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Neural interfaces for somatosensory feedback: bringing life to a prosthesis

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Abstract

Purpose of review—When an individual loses a limb, he/she loses touch with the world and with the people around him/her. Somatosensation is critical to the feeling of connection and control of one's own body. Decades of attempts to replace lost somatosensation by sensory substitutions have been ineffective outside of the laboratory. This review discusses important recent results demonstrating chronic somatosensory restoration through direct peripheral nerve stimulation.

Recent findings—Stimulation of peripheral nerves results in somatosensory perception on the phantom limb. Sensations are localized to several independent and functionally relevant locations, such as the fingertips, thenar eminence, ulnar border and dorsal surface. Patterns in stimulation intensity change the perception experience by the user, opening new dimensions on neuromodulation.

Summary—Neural interfaces with sophisticated stimulation paradigms create a user's perception of his/her hand to touch and manipulate objects. The pattern of intensity and frequency of stimulation is critical to the quality and intensity of perceived sensation. Restoring feeling has allowed the individuals to, 'feel [my] hand for the first time since the accident,' and 'feel [my] wife touch my hand'. Individuals using a prosthetic hand with sensation can pull cherries and grapes from the stem, open water bottles and move objects without destroying these objects – all while audio and visually deprived. After regaining sensation, phantom pain is eliminated in individuals that had frequent, sometimes debilitating, pain following limb loss. With over 5 subject-years of experience, this work is leading the evolution of a new era in prostheses. Somatosensory prosthetics as a standard procedure to augment and restore somatosensation are now within our reach.

Keywords

amputation; electrode; peripheral nerve; phantom pain; sensory feedback; somatosensation; stimulation

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

When an individual loses a limb, he/she loses touch with the world and people around him/her. Somatosensation is critical to the feeling of connection and control of one's own body. Loss of somatosensation may be even more devastating than loss of hand function.

Advanced anthropomorphic mechatronics in sophisticated prostheses will require somatosensory feedback to operate the devices in more than a rudimentary, preprogrammed set of motions. Without sensory connection to the prosthesis, it remains only an adaptive tool, not a replacement for the hand. Rejection and abandonment of prostheses ranges from 40 to 60% of limb loss individuals [1,2] with sensory feedback reported as a key factor for abandonment [2,3] and a consumer design priority [4].

Somatosensation [5,6] arises from a complex system of biological organs that respond to external inputs and body state. The sensors include rapidly and slowly adapting mechanoreceptors, temperature, stretch, pain, tendon tension, muscle bag and chain fibers, and joint sensors. These receptors are found in the skin, muscles, tendons, joints, epithelial tissues, bones, organs and cardiovascular system. It is ubiquitous. The only normal experiences that give a sense of its loss include the numbness following prolonged skin exposure to cold temperatures; local anesthetics for a dental procedure; or upon waking after occluding blood flow to the arm while sleeping, resulting in a 'dead limb' in the morning. Replacing somatosensory perception will require complex restoration of many different, coordinated signals. The peripheral nervous system is a common pathway of these signals. Direct stimulation of peripheral nerves with appropriate patterns of information can restore the perception of somatosensation.

SOMATOSENSATION FOR PROSTHESES

Benefits

Embodiment is the experience of incorporating the prosthesis into one's body image and actually perceives the prosthesis as part of themselves [7–11]. Without embodiment, a prosthesis is an artificial tool attached to the end of the residual limb. When embodied, the prosthesis feels either like it is their hand or that their phantom is directly in the prosthesis [12]. Embodiment provides the individual the sense of being whole again. Practically, the perception of their hand performing a task is easier to control than an attached, disembodied tool [13]. Techniques for promoting embodiment include mirror box therapy [14], robotic therapies [15] and task-oriented focus on use of the prosthetic rather than the prosthesis itself [16]. These techniques demonstrated improvement, but without sensation, the visual experience of the prosthesis interacting with the environment is incongruous with the perceived experience, thereby disrupting the sense of embodiment [17,18]. Even one's own body will feel disembodied and foreign with the loss of sensation, such as in hemineglect following stroke [19]. Recent functional magnetic resonance imaging studies, however, show that sensation is related to restoring a sense of embodiment following limb loss [20].

Somatosensation is necessary for arbitrary control of sophisticated and complex prostheses, especially with the additional goal of reducing, not increasing, reliance on vision. Somatosensation is important to normal motor function [21–25]. Study of a single degree of

freedom task with able-bodied individuals shows that proprioception is necessary to improve performance even when vision is present and is more important as the task difficulty increases [26]. The importance of somatosensation and motor function is evident in other disorders [27] such as stroke [28,29] and large axon neuropathies resulting in loss of somatosensation [30]. Even with a normally functioning motor system of an intact hand, patients with large axon neuropathies have exceptional difficulty controlling their otherwise intact limb. This results in extremely high cognitive load and poor performance. Even the cortical representations of motor commands are degraded with the lack of somatosensory feedback [31]. Therefore, it is not very likely that even perfect mechatronics will function well without somatosensation. Given that increasing task complexity has increasing reliance on somatosensation, the significant investment in mechatronics would paradoxically provide less value and function to the user as the added degrees of freedom become exceedingly difficult for the user to control. Even the most complex hands will essentially be preprogrammed, patterned movement.

The psychological impact of limb loss is debilitating. Depression and posttraumatic stress are common following traumatic limb loss [32–36], correlated with long-term psychosocial adjustment [37,38], more prevalent following upper extremity amputation than lower extremity amputation [39,40]. Psychotherapy is a recommended care following limb loss [41–43]. Depression can lead to self-destructive behavior [36], disengagement from society [44], lost productivity [45,46], pharmacological dependence [47] and stress on family units [48]. Depending on the cultural background, limb loss makes one feel defective or less of a human. The lack of tactile interaction with a family member results in a feeling of disconnection and lack of intimacy [49,50]. The use of a prosthesis provides a sense of normalcy and improvement in psychosocial interaction as users reported a reduced awareness of being different [51]. As restoring sensation is expected to increase embodiment and connection, it is expected to further alleviate psychosocial effects of traumatic limb loss.

Pain is often associated with limb loss [52,53]. The physical and neurological cause of pain is complex and an active area of research. There is evidence that underlying dysfunction of somatosensation is related to the chronic pain of complex regional pain syndrome [54]. Pain, however, is a complex phenomenon with many interrelated causes that can range from neurogenic from activity of pain fibers within a sensitive neuroma and other peripheral activity [55], to changes in central connectivity resulting from loss of sensory input [56]. Pain can result in reduced quality of life [57] including loss of productivity, further deepening depression and additional medication costs with associated risks of dependency [47].

Body-powered versus electrically powered prostheses and somatosensation

Body-powered prostheses are often preferred over more functional electrical devices because the user can ‘feel’ the grip interaction with objects via referred sensation through the body harness operating the prosthesis [58]. The representative sensory information does not directly match the user’s visual experience of the prosthesis, but does provide a sense of control and connection to the device. Despite the negative aspects of body-powered prostheses, including being limited to one active degree of freedom [59], limited range of

motion [58,60] (e.g. reaching over shoulder can be nonfunctional), and cumbersome and uncomfortable nature of the body harness, 35% of users still prefer the body-powered prosthesis, possibly for improved feedback and referred sensation [4,58]. Powered prostheses have many functional advantages to body-powered devices, but unfortunately, the only somatosensory feedback is the forces applied to the residual limb through the socket, the audible feedback of the motors and visual feedback. Prosthetic choice is often a choice between either function or sensation [58].

NEURAL INTERFACES ARE NEEDED TO RESTORE SOMATOSENSATION

Several sensory substitution techniques not requiring implanted components have been developed [62–64]. These include sensory substitution with cutaneous electrical stimulation [63], vibration on the skin surface [65–68], skin stretch [69,70] and tendon vibration [71,72] for proprioception, and targeted sensory reinnervation [12,73,74]. In laboratory settings, these have been successful, but none have been sufficiently robust or effective in everyday use for widespread adoption in commercially available prosthetics.

When the limb is lost, only the sensory end organs are lost. The nerves connecting those organs to the brain are functioning normally [75,76]. Artificial activation of these pathways results in the perception of sensation as though it was from the missing limb. There are several locations to interact with the residual somatosensory system [77]. Preclinical work in brain [78], dorsal root ganglion [79,80] and intraspinal microstimulation [81] approaches are progressing, but peripheral interfaces have achieved chronic clinical demonstration [82[■], 83[■]].

There are several options being explored for peripheral nerve interfaces [84,85]. Most often, peripheral interfaces focus on the physical interaction and location of electrical contacts. Although infrequently discussed, the electromagnetic interaction with the nerve is equally important to the functional result of somatosensory stimulation.

Physical interaction

Generally, peripheral nerve interfaces can be divided into extraneural and intraneural categories. Extraneural electrodes surround a peripheral nerve, but do not insert elements within the nerve, causing the least disturbance to the neural tissue. Circular, self-sizing electrodes, such as the spiral [86] and helical electrode [87], have been stable in clinical applications for decades [88–90]. A circular configuration has the minimum surface area to interact with the neural tissue. To increase the surface area and proximity to more of the neural tissues while not penetrating the nerve, another class of extraneural electrodes maintains an elongated or rectangular configuration for the nerve. The Flat Interface Nerve Electrode (FINE) [91] has shown fascicular level selectivity for stimulation [91–93] and recording capabilities [94]. The spiral and FINE electrodes have been in clinical trials with limb loss individuals for over 3 years [82[■],83[■]].

Intraneural interfaces physically insert electrical contacts within the nerve. The least invasive designs penetrate the epineurium, but not the perineurium. Two examples include the Slowly Penetrating Interfascicular Nerve Electrode [95] and the grove electrode [96]. The most

invasive penetrates the perineurium to place components inside the fascicle. Examples include the Longitudinal IntraFascicular Electrode (LIFE) [97,98], Transverse Intrafascicular Multichannel Electrode (TIME) [99] and Utah Slanted Electrode Array [100].

The perineurium is a living cellular membrane that helps maintain a blood–nerve barrier within the fascicle and maintains the chemical balances with the fascicle for proper nerve function [101]. The objective of increasing intimacy is a one-to-one relationship between contacts and axons. There is a stochastic distribution of Nodes of Ranvier and axon sizes that results in a distributed recruitment within the nerve limiting the maximum effective electrode density [102,103]. When placing electrodes within the nerve, there are spatial constraints that limit the number of electrodes within the constrained fascicle [101], especially when considering inflammatory response characteristics [104, 105[■],106,107], which will further reduce the intimacy of contacts with axons. Prior short-term applications of intrafascicular approaches showed increasing stimulation thresholds [108,109[■]]. The number of reported sensory locations and perceptions elicited was similar to long-term extraneural approaches [82[■],83[■],110[■]]. The functional performance of an intrafascicular approach is similar to the extraneural approach [107].

Electromagnetic interaction

In addition to physical proximity, a second powerful tool that is often not considered is the manipulation and design of the spatiotemporal electromagnetic field. Multiple electrical contacts in electrodes like the FINE [111–113] allow for the summation of electrical fields to shape and move areas of activation within the nerve. Therefore, the sensory locations are not limited to the number of electrical contacts. It has been demonstrated clinically that additional sensory perceptions are possible [82[■]] and the number of additional sensations possible is an active area of research.

Pulse shapes

The magnitude of the electrical fields decays by a factor of $1/r$, where r is the distance from the electrode. Nerve activation is proportional to the rate of change of the voltage difference along the axon [114]. Hence, with simple square pulses, closer, larger, myelinated axons will be activated before smaller, distant and unmyelinated axons. However, axonal excitation is also controlled by the nonlinear dynamics of the membrane channels [115] that can be manipulated by changing the shape of the pulse. Types of waveforms that have been explored include quasi-trapezoidal pulses designed to recruit small axons before the large [116] and ramp pulses to activate more distal axons before closer axons [117]. To minimize the power requirements for implanted devices, exponential-shaped waveforms activate the larger and closer axons in the same order, but with minimized energy [118,119].

Frequency modulation

Axons convey information by spikes. In any single axon, the information is carried out by the spike rate or frequency. Changing stimulation frequency in somatosensory applications is related to intensity [120] and bursting pulse trains can change resulting sensory perceptions [82[■]].

Patterned stimulation intensity

In populations of axons, additional information is conveyed by the relative timing and rates of spikes on different axons. In patterned frequency paradigms, stimulation strength is typically maintained constant for all pulses, resulting in synchronous activity in the entire axon population. This does not convey the complex information possible with relative differences in timing and frequency of spikes between axons. This type of information is exemplified by the difference in rapidly and slowly adapting fibers in response to a touching an object. The rapidly adapting fibers burst at contact and release only. The slowly adapting fibers respond with a more continuous spiking with spike frequency proportional to applied pressure. To duplicate the pattern of fiber activity, there are several tools including patterned stimulation intensity (PSI) [82²²] and patterned field distribution of the stimulation. In each paradigm, shift in the field between stimulation pulses changes the axons activated with each pulse, and hence creates a nonsynchronous activity in a population. If controlled properly, this information can be sufficient to restore several different somatosensation percepts [82²²].

Class III medical device status

Implanted devices are regulated by the Food and Drug Administration as, Class III devices (U.S. regulation 21 CFR 860). This is a significant shift from the Class I designation of traditional prostheses. Class III devices require significant oversight and regulation, which increases cost and complexity. This will be difficult to manage in the relatively small limb-loss market. Powered prostheses are already expensive and require extensive justification to the Centers for Medicare & Medicaid Services (CMS) and other third-party payers. It is important to show that the added cost of somatosensation is justified. Studies and quantification of pain relief, return to work, lower abandonment and improved psychological outlook will be important to CMS. It will also be important to develop and leverage device technology that has applications in larger market segments. Defense Advanced Research Projects Agency investment through several initiatives, including the 'Revolutionizing Prosthetics,' 'RE-NET,' and 'HAPTIX' programs have been critical to help offset the development costs and show the value of somatosensory restoration.

CLINICAL DEMONSTRATIONS OF SOMATOSENSTORY RESTORATION

There are a growing number of studies providing evidence of the importance and capability of providing sensation through neural interfaces and electrical stimulation. The concept was first demonstrated by Frank Clippinger in 1974 with single channel cuff electrodes placed around the median nerves for the upper extremity [121] and the femoral nerve in the lower extremities [122]. Sensation was perceived on the phantom, but was generally diffuse sensation, unstable, and the quality of the sensation was generally described as paresthesia. Nerve stimulation for somatosensory restoration was then largely ignored until 2005 when a series of articles was published describing the acute trials with the LIFE electrodes placed in the median nerve [120,123,124]. There were localized sensory percepts with perceptual intensity proportional to stimulation frequency and a spread of sensory area with increased stimulation intensity. Even 25 years postinjury, an individual could still feel localized sensation with the phantom. The sensory changes associated with brain plasticity following

limb loss were not permanent and the cortical hand representation remains. In further acute trials, a TIME also showed four points of sensation, a graded perceptual response and basic object discrimination based on relative sensor activation [109[■]].

Extraneural electrodes have shown the first long-term, stable, multineur, multichannel restoration of sensation [82[■],83[■],110[■]]. Individuals have been implanted for more than 3 years with FINEs on the median, ulnar, and radial nerves and spiral electrodes on the radial or ulnar nerve. The extraneural electrodes were able to produce highly localized sensations from each of the contacts and these were distributed over the entire hand. In one individual, the electrodes are implanted in the forearm and in second individual, they are in the upper arm. More than 90% of the eight electrical contacts around each nerve produced somatosensation at unique locations. There is a maintained somatotopic organization of somatosensation from the hand to at least the middle upper arm. These locations and stimulation thresholds have been stable for the entire duration of the implant. Adding fields from multiple electrodes produce sensation at additional locations on the hand. The stimulation thresholds and electrode impedances were stable for the entire 2-year pulse duration of the implant and are still ongoing at the time of this article [83[■]].

Different PSIs result in the individual reporting several different qualities of sensation at a single location on the hand [82[■]]. Several of these sensations were described by the individual as being very ‘natural.’ Different stimulation patterns resulted in sensations such as constant pressure, pulsing pressure, buzzing, tapping, flutter, sandpaper and motion.

Functionally, sensory feedback improves the user’s fine control of a traditional myoelectric device [82[■]]. The user could perform delicate tasks without visual or audio feedback, relying entirely on stimulated somatosensation. These tasks were often difficult or not possible even with visual and auditory feedback.

Chronic phantom pain that had not been resolved with medication or other desensitization therapy was reduced immediately and virtually eliminated within 6 months of the start of the somatosensory stimulation trial [82[■]]. Stimulation was applied only in the laboratory, which was every 2 weeks for about 6 h per session. Pain relief, however, persisted even without stimulation.

CONCLUSION

Chronic restoration of somatosensation has been shown for individuals with limb loss [82[■], 83[■],110[■]]. Neural interfaces with sophisticated stimulation paradigms create a user’s perception of his/her hand to touch and manipulate objects. Multichannel stimulation of the peripheral nerve can control location and size of somatosensation perception. The pattern of intensity and frequency of stimulation is critical to the quality and intensity of perceived sensation. Restoring feeling has allowed the individuals to, ‘feel [my] hand for the first time since the accident,’ and ‘feel [my] wife touch my hand’. These individuals using a prosthetic hand with sensation can pull cherries and grapes from the stem, open water bottles and move objects without destroying these objects – all while audio and visually deprived. After regaining sensation, phantom pain is eliminated in individuals that had frequent, sometimes

debilitating, pain following limb loss. There are several technologies in development, but extraneural peripheral nerve interfaces have been stable for more than 3 years in two different studies [82[■],110[■]]. Restoration of somatosensation following limb loss is now tangible.

This review has focused on upper limb loss. There is a more substantial population and need for individuals with lower limb loss. Stimulation of lower extremity peripheral nerves is expected to similarly produce sensation in the phantom foot. Sensation would be valuable to restore a sense of ground strike, foot position, and center of pressure during standing and locomotion.

In addition to the value in prosthetics, these reports drive important research questions in neurology. A few specific patterns of stimulation intensity alter the quality of the perceptual experience. It is unlikely that the patterns reproduce the exact neural activity of the intact somatosensory system. The somatosensory processing system, however, can accommodate a small amount of noise or error and recognize a pattern based on prior experience. The important questions yet to address are how much noise is acceptable to still achieve accurate classification; how many different perceptions can be recognized; and how does learning with long-term constant application of stimulation patterns change the ‘naturalness’ and recognition of different sensory perceptions.

The highlighted recent literature shows over 7 subject-years of stable, complex somatosensory restoration. This is the beginning of a new era of prostheses, and more broadly, somatosensory neuromodulation and research.

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KEY POINTS

- Stimulation of peripheral nerves with extraneural cuff-type electrodes on residual nerves in upper limb loss individuals provides localized sensations over the entire hand in a somatotopic representation.
- Restored somatosensation improves fine control of a myoelectric prosthesis, embodiment of the prosthesis and reduction of phantom pain.
- Peripheral nerve cuff electrodes are stable for more than 3 years in individuals with limb loss.
- Patterns of stimulation intensity change the quality of the perceptions experienced by the user as a single location. The perceptions can change from artificial paresthesia to pressures that an individual will describe as normal.