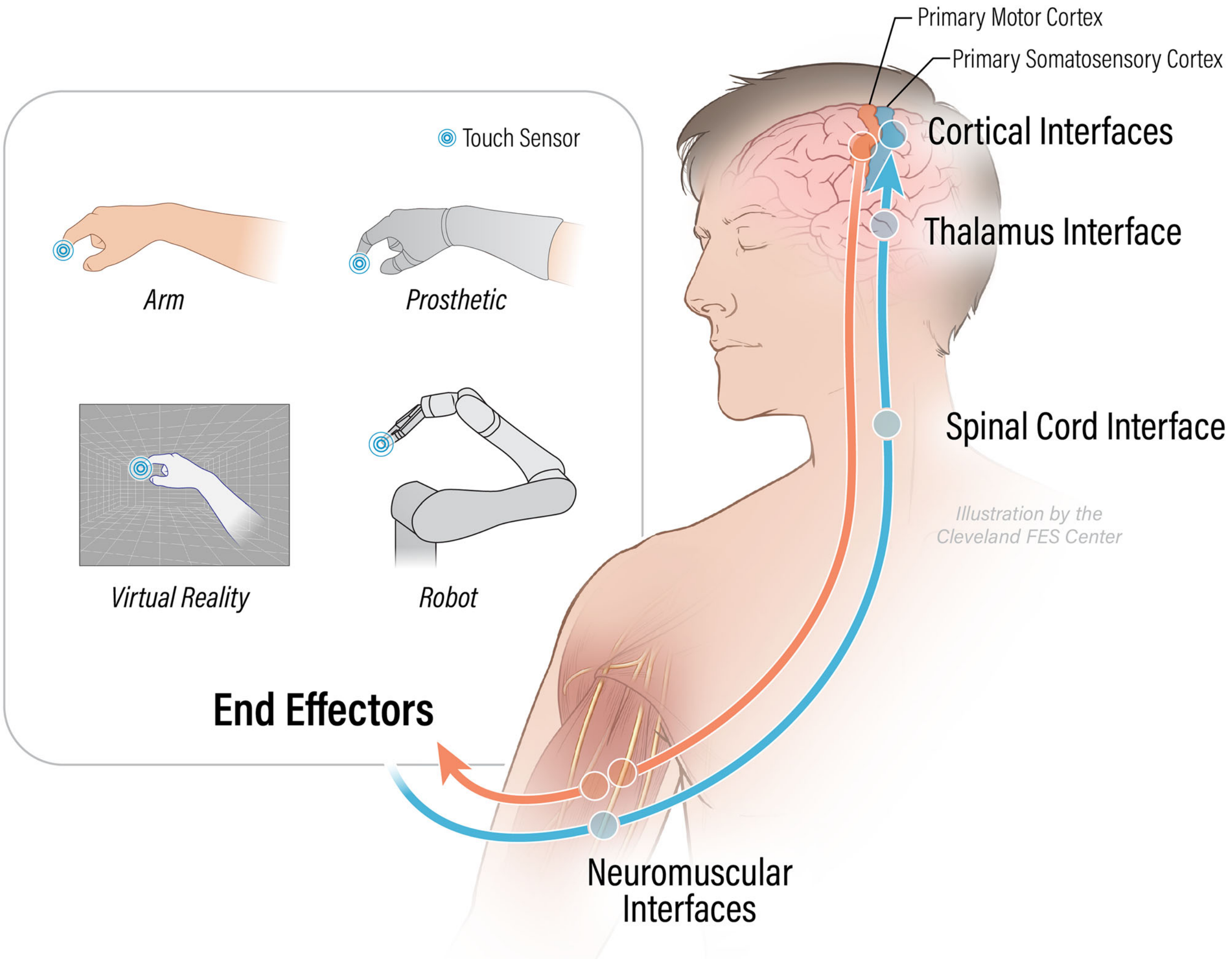

Figure 1. Somatosensory neuroprostheses integrate with motor neuroprostheses or assistive devices to provide touch, proprioception, and/or other forms of somatosensation to the user. The user controls movements of their own body, a prosthetic device, a robot, or an avatar in virtual reality via signals from their brain, nerves, and/or muscles. Interactions of these end effectors with the environment, objects, or other people activate sensors placed on the end effector. Signals from the sensor(s) modulate neurostimulation applied through neural interfaces placed along the somatosensory pathway to provide real-time, closed-loop sensory feedback to aid in task performance, improve user experience, and enhance immersion and/or social connection.

More invasive electrodes are generally thought to be more selective in recruiting specific neural populations, although selectivity varies across studies, participants, and electrodes (M. A. Gonzalez et al., 2022).

Spinal cord stimulation (SCS) for sensory restoration is typically applied with commercially available multichannel leads inserted into the epidural space on the dorsal side of the spinal cord (D. Tan et al., 2016; Chandrasekaran et al., 2020; Nanivadekar et al., 2023; Fig. 2). These SCS leads are also used clinically to manage pain that is refractory to pharmacological treatment (North et al., 1995, 2005; Kumar et al., 2007, 2008; Liem et al., 2013; Eldabe et al., 2015; Morgalla et al., 2018; Hunter et al., 2019).

Brain stimulation to produce sensation can also involve multiple types of interfaces. The most common cortical target for stimulation in humans is the primary somatosensory cortex (S1), typically the hand area of Brodmann's area 1. Area 1 is commonly targeted because it is on the gyrus and can be easily accessed by surface probes (Boldrey and Penfield, 1937; Ojemann and Silbergeld, 1995), electrocorticography (ECoG) electrodes (Johnson et al., 2013; Hiremath et al., 2017; B. Lee et al., 2018), and intracortical microelectrode arrays (Flesher et al., 2016, 2021; Armenta Salas et al., 2018; Fifer et al., 2022; Greenspon et al., 2023a; Fig. 2). Brodmann's area 3b, which typically resides on the posterior side of the central sulcus in humans and NHPs, has been targeted using stereoelectroencephalography (sEEG) depth electrodes (Chandrasekaran et al., 2021) to evoke tactile percepts. Brodmann's area 2, which receives both proprioceptive and tactile inputs, has also been explored as a location to restore somatosensory percepts (Zaaimi et al., 2013). All of these different approaches could be exploited singularly or in combination (Herring et al., 2023), depending on the residual pathways and needs of a potential neuroprosthesis user. See Table 1 for an overview of key studies related to each neural interface.

Surgical strategies to restore sensation

As an alternative to electrically stimulating the nervous system, research groups are partnering with physicians to develop innovative surgical techniques to help restore tactile and proprioceptive sensations. These surgical strategies leverage intact nerves and the body's ability to heal to generate new neural interfacing locations. The surgical constructs can then be coupled with prosthetic or robotic devices and/or neuromuscular

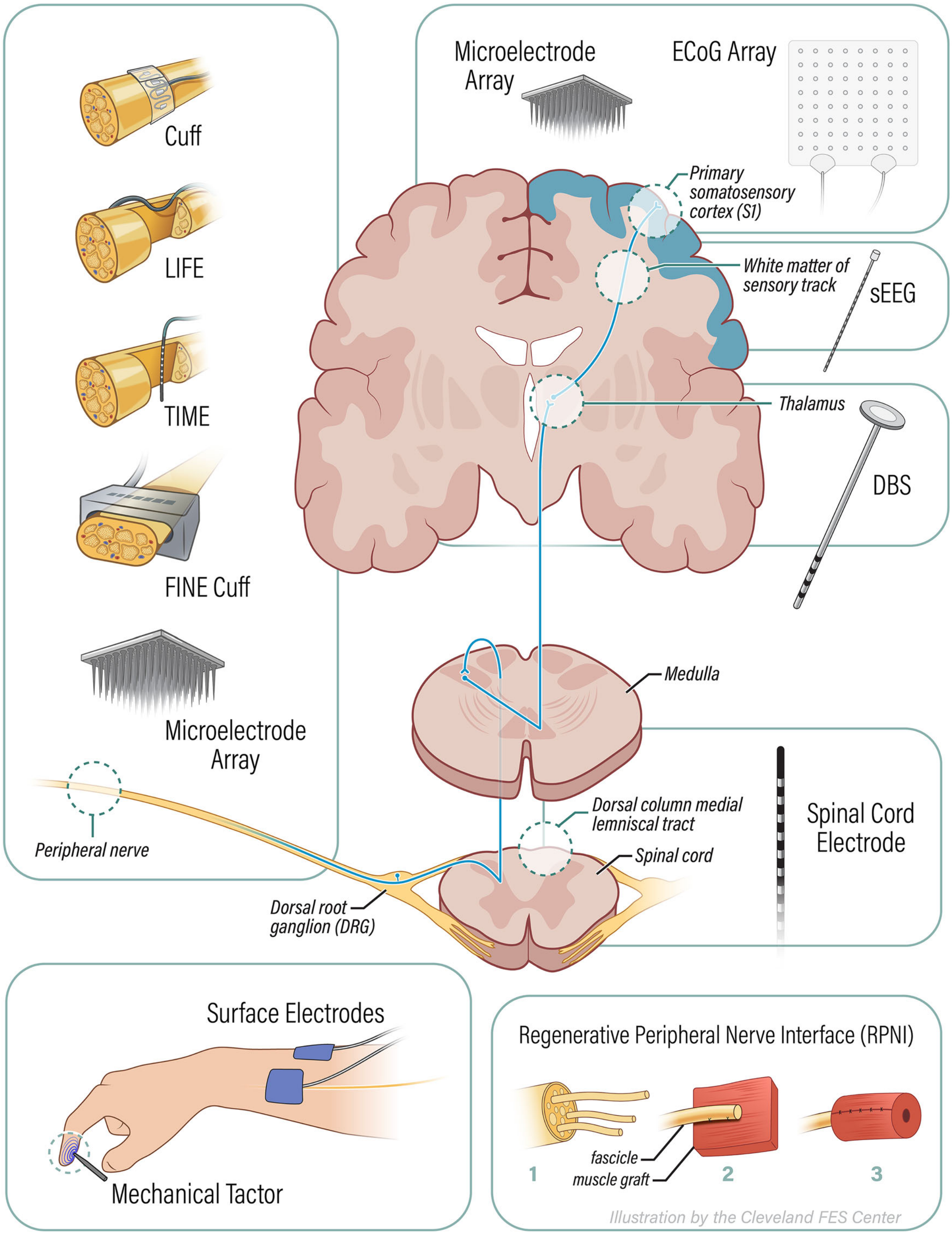

Figure 2. Neural interfaces for somatosensory neuroprostheses. Neural stimulation can be applied through interfaces placed along the somatosensory pathway to provide somatosensory feedback to neuroprosthesis users. A mechanical tactor, vibrating unit, or other mechanical device can activate the mechanoreceptors in the skin to produce touch. Surface electrodes placed over nerves in the hand, foot, arm, or leg can evoke sensation corresponding to the innervation territory of the activated nerve. PNS can be applied through implanted peripheral nerve interfaces, including an extraneural cuff electrode, the longitudinal intrafascicular electrode (LIFE), transverse intrafascicular electrode (TIME), flat interface nerve electrode (FINE or C-FINE), and microelectrode arrays. Surgical constructs can also be used to generate feedback, such as the regenerative peripheral nerve interface (RPNI), in which nerve fascicles are individually inserted into muscle grafts. Stimulation in the spinal cord can be applied via spinal cord leads inserted into the epidural space, near the dorsal root ganglia (DRG), or dorsal column medial lemniscal tract carrying sensory information to the brain. Brain stimulation can be applied via deep brain stimulation electrodes (placed near the thalamus), stereoelectroencephalography (sEEG) leads (placed in sulci or near white matter tracts), electrocorticography (ECoG) grids (placed on the brain surface), or intracortical microelectrode arrays (inserted into primary somatosensory cortex).

interfaces to restore bidirectional sensation and control to people with disabilities. For example, targeted sensory reinnervation (TSR) is a surgical approach where mixed nerves containing sensory axons are sutured to cutaneous nerve branches enabling reinnervation of the overlaying skin (Hebert et al., 2014a,b). When this area of skin is mechanically stimulated, users feel sensations that are referred to the region of the body typically innervated by the rerouted nerve (Kuiken

Table 1. Summary of electrical stimulation approaches for somatosensory neuroprostheses

Location	Interface type	Patient population	Stimulation approach	Key studies
Skin surface	Surface electrodes	Able-bodied	Single channel, multichannel	Tashiro and Higashiyama, 1981; Geng et al., 2012; Ng et al., 2020; Mesias et al., 2023
Peripheral nerve	Nerve cuff, FINE	Amputation	Single channel, multichannel, biomimetic	D. W. Tan et al., 2014, 2015; Ortiz-Catalan et al., 2014; Graczyk et al., 2016, 2022; Christie et al., 2017, 2020; Charkhkar et al., 2018, 2020; Schiefer et al., 2018; Ackerley et al., 2018; Graczyk, 2018; Cuberovic et al., 2019
	LIFE	Amputation	Single channel	Dhillon et al., 2005; Overstreet et al., 2019
	TIME	Amputation	Single channel, multichannel, biomimetic	Raspopovic et al., 2014; Oddo et al., 2016; Valle et al., 2018a,b; Strauss et al., 2019; Clemente et al., 2019; D'Anna et al., 2019; Petrini et al., 2019b; Valle et al., 2020, 2021, 2024
	Microelectrode array	Amputation	Single channel, multichannel, biomimetic	Clark et al., 2014; Davis et al., 2016; Wendelken et al., 2017; George et al., 2019; Page et al., 2021
	RPNI	Amputation	Single channel, multichannel	M. A. Gonzalez et al., 2022, 2024; Vu et al., 2022
	AMI	Amputation	Single channel	Clites et al., 2018; Carty and Herr, 2021; Srinivasan et al., 2017
Spinal cord	SCS	Amputation	Single channel	Chandrasekaran et al., 2020; Nanivadekar et al., 2023
Thalamus	DBS	Tremor and epilepsy	Single channel, multichannel	Ohara et al., 2004; E. Heming et al., 2010; E. A. Heming et al., 2011; Swan et al., 2018
Cortex	sEEG and ECOG	SCI	Single channel	Hiremath et al., 2017; Chandrasekaran et al., 2021
	Microelectrode array	SCI	Single channel, multichannel, biomimetic	Flesher et al., 2016, 2021; Armenta Salas et al., 2018; Bjånes et al., 2022; Fifer et al., 2022; Greenspon et al., 2023a,b, Valle et al., 2024

The location of the neural interface, the interface type, the patient population, and the stimulation methodology for each key study is presented.

et al., 2007a,b; Marasco et al., 2009; Schultz et al., 2009; Hebert et al., 2014b; Serino et al., 2017).

Another surgical approach for reinnervation is the regenerative peripheral nerve interface (RPNI; Fig. 2). In this approach, nerve endings are sutured to small muscle grafts placed internal to the body to amplify electromyography (EMG) signals for prosthetic control and to reduce postamputation pain (Vu et al., 2020, 2023; Kubiak et al., 2022; C. Lee et al., 2022; J. C. Lee et al., 2024). Electrical stimulation of RPNIs has also been used to provide sensation to amputees, indicating their potential to be used in tandem with motor control to improve prosthetic use (M. A. Gonzalez et al., 2022, 2024; Vu et al., 2022). However, the RPNI approach involves stimulating muscle tissue rather than skin, which may feel less natural. To address this issue, similar constructs can be created by attaching sensory nerves to small de-epithelialized skin grafts placed internal to the body (Dermal Sensory Regenerative Peripheral Nerve Interfaces, DS-RPNI; Sando et al., 2023). Examples of the DS-RPNI approach in the literature are limited to animal models, so the naturalness of the produced sensation is currently unknown. For restoring proprioception, researchers have developed the agonist–antagonist myoneural interface (AMI), which is a surgical construct for postamputation sensation and prosthesis control in which agonist–antagonist muscle pairs in the residual limb are mechanically coupled to preserve normal muscle dynamics and proprioceptive signals (Srinivasan et al., 2017; Clites et al., 2018; Carty and Herr, 2021).

Percepts evoked by somatosensory neuroprostheses

Stimulation of the somatosensory nervous system evokes percepts that are described as originating in the area of the body innervated by the stimulated neural structure. Peripheral nerve interfaces and spinal cord interfaces have been used to produce sensation in the upper and lower limbs, typically for people with upper and lower limb loss, respectively (Raspopovic et al., 2014; D. W. Tan et al., 2014; Charkhkar et al., 2018; Petrini et al., 2019a; Chandrasekaran et al., 2020; Nanivadekar et al., 2023). Percept sizes range from several millimeter in diameter or individual finger segments to whole digits, large sections of the hand or foot, or large areas of the limb (Clark et al., 2014; Raspopovic et al., 2014; D. W. Tan et al., 2014). Percept sizes can vary across electrodes in the same participant and even across contacts in the same electrode array (D. W. Tan et al., 2014; Chandrasekaran et al., 2020). In general, the location of the percept follows the innervation territory of the nerve for peripheral nerve stimulation (PNS) or the dermatome for SCS (D. W. Tan et al., 2014, 2015; Nanivadekar et al., 2023). SCS tends to evoke larger and more proximal percepts than PNS (Chandrasekaran et al., 2020; Nanivadekar et al., 2023). Intracortical microstimulation (ICMS) has thus far only been used to evoke sensation in the upper limb, in part because the lower limb representations in the somatosensory cortex are located in interhemispheric regions that are difficult to access surgically with currently-approved technologies. Perceived sensations from ICMS are typically localized to the hand, with sizes varying from <1 mm in diameter to large sections of the hand or arm. However, ICMS-evoked percepts are typically the size of a fingertip or smaller (Flesher et al., 2016; Armenta Salas et al., 2018; Fifer et al., 2022; Greenspon et al., 2023a; Herring et al., 2023).

All neural interfaces tested in humans thus far can provide a range of perceived intensities from barely perceptible up to very intense percepts that border on uncomfortable. Furthermore, research participants are able to discriminate different intensity levels, although the resolution of this discrimination varies widely based on many factors, including the stimulation paradigm and which stimulation parameter(s) are varying (Flesher et al., 2016; Graczyk et al., 2016; Fifer et al., 2022; M. Gonzalez et al., 2022). In cases where intact sensation can serve as a comparison, the range of perceived intensities can be matched to forces used in everyday object interactions (Graczyk et al., 2016; Greenspon et al., 2023a).

The perceptual qualities evoked by sensory neuroprostheses are commonly described with words such as "touch," "vibration," "tingling," "pressure," "sharp," "electrical," "tapping," "buzzing," and "movement" (Clark et al., 2014; D. W. Tan et al., 2014; Flesher et al., 2016; Armenta Salas et al., 2018; L. H. Kim et al., 2018; Cuberovic et al., 2019; Chandrasekaran et al., 2020; C. L. Hughes et al., 2021a; Graczyk et al., 2022; Graczyk and Tyler, 2023). Sensations from sensory neurostimulation are most frequently reported to be paresthetic, though for some contacts and participants, evoked sensation is described as "naturalistic," "possibly natural," or "natural" (D. W. Tan et al., 2014; Flesher et al., 2016; Valle et al., 2018a; Chandrasekaran et al., 2020). Converting these paresthetic sensations to more natural ones is a major goal of ongoing research, since this would likely drive increased acceptance by users. Therefore, considerable effort is devoted to the development of novel stimulation paradigms for somatosensory feedback restoration.

Development of Neurostimulation Paradigms

Single-channel stimulation

Most clinical studies to date have focused on characterizing the perceptual response to single-channel stimulation, in which stimulation is applied through a single electrode contact at a time. Stimulation patterns generally consist of trains of biphasic, square-wave, charge-balanced stimulation pulses, which can be described by sets of parameters: pulse amplitude, pulse width, pulse frequency, and train duration (Fig. 3*A*; Bjånes and Moritz, 2021). Pulses are typically cathodic leading, due to their enhanced sensitivity and lower detection thresholds (S. Kim et al., 2015; Stieger et al., 2022). Many studies have explored the relationship between single-channel stimulation parameters and the evoked sensation.

The stimulation channel, or electrode contact delivering current, changes the projected field location because of the somatotopy observed throughout much of the nervous system (Clark et al., 2014; D. W. Tan et al., 2015; Flesher et al., 2016; Charkhkar et al., 2018; Greenspon et al., 2023b). While small changes in projected field location may occur over time (D. W. Tan et al., 2015; Chandrasekaran et al., 2020) or with prolonged training (Cuberovic et al., 2019), projected field locations cannot be entirely remapped, suggesting a relatively stable somatotopic map in adults (Ortiz-Catalan et al., 2020).

Pulse amplitude and pulse width refer to the height and width, respectively, of the first (typically cathodic) phase of the pulse (Shannon, 1992; Merrill et al., 2005; Rajan et al., 2015). Pulse amplitude and pulse width are often used to modulate the perceived intensity and/or the size of the projected fields (D. W. Tan et al., 2014; Flesher et al., 2016; Graczyk et al., 2016; Valle et al., 2018b; Greenspon et al., 2023a,b; Nanivadekar et al., 2023; M. A. Gonzalez et al., 2024).

Pulse frequency, the rate at which stimulation pulses are delivered, also modulates the perceived intensity (Dhillon et al., 2005; Graczyk et al., 2016). However, the relationship between pulse frequency and perception is more complex than that of pulse width or pulse amplitude because pulse frequency can also change the quality of the percept (C. L. Hughes et al., 2021a; Graczyk et al., 2022). For example, a PNS study showed that stimulation below 50 Hz evoked sensations described as "tapping" and "pulsing," while stimulation above 50 Hz evoked sensations described as "tingling" and "buzzing" (Graczyk et al., 2022). Similarly, an ICMS study showed 20 Hz frequencies evoked sensations of "pressure," "tapping," and "touch," while 100 Hz frequencies evoked sensations of "buzzing" and "vibrating" (C. L. Hughes et al., 2021a). In addition, the perceived frequency of sensation evoked by PNS was only discriminable below ∼50 Hz (Graczyk et al., 2022). With ICMS, frequency modulation yields inconsistent effects across electrodes even in the same cortical region and is currently thought to be network/neuron specific (Callier et al., 2020; C. L. Hughes et al., 2021a).

The final parameter, train duration, is the time interval during which stimulation pulses are applied. Train duration can modulate the perceived intensity. On short time scales (<3 s), train duration increases the perceived intensity (Graczyk, 2018; C. L. Hughes et al., 2021a). Train durations on longer time scales (>3 s) can lead to attenuation of the perceived intensity throughout the stimulus (i.e., perceptual adaptation; Graczyk et al., 2018a; C. L. Hughes et al., 2022).

All of these stimulation parameters can also be dynamically modulated over the course of milliseconds, seconds, or minutes to communicate different types of sensory information. Work is ongoing to determine how to best encode a complex, time-varying sensory input (such as from a prosthetic hand or other end effector) into patterns of stimulation parameters. This complexity only increases when attempting to evoke multiple sensory percepts simultaneously.

For functional applications, most studies that provide sensory neurostimulation in real-time linearly map a sensor signal to a single stimulation parameter, such as pulse amplitude (Flesher et al., 2016; Petrini et al., 2019b; Ortiz-Catalan et al., 2020) or pulse frequency (Davis et al., 2016; Schiefer et al., 2016, 2018), to vary the intensity of the stimulation across time (Fig. 3*B*). In practice, some of these decisions about manipulating pulse amplitude or pulse width are driven by hardware design considerations in the stimulators themselves. The stimulation channel is typically selected such that the sensor position is matched as closely as possible to the projected field (i.e., perceived sensory location) in order to convey more intuitive feedback (Graczyk et al., 2018b; Schiefer et al., 2018; Flesher et al., 2021).

Biomimetic stimulation

The human hand is innervated by tens of thousands of mechanoreceptive afferents, each of which conveys different (albeit overlapping) information about grasped objects (Fig. 3*C*, left; Johansson and Flanagan, 2009). Each afferent responds in a distinct temporal firing pattern to a given stimulus, based on the type of afferent and the properties of the input stimulus (Saal et al., 2017). For example, certain mechanoreceptors fire in response to changes in a stimulus and display onset and/or offset transients during contact events (i.e., rapidly adapting receptors). Other mechanoreceptors (i.e., slowly adapting receptors) produce sustained firing throughout the duration of a stimulus and tend to increase their firing rate in response to increased input (Johansson and Flanagan, 2009). The information is integrated as it ascends the neuroaxis (Pei et al., 2009; Callier et al., 2019; Suresh et al., 2021). However, most sensory neuroprosthetic devices stimulate with simple stimulation paradigms that induce the same firing pattern in relatively large populations of neurons instead of imitating the complex neural coding of natural human touch (Donati and Valle, 2024). ICMS is further complicated by the difficulty in replicating temporally dynamic, nonstationary properties observed in normal brain networks. This unnatural activation is believed to underlie the paresthesia reported in most sensory neurostimulation studies.

To address this problem, many research groups are developing "biomimetic" stimulation approaches, which imitate the intact nervous system's activity during somatosensory function (Saal et al., 2017; Okorokova et al., 2018; Fig. 3*C*, right). To completely restore the natural neural activity of touch would require hundreds, if not thousands, of stimulating channels. While we cannot completely reproduce natural patterns of neuronal activation with current neurostimulation technology, we can leverage key principles of somatosensory neural coding in the development of biomimetic stimulation paradigms for sensory neuroprostheses. The biomimetic approach assumes that stimulation paradigms that closely replicate the neural patterns of natural touch will lead to more natural-feeling percepts than traditional neurostimulation approaches. Biomimetic stimulation

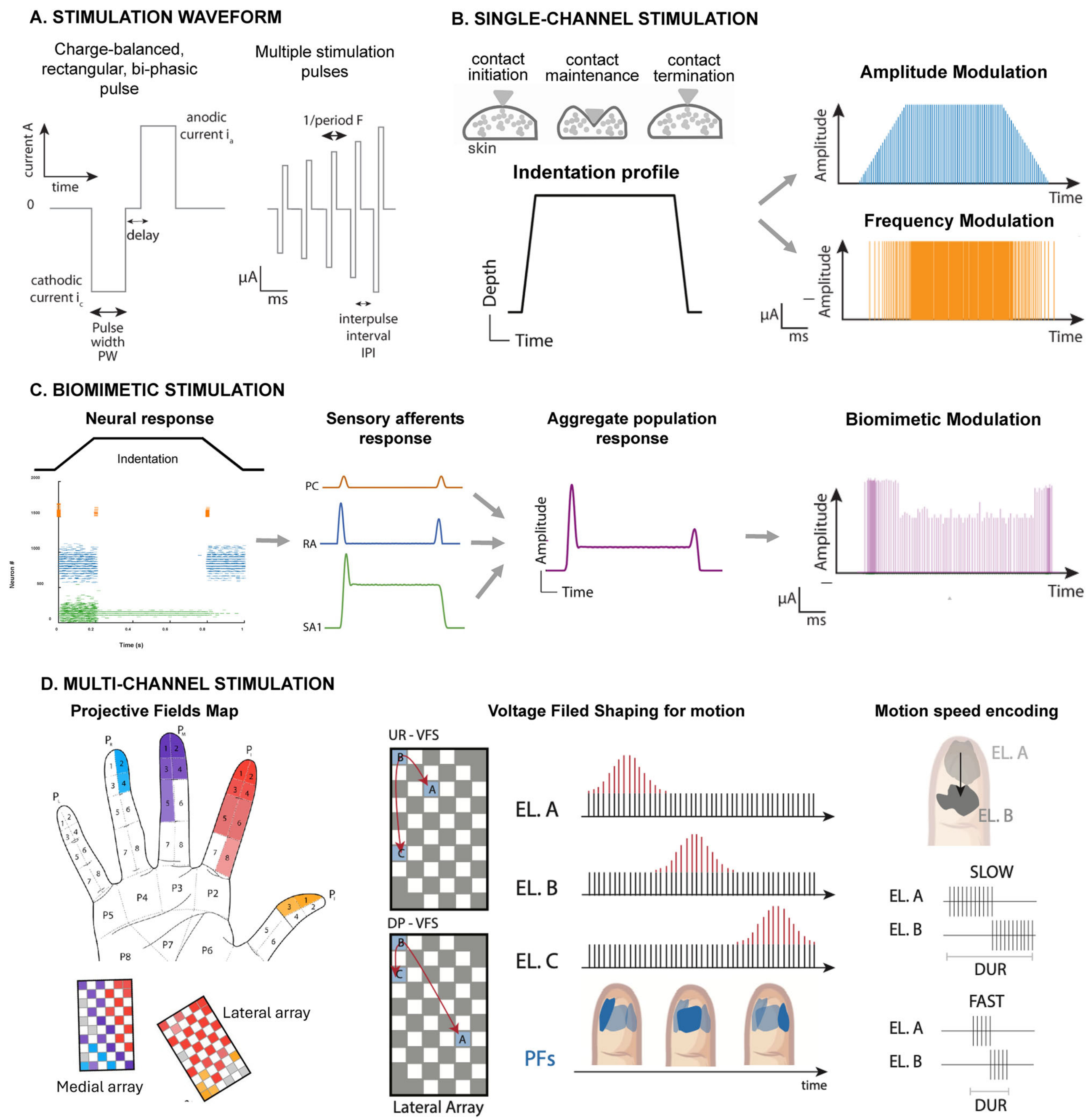

Figure 3. Neurostimulation paradigms for somatosensory neuroprostheses. ***A***, Stimulation waveforms. Neurostimulation is applied as trains of charge-balanced, rectangular, biphasic, cathode-first pulses. Each stimulation pulse can be described by its pulse amplitude and pulse width. The stimulation frequency is the inverse of the interpulse interval. ***B***, Single-channel stimulation approaches. An example tactile indentation (left) can be encoded into neurostimulation via either amplitude modulation (blue) or frequency modulation (orange). ***C***, Biomimetic stimulation. Normal touch produces dynamic firing patterns in hundreds of mechanoreceptive afferents (left). The responses across activated neurons can be aggregated on the basis of afferent type: slowly adapting type 1 (SA1, green), rapidly adapting type 1 (RA, blue), and Pacinian (PC, orange). These afferent subtype responses can then be added to form the aggregate population response (purple). Biomimetic stimulation replicates the aggregate population response (right). ***D***, Multichannel stimulation approaches. The projected fields of individual stimulation channels demonstrate somatotopic organization in the cortex (left). Stimulating multiple electrodes in sequence (middle) produces the sensation of movement across the finger. The duration and overlap of the pulse trains can also be varied (right) to control the speed of the perceived motion. Reproduced from Donati and Valle (2024), Valle et al. (2024), and Saal (2015).

may also be more intuitively processed, require less learning, and promote improved neuroprosthetic function, adoption, and user experience.

Recent work provides evidence that biomimetic neural stimulation produces more natural and functional somatosensory feedback (Fig. 3C). In PNS studies with upper and lower limb amputations, biomimetic stimulation evoked more natural percepts (Graczyk, 2018; Valle et al., 2018a, 2024) and improved functional task performance (Valle et al., 2018a, 2024; George et al., 2019). In the brain, multichannel biomimetic ICMS conveyed finely graded force feedback that more closely approximated natural touch sensitivity (Greenspon et al., 2023a). In addition, when percepts evoked by linear and biomimetic stimulation trains were directly compared with the percepts evoked by mechanical stimulation of the hand, biomimetic trains were routinely chosen as feeling more like the mechanical input.

Multichannel stimulation

Multichannel electrical stimulation patterns have emerged to encode both spatial and temporal information into the nervous system (Schiefer et al., 2018; Strauss et al., 2019; Greenspon et al., 2023a; Valle et al., 2024; Fig. 3*D*). Multichannel stimulation adds an additional layer of complexity to stimulation paradigm design, as pulses across channels can either overlap in time or be temporally separated (interleaved). If the stimulation pulses across channels overlap in time, the electrical fields interact, and the resulting combined voltage field can activate a different neural population than could be activated via stimulation through each channel individually (Sweeney et al., 1990; Polasek et al., 2009; Brill and Tyler, 2011; Hokanson et al., 2018; Tebcherani et al., 2024). This approach, called field shaping or current steering, can be used to produce new or different sensory locations (Cuberovic, 2020; Bjånes et al., 2022; Greenspon et al., 2023b; M. A. Gonzalez et al., 2024). If the stimulation pulses across channels do not overlap (i.e., are interleaved), then the goal is to recruit multiple discrete neural populations at different points in time (Tebcherani et al., 2024). If the pulses across channels are interleaved while the pulse train intervals overlap, all associated sensory percepts are electrically independent while being perceptually simultaneous. This interleaved approach has commonly been used in studies of PNS to provide sensory feedback from multiple locations on the hand or foot during closed-loop neuroprosthesis use (Graczyk et al., 2018b; Schiefer et al., 2018; Charkhkar et al., 2020; Christie et al., 2020).

Several studies using ICMS of S1 have investigated the effects of stimulating multiple electrodes simultaneously (synchronously or interleaved) and in sequence to expand the functionality of cortical sensory neuroprostheses. Studies investigating simultaneous multielectrode stimulation demonstrated increased dynamic range of intensity per electrode and increased intensity resolution (Greenspon et al., 2023a), which suggests that this paradigm can convey force information from a bionic hand over a wider range and with greater specificity. Multichannel stimulation also resulted in increased somatotopic coverage (Bjånes et al., 2022), improved localizability (Greenspon et al., 2023b), faster reaction times (Bjånes et al., 2022), and more natural perceived sensations (Bjånes et al., 2022).

Spatiotemporal patterning through multiple electrodes can produce complex sensations, including movement of an object across the skin, edges, and curvatures (Valle et al., 2024). Sequentially delivering stimulation through electrodes with spatially discontinuous projected fields can evoke the sensation of an object moving across the skin in different directions and at different speeds (Scarpelli et al., 2020; Valle et al., 2024). Stimulating multiple electrodes whose projected fields were arranged in a line elicited sensation of edges on the skin, and varying the alignment of the projected fields resulted in edges at different orientations, arbitrary tactile shapes, and curvatures (Valle et al., 2024). Thus, principled spatiotemporal patterning of neurostimulation can be used to evoke rich and complex sensations that expand the repertoire of producible sensations for sensory neuroprostheses.

Impacts of Restored Sensation in Clinical Populations

Limb amputation

There are >57.7 million people living with limb amputation worldwide, and rates of acquired amputation range from 1.2 to 4.4 per 10,000 people (Ephraim et al., 2003; McDonald et al., 2021). In the United States, there are >2 million people living with limb loss, ∼50% of whom have undergone a major limb amputation (Ziegler-graham et al., 2008). Current clinically available prostheses do not restore intuitive sensory feedback to users. While commercially available upper extremity (UE) prostheses can provide simple elbow, wrist, and grasp movements controlled via EMG signals from the residual muscles (Deijs et al., 2016; Segil et al., 2017; Lukyanenko et al., 2021), the lack of tactile or proprioceptive feedback makes precise movements and dexterous grasp challenging. People with lower extremity (LE) amputation must rely on very limited and uncomfortable haptic information from the stump-socket interaction and thus experience significant impairments, such as an increased risk of falls (Miller et al., 2001), impaired balance (Billot et al., 2013), and decreased mobility (Nolan et al., 2010). In addition, both upper and lower limb amputees frequently perceive the prosthesis as an external object (i.e., low embodiment; Engdahl et al., 2020; Bekrater-Bodmann, 2021) and experience increased cognitive burden during prosthesis use (Williams et al., 2006; Rackerby et al., 2022). Prior studies have suggested that the lack of sensory feedback in commercial devices is one of the factors contributing to prosthesis nonuse and abandonment (Biddiss and Chau, 2007; Smail et al., 2021).

Sensory neuroprostheses targeting the peripheral nerve to restore somatosensation to people with UE amputation have advanced nearly to the point of clinical adoption. Several research groups have demonstrated the potential of neural stimulation to provide intuitive touch and proprioceptive sensation that is perceived to originate from the missing hand and arm. While some studies are developing noninvasive approaches (L. Osborn et al., 2018), many studies have investigated the capabilities of implantable neural interfaces, which provide a direct connection between the prosthesis and the peripheral afferents governing somatosensory perception (Raspopovic et al., 2021). Providing sensory feedback using neural stimulation has been shown to improve prosthesis control (Schiefer et al., 2016; Valle et al., 2018a; Clemente et al., 2019), prosthesis embodiment (Graczyk et al., 2018b; Rognini et al., 2018; Schofield et al., 2020), active prosthesis usage (Graczyk et al., 2018b), visuohaptic integration (Risso et al., 2019), hand posture identification (Segil et al., 2020), and object identification (Raspopovic et al., 2014; Schiefer et al., 2018). For example, one study demonstrated a 25–50% improvement in object identification performance when touch and proprioceptive information were provided from the prosthesis (Schiefer et al., 2018). In addition, sensory feedback has been shown to reduce abnormal representations of the phantom limb (Graczyk et al., 2018b; Valle et al., 2018a; Cuberovic et al., 2019) and to reduce phantom limb pain by up to 70% (D. W. Tan et al., 2014; Page et al., 2018; Petrini et al., 2019b; Nanivadekar et al., 2023). Restored sensation also improves confidence in prosthesis use and decreases the cognitive burden of prosthesis use (Schiefer et al., 2016; Graczyk et al., 2018b, 2019).

Although the development of LE prostheses to provide users with active control of the prosthesis and sensory feedback began more recently than similar efforts for UE prostheses, several research groups are making significant advancements toward addressing this challenge (Hargrove et al., 2013, 2015; Charkhkar et al., 2018; Petrini et al., 2019c). Approaches to provide sensation to lower limb prosthesis users include noninvasive stimulation (Basla et al., 2022), surgical approaches (Clites et al., 2018), SCS (Nanivadekar et al., 2023), and direct nerve stimulation via implanted interfaces (Charkhkar et al., 2018; Preatoni et al., 2021). Neurostimulation can restore tactile and position information from the prosthetic foot and ankle that is somatotopic and intuitive to use (Charkhkar et al., 2018). Providing sensation from the prosthetic foot via PNS has been shown to improve mobility on stairs and ladders, increase walking speed, and reduce falls in response to unexpected obstacles (Petrini et al., 2019a,c; Christie et al., 2020). For example, one study demonstrated an improvement in walking speed of 3.5–5.7 m/min with sensory feedback (Petrini et al., 2019a). In addition, restored sensation in the prosthetic leg improves postural stability and balance (Charkhkar et al., 2020; Shell et al., 2021). Studies have also shown that using a lower limb prosthesis with sensation improves the confidence of the user (Preatoni et al., 2021; Valle et al., 2021), increases embodiment (Petrini et al., 2019c; Preatoni et al., 2021), and lowers cognitive load associated with prosthesis use (Petrini et al., 2019c; Preatoni et al., 2021). Restored sensory feedback also improved the kinematics of overground walking and stair ascent, such as increasing stride length and reducing prosthetic leg stance time, demonstrating that the gait pattern with the prosthesis became more similar to normal, unimpaired gait (Valle et al., 2021). The results from these proof-of-concept cases provide the rationale for larger population studies investigating the clinical utility of neuroprostheses that restore sensory feedback in LE amputees. These works pave the way for further investigations about how the brain interprets different artificial feedback strategies and for the development of fully implantable sensory-enhanced arm and leg neuroprostheses, which could drastically ameliorate quality of life in people with amputation.

Spinal cord injury

SCI resulting in paralysis affects over 296,000 people in the United States with over 17,900 new cases each year (National Spinal Cord Injury Statistical Center, 2021). Worldwide, incidence of SCI ranges from 5.1 to 150.5 cases per million people (Kang et al., 2017; Jazayeri et al., 2023). Incomplete and complete tetraplegia have accounted, respectively, for 47 and 12% of all SCI cases since 2015, with <1% of all cases achieving full recovery (National Spinal Cord Injury Statistical Center, 2021). Chronic tetraplegia due to SCI impedes general function and independence, resulting in lower quality of life and lower social integration. The loss of independence also places a burden on the family and/or caregivers of the person with SCI, who typically must perform all ADLs for them, including feeding, bathing, dressing, and bladder and bowel care. Most people with SCI, including those with incomplete injuries, have deficits in somatosensation, including reduced sensitivity or acuity in touch, vibration, temperature, and/or pain modalities (Finnerup et al., 2003).

Restoring arm function is a top clinical priority for people with high cervical SCI (Anderson, 2004; Huh and Ko, 2020). Intracortical brain machine interfaces (BMIs) can decode movement intent in people with tetraplegia to control the movement of end effectors such as virtual arms and robotic limbs (Collinger et al., 2013; Wodlinger et al., 2015; Bouton et al., 2016; Ajiboye et al., 2017; Downey et al., 2017; Young et al., 2019; Handelman et al., 2022). However, the dexterity of the BMI movements is limited by the absence of somatosensory feedback (Augurelle et al., 2003; Johansson and Flanagan, 2009; C. Hughes et al., 2020). Several research groups are developing somatosensory neuroprostheses that apply ICMS to the somatosensory cortex to evoke tactile and proprioceptive percepts in human clinical trials (Flesher et al., 2016; Armenta Salas et al., 2018; Fifer et al., 2022; Greenspon et al., 2023b; Herring et al., 2023). These evoked sensations can be mapped to sensorized robotic arms under BMI control (Flesher et al., 2021). In a prior study, the addition of somatosensory feedback improved the participant's ability to reach and grasp objects (Flesher et al., 2021). The tactile feedback indicating object contact enabled the participant to complete the Action Research Arm Task—a clinical assessment of upper limb function—twice as fast as the same system without somatosensory feedback (Flesher et al., 2021). In another study, bioinspired ICMS improved accuracy on a virtual object identification task (L. E. Osborn et al., 2021).

Chronic pain

Several neurostimulation systems have been clinically deployed to treat chronic pain. Neuromodulation technology is often used to treat chronic pain when pharmacological, psychological, and surgical interventions fail to control the pain (North et al., 1995; Kumar et al., 2007; Knotkova et al., 2021). The most prominent technology in the pain therapy industry is SCS (Grider et al., 2016). SCS is most commonly used to treat back and leg pain, though studies have also investigated treatment of arm and neck pain more recently (Taylor et al., 2005; Vallejo et al., 2007). PNS is also gaining popularity as an approach to treat chronic pain clinically (Xu et al., 2021).

An important application of neurostimulation for pain mitigation in the context of sensory neuroprostheses is phantom limb pain. Although ∼98% of people with amputation experience phantom sensation (Giummarra et al., 2007), which is the sense that the lost body part is still present, 50–80% of these people have painful experiences of the phantom limb (i.e., phantom pain; Sherman and Sherman, 1983; Kooijman et al., 2000; Desmond and MacLachlan, 2010). These painful phantom sensations are commonly described as "throbbing," "piercing," and "needle-like" sensations (Ramachandran and Hirstein, 1998; Grüsser et al., 2001). Although it is not completely understood why phantom limb pain occurs, factors that may influence the occurrence and extent of phantom pain include ectopic discharges from stump neuromas, increased excitability of injured nerves and dorsal root ganglia, and spinal or supraspinal neuroplastic changes (Harwood et al., 1992; Vaso et al., 2014; Petersen et al., 2019).

Several studies have investigated the effect of sensory neuroprostheses on phantom and postamputation pain. Surface stimulation is commonly applied to the residual limb to treat the phantom pain (Dietrich et al., 2012, 2018). Stimulation therapy through implanted peripheral nerve interfaces has also demonstrated the ability to alleviate phantom limb pain, and the reduction in phantom limb pain persisted over several weeks following the cessation of the treatment (D. W. Tan et al., 2014; Page et al., 2018; Petrini et al., 2019b). In addition, research systems that provide SCS as sensory feedback during LE prosthesis use demonstrated significant improvements in pain throughout the study, with pain reductions of 70% on average (Nanivadekar et al., 2023).

Translation of Somatosensory Neuroprostheses

Current challenges for somatosensory neuroprostheses

The overarching goal of somatosensory neuroprostheses is to "write" information to the sensory nervous system that can be interpreted and effectively utilized by downstream processes, including motor circuits, decision-making and other cognitive processes, and multisensory integration. However, the ability of sensory neuroprostheses to achieve this goal and engage with these processes is limited by the field's understanding of what information should be "written"—that is, the normal neural language of touch, proprioception, and other forms of somatosensation. Without a complete understanding of what neural codes to replicate, sensory stimulation technology will never fully engage with these circuits or fully replace natural sensation. Advancements in the neuroscientific understanding of somatosensory neural coding at all levels of the somatosensory pathway are necessary to continue to improve sensory stimulation paradigms and approaches.

Numerous neural interfacing technologies have shown initial feasibility in restoring sensation to humans (Table 1). However, most studies of somatosensory neuroprostheses have been conducted with small participant populations ($n = 1–5$), for relatively short durations (several weeks to several months), and in laboratory settings. All these factors make it difficult to synthesize findings across studies, make generalizations to larger patient populations, and ultimately translate these techniques to clinical practice. Most studies involve small participant cohorts due to difficulty in recruiting eligible participants and the high cost of performing studies involving surgical implantation of electrodes. The duration of studies is generally limited by electrode longevity and stability concerns (Christie et al., 2017; C. L. Hughes et al., 2021b; Woeppel et al., 2021) and by limitations dictated by regulatory agencies overseeing these studies. In the United States, for example, regulatory approval is simpler for implants that are <30 d in duration, so many studies require device explanation after less than month. However, studies have begun reporting electrode stability and consistent outcomes over years to decades (D. W. Tan et al., 2014, 2015; Christie et al., 2017; C. L. Hughes et al., 2021b), demonstrating the possibility for longer-term studies moving forward. Studies with larger sample sizes and longer implant durations would help somatosensory neuroprostheses reach translation.

Current progress toward translation

Most assessments of sensory neuroprostheses have thus far been conducted in the clinic or laboratory setting. Studies are typically conducted in the laboratory because the neurostimulators and devices involved are custom research devices that require expert knowledge to operate. These research systems typically are not user-friendly enough to be used autonomously by participants at home without researcher intervention. However, the next critical step toward translation of somatosensory neuroprosthetic technology is determining how sensory neuroprostheses are used in the home and community. Home studies provide a unique view into how and to what extent these devices will be used once commercially available because neuroprosthesis use is voluntarily chosen by users rather than directed by a research team. These studies also offer the opportunity to study long-term impacts of sensory neuroprostheses that are not likely to emerge over short, intermittent periods of use in the lab environment.

Several long-term home studies of UE sensory neuroprostheses have been conducted, in which people with UE amputation used sensory-enabled prosthetic hands in their homes and communities for up to 7 years. These studies demonstrated increased prosthesis wear time and improved task performance when sensation was provided compared with when it was not (Graczyk et al., 2018b; Middleton and Ortiz-Catalan, 2020). These studies also showed enhanced user experience when sensation was provided long-term, such as improving prosthesis embodiment, increasing confidence in prosthesis use, and increasing the willingness of participants to engage in social interactions with the prosthesis, such as shaking hands (Graczyk et al., 2018b, 2019; Cuberovic et al., 2019; Middleton and Ortiz-Catalan, 2020). Improvements were also seen in domains such as self-esteem, perceived disability, and quality of life (Graczyk et al., 2018b, 2019; Middleton and Ortiz-Catalan, 2020; Ortiz-Catalan et al., 2023). Interestingly, the perceived quality and naturalness of the evoked sensation was shown to improve through daily home use, though perceived sensory locations were not as malleable (Cuberovic et al., 2019; Ortiz-Catalan et al., 2020; Schofield et al., 2020). Studies have also shown improvements in phantom limb sensory experience and decreases in phantom limb pain after daily use of sensory neuroprostheses (Cuberovic et al., 2019; Middleton and Ortiz-Catalan, 2020).

One study examined home use of an LE sensory neuroprosthesis for 31 weeks and demonstrated improved sensorimotor integration of the prosthesis and improved prosthesis experience (Schmitt et al., 2023). In another study, participants briefly used a lower limb sensory neuroprosthesis to walk over sand in an outdoor environment. This study showed improved walking speed, improved confidence in the prosthesis, and lower cognitive effort when sensation was enabled (Petrini et al., 2019a). Thus far, there have been no home studies of sensory neuroprostheses for persons with SCI or paralysis. However, this is an active area of research and development. Nonetheless, the strong positive results from the sensory neuroprosthesis home studies to date provide justification for continued translation efforts.

Future translation of somatosensory neuroprostheses

Translation of sensory neuroprostheses may be aided by leveraging partnerships with medical device companies, such as those that already produce and market implantable spinal cord stimulators for chronic pain mitigation. These devices have already undergone significant technical development and clinical testing and have received appropriate regulatory approvals for commercialization (such as FDA 510K approval in the United States). Through partnerships with these companies, these technologies could be modified to support closed-loop, bidirectional sensorimotor restoration for rehabilitation applications. For example, a recently developed neuroprosthesis for sensory restoration and intuitive control of prosthetic hands was built in partnership with a medical device company on a platform originally developed for SCS (Lambrecht et al., 2024). Another commercialization approach involves partnering with manufacturers of research neurostimulation systems to conduct pivotal trials to acquire sufficient safety and efficacy data to enable premarket approval. For clinical applications involving prosthetic devices, it may be advantageous to partner with prosthetic device manufacturers to enable efficient translation of sensory neuroprostheses. In this approach, the neuroprosthesis could be included as a component of the overall prosthetic system, which could help address challenges with insurance coding and reimbursement.

Several challenges remain to be addressed before sensory neuroprostheses can be translated to commercial use. One major challenge is demonstrating sufficient clinical benefit to warrant the high cost of the device and associated procedures. Sensory neuroprostheses are currently very expensive, as a full system involves neural interfaces, neurostimulators, sensors, and often customized prosthetic or robotic devices (Fig. 1). Neuroprostheses that require implanted interfaces are even more costly due to the surgical and clinical care costs. Invasive interfaces also put the user at risk of infection and other medical complications, which was reported to be a concern for future adoption of these types of devices for 20% of amputees, but nearly all clinicians and regulators in a recent survey study (Rekant et al., 2022). While sensory neuroprostheses improve object interactions compared with assistive devices without sensation (Schiefer et al., 2018; Flesher et al., 2021; L. E. Osborn et al., 2021), these functional improvements may be seen as too incremental by funding organizations, insurance companies, and consumers to merit the additional costs and risks of these devices (Rekant et al., 2022). In fact, the largest and most consistent benefits of sensory neuroprostheses appear to be their psychological benefits, such as enhanced embodiment, confidence, and quality of life (Graczyk et al., 2018b; Preatoni et al., 2021; Valle et al., 2021). However, these outcomes are difficult to measure, and variability in outcome metrics across studies makes it difficult to synthesize findings across studies or generalize conclusions. Standardization of outcome measures across studies would help the field make comparisons across technologies and approaches and to synthesize findings to support future commercialization efforts.

Because clinical studies to date have been proof-of-concept studies to demonstrate technological feasibility and have small sample sizes, sufficient data has not yet been collected on the safety and efficacy of these neuroprosthetic systems, which is crucial for obtaining necessary medical certifications. Commercialization of sensory neuroprostheses is further challenged by the relatively small patient populations, which complicates the return on investment for a company marketing the product and limits the extent to which economy of scale can save on manufacturing costs. Worldwide, regulatory procedures are stringent and costly, and when factoring in the customization of devices and the need for smaller volumes, the economic burden on end users can be significant. This could impede the widespread adoption of these technologies. Another concern is the generalizability of the technology across participants. Most research systems are custom-tuned for each participant, but this configuration process is time consuming and requires specialized training. However, artificial intelligence approaches may be able to help with the configuration process in future systems.

The future of somatosensory neuroprostheses lies in personalized therapies involving the combined use of neural interfacing technologies and surgical approaches, which will be collaboratively selected by the patient and their care team depending on the patient's neurological injury or disorder, as well as their goals and needs. To enable translation, future somatosensory neuroprostheses must be effective, affordable, portable, minimally invasive, customizable, and easy to use. Improved neuroscientific understanding of somatosensory neural coding and integration will enable continued innovation in neurostimulation paradigms, which will further enhance the capabilities and benefits of somatosensory neuroprostheses. The significant advancements in the field over the past decade, as well as continued investment in and enthusiasm for ongoing research in this area, provide hope that somatosensory neuroprostheses could achieve translation in the next 5–10 years.

References

Abraira VE, Ginty DD (2013) The sensory neurons of touch. Neuron 79:618–639.

Ackerley R, Wasling HB, Ortiz-Catalan M, Brånemark R, Wessberg J (2018) Case studies in neuroscience: sensations elicited and discrimination ability from nerve cuff stimulation in an amputee over time. J Neurophysiol 120:291–295.

Ajiboye AB, et al. (2017) Restoration of reaching and grasping movements through brain-controlled muscle stimulation in a person with tetraplegia: a proof-of-concept demonstration. Lancet 389:1821–1830.

Anani AB, Ikeda K, Korner LM (1977) Human ability to discriminate various parameters in afferent electrical nerve-stimulation with particular reference to prostheses sensory feedback. Med Biol Eng Comput 15:363–373.

Anderson KD (2004) Targeting recovery: priorities of the spinal cord-injured population. J Neurotrauma 21:1371–1383.

Armenta Salas M, et al. (2018) Proprioceptive and cutaneous sensations in humans elicited by intracortical microstimulation. Elife 7:e32904.

Augurelle A-S, Smith AM, Lejeune T, Thonnard J-L (2003) Importance of cutaneous feedback in maintaining a secure grip during manipulation of hand-held objects. J Neurophysiol 89:665–671.

Ayers CA, Fisher LE, Gaunt RA, Weber DJ (2016) Microstimulation of the lumbar DRG recruits primary afferent neurons in localized regions of lower limb. J Neurophysiol 116:51–60.

Baker CM, et al. (2018) A connectomic atlas of the human cerebrum—chapter 3: the motor, premotor, and sensory cortices. Oper Neurosurg 15:S75–S121.

Basla C, Chee L, Valle G, Raspopovic S (2022) A non-invasive wearable sensory leg neuroprosthesis: mechanical, electrical and functional validation. J Neural Eng 19:016008.

Bekrater-Bodmann R (2021) Factors associated with prosthesis embodiment and its importance for prosthetic satisfaction in lower limb amputees. Front Neurorobot 14:604376.

Bensmaïa SJ, Craig JC, Yoshioka T, Johnson KO (2006) SA1 and RA afferent responses to static and vibrating gratings. J Neurophysiol 95:1771–1782.

Bensmaïa S, Hollins M, Yau J, Carolina N, Hill C, Carolina N (2005) Vibrotactile intensity and frequency information in the Pacinian system: a psychophysical model. Percept Psychophys 67:828–841.

Bensmaia SJ, Hollins M (2003) The vibrations of texture. Somatosens Mot Res 20:33–43.

Bensmaia SJ, Tyler DJ, Micera S (2023) Restoration of sensory information via bionic hands. Nat Biomed Eng 7:443–455.

Bensmaia SJ, Yau JM (2011) The organization and function of the somatosensory cortex. In: *The handbook of touch* (Hertenstein MJ, Weiss SJ, eds), pp 161–188. New York, NY: Springer Publishing Company, LLC.

Biddiss E, Chau T (2007) Upper-limb prosthetics: critical factors in device abandonment. Am J Phys Med Rehabil 86:977–987.

Billot M, Handrigan GA, Simoneau M, Corbeil P, Teasdale N (2013) Short term alteration of balance control after a reduction of plantar mechanoreceptor sensation through cooling. Neurosci Lett 535:40–44.

Bjånes DA, Bashford L, Pejsa K, Lee B, Liu CY, Andersen RA (2022) Multi-channel intra-cortical micro-stimulation yields quick reaction times and evokes natural somatosensations in a human participant. medRxiv:2022.08.08.22278389. Available at: https://www.medrxiv.org/content/10.1101/2022.08.08.22278389v1%0Ahttps://www.medrxiv.org/content/10.1101/2022.08.08.22278389v1.abstract

Bjånes DA, Moritz CT (2021) Chapter 15 - Design of intracortical microstimulation patterns to control the location, intensity, and quality of evoked sensations in human and animal models. In: *Somatosensory feedback for neuroprosthetics* (Guclu B, ed), pp 479–506. San Diego, CA: Academic Press.

Björnsdotter M, Löken L, Olausson H, Vallbo Å, Wessberg J (2009) Somatotopic organization of gentle touch processing in the posterior insular cortex. J Neurosci 29:9314–9320.

Boldrey E, Penfield W (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 60: 389–443.

Bouton CE, et al. (2016) Restoring cortical control of functional movement in a human with quadriplegia. Nature 533:247–250.

Brill N, Tyler D (2011) Optimizing nerve cuff stimulation of targeted regions through use of genetic algorithms. In 2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society 5811–5814.

Burgess PR, Mei J, Tuckett RP, Horch KW, Ballinger CM, Poulos DA (1983) The neural signal for skin indentation depth. I. Changing indentations. J Neurosci 3:1572–1585.

Callier T, Brantly NW, Caravelli A, Bensmaia SJ (2020) The frequency of cortical microstimulation shapes artificial touch. Proc Natl Acad Sci U S A 117:1191–1200.

Callier T, Suresh AK, Bensmaia SJ (2019) Neural coding of contact events in somatosensory cortex. Cereb Cortex 29:4613–4627.

Carty MJ, Herr HM (2021) The agonist-antagonist myoneural interface. Hand Clin 37:435–445.

Chandrasekaran S, et al. (2021) Evoking highly focal percepts in the fingertips through targeted stimulation of sulcal regions of the brain for sensory restoration. Brain Stimul 14:1184–1196.

Chandrasekaran S, Nanivadekar AC, McKernan G, Helm ER, Boninger ML, Collinger JL, Gaunt RA, Fisher LE (2020) Sensory restoration by epidural stimulation of the lateral spinal cord in upper-limb amputees. Elife 9:1–26.

Charkhkar H, Christie BP, Triolo RJ (2020) Sensory neuroprosthesis improves postural stability during sensory organization test in lower-limb amputees. Sci Rep 10:6984.
Charkhkar H, Shell CE, Marasco PD, Pinault GJ, Tyler DJ, Triolo RJ (2018) High-density peripheral nerve cuffs restore natural sensation to individuals with lower-limb amputations. J Neural Eng 15:056002.
Christie BP, Charkhkar H, Shell CE, Burant CJ, Tyler DJ, Triolo RJ (2020) Ambulatory searching task reveals importance of somatosensation for lower-limb amputees. Sci Rep 10:10216.
Christie BP, Freeberg M, Memberg WD, Pinault GJC, Hoyen HA, Tyler DJ, Triolo RJ (2017) Long-term stability of stimulating spiral nerve cuff electrodes on human peripheral nerves. J Neuroeng Rehabil 14:70.
Clark GA, Wendelken S, Page DM, Davis T, Wark HA, Normann RA, Warren DJ, Hutchinson DT (2014) Using multiple high-count electrode arrays in human median and ulnar nerves to restore sensorimotor function after previous transradial amputation of the hand. In: 2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC 2014, pp 1977–1980.
Clemente F, et al. (2019) Intraneural sensory feedback restores grip force control and motor coordination while using a prosthetic hand. J Neural Eng 16:026034.
Clemente F, D'Alonzo M, Controzzi M, Edin BB, Cipriani C (2016) Non-invasive, temporally discrete feedback of object contact and release improves grasp control of closed-loop myoelectric transradial prostheses. IEEE Trans Neural Syst Rehabil Eng 24:1314–1322.
Clites TR, Carty MJ, Ullauri JB, Carney ME, Mooney LM, Duval J-F, Srinivasan SS, Herr HM (2018) Proprioception from a neurally controlled lower-extremity prosthesis. Sci Transl Med 10:eaap8373.
Cohen RH, Vierck CJ (1993) Relationships between touch sensations and estimated population responses of peripheral afferent mechanoreceptors. Exp Brain Res 94:120–130.
Collinger JL, Wodlinger B, Downey JE, Wang W, Tyler-Kabara EC, Weber DJ, McMorland AJ, Velliste M, Boninger ML, Schwartz AB (2013) High-performance neuroprosthetic control by an individual with tetraplegia. Lancet 6736:1–8.
Crossman MW (1996) Sensory deprivation in spinal cord injury - an essay. Spinal Cord 34:573–577.
Cuberovic I (2020) Understanding factors affecting perception and utilization of artificial sensory location.
Cuberovic I, Gill A, Resnik LJ, Tyler DJ, Graczyk EL (2019) Learning of artificial sensation through long-term home use of a sensory-enabled prosthesis. Front Neurosci 13:853.
D'Anna E, et al. (2019) A closed-loop hand prosthesis with simultaneous intraneural tactile and position feedback. Sci Robot 4:eaau8892.
Davis TS, Wark HACC, Hutchinson DT, Warren DJ, O'Neill K, Scheinblum T, Clark GA, Normann RA, Greger B (2016) Restoring motor control and sensory feedback in people with upper extremity amputations using arrays of 96 microelectrodes implanted in the median and ulnar nerves. J Neural Eng 13:036001.
Deijs M, Bongers RM, Ringeling-Van Leusen NDM, Van Der Sluis CK (2016) Flexible and static wrist units in upper limb prosthesis users: functionality scores, user satisfaction and compensatory movements. J Neuroeng Rehabil 13:1–13.
Delhaye BP, Long KH, Bensmaia SJ (2018) Neural basis of touch and proprioception in primate cortex. Compr Physiol 8:1575–1602.
Desmond DM, MacLachlan M (2010) Prevalence and characteristics of phantom limb pain and residual limb pain in the long term after upper limb amputation. Int J Rehabil Res 33:279–282.
Dhillon GS, Horch KW (2005) Direct neural sensory feedback and control of a prosthetic arm. IEEE Trans Neural Syst Rehabil Eng 13:468–472.
Dhillon GS, Krüger TB, Sandhu JS, Horch KW, Kruger TB, Sandhu JS, Horch KW (2005) Effects of short-term training on sensory and motor function in severed nerves of long-term human amputees. J Neurophysiol 93:2625–2633.
Dietrich C, Nehrdich S, Seifert S, Blume KR, Miltner WHR, Hofmann GO, Weiss T (2018) Leg prosthesis with somatosensory feedback reduces phantom limb pain and increases functionality. Front Neurol 9:270.
Dietrich C, Walter-Walsh K, Preissler S, Hofmann GO, Witte OW, Miltner WHR, Weiss T (2012) Sensory feedback prosthesis reduces phantom limb pain: proof of a principle. Neurosci Lett 507:97–100.
Donati E, Valle G (2024) Neuromorphic hardware for somatosensory neuroprostheses. Nat Commun 15:556.
Downey JE, Brane L, Gaunt RA, Tyler-Kabara EC, Boninger ML, Collinger JL (2017) Motor cortical activity changes during neuroprosthetic-controlled object interaction. Sci Rep 7:16947.
Eldabe S, Burger K, Moser H, Klase D, Schu S, Wahlstedt A, Vanderick B, Francois E, Kramer J, Subbaroyan J (2015) Dorsal root ganglion (DRG) stimulation in the treatment of phantom limb pain (PLP). Neuromodulation 18:610–616.
Elzahaf RA, Tashani OA, Unsworth BA, Johnson MI (2012) The prevalence of chronic pain with an analysis of countries with a human development index less than 0.9: a systematic review without meta-analysis. Curr Med Res Opin 28:1221–1229.
Engdahl SM, Meehan SK, Gates DH (2020) Differential experiences of embodiment between body-powered and myoelectric prosthesis users. Sci Rep 10:15471.
Ephraim PL, Dillingham TR, Sector M, Pezzin LE, MacKenzie EJ (2003) Epidemiology of limb loss and congenital limb deficiency: a review of the literature. Arch Phys Med Rehabil 84:747–761.
Field T (2010) Touch for socioemotional and physical well-being: a review. Dev Rev 30:367–383.
Fifer MS, et al. (2022) Intracortical somatosensory stimulation to elicit fingertip sensations in an individual with spinal cord injury. Neurology 98: e679–e687.
Finnerup NB, Johannesen IL, Fuglsang-Frederiksen A, Bach FW, Jensen TS (2003) Sensory function in spinal cord injury patients with and without central pain. Brain 126:57–70.
Fisher LE, Ayers CA, Ciollaro M, Ventura V, Weber DJ, Gaunt RG (2014) Chronic recruitment of primary afferent neurons by microstimulation in the feline dorsal root ganglia. J Neural Eng 11:036007.
Flesher SN, Collinger JL, Foldes ST, Weiss JM, Downey JE, Tyler-Kabara EC, Bensmaia SJ, Schwartz AB, Boninger ML, Gaunt RA (2016) Intracortical microstimulation of human somatosensory cortex. Sci Transl Med 8: 361ra141.
Flesher SN, Downey JE, Weiss JM, Hughes CL, Herrera AJ, Tyler-Kabara EC, Boninger ML, Collinger JL, Gaunt RA (2021) A brain-computer interface that evokes tactile sensations improves robotic arm control. Sci Transl Med 836:831–836.
Freeberg MJ, Stone MA, Triolo RJ, Tyler DJ (2017) The design of and chronic tissue response to a composite nerve electrode with patterned stiffness. J Neural Eng 14:036022.
Gallace A, Spence C (2010) The science of interpersonal touch: an overview. Neurosci Biobehav Rev 34:246–259.
Gardner EP, Kandel ER (2013) Touch. In: *Principles of neural science* (Kandel ER, Schwartz JH, Jessell TM, eds) Ed 5, pp 451. New York, NY: McGraw-Hill.
Gardner E, Martin J, Jessell TM (2013) The bodily senses. In: *Principles of neural science* (Kandel ER, Schwartz JH, Jessel TM, eds) Ed 5, pp 430–450. New York, NY: McGraw-Hill.
Geng B, Yoshida K, Petrini L, Jensen W (2012) Evaluation of sensation evoked by electrocutaneous stimulation on forearm in nondisabled subjects. J Rehabil Res Dev 49:297–308.
Gentsch A, Crucianelli L, Jenkinson P, Fotopoulou A (2016) The touched self: affective touch and body awareness in health and disease. In: *Affective touch and the neurophysiology of CT afferents* (Olausson H, Wessberg J, Morrison I, McGlone F, eds), pp 355–384. New York, NY: Springer.
George JA, et al. (2019) Biomimetic sensory feedback through peripheral nerve stimulation improves dexterous use of a bionic hand. Sci Robot 4: eaax2352.
Ghez C, Gordon J, Ghilardi, Felice M, Sainburg R (2001) Contribution of vision and proprioception in arm movement. Strateg Plan Mot Syst. 1–16 Available at: http://ghez.org/Ghez+CogNs_I.PDF%5Cnpapers2://publication/uuid/2814DB82-A4AC-4DD4-BC0E-D70655E30468
Giummarra MJ, Gibson SJ, Georgiou-Karistianis N, Bradshaw JL (2007) Central mechanisms in phantom limb perception: the past, present and future. Brain Res Rev 54:219–232.
Gonzalez M, Bismuth A, Lee C, Chestek CA, Gates DH (2022) Artificial referred sensation in upper and lower limb prosthesis users: a systematic review. J Neural Eng 19:051001.
Gonzalez MA, Nwokeabia C, Vaskov AK, Vu PP, Lu CW, Patil PG, Cederna PS, Chestek CA, Gates DH (2024) Electrical stimulation of regenerative peripheral nerve interfaces (RPNIs) induces referred sensations in people with upper limb loss. IEEE Trans Neural Syst Rehabil Eng 32:339–349.
Gonzalez MA, Vu PP, Vaskov AK, Cederna PS, Chestek CA, Gates DH (2022) Characterizing sensory thresholds and intensity sensitivity of regenerative

peripheral nerve interfaces: a case study. In 2022 International Conference on Rehabilitation Robotics (ICORR). 1–6.

Graczyk EL, et al. (2016) The neural basis of perceived intensity in natural and artificial touch. Sci Transl Med 8:362ra142.

Graczyk EL (2018) Natural perceptual characteristics and psychosocial impacts of touch evoked by peripheral nerve stimulation. Available at: http://rave.ohiolink.edu/etdc/view?acc_num=case1522943665759439 [Accessed October 2, 2018].

Graczyk EL, Christie BP, He Q, Tyler DJ, Bensmaia SJ (2022) Frequency shapes the quality of tactile percepts evoked through electrical stimulation of the nerves. J Neurosci 42:2052–2064.

Graczyk EL, Delhaye BP, Schiefer MA, Bensmaia SJ, Tyler DJ (2018a) Sensory adaptation to electrical stimulation of the somatosensory nerves. J Neural Eng 15:046002.

Graczyk EL, Gill A, Tyler DJ, Resnik LJ (2019) The benefits of sensation on the experience of a hand: a qualitative case series. PLoS One 14:e0211469.

Graczyk EL, Resnik L, Schiefer MA, Schmitt MS, Tyler DJ (2018b) Home use of a neural-connected sensory prosthesis provides the functional and psychosocial experience of having a hand again. Sci Rep 8:9866.

Graczyk EL, Tyler DJ (2023) Somatosensory neuromodulation with a focus towards clinical systems. In: *Handbook of neuroengineering* (Thakor NV, ed), pp 3297–3351. Singapore: Springer Nature Singapore Pte Ltd.

Greenspon CM, et al. (2023a) Biomimetic multi-channel microstimulation of somatosensory cortex conveys high resolution force feedback for bionic hands. bioRxiv Prepr Serv Biol. Available at: http://www.ncbi.nlm.nih.gov/pubmed/36824713%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC9949113

Greenspon CM, et al. (2023b) Tessellation of artificial touch via microstimulation of human somatosensory cortex. bioRxiv Prepr Serv Biol. Available at: http://www.ncbi.nlm.nih.gov/pubmed/37425877%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC10327055

Grider J, et al. (2016) Effectiveness of spinal cord stimulation in chronic spinal pain: a systematic review. Pain Physician 19:33–54.

Grüsser SM, Winter C, Mühlnickel W, Denke C, Karl A, Villringer K, Flor H (2001) The relationship of perceptual phenomena and cortical reorganization in upper extremity amputees. Neuroscience 102:263–272.

Handelman DA, et al. (2022) Shared control of bimanual robotic limbs with a brain-machine interface for self-feeding. Front Neurorobot 16:918001.

Hargrove LJ, Simon AM, Young AJ, Lipschutz RD, Finucane SB, Smith DG, Kuiken TA (2013) Robotic leg control with EMG decoding in an amputee with nerve transfers. N Engl J Med 369:1237–1242.

Hargrove LJ, Young AJ, Simon AM, Fey NP, Lipschutz RD, Finucane SB, Halsne EG, Ingraham KA, Kuiken TA (2015) Intuitive control of a powered prosthetic leg during ambulation: a randomized clinical trial. J Am Med Assoc 313:2244–2252.

Harwood DD, Hanumanthu S, Stoudemire A (1992) Pathophysiology and management of phantom limb pain. Gen Hosp Psychiatry 14:107–118.

Hauser SC, McIntyre S, Israr A, Olausson H, Gerling GJ (2019) Uncovering human-to-human physical interactions that underlie emotional and affective touch communication. IEEE World Haptics Conf. 407–412.

Hebert JS, Elzinga K, Chan KM, Olson J, Morhart M (2014a) Updates in targeted sensory reinnervation for upper limb amputation. Curr Surg Rep 2:45.

Hebert JS, Olson JL, Morhart MJ, Dawson MR, Marasco PD, Kuiken TA, Chan KM (2014b) Novel targeted sensory reinnervation technique to restore functional hand sensation after transhumeral amputation. IEEE Trans Neural Syst Rehabil Eng 22:765–773.

Heming EA, Choo R, Davies JN, Kiss ZHT (2011) Designing a thalamic somatosensory neural prosthesis: consistency and persistence of percepts evoked by electrical stimulation. IEEE Trans Neural Syst Rehabil Eng 19:477–482.

Heming E, Sanden A, Kiss Z (2010) Designing a somatosensory neural prosthesis: percepts evoked by different patterns of thalamic stimulation. J Neural Eng 7:064001.

Herring EZ, et al. (2023) Reconnecting the hand and arm to the brain: efficacy of neural interfaces for sensorimotor restoration after tetraplegia. Neurosurgery 94:864–874.

Hertenstein MJ, Holmes R, McCullough M, Keltner D (2009) The communication of emotion via touch. Emotion 9:566–573.

Hiremath SV, et al. (2017) Human perception of electrical stimulation on the surface of somatosensory cortex. PLoS One 12:e0176020.

Hokanson JA, Gaunt RA, Weber DJ (2018) Effects of synchronous electrode pulses on neural recruitment during multichannel microstimulation. Sci Rep 8:13067.

Hughes CL, Flesher SN, Gaunt RA (2022) Effects of stimulus pulse rate on somatosensory adaptation in the human cortex. Brain Stimul 15:987–995.

Hughes CL, Flesher SN, Weiss JM, Boninger M, Collinger JL, Gaunt RA (2021a) Perception of microstimulation frequency in human somatosensory cortex. Elife 10:e65128.

Hughes CL, Flesher SN, Weiss JM, Downey JE, Boninger M, Collinger JL, Gaunt RA (2021b) Neural stimulation and recording performance in human sensorimotor cortex over 1500 days. J Neural Eng 18:045012.

Hughes C, Herrera A, Gaunt R, Collinger J (2020) Chapter 13 - Bidirectional brain-computer interfaces. In: *Handbook of clinical neurology* (Ramsey NF, del R. Millan J, eds) Ed 1168, pp 163–181. Cambridge, MA: Elsevier B.V.

Huh S, Ko HY (2020) Recovery target priorities of people with spinal cord injuries in Korea compared with other countries: a survey. Spinal Cord 58:998–1003.

Hunter CW, et al. (2019) DRG FOCUS: a multicenter study evaluating dorsal root ganglion stimulation and predictors for trial success. Neuromodulation 22:61–79.

Jazayeri SB, et al. (2023) Incidence of traumatic spinal cord injury worldwide: a systematic review, data integration, and update. World Neurosurgery: X 18:100171.

Jenmalm P, Johansson RS (1997) Visual and somatosensory information about object shape control manipulative fingertip forces. J Neurosci 17: 4486–4499.

Johansson RS, Flanagan JR (2009) Coding and use of tactile signals from the fingertips in object manipulation tasks. Nat Rev Neurosci 10:345–359.

Johansson RS, Häger C, Riso R (1992) Somatosensory control of precision grip during unpredictable pulling loads. Exp Brain Res 89:192–203.

Johnson LA, Wander JD, Sarma D, Su DK, Fetz EE, Ojemann JG (2013) Direct electrical stimulation of the somatosensory cortex in humans using electrocorticography electrodes: a qualitative and quantitative report. J Neural Eng 10:036021.

Kang Y, Ding H, Zhou H, Wei Z, Liu L, Pan D, Feng S (2017) Epidemiology of worldwide spinal cord injury: a literature review. J Neurorestoratology 6: 1–9.

Kim S, Callier T, Tabot GA, Gaunt RA, Tenore FV, Bensmaia SJ (2015) Behavioral assessment of sensitivity to intracortical microstimulation of primate somatosensory cortex. Proc Natl Acad Sci U S A 112:15202–15207.

Kim LH, McLeod RS, Kiss ZHT (2018) A new psychometric questionnaire for reporting of somatosensory percepts. J Neural Eng 15:013002.

Klatzky RL, Lederman SJ, Metzger VA (1985) Identifying objects by touch: an "expert system". Percept Psychophys 37:299–302.

Knotkova H, Hamani C, Sivanesan E, Le Beuffe MFE, Moon JY, Cohen SP, Huntoon MA (2021) Neuromodulation for chronic pain. Lancet 397: 2111–2124.

Kooijman CM, Dijkstra PU, Geertzen JHB, Elzinga A, Van Der Schans CP (2000) Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. Pain 87:33–41.

Kubiak CA, Adidharma W, Kung TA, Kemp SWP, Cederna PS, Vemuri C (2022) Decreasing postamputation pain with the regenerative peripheral nerve interface (RPNI). Ann Vasc Surg 79:421–426.

Kuiken TA, Marasco PD, Lock BA, Harden RN, Dewald JPA (2007a) Redirection of cutaneous sensation from the hand to the chest skin of human amputees with targeted reinnervation. Proc Natl Acad Sci U S A 104:20061–20066.

Kuiken TA, Miller LA, Lipschutz RD, Lock BA, Stubblefield K, Marasco PD, Zhou P, Dumanian GA (2007b) Targeted reinnervation for enhanced prosthetic arm function in a woman with a proximal amputation: a case study. Lancet 369:371–380.

Kumar K, et al. (2007) Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain 132:179–188.

Kumar K, et al. (2008) The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. Neurosurgery 63:762–770.

Lambrecht JM, Cady SR, Peterson EJ, Dunning JL, Dinsmoor DA, Pape F, Graczyk EL, Tyler DJ (2024) A distributed, high-channel-count, implanted bidirectional system for restoration of somatosensation and myoelectric control. J Neural Eng 21:036049.

Lederman SJ, Klatzky RL (1990) Haptic classification of common objects: knowledge-driven exploration. Cogn Psychol 22:421–459.

Lee B, et al. (2018) Engineering artificial somatosensation through cortical stimulation in humans. Front Syst Neurosci 12:24.
Lee BB, Cripps RA, Fitzharris M, Wing PC (2013) The global map for traumatic spinal cord injury epidemiology: update 2011, global incidence rate. Spinal Cord 52:110–116.
Lee JC, Kemp SWP, Kung TA (2024) Regenerative peripheral nerve interface surgery for the management of chronic posttraumatic neuropathic pain. Semin Plast Surg 38:19–24.
Lee C, Vaskov AK, Gonzalez MA, Vu PP, Davis AJ, Cederna PS, Chestek CA, Gates DH (2022) Use of regenerative peripheral nerve interfaces and intramuscular electrodes to improve prosthetic grasp selection: a case study. J Neural Eng 19:066010.
Lenggenhager B, Pazzaglia M, Scivoletto G, Molinari M, Aglioti SM (2012) The sense of the body in individuals with spinal cord injury. PLoS One 7:e50757.
Liem L, et al. (2013) A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. Neuromodulation 16:471–482.
Lukyanenko P, Dewald HA, Lambrecht J, Kirsch RF, Tyler DJ, Williams MR (2021) Stable, simultaneous and proportional 4-DoF prosthetic hand control via synergy-inspired linear interpolation: a case series. J Neuroeng Rehabil 18:50.
Makin TR, de Vignemont F, Faisal AA (2017) Neurocognitive considerations to the embodiment of technology. Nat Biomed Eng 1:0014.
Marasco PD, Schultz AE, Kuiken TA (2009) Sensory capacity of reinnervated skin after redirection of amputated upper limb nerves to the chest. Brain 132:1441–1448.
McDonald CL, Westcott-Mccoy S, Weaver MR, Haagsma J, Kartin D (2021) Global prevalence of traumatic non-fatal limb amputation. Prosthet Orthot Int 45:105–114.
McIntyre S, Moungou A, Boehme R, Isager PM, Lau F, Israr A, Lumpkin EA, Abnousi F, Olausson H (2019) Affective touch communication in close adult relationships. IEEE World Haptics Conf. 175–180.
Merrill DR, Bikson M, Jefferys JGR (2005) Electrical stimulation of excitable tissue: design of efficacious and safe protocols. J Neurosci Methods 141: 171–198.
Mesias L, Gormez MA, Tyler DJ, Makowski NS, Graczyk EL, Fu MJ (2023) Distally-referred surface electrical nerve stimulation (DR-SENS) for haptic feedback. J Neural Eng 20:066034.
Middleton A, Ortiz-Catalan M (2020) Neuromusculoskeletal arm prostheses: personal and social implications of living with an intimately integrated bionic arm. Front Neurorobot 14:39.
Miller WC, Speechley M, Deathe B (2001) The prevalence and risk factors of falling and fear of falling among lower extremity amputees. Arch Phys Med Rehabil 82:1031–1037.
Monzée J, Lamarre Y, Smith AM (2003) The effects of digital anesthesia on force control using a precision grip. J Neurophysiol 89:672–683.
Morgalla MH, Fortunato M, Lepski G, Chander BS (2018) Dorsal root ganglion stimulation (DRGS) for the treatment of chronic neuropathic pain: a single-center study with long-term prospective results in 62 cases. Pain Physician 21:E377–E387.
Nanivadekar AC, et al. (2023) Restoration of sensory feedback from the foot and reduction of phantom limb pain via closed-loop spinal cord stimulation. Nat Biomed Eng 1–12.
Nanivadekar AC, Ayers CA, Gaunt RA, Weber DJ, Fisher LE (2020) Selectivity of afferent microstimulation at the DRG using epineural and penetrating electrode arrays. J Neural Eng 17:016011.
National Spinal Cord Injury Statistical Center (2021) Spinal cord injury facts and figures at a glance. J Spinal Cord Med 36:1–2.
Ng KKW, Olausson C, Vickery RM, Birznieks I (2020) Temporal patterns in electrical nerve stimulation: burst gap code shapes tactile frequency perception. PLoS One 15:e0237440.
Nolan M, Nitz J, Choy NL, Illing S (2010) Age-related changes in musculoskeletal function, balance and mobility measures in men aged 3080 years. Aging Male 13:194–201.
North RB, Kidd DH, Farrokhi F, Piantadosi SA (2005) Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. Neurosurgery 56:98–106.
North RB, Kidd DH, Piantadosi S (1995) Spinal cord stimulation versus reoperation for failed back surgery syndrome: a prospective, randomized study design. In: *Advances in stereotactic and functional neurosurgery 11* (Meyerson BA, Ostertag C, eds) Vol. 64, pp. 106–108. Vienna, Austria: Springer Vienna.
Nowak DA, Glauser S, Hermsdorfer J (2004) How predictive is grip force control in the complete absence of somatosensory feedback? Brain 127:182–192.
Oddo CM, et al. (2016) Intraneural stimulation elicits discrimination of textural features by artificial fingertip in intact and amputee humans. Elife 5: e09148.
Ohara S, Weiss N, Lenz FA (2004) Microstimulation in the region of the human thalamic principal somatic sensory nucleus evokes sensations like those of mechanical stimulation and movement. J Neurophysiol 91: 736–745.
Ojemann JO, Silbergeld DL (1995) Cortical stimulation mapping of phantom limb rolandic cortex: case report. J Neurosurg 82:641–644.
Okorokova E, He Q, Bensmaia S (2018) Biomimetic encoding model for restoring touch in bionic hands through a nerve interface. J Neural Eng 15:10.
Ortiz-Catalan M, et al. (2023) A highly integrated bionic hand with neural control and feedback for use in daily life. Sci Robot 8:eadf7360.
Ortiz-Catalan M, Håkansson B, Brånemark R (2014) An osseointegrated human-machine gateway for long-term sensory feedback and motor control of artificial limbs. Sci Transl Med 6:257re6.
Ortiz-Catalan M, Mastinu E, Greenspon CM, Bensmaia SJ (2020) Chronic use of a sensitized bionic hand does not remap the sense of touch. Cell Rep 33: 108539.
Osborn LE, et al. (2021) Intracortical microstimulation of somatosensory cortex enables object identification through perceived sensations. Proc Annu Int Conf IEEE Eng Med Biol Soc EMBS. 6259–6262.
Osborn L, Betthauser J, Kaliki R, Thakor N (2018) Targeted transcutaneous electrical nerve stimulation for phantom limb sensory feedback. 2017 IEEE Biomed Circuits Syst Conf BioCAS 2017 - Proc 2018-Janua:1.
Overstreet CK, Cheng J, Keefer EW (2019) Fascicle specific targeting for selective peripheral nerve stimulation. J Neural Eng 16:066040.
Page DM, George JA, Kluger DT, Duncan C, Wendelken S, Davis T, Hutchinson DT, Clark GA (2018) Motor control and sensory feedback enhance prosthesis embodiment and reduce phantom pain after long-term hand amputation. Front Hum Neurosci 12:352.
Page DM, George JA, Wendelken SM, Davis TS, Kluger DT, Hutchinson DT, Clark GA (2021) Discriminability of multiple cutaneous and proprioceptive hand percepts evoked by intraneural stimulation with Utah slanted electrode arrays in human amputees. J Neuroeng Rehabil 18:12.
Pei Y-C, Denchev PV, Hsiao SS, Craig JC, Bensmaia SJ (2009) Convergence of submodality-specific input onto neurons in primary somatosensory cortex. J Neurophysiol 102:1843–1853.
Perry SD, Mcilroy WE, Maki BE (2000) The role of plantar cutaneous mechanoreceptors in the control of compensatory stepping reactions evoked by unpredictable, multi-directional perturbation. Brain Res 877: 401–406.
Petersen BA, Nanivadekar AC, Chandrasekaran S, Fisher LE (2019) Phantom limb pain: peripheral neuromodulatory and neuroprosthetic approaches to treatment. Muscle Nerve 59:154–167.
Petrini FM, et al. (2019a) Sensory feedback restoration in leg amputees improves walking speed, metabolic cost and phantom pain. Nat Med 25:1356–1363.
Petrini FM, et al. (2019b) Six-month assessment of a hand prosthesis with intraneural tactile feedback. Ann Neurol 85:137–154.
Petrini FM, et al. (2019c) Enhancing functional abilities and cognitive integration of the lower limb prosthesis. Sci Transl Med 11:eaav8939.
Pfeiffer EA (1968) Electrical stimulation of sensory nerves with skin electrodes for research, diagnosis, communication and behavioral conditioning: a survey. Med Biol Eng 6:637–651.
Polasek KH, Hoyen HA, Keith MW, Kirsch RF, Tyler DJ (2009) Stimulation stability and selectivity of chronically implanted multicontact nerve cuff electrodes in the human upper extremity. IEEE Trans Neural Syst Rehabil Eng 17:428–437.
Preatoni G, Valle G, Petrini FM, Raspopovic S (2021) Lightening the perceived prosthesis weight with neural embodiment promoted by sensory feedback. Curr Biol 31:1065–1071.e4.
Proske U, Gandevia SC (2012) The proprioceptive senses: their roles in signaling body shape, body position and movement, and muscle force. Physiol Rev 92:1651–1697.
Rackerby R, Lukosch S, Munro D (2022) Understanding and measuring the cognitive load of amputees for rehabilitation and prosthesis development. Arch Rehabil Res Clin Transl 4:100216.
Rajan AT, Boback JL, Dammann JF, Tenore FV, Wester BA, Otto KJ, Gaunt RA, Bensmaia SJ (2015) The effects of chronic intracortical microstimulation on neural tissue and fine motor behavior. J Neural Eng 12:066018.

Ramachandran VS, Hirstein W (1998) The perception of phantom limbs. The D. O. Hebb lecture. Brain 121:1603–1630.
Rappl LM (2008) Physiological changes in tissues denervated by spinal cord injury tissues and possible effects on wound healing. Int Wound J 5:435–444.
Raspopovic S, et al. (2014) Restoring natural sensory feedback in real-time bidirectional hand prostheses. Sci Transl Med 6:222ra19.
Raspopovic S, Valle G, Petrini FM (2021) Sensory feedback for limb prostheses in amputees. Nat Mater 20:925–939.
Rekant J, Fisher LE, Boninger ML, Gaunt RA, Collinger JL (2022) Amputee, clinician, and regulator perspectives on current and prospective upper extremity prosthetic technologies. Assist Technol 35:258–270.
Risso G, et al. (2019) Optimal integration of intraneural somatosensory feedback with visual information: a single-case study. Sci Rep 9:7916.
Rognini G, et al. (2018) Multisensory bionic limb to achieve prosthesis embodiment and reduce distorted phantom limb perceptions. J Neurol Neurosurg Psychiatry 90:833–836.
Roll R, Kavounoudias A, Roll JP (2002) Cutaneous afferents from human plantar sole contribute to body posture awareness. Neuroreport 13:1957–1961.
Saal HP, Delhaye BP, Rayhaun BC, Bensmaia SJ (2017) Simulating tactile signals from the whole hand with millisecond precision. Proc Natl Acad Sci U S A 114:E5693–E5702.
Sainburg RL, Poizner H, Ghez C (1993) Loss of proprioception produces deficits in interjoint coordination. J Neurophysiol 70:2136–2147.
Sando IC, et al. (2023) Dermal sensory regenerative peripheral nerve interface for reestablishing sensory nerve feedback in peripheral afferents in the rat. Plast Reconstr Surg 151:804E–813E.
Saudabayev A, Rysbek Z, Khassenova R, Varol HA (2018) Human grasping database for activities of daily living with depth, color and kinematic data streams. Sci Data 5:180101.
Scarpelli A, Demofonti A, Terracina F, Ciancio AL, Zollo L (2020) Evoking apparent moving sensation in the hand via transcutaneous electrical nerve stimulation. Front Neurosci 14:534.
Schiefer MA, Graczyk EL, Sidik S, Tan DW, Tyler DJ (2018) Artificial tactile and proprioceptive feedback improves performance and confidence on object identification tasks. PLoS One 13:e0207659.
Schiefer MA, Tan DW, Sidek SM, Tyler DJ (2016) Sensory feedback by peripheral nerve stimulation improves task performance in individuals with upper limb loss using a myoelectric prosthesis. J Neural Eng 13:016001.
Schmid AC, Chien JH, Greenspan JD, Garonzik I, Weiss N, Ohara S, Lenz FA (2016) Neuronal responses to tactile stimuli and tactile sensations evoked by microstimulation in the human thalamic principal somatic sensory nucleus (ventral caudal). J Neurophysiol 115:2421–2433.
Schmitt MS, Wright JD, Triolo RJ, Charkhkar H, Graczyk EL (2023) The experience of sensorimotor integration of a lower limb sensory neuroprosthesis: a qualitative case study. Front Hum Neurosci 16:1074033.
Schofield JS, Shell CE, Beckler DT, Thumser ZC, Marasco PD (2020) Long-term home-use of sensory-motor-integrated bidirectional bionic prosthetic arms promotes functional, perceptual, and cognitive changes. Front Neurosci 14:120.
Schultz AE, Marasco PD, Kuiken TA (2009) Vibrotactile detection thresholds for chest skin of amputees following targeted reinnervation surgery. Brain Res 1251:121–129.
Segil JL, Cuberovic I, Graczyk EL, Weir RFF, Tyler D (2020) Combination of simultaneous artificial sensory percepts to identify prosthetic hand postures: a case study. Sci Rep 10:6576.
Segil JL, Huddle SA, Weir RF (2017) Functional assessment of a myoelectric postural controller and multi-functional prosthetic hand by persons with trans-radial limb loss. IEEE Trans Neural Syst Rehabil Eng 25:618–627.
Serino A, et al. (2017) Upper limb cortical maps in amputees with targeted muscle and sensory reinnervation. Brain 140:2993–3011.
Shannon RV (1992) A model of safe levels for electrical stimulation. IEEE Trans Biomed Eng 39:424–426.
Shell CE, Christie BP, Marasco PD, Charkhkar H, Triolo RJ, Valle G, Shell CE (2021) Lower-limb amputees adjust quiet stance in response to manipulations of plantar sensation. Front Neurosci 15:611926.
Sherman RA, Sherman C (1983) Prevalence and characteristics of chronic phantom limb pain among American veterans: results of a trial survey. Am J Phys Med 62:227–238.
Smail LC, Neal C, Wilkins C, Packham TL (2021) Comfort and function remain key factors in upper limb prosthetic abandonment: findings of a scoping review. Disabil Rehabil Assist Technol 16:821–830.
Soden R, Walsh J, Craven M, Rutkowski S, Yeo J (2000) Causes of death after spinal cord injury. Spinal Cord 38:604–610.
Srinivasan SS, Carty MJ, Calvaresi PW, Clites TR, Maimon BE, Taylor CR, Zorzos AN, Herr H (2017) On prosthetic control: a regenerative agonist-antagonist myoneural interface. Sci Robot 2:eaan2971.
Sritharan SY, Richardson AG, Weigand PK, Planell-Mendez I, Liu X, Zhu H, Zhang M, Van Der Spiegel J, Lucas TH (2016) Somatosensory encoding with cuneate nucleus microstimulation: detection of artificial stimuli. Proc Annu Int Conf IEEE Eng Med Biol Soc EMBS 2016-Octob:4719–4722.
Stieger KC, Eles JR, Ludwig KA, Kozai TDY (2022) Intracortical microstimulation pulse waveform and frequency recruits distinct spatiotemporal patterns of cortical neuron and neuropil activation. J Neural Eng 19:026024.
Strauss I, et al. (2019) Characterization of multi-channel intraneural stimulation in transradial amputees. Sci Rep 9:19258.
Suresh AK, Greenspon CM, He Q, Rosenow JM, Miller LE, Bensmaia SJ (2021) Sensory computations in the cuneate nucleus of macaques. Proc Natl Acad Sci U S A 118:e2115772118.
Swan BD, Gasperson LB, Krucoff MO, Grill WM, Turner DA (2018) Sensory percepts induced by microwire array and DBS microstimulation in human sensory thalamus. Brain Stimul 11:416–422.
Sweeney JD, Ksienski DA, Mortimer JT (1990) A nerve cuff technique for selective excitation of peripheral nerve trunk regions. IEEE Trans Biomed Eng 37:706–715.
Tan DW, Schiefer MA, Keith MW, Anderson JR, Tyler DJ (2015) Stability and selectivity of a chronic, multi-contact cuff electrode for sensory stimulation in a human amputee. J Neural Eng 12:859–862.
Tan DW, Schiefer MA, Keith MW, Anderson JR, Tyler J, Tyler DJ (2014) A neural interface provides long-term stable natural touch perception. Sci Transl Med 6:257ra138.
Tan D, Tyler D, Sweet J, Miller J (2016) Intensity modulation: a novel approach to percept control in spinal cord stimulation. Neuromodulation 19:254–259.
Tashiro T, Higashiyama A (1981) The perceptual properties of electrocutaneous stimulation: sensory quality, subjective intensity, and intensity-duration relation. Percept Psychophys 30:579–586.
Taylor RS, Van Buyten J-P, Buchser E (2005) Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: a systematic review and analysis of prognostic factors. Spine 30:152–160.
Tebcherani TM, Loparo KA, Fellow L, Kaffashi F, Dustin J, Graczyk EL (2024) Interleaved multi-contact peripheral nerve stimulation to enhance reproduction of tactile sensation: a computational modeling study. IEEE Trans Neural Syst Rehabil Eng 32:2302–2313.
Valle G, et al. (2018a) Biomimetic intraneural sensory feedback enhances sensation naturalness, tactile sensitivity, and manual dexterity in a bidirectional prosthesis. Neuron 100:37–45.e7.
Valle G, et al. (2018b) Comparison of linear frequency and amplitude modulation for intraneural sensory feedback in bidirectional hand prostheses. Sci Rep 8:16666.
Valle G, et al. (2024) Biomimetic computer-to-brain communication enhancing naturalistic touch sensations via peripheral nerve stimulation. Nat Commun 15:1151.
Valle G, Saliji A, Fogle E, Cimolato A, Petrini FM, Raspopovic S (2021) Mechanisms of neuro-robotic prosthesis operation in leg amputees. Sci Adv 7:eabd8354.
Valle G, Strauss I, D'Anna E, Granata G, Di Iorio R, Stieglitz T, Rossini PM, Raspopovic S, Petrini FM, Micera S (2020) Sensitivity to temporal parameters of intraneural tactile sensory feedback. J Neuroeng Rehabil 17:110.
Vallejo R, Kramer J, Benyamin R (2007) Neuromodulation of the cervical spinal cord in the treatment of chronic intractable neck and upper extremity pain: a case series and review of the literature. Pain Physician 10:305–311.
Vaso A, Adahan H-M, Gjika A, Zahaj S, Zhurda T, Vyshka G, Devor M (2014) Peripheral nervous system origin of phantom limb pain. Pain 155:1384–1391.
Vastano R, Costantini M, Alexander WH, Widerstrom-Noga E (2022) Multisensory integration in humans with spinal cord injury. Sci Rep 12:22156.
Vu PP, et al. (2020) A regenerative peripheral nerve interface allows real-time control of an artificial hand in upper limb amputees. Sci Transl Med 12:eaay2857.

Vu PP, et al. (2023) Long-term upper-extremity prosthetic control using regenerative peripheral nerve interfaces and implanted EMG electrodes. J Neural Eng 20:026039.
Vu PP, Lu CW, Vaskov AK, Gates DH, Gillespie RB, Kemp SWP, Patil PG, Chestek CA, Cederna PS, Kung TA (2022) Restoration of proprioceptive and cutaneous sensation using regenerative peripheral nerve interfaces in humans with upper limb amputations. Plast Reconstr Surg 149:1149e–1154e.
Walters ET, Williams ACC (2019) Evolution of mechanisms and behaviour important for pain. Philos Trans R Soc Lond B Biol Sci 374:20190275.
Weber AI, Saal HP, Lieber JD, Cheng J, Manfredi LR, Dammann JF (2013) Spatial and temporal codes mediate the tactile perception of natural textures. Proc Natl Acad Sci U S A 110:17107–17112.
Wendelken S, Page DM, Davis T, Wark HAC, Kluger DT, Duncan C, Warren DJ, Hutchinson DT, Clark GA (2017) Restoration of motor control and proprioceptive and cutaneous sensation in humans with prior upper-limb amputation via multiple Utah Slanted Electrode Arrays (USEAs) implanted in residual peripheral arm nerves. J Neuroeng Rehabil 14:121.
Williams RM, Turner AP, Orendurff M, Segal AD, Klute GK, Pecoraro J, Czerniecki J (2006) Does having a computerized prosthetic knee influence cognitive performance during amputee walking? Arch Phys Med Rehabil 87:989–994.
Wodlinger B, Downey JE, Tyler-Kabara EC, Schwartz AB, Boninger M, Collinger JL (2015) Ten-dimensional anthropomorphic arm control in a human brain - machine interface: difficulties, solutions, and limitations. J Neural Eng 12:016011.
Woeppel K, Hughes C, Herrera AJ, Eles J, Elizabeth C, Gaunt RA, Collinger JL, Cui XT (2021) Explant analysis of Utah electrode arrays implanted in human cortex for brain-computer-interfaces. Front Bioeng Biotechnol 9:759711.
Xu J, et al. (2021) Peripheral nerve stimulation in pain management: a systematic review. Pain Physician 24:E131–E152.
Young D, et al. (2019) Closed-loop cortical control of virtual reach and posture using Cartesian and joint velocity commands. J Neural Eng 16: 026011.
Zaaimi B, Ruiz-Torres R, Solla SA, Miller LE (2013) Multi-electrode stimulation in somatosensory cortex increases probability of detection. J Neural Eng 10:056013.
Ziegler-Graham K, Mackenzie EJ, Ephraim PL, Travison TG, Brookmeyer R (2008) Estimating the prevalence of limb loss in the United States: 2005 to 2050. Arch Phys Med Rehabil 89:422–429.