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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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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 lost 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) [82■■] 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 [82■■].

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, multinerve, 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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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Biddiss, Ea, Chau, TT. Upper limb prosthesis use and abandonment: a survey of the last 25 years. Prosthet Orthot Int. 2007; 31:236–257. [PubMed: 17979010]
2. Resnik L, Meucci MR, Lieberman-Klinger S, et al. Advanced upper limb prosthetic devices: implications for upper limb prosthetic rehabilitation. Arch Phys Med Rehabil. 2012; 93:710–717. [PubMed: 22464092]

3. Biddiss E, Chau T. Upper-limb prosthetics: critical factors in device abandonment. Am J Phys Med Rehabil. 2007; 86:977–987. [PubMed: 18090439]
4. Biddiss E, Beaton D, Chau T. Consumer design priorities for upper limb prosthetics. Disabil Rehabil Assist Technol. 2007; 2:346–357. [PubMed: 19263565]
5. McCloskey DI. Kinesthetic sensibility. Physiol Rev. 1978; 58:763–820. [PubMed: 360251]
6. Proske U, Gandevia SC. The kinaesthetic senses. J Physiol. 2009; 587:4139–4146. [PubMed: 19581378]
7. Longo MR, Schüür F, Kammers MPM, et al. What is embodiment? A psychometric approach. Cognition. 2008; 107:978–998. [PubMed: 18262508]
8. De Vignemont F. Embodiment, ownership and disownership. Conscious Cogn. 2011; 20:82–93. [PubMed: 20943417]
9. Murray, CD. Embodiment and Prosthetics. In: Gallagher, P.Desmond, D., MacLachlan, M., editors. Psychoprosthetics. Springer; 2008. p. 119-129.
10. Tsakiris M. My body in the brain: a neurocognitive model of body-ownership. Neuropsychologia. 2010; 48:703–712. [PubMed: 19819247]
11. Limerick H, Coyle D, Moore JW. The experience of agency in human-computer interactions: a review. Front Hum Neurosci. 2014; 8:1–10. [PubMed: 24474914]
12. Marasco PD, Kim K, Colgate JE, et al. Robotic touch shifts perception of embodiment to a prosthesis in targeted reinnervation amputees. Brain. 2011; 134:747–758. [PubMed: 21252109]
13. Velliste M, Perel S, Spalding MC, et al. Cortical control of a robotic arm for self-feeding. Nature. 2008; 453:1098–1101. [PubMed: 18509337]
14. Ezendam D, Bongers RM, Jannink MJa. Systematic review of the effectiveness of mirror therapy in upper extremity function. Disabil Rehabil. 2009; 31:2135–2149. [PubMed: 19903124]
15. Hellman RB, Chang E, Tanner J, et al. A robot hand testbed designed for enhancing embodiment and functional neurorehabilitation of body schema in subjects with upper limb impairment or loss. Front Hum Neurosci. 2015; 9:1–10. [PubMed: 25653611]
16. Mills FB. A phenomenological approach to psychoprosthetics. Disabil Rehabil. 2012; 35:1–7. [PubMed: 22607157]
17. Giummarra MJ, Gibson SJ, Georgiou-Karistianis N, Bradshaw JL. Mechanisms underlying embodiment, disembodiment and loss of embodiment. Neurosci Biobehav Rev. 2008; 32:143–160. [PubMed: 17707508]
18. Giummarra MJ, Gibson SJ, Georgiou-Karistianis N, Bradshaw JL. Central mechanisms in phantom limb perception: the past, present and future. Brain Res Rev. 2007; 54:219–232. [PubMed: 17500095]
19. Buxbaum LJ. On the right (and left) track: twenty years of progress in studying hemispatial neglect. Cogn Neuropsychol. 2006; 23:184–201. [PubMed: 21049327]
20. Schmalzl L, Kalckert A, Ragnö C, Ehrsson HH. Neural correlates of the rubber hand illusion in amputees: a report of two cases. Neurocase. 2014; 20:407–420. [PubMed: 23682688]
21. Proske U, Gandevia SC. The proprioceptive senses: their roles in signaling body shape, body position and movement, and muscle force. Physiol Rev. 2012; 92:1651–1697. [PubMed: 23073629]
22. Cordo PJ, Flanders M. Sensory control of target acquisition. Trends Neurosci. 1989; 12:110–117. [PubMed: 2469217]
23. Cordo PJ, Horn J-L, Künster D, et al. Contributions of skin and muscle afferent input to movement sense in the human hand. J Neurophysiol. 2011; 105:1879–1888. [PubMed: 21307315]
24. Cullen KE. The neural encoding of self-motion. Curr Opin Neurobiol. 2011; 21:587–595. [PubMed: 21689924]
25. Johansson RS, Flanagan JR. Coding and use of tactile signals from the fingertips in object manipulation tasks. Nat Rev Neurosci. 2009; 10:345–359. [PubMed: 19352402]
26. Blank A, Okamura AM, Kuchenbecker KJ. Identifying the role of proprioception in upper-limb prosthesis control. ACM Trans Appl Percept. 2010; 7:1–23.
27. Dietz V. Proprioception and locomotor disorders. Nat Rev Neurosci. 2002; 3:781–790. [PubMed: 12360322]

28. Campfens SF, Zandvliet SB, Meskers CGM, et al. Poor motor function is associated with reduced sensory processing after stroke. Exp Brain Res. 2015; 233:1339–1349. [PubMed: 25651979]
29. Sullivan JE, Hedman LD. Sensory dysfunction following stroke: incidence, significance, examination, and intervention. Top Stroke Rehabil. 2008; 15:200–217. [PubMed: 18647725]
30. Sanes JN, Mauritz KH, Evarts EV, et al. Motor deficits in patients with large-fiber sensory neuropathy. Proc Natl Acad Sci. 1984; 81:979–982. [PubMed: 6322181]
31. Galán F, Baker MR, Alter K, Baker SN. Degraded EEG decoding of wrist movements in absence of kinaesthetic feedback. Hum Brain Mapp. 2015; 36:643–654. [PubMed: 25307551]
32. Mckechnie PS, John A. Anxiety and depression following traumatic limb amputation: a systematic review. Injury. 2014; 45:1859–1866. [PubMed: 25294119]
33. Desmond DM, MacLachlan M. Affective distress and amputation-related pain among older men with long-term, traumatic limb amputations. J Pain Symptom Manage. 2006; 31:362–368. [PubMed: 16632084]
34. Cavanagh SR, Shin LM, Karamouz N, Rauch SL. Psychiatric and emotional sequelae of surgical amputation. Psychosomatics. 2006; 47:459–464. [PubMed: 17116945]
35. Vincent HK, Horodyski M, Vincent KR, et al. Psychological distress after orthopedic trauma: prevalence in patients and implications for rehabilitation. PM&R. 2015; 7:978–989. [PubMed: 25772720]
36. Shukla GD, Sahu SC, Tripathi RP, Gupta DK. A psychiatric study of amputees. Br J Psychiatry. 1982; 141:50–53. [PubMed: 7116072]
37. Dogu B, Kuran B, Sirzai H, et al. The relationship between hand function, depression, and the psychological impact of trauma in patients with traumatic hand injury. Int J Rehabil Res. 2014; 37:105–109. [PubMed: 24276593]
38. Bailey R, Kaskutas V, Fox I, et al. Effect of upper extremity nerve damage on activity participation, pain, depression, and quality of life. J Hand Surg Am. 2009; 34:1682–1688. [PubMed: 19896011]
39. Cheung E, Alvaro R, Colotla Va. Psychological distress in workers with traumatic upper or lower limb amputations following industrial injuries. Rehabil Psychol. 2003; 48:109–112.
40. Desteli EE, ˙Imren Y, Erdoğan M, et al. Comparison of upper limb amputees and lower limb amputees: a psychosocial perspective. Eur J Trauma Emerg Surg. 2014; 40:735–739. [PubMed: 26814792]
41. Copuroglu C, Ozcan M, Yilmaz B, et al. Acute stress disorder and posttraumatic stress disorder following traumatic amputation. Acta Orthop Belg. 2010; 76:90–93. [PubMed: 20306971]
42. Galanakos SP, Bot AGJ, Zoubos AB, Soucacos PN. Psychological and social consequences after reconstruction of upper extremity trauma: Methods of detection and management. J Reconstr Microsurg. 2014; 30:193–206. [PubMed: 24347334]
43. Hannah SD. Psychosocial issues after a traumatic hand injury: Facilitating adjustment. J Hand Ther. 2011; 24:95–103. [PubMed: 21236639]
44. Herbert BM, Pollatos O. The body in the mind: on the relationship between interoception and embodiment. Top Cogn Sci. 2012; 4:692–704. [PubMed: 22389201]
45. Bruyns CNP, Jaquet JB, Schreuders TaR, et al. Predictors for return to work in patients with median and ulnar nerve injuries. J Hand Surg Am. 2003; 28:28–34. [PubMed: 12563634]
46. Clay FJ, Newstead SV, McClure RJ. A systematic review of early prognostic factors for return to work following acute orthopaedic trauma. Injury. 2010; 41:787–803. [PubMed: 20435304]
47. Helmerhorst GTT, Vranceanu A, Vrahas M, et al. Risk factors for continued opioid use one to two months after surgery for musculoskeletal trauma. J Bone Joint Surg Am. 2014; 96:495–499. [PubMed: 24647506]
48. Moradi A, Ebrahimzadeh MH, Soroush MR. Quality of life of caregiver spouses of veterans with bilateral lower extremity amputations. Trauma Mon. 2015; 20:1–6.
49. Geertzen JHB, Van Es CG, Dijkstra PU. Sexuality and amputation: a systematic literature review. Disabil Rehabil. 2009; 31:522–527. [PubMed: 19117187]
50. Ide M. Sexuality in persons with limb amputation: a meaningful discussion of re-integration. Disabil Rehabil. 2004; 26:939–943. [PubMed: 15497925]

51. Saradjian A, Thompson AR, Datta D. The experience of men using an upper limb prosthesis following amputation: positive coping and minimizing feeling different. Disabil Rehabil. 2008; 30:871–883. [PubMed: 17852212]
52. Kooijman CM, Dijkstra PU, Geertzen JHB, et al. Phantom pain and phantom sensations in upper limb amputees: an epidemiological study. Pain. 2000; 87:33–41. [PubMed: 10863043]
53. Wolff A, Vanduynhoven E, Van Kleef M, et al. Phantom pain. Pain Pract. 2011; 11:403–413. [PubMed: 21447079]
54. Gierthmühlen J, Binder A, Baron R. Mechanism-based treatment in complex regional pain syndromes. Nat Rev Neurol. 2014; 10:1–11. [PubMed: 24323047]
55. Vaso A, Adahan H-M, Gjika A, et al. Peripheral nervous system origin of phantom limb pain. Pain. 2014; 155:1384–1391. [PubMed: 24769187]
56. Makin TR, Scholz J, Filippini N, et al. Phantom pain is associated with preserved structure and function in the former hand area. Nat Commun. 2013; 4:1570. [PubMed: 23463013]
57. Desmond DM, MacLachlan M. Prevalence and characteristics of phantom limb pain and residual limb pain in the long term after upper limb amputation. Int J Rehabil Res. 2010; 33:279–282. [PubMed: 20101187]
58. Carey SL, Lura DJ, Highsmith MJ. Differences in myoelectric and body-powered upper-limb prostheses: systematic literature review. J Rehabil Res Dev. 2015; 52:247–262. [PubMed: 26230500]
59. Berning K, Cohick S, Johnson R, et al. Comparison of body-powered voluntary opening and voluntary closing prehensor for activities of daily living. J Rehabil Res Dev. 2014; 51:253–262. [PubMed: 24933723]
60. Stein RB, Walley M. Functional comparison of upper extremity amputees using myoelectric and conventional prostheses. Arch Phys Med Rehabil. 1983; 64:243–248. [PubMed: 6860093]
61. Reference deleted.
62. Lundborg G, Rosen B. Sensory substitution in prosthetics. Hand Clin. 2001; 17:481–488. [PubMed: 11599215]
63. Visell Y. Tactile sensory substitution: models for enaction in HCI. Interact Comput. 2009; 21:38–53.
64. Hsiao SS, Fettiplace M, Darbandi B. Sensory feedback for upper limb prostheses. Prog Brain Res. 2011; 192:69–81. [PubMed: 21763519]
65. Clemente F, Cipriani C. A novel device for multimodal sensory feedback in hand prosthetics: design and preliminary prototype. 2014 IEEE Haptics Symp. 2014:569–573.
66. D’Alonzo M, Cipriani C. Vibrotactile sensory substitution elicits feeling of ownership of an alien hand. PLoS One. 2012; 7:e50756. [PubMed: 23226375]
67. Cipriani C, D’Alonzo M, Carrozza MC. A miniature vibrotactile sensory substitution device for multifingered hand prosthetics. IEEE Trans Biomed Eng. 2012; 59:400–408. [PubMed: 22042125]
68. Rombokas E, Stepp CE, Chang C, et al. Vibrotactile sensory substitution for electromyographic control of object manipulation. IEEE Trans Biomed Eng. 2013; 60:2226–2232. [PubMed: 23508245]
69. Wheeler J, Bark K, Savall J, Cutkosky M. Investigation of rotational skin stretch for proprioceptive feedback with application to myoelectric systems. IEEE Trans Neural Syst Rehabil Eng. 2010; 18:58–66. [PubMed: 20071271]
70. Collins DF, Refshauge KM, Todd G, Gandevia SC. Cutaneous receptors contribute to kinesthesia at the index finger, elbow, and knee. J Neurophysiol. 2005; 94:1699–1706. [PubMed: 15917323]
71. Thyrion C, Roll J-P. Predicting any arm movement feedback to induce three-dimensional illusory movements in humans. J Neurophysiol. 2010; 104:949–959. [PubMed: 20538782]
72. Bark K, Wheeler JW, Premakumar S, Cutkosky MR. Comparison of skin stretch and vibrotactile stimulation for feedback of proprioceptive information. Symp Haptics Interfaces Virtual Environ Teleoperator Syst 2008 #x02013; Proceedings, Haptics. 2008:71–78.
73. Hebert JS, Elzinga K, Chan KM, et al. Updates in targeted sensory reinnervation for upper limb amputation. Curr Surg Reports. 2014; 2:45.

74. Marasco PD, Schultz AE, Kuiken Ta. Sensory capacity of reinnervated skin after redirection of amputated upper limb nerves to the chest. Brain. 2009; 132:1441–1448. [PubMed: 19369486]

75. McGlone F, Reilly D. The cutaneous sensory system. Neurosci Biobehav Rev. 2010; 34:148–159. [PubMed: 19712693]

76. Lumpkin, Ea, Caterina, MJ. Mechanisms of sensory transduction in the skin. Nature. 2007; 445:858–865. [PubMed: 17314972]

77. Weber DJ, Friesen R, Miller LE. Interfacing the somatosensory system to restore touch and proprioception: essential considerations. J Mot Behav. 2012; 44:403–418. [PubMed: 23237464]

78. Bensmaia SJ, Miller LE. Restoring sensorimotor function through intracortical interfaces: progress and looming challenges. Nat Rev Neurosci. 2014; 15:313–325. [PubMed: 24739786]

79. Weber DJ, London BM, Hokanson Ja, et al. Limb-state information encoded by peripheral and central somatosensory neurons: implications for an afferent interface. IEEE Trans Neural Syst Rehabil Eng. 2011; 19:501–513. [PubMed: 21878419]

80. Weber DJ, Stein RB, Everaert DG, Prochazka A. Decoding sensory feedback from firing rates of afferent ensembles recorded in cat dorsal root ganglia in normal locomotion. IEEE Trans Neural Syst Rehabil Eng. 2006; 14:240–243. [PubMed: 16792303]

81. Gaunt, Ra, Prochazka, A., Mushahwar, VK., et al. Intraspinal microstimulation excites multisegmental sensory afferents at lower stimulus levels than local alpha-motoneuron responses. J Neurophysiol. 2006; 96:2995–3005. [PubMed: 16943320]

82■■. Tan DW, Schiefer Ma, Keith MW, et al. A neural interface provides long-term stable natural touch perception. Sci Transl Med. 2014; 6:257ra138. This is the first chronic demonstrating of multiple electrodes with multiple points on a single nerve providing stable, somatotopically organized restoration of sensation, repeated in multiple individuals, improve control of a myoelectric prosthesis in fine manipulation tasks and manage phantom pain. The sensation at each point was graded with stimulation frequency and strength. More importantly, it introduces for the first time that PSI can dramatically change the sensation perceived by the individual.

83■. Tan D, Schiefer M, Keith MW, et al. Stability and selectivity of a chronic, multicontact cuff electrode for sensory stimulation in a human amputee. J Neural Eng. 2015; 12:026002. Shows the stable location and threshold of stimulation for somatosensory restoration with extraneural cuff electrodes for more than 3 years. [PubMed: 25627310]

84. Rutten WLC. Selective electrical interfaces with the nervous system. Annu Rev Biomed Eng. 2002; 4:407–452. [PubMed: 12117764]

85. Navarro X, Krueger TB, Lago N, et al. A critical review of interfaces with the peripheral nervous system for the control of neuroprostheses and hybrid bionic systems. J Peripher Nerv Syst. 2005; 10:229–258. [PubMed: 16221284]

86. Naples GG, Mortimer JT, Scheiner A, Sweeney JD. A spiral nerve cuff electrode for peripheral nerve stimulation. IEEE Trans Biomed Eng. 1988; 35:905–916. [PubMed: 3198136]

87. Agnew WF, McCreery DB, Yuen TGH, Bullara LA. Histologic and physiologic evaluation of electrically stimulated peripheral nerve: Considerations for the selection of parameters. Ann Biomed Eng. 1989; 17:39–60. [PubMed: 2537589]

88. Polasek KH, Hoyen HA, Keith MW, et al. Stimulation stability and selectivity of chronically implanted multicontact nerve cuff electrodes in the human upper extremity. IEEE Trans Neural Syst Rehabil Eng. 2009; 17:428–437. [PubMed: 19775987]

89. Groves DA, Brown VJ. Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neurosci Biobehav Rev. 2005; 29:493–500. [PubMed: 15820552]

90. Fisher LE, Tyler DJ, Anderson JS, Triolo RJ. Chronic stability and selectivity of four-contact spiral nerve-cuff electrodes in stimulating the human femoral nerve. J Neural Eng. 2009; 6:046010. [PubMed: 19602729]

91. Tyler DJ, Durand DM. Functionally selective peripheral nerve stimulation with a flat interface nerve electrode. IEEE Trans Neural Syst Rehabil Eng. 2002; 10:294–303. [PubMed: 12611367]

92. Schiefer MA, Triolo RJ, Tyler DJ. A model of selective activation of the femoral nerve with a flat interface nerve electrode for a lower extremity neuroprosthesis. IEEE Trans Neural Syst Rehabil Eng. 2008; 16:195–204. [PubMed: 18403289]

93. Schiefer, Ma, Freeberg, M., Pinault, GJC., et al. Selective activation of the human tibial and common peroneal nerves with a flat interface nerve electrode. J Neural Eng. 2013; 10:056006. [PubMed: 23918148]

94. Yoo PB, Durand DM. Selective recording of the canine hypoglossal nerve using a multicontact flat interface nerve electrode. IEEE Trans Biomed Eng. 2005; 52:1461–1469. [PubMed: 16119242]

95. Tyler DJ, Durand DM. A slowly penetrating interfascicular nerve electrode for selective activation of peripheral nerves. IEEE Trans Rehabil Eng. 1997; 5:51–61. [PubMed: 9086385]

96. Koole P, Holsheimer J, Struijk JJ, Verloop AJ. Recruitment characteristics of nerve fascicles stimulated by a multigroove electrode. IEEE Trans Rehabil Eng. 1997; 5:40–50. [PubMed: 9086384]

97. Yoshida K, Horch KW. Selective stimulation of peripheral nerve fibers using dual intrafascicular electrodes. IEEE Trans Biomed Eng. 1993; 40:492. [PubMed: 8225338]

98. Thota AK, Kuntaegowdanahalli S, Starosciak AK, et al. A system and method to interface with multiple groups of axons in several fascicles of peripheral nerves. J Neurosci Methods. 2015; 244:78–84. [PubMed: 25092497]

99. Boretius T, Badia J, Pascual-Font A, et al. A transverse intrafascicular multichannel electrode (TIME) to interface with the peripheral nerve. Biosens Bioelectron. 2010; 26:62–69. [PubMed: 20627510]

100. Wark, HaC, Sharma, R., Mathews, KS., et al. A new high-density (25 electrodes/mm2) penetrating microelectrode array for recording and stimulating submillimeter neuroanatomical structures. J Neural Eng. 2013; 10:045003. [PubMed: 23723133]

101. Peters, A., Palay, SL., deF Webster, H. The Fine Structure of the Nervous System: Neurons and Their Supporting Cells. Oxford University Press; 1991. p. 384-394.

102. Grinberg Y, Schiefer MA, Tyler DJ, Gustafson KJ. Fascicular perineurium thickness, size, and position affect model predictions of neural excitation. IEEE Trans Neural Syst Rehabil Eng. 2008; 16:572–581. [PubMed: 19144589]

103. Rutten WL, van Wier HJ, Put JH. Sensitivity and selectivity of intraneural stimulation using a silicon electrode array. IEEE Trans Biomed Eng. 1991; 38:192–198. [PubMed: 2066129]

104. Lago N, Yoshida K, Koch KP, Navarro X. Assessment of biocompatibility of chronically implanted polyimide and platinum intrafascicular electrodes. IEEE Trans Biomed Eng. 2007; 54:281–290. [PubMed: 17278585]

105■. Christensen MB, Pearce SM, Ledbetter NM, et al. The foreign body response to the Utah slant electrode array in the cat sciatic nerve. Acta Biomater. 2014; 10:4650–4660. This article describes the most detailed analysis to date of the penetrating, intrafascicular electrode arrays. It demonstrates the influence of the penetrating array on nerve tissue, including presence of degenerating and regenerating neurons. There still remains debate as to the long-term stability of the approach of crossing the perineurium and chronic effects of the changes in the nerve. [PubMed: 25042798]

106. Branner A, Stein RBB, Fernandez E, et al. Long-term stimulation and recording with a penetrating microelectrode array in cat sciatic nerve. Biomed Eng IEEE Trans. 2004; 51:146–157.

107. Grill Warren M, Norman S, Sharon E, Bellamkonda Ravi V, et al. Implanted neural interfaces: biochallenges and engineered solutions. Biomed Eng (NY). 2009; 11:1.

108. Rossini PM, Micera S, Benvenuto A, et al. Double nerve intraneural interface implant on a human amputee for robotic hand control. Clin Neurophysiol. 2010; 121:777–783. [PubMed: 20110193]

109■. Raspopovic S, Capogrosso M, Petrini FM, et al. Restoring natural sensory feedback in real-time bidirectional hand prostheses. Sci Transl Med. 2014; 6:222ra19. Implant of TIME intrafascicular electrodes for 4 weeks. Three locations of sensation are reported and they show the individual could distinguish multiple levels of sensation. The individual could distinguish a large object from small object by distinguishing the number of sensory locations active simultaneously when grasping the object.

110■■. Ortiz-Catalan M, Håkansson B, Brånemark R. An osseointegrated human-machine gateway for long-term sensory feedback and motor control of artificial limbs. Sci Transl Med. 2014; 6:1–8. Most important in this article is the demonstration of the long-term stability of an osseointegrated attachment for the prosthesis. In addition, they included a connector system in the osseointegrated post that connected internal electromyography recordings for highly improved control. They also attached a spiral extraneural electrode on the ulnar nerve and demonstrated long-term sensation to the ulnar territory of the hand.

111. Schiefer MA, Polasek KH, Triolo RJ, et al. Selective stimulation of the human femoral nerve with a flat interface nerve electrode. J Neural Eng. 2010; 7:26006. [PubMed: 20208125]
112. Schiefer MA, Tyler DJ, Triolo RJ. Probabilistic modeling of selective stimulation of the human sciatic nerve with a flat interface nerve electrode. J Comput Neurosci. 2012; 33:179–190. [PubMed: 22222951]
113. Brill N, Tyler D. Optimizing nerve cuff stimulation of targeted regions through use of genetic algorithms. Conf Proc IEEE Eng Med Biol Soc. 2011; 2011:5811–5814. [PubMed: 22255661]
114. Rattay F, Aberham M. Modeling axon membranes for functional electrical stimulation. IEEE Trans Biomed Eng. 1993; 40:1201–1209. [PubMed: 8125496]
115. Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol. 1952; 117:500–544. [PubMed: 12991237]
116. Fang ZP, Mortimer JT. Selective activation of small motor axous by quasitrapezoidal current pulses. IEEE Trans Biomed Eng. 1991; 38:168–174. [PubMed: 2066126]
117. Grill WM, Mortimer JT. Inversion of the current-distance relationship by transient depolarization. IEEE Trans Biomed Eng. 1997; 44:1–9. [PubMed: 9214779]
118. Krouchev NI, Danner SM, Vinet A, et al. Energy-optimal electrical-stimulation pulses shaped by the least-action principle. PLoS One. 2014; 9:e90480. [PubMed: 24625822]
119. Wongsarnpigoon A, Grill WM. Energy-efficient waveform shapes for neural stimulation revealed with a genetic algorithm. J Neural Eng. 2010; 7:046009. [PubMed: 20571186]
120. Dhillon GS, Horch KW. Direct neural sensory feedback and control of a prosthetic arm. IEEE Trans Neural Syst Rehabil Eng. 2005; 13:468–472. [PubMed: 16425828]
121. Clippinger FW, Avery R, Titus BR. A sensory feedback system for an upper-limb amputation prosthesis. Bull Prosthet Res. 1973:247–258.
122. Clippinger FW, Seaber AV, McElhaney JH, et al. Afferent sensory feedback for lower extremity prosthesis. Clin Orthop Relat Res. 1982; 169:202–206.
123. Dhillon GS, Lawrence SM, Hutchinson DT, Horch KW. Residual function in peripheral nerve stumps of amputees: implications for neural control of artificial limbs. J Hand Surg Am. 2004; 29:605–615. discussion 616–8. [PubMed: 15249083]
124. Dhillon GS, Kruger TB, Sandhu JS, Horch KW. Effects of short-term training on sensory and motor function in severed nerves of long-term human amputees. J Neurophysiol. 2005; 93:2625–2633. [PubMed: 15846000]

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.