Restoration of Proprioceptive and Cutaneous Sensation Using Regenerative Peripheral Nerve Interfaces in Humans with Upper Limb Amputations

Philip P. Vu, Ph.D.
Charles W. Lu, M.S.E.
Alex K. Vaskov, M.S.
Deanna H. Gates, Ph.D.
R. Brent Gillespie, Ph.D.
Stephen W. P. Kemp, Ph.D.
Parag G. Patil, M.D., Ph.D.
Cynthia A. Chestek, Ph.D.
Paul S. Cederna, M.D.
Theodore A. Kung, M.D.

Ann Arbor, Mich.

Summary: Without meaningful and intuitive sensory feedback, even the most advanced prosthetic limbs remain insensate and impose an enormous cognitive burden during use. The regenerative peripheral nerve interface can serve as a novel bidirectional motor and sensory neuroprosthetic interface. In previous human studies, regenerative peripheral nerve interfaces demonstrated stable high-amplitude motor electromyography signals with excellent signal-to-noise ratio for prosthetic control. In addition, they can treat and prevent postamputation pain by mitigating neuroma formation. In this study, the authors investigated whether electrical stimulation applied to regenerative peripheral nerve interfaces could produce appreciable proprioceptive and/or tactile sensations in two participants with upper limb amputations. Stimulation of the interfaces resulted in both participants reporting proprioceptive sensations in the phantom hand. Specifically, stimulation of participant 1's median nerve regenerative peripheral nerve interface activated a flexion sensation in the thumb or index finger, whereas stimulation of the ulnar nerve interface evoked a flexion sensation of the ring or small finger. Likewise, stimulation of one of participant 2's ulnar nerve interfaces produced a sensation of flexion at the ring finger distal interphalangeal joint. In addition, stimulation of participant 2's other ulnar nerve interface and the median nerve interface resulted in perceived cutaneous sensations that corresponded to each nerve's respective dermatome. These results suggest that regenerative peripheral nerve interfaces have the potential to restore proprioceptive and cutaneous sensory feedback that could significantly improve prosthesis use and embodiment. (*Plast. Reconstr. Surg.* 149: 1149e, 2022.)

Modern robotic technology has provided amputation patients the ability to mimic basic movements and function of the human upper extremity.[1] Prosthetic users rely primarily on visual and auditory feedback to improve prosthetic control and function.[2] These necessary adaptations impose high cognitive load during prosthetic use and are known risk factors for prosthesis abandonment.[3] The ability to provide proprioceptive and cutaneous feedback is essential to optimize functional performance and embodiment of prosthetic limbs.[4–6] Some neural interfaces have demonstrated the potential to evoke meaningful sensory feedback to enhance prosthetic use,[7–11] but none are able to reliably provide both motor and sensory modalities through one interface. The regenerative peripheral nerve interface is a biologic nerve interface that transduces neural signals by allowing a residual peripheral nerve to reinnervate a free skeletal muscle graft. They demonstrate high-amplitude motor

From the Department of Biomedical Engineering, Department of Surgery, Section of Plastic Surgery, Department of Mechanical Engineering, Robotics Institute, School of Kinesiology, Department of Electrical Engineering and Computer Science, Neuroscience Graduate Program, and Department of Neurosurgery, University of Michigan.
Received for publication April 22, 2020; accepted August 13, 2021.

DOI: 10.1097/PRS.0000000000009153

Disclosure: *None of the authors has any financial interest to declare in relation to the content of this article.*

Related digital media are available in the full-text version of the article on www.PRSJournal.com.

electromyography signals for prosthetic control and provide sufficient signal specificity for independent movements of artificial fingers.[12] In this study, we sought to characterize the potential afferent sensory capabilities of the regenerative peripheral nerve interface with the overall goal of developing a reliable bidirectional prosthetic interface.

METHODS

The institutional review board at the University of Michigan approved this study, and each participant provided written and informed consent. Electrode implantation surgery was performed under an investigational device exemption from the U.S. Food and Drug Administration.

Participant 1 was a 30-year-old man who previously sustained a traumatic amputation of the right hand resulting in right wrist disarticulation. Subsequently, participant 1 underwent resection of symptomatic median, ulnar, and dorsal radial sensory nerve neuromas in his distal forearm; one regenerative peripheral nerve interface was created on each of these nerves (Fig. 1). In 2018, he underwent implantation of eight indwelling bipolar electrodes; one each in the median and ulnar nerve regenerative peripheral nerve interfaces, and six into intact forearm muscles associated with finger and wrist movements.[12] Figure 2 shows an example of a bipolar electrode implanted in participant 1's median nerve interface.

Participant 2 was a 53-year-old woman whose right hand required a partial hand amputation after an intravenous extravasation injury resulting in progressive contracture and loss of functionality. Consequently, she underwent a distal transradial amputation. One regenerative peripheral nerve interface was created on each of the median and radial nerves, and an intraneural dissection of the ulnar nerve was performed to create two ulnar nerve interfaces (Fig. 1). One year after the regenerative peripheral nerve interface surgery, she elected to undergo implantation of indwelling bipolar electrodes. Eight electrodes were implanted, one in each median and ulnar interface and five in intact forearm muscles.[12]

Each bipolar electrode was implanted by creating a small 3- to 4-mm window in the muscle component of the regenerative peripheral nerve interface or intact muscle belly with scissors. The electrode was inserted bluntly into the substance of the muscle and fastened by placing an absorbable stitch to secure the proximal wire to reduce motion at the electrode-muscle interface. The wire was passed proximally using a tendon passer instrument to exit percutaneously to a housing unit that was affixed to the skin with adhesive. To prevent infection, the electrode wire, connectors, and exit sites were cleaned with 70% isopropyl alcohol. All external components were covered with a soft dressing and transparent tape. Cleaning and dressing changes were performed every 3 days.

Study patients participated in experimental stimulation sessions approximately 1 month after indwelling electrode placement and once per month thereafter as dictated by our U.S. Food and Drug Administration–approved investigational device exemption protocol. Participant 1 was implanted for 12 months and had seven stimulation sessions. Participant 2 remains implanted at the time of writing and has had 15 stimulation sessions. Regenerative peripheral nerve interfaces on the median and ulnar nerves were stimulated for 3 to 5 seconds with a biphasic square wave using a human-grade stimulator [for participant 1, DS7A (Digitimer, Ft. Lauderdale, Fla.); for participant 2, Neuro Omega (Alpha Omega, Alpharetta, Ga.)]. Stimulation parameter settings were as follows: frequency, 20 to 100 Hz; pulse width, 100 or 200 μsec; and amplitude, 1 to 4 mA. Parameters were set at low values and linearly incremented one at a time until subjects reported a subjective sensory perception. Sensory perception thresholds were measured by adjusting the amplitude intensity parameter and fixing the frequency at 20 Hz and pulse width at 200 μsec for participant 1 and 100 μsec for participant 2. Increments of 0.1 mA were applied until subject reported perception of sensation. To test the effects of frequency, frequency was set at 20 Hz and adjusted by increments of 20 Hz with the amplitude intensity set just above perception threshold and the pulse width fixed at values mentioned earlier. Subjects reported on perceived sensations after each increment.

Participants were blinded to the electrode contact associated with each regenerative peripheral nerve interface and which contact was stimulated for each trial. They reported where they felt the stimulation on a sketched drawing of an ipsilateral hand and arm, and on the researcher's ipsilateral hand. [**See Video (online)**, which demonstrates the method of stimulation and reporting of sensation.] Regenerative peripheral nerve interfaces were stimulated in a pseudorandom order. The quality, location, and associated stimulation parameters were recorded. Using MATLAB (MathWorks, Natick, Mass.), linear regression. models were fitted to test for increasing or decreasing trends in sensory perception thresholds across time.

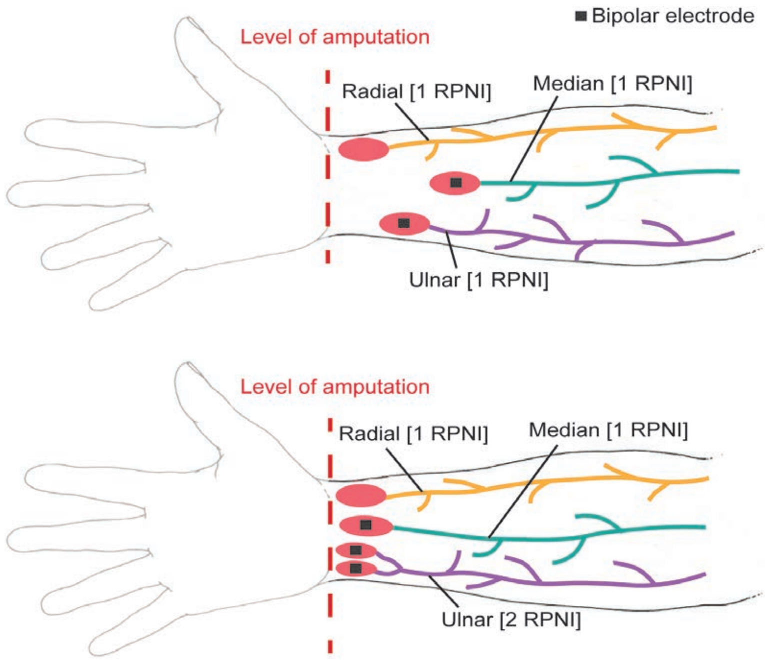

Fig. 1. Illustrations of regenerative peripheral nerve interface (*RPNI*) surgical creation and electrode placement. (*Above*) Participant 1 had three interfaces created, one on each of the median, ulnar, and radial nerves. A bipolar electrode was surgically implanted into each of the median and ulnar interfaces 1 year after regenerative peripheral nerve interface surgery (*black rectangle*). (*Below*) Participant 2 had four interfaces created, one on each of the median and radial nerve and two on the ulnar nerve. Bipolar electrodes were surgically placed in each ulnar interface and the median interface.

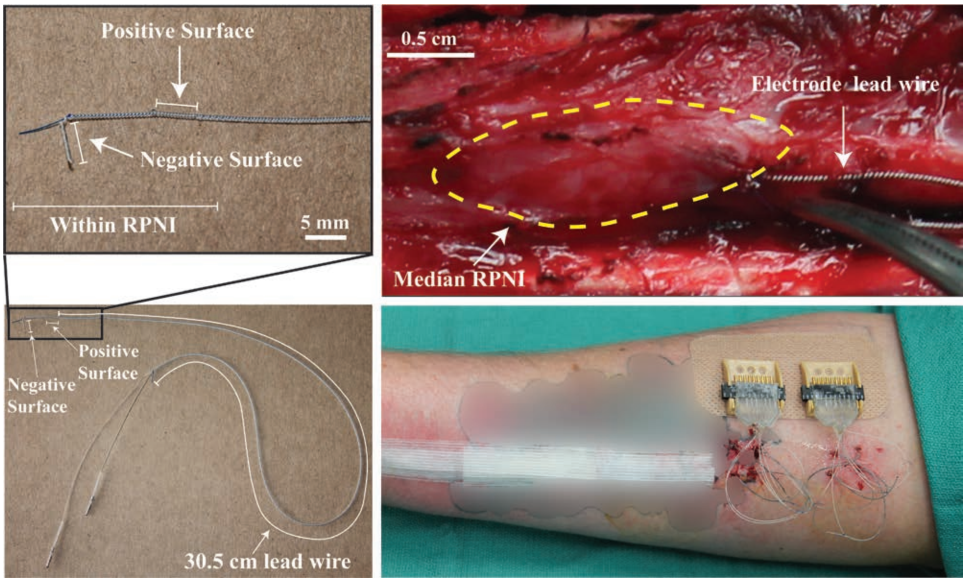

Fig. 2. Surgical electrode implantation for participant 1. (*Above, left*) Example of a 30.5-cm bipolar electrode wire before implantation for participant 1. Rectangular inset shows the 5-mm positive and negative surfaces of the electrode contacts with a 10-mm gap between contacts. The bipolar electrode lead length for participant 2 was 60 cm (not shown). (*Above, right*) Implanted wire insertion into an individual regenerative peripheral nerve interface (*RPNI*) (*dashed line*). (*Below, right*) Final connector setup after all electrodes were implanted.

RESULTS

Anatomically appropriate proprioceptive sensations were reported when stimulating participant 1's median and ulnar nerve regenerative peripheral nerve interfaces. Participant 1 reported a sensation of flexion in his phantom thumb or index finger when stimulating the median nerve interface. When stimulating the ulnar nerve interface, a flexion sensation was felt in his phantom small or ring finger (Fig. 3, *left*, and Table 1). Participant 2 reported both proprioceptive and cutaneous sensations. Stimulation of participant 2's ulnar nerve interface 2 invoked a proprioceptive sensation at the distal interphalangeal joint of the phantom ring finger. In addition to proprioceptive sensations, stimulation of participant 2's median and ulnar nerve interfaces evoked sensations consistent with the dermatome of each nerve, respectively. Stimulation of the median nerve interface produced cutaneous sensations described as tingling at the base of her phantom thumb. Similarly, stimulation of ulnar nerve interface 1 produced a tingling cutaneous sensation along the ulnar aspect of the small finger and palm (Fig. 3, *right*, and Table 1).

Sensory perception thresholds were recorded across sessions in both participants. [**See Figure, Supplemental Digital Content 1**, which shows (*left*) participant 1's sensory perception amplitude thresholds measured up to 271 days after electrode implantation. *Blue circles* indicate amplitude thresholds for the ulnar nerve regenerative peripheral nerve interface, and *yellow squares* represent amplitude thresholds for the median nerve interface. Linear regression models were fitted and are displayed as *yellow* and *blue lines*. There was no significant change in slopes for the median or ulnar nerve interface over time ($p = 0.30$, 0.83, respectively). (*Right*) Participant 2's sensory perception amplitude thresholds measured up to 437 days after electrode implantation. *Blue circles* and *red diamonds* represent amplitude thresholds for the two ulnar nerve interfaces, while *yellow squares* represent the median interface. Linear regression models were fitted and are displayed as *yellow*, *blue*, and *red lines*. There was no significant change in the slope for the median interface ($p = 0.45$). However, ulnar nerve regenerative peripheral nerve interfaces 1 and 2 showed a gradual change in slope ($p < 0.05$), ***http://links.lww.com/PRS/F64***.] In participant 1, the median and ulnar nerve regenerative peripheral nerve interface perception thresholds did not change throughout the study period (271 days). In participant 2, the median interface perception thresholds also remained steady (437 days). However, participant 2's ulnar nerve regenerative peripheral nerve interface 1 and 2 sensory perception thresholds decreased gradually over time ($p < 0.05$), indicating that less stimulation was necessary to evoke sensory perceptions as the study progressed. Across sessions, participant 2 remained

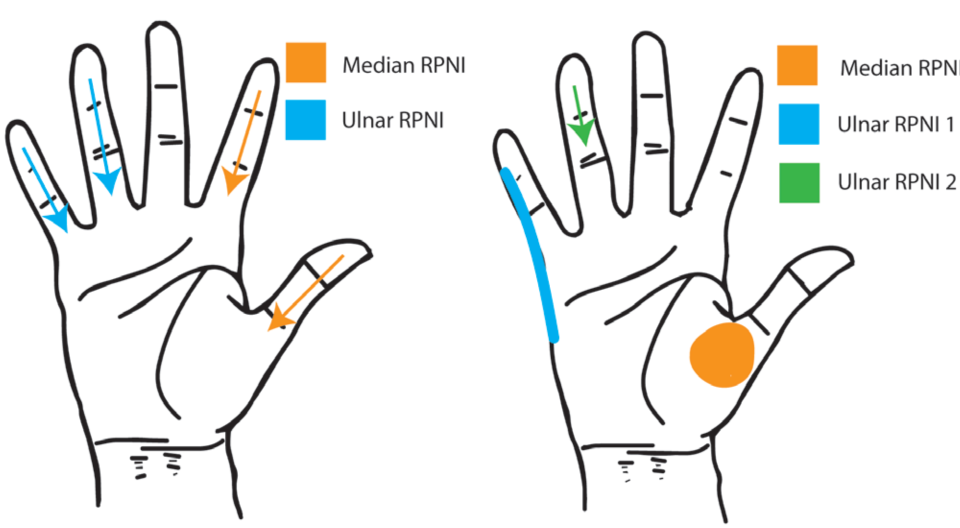

Fig. 3. Sensory map of invoked sensory modalities from electrical stimulation. (*Left*) Patient 1's sensory map during regenerative peripheral nerve interface stimulation. *Orange* and *blue arrows* indicate movement occurred in the referred phantom limb. (*Right*) Patient 2's sensory map showing location of proprioceptive and cutaneous sensations during regenerative peripheral nerve interface stimulation. Cutaneous sensations were reported in the dermatomes corresponding to the peripheral nerve that was stimulated.

Table 1. Summary of Stimulation Parameters and Perceived Sensations

Participant	RPNI Name	Nerve	Stimulation Parameters	Perceived Sensation
P1	Median RPNI	Median	3.0 mA, 20 Hz, 200 μsec	Flexion at the phantom thumb or index finger
	Ulnar RPNI	Ulnar	1.0 mA, 20 Hz, 200 μsec	Flexion at the small or ring finger
P2	Median RPNI	Median	2.0 mA, 100 Hz, 100 μsec	Tingling near base of thumb
	Ulnar RPNI 1	Ulnar	1.5 mA, 100 Hz, 100 μsec	Tingling near edge of small finger and palm
	Ulnar RPNI 2	Ulnar	1.5 mA, 100Hz, 100 μsec	Flexion at DIP joint of ring finger

RPNI, regenerative peripheral nerve interface; DIP, distal interphalangeal.

consistent with reporting the same sensations and perceived location when stimulating each interface. For participant 1, evoked sensations were different when the first testing session was compared to later testing sessions. Stimulating the ulnar interface at low amplitudes produced flexion sensations in the phantom index and middle fingers, whereas stimulating at higher amplitudes yielded flexion sensations in the phantom ring and small fingers. In later sessions, stimulation at low or high amplitudes only provided flexions in the ring and small fingers.

DISCUSSION

This preliminary report demonstrates that regenerative peripheral nerve interfaces can be used to mimic proprioceptive and cutaneous sensations in participants with upper limb amputations. Electrical stimulation resulted in meaningful afferent percepts that were repeatedly experienced in the phantom hand. Our previous human study using ultrasound imaging revealed contractions of the regenerative peripheral nerve interfaces during volitional movements, indicating that efferent motor nerves have successfully reinnervated the muscle graft.[12] In this study, demonstration of proprioceptive sensation suggests that afferent sensory muscle spindle fibers have also reinnervated within the interface. For future studies, established methods of quantifying proprioception[11] will be utilized to explore the functional benefits of regenerative peripheral nerve interface stimulation during physical use of a prosthesis.

For regenerative peripheral nerve interfaces facilitating cutaneous percepts, this may occur through direct afferent depolarization of free sensory nerve endings enclosed within the interface. We hypothesize that regenerative peripheral nerve interfaces provide physical and neurotrophic protection to regenerating cutaneous sensory nerve fibers which subsequently results in mitigation of neuroma formation.[13–16] Most notably, stimulation of participant 2's two ulnar interfaces created from intraneural dissection of the ulnar nerve demonstrated a separation of proprioceptive and cutaneous nerve fibers. This suggests that the ulnar nerve had been divided into its superficial (sensory) and deep (motor) branches, which allows the ability to perceive sensory feedback (afferent) and facilitate prosthetic control (efferent) independently.

These initial results encourage further investigation into the potential for regenerative peripheral nerve interfaces to provide naturalistic sensory feedback to enhance the use of an advanced prosthetic device. Previous studies have shown that a neuroprosthetic interface providing proprioceptive or cutaneous sensory feedback will improve a participant's functional performance with a prosthetic limb.[7,10,11,17] Conceptually, regenerative peripheral nerve interfaces in the residual limb may be interfaced directly with existing force sensors built into a prosthetic device that would provide varying levels of stimulation. An increase in force detected on the fingertips of a prosthetic hand could result in increased electrical stimulation that is transduced by interfaces into the perception of graded sensory feedback. Future studies will focus on combining the capture of efferent motor signals, while simultaneously stimulating regenerative peripheral nerve interfaces within the residual limb. Application of an implantable wireless system that concurrently transmits motor commands while receiving sensory feedback from prosthetic sensors will revolutionize prosthetic functionality and rehabilitation after limb loss.

Theodore A. Kung, M.D.
A. Alfred Taubman Health Care Center
1500 East Medical Center Drive
Ann Arbor, Mich. 48109
thekung@med.umich.edu
Instagram: @theodorekungmd

ACKNOWLEDGMENTS

This work was supported by the Defense Advanced Research Projects Agency's Biological Technologies Office Hand Proprioception and Touch Interfaces program through the agency's Contracts Management Office (grant/contract no. N66001-16-1-4006) and by the National Institute of Neurological Disorders *and Stroke, National Institutes of Health (award no. R01NS105132). P.P.V. was supported by the National Science Foundation Graduate Research Fellowship Program (award no. DGE 1256260).*

DISCLAIMER

The opinions expressed in this article are the authors' own and do not reflect the views of the U.S. Department of Defense, National Institutes of Health, or the National Science Foundation.

REFERENCES

1. Belter JT, Segil JL, Dollar AM, Weir RF. Mechanical design and performance specifications of anthropomorphic prosthetic hands: A review. *J Rehabil Res Dev.* 2013;50:599–618.
2. Childress DS. Historical aspects of powered limb prostheses. *Clinical Prosthetics & Orthotics* 1985;9:2–13.
3. Biddiss E, Chau T. Upper-limb prosthetics: Critical factors in device abandonment. *Am J Phys Med Rehabil.* 2007;86:977–987.
4. Marasco PD, Kim K, Colgate JE, Peshkin MA, Kuiken TA. Robotic touch shifts perception of embodiment to a prosthesis in targeted reinnervation amputees. *Brain* 2011;134:747–758.
5. Augurelle AS, Smith AM, Lejeune T, Thonnard JL. Importance of cutaneous feedback in maintaining a secure grip during manipulation of hand-held objects. *J Neurophysiol.* 2003;89:665–671.
6. Robles-De-La-Torre G. The importance of the sense of touch in virtual and real environments. *IEEE MultiMedia* 2006;13:24–30.
7. Tan DW, Schiefer MA, Keith MW, Anderson JR, Tyler J, Tyler DJ. A neural interface provides long-term stable natural touch perception. *Sci Transl Med.* 2014;6:257ra138.
8. Davis TS, Wark HA, Hutchinson DT, et al. 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.* 2016;13:036001.
9. 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.
10. Raspopovic S, Capogrosso M, Petrini FM, et al. Restoring natural sensory feedback in real-time bidirectional hand prostheses. *Sci Transl Med.* 2014;6:222ra19.
11. D'Anna E, Valle G, Mazzoni A, et al. A closed-loop hand prosthesis with simultaneous intraneural tactile and position feedback. *Sci Robot* 2019;4:eaau8892.
12. Vu PP, Vaskov AK, Irwin ZT, et al. A regenerative peripheral nerve interface allows real-time control of an artificial hand in upper limb amputees. *Sci Transl Med.* 2020;12:eaay2857.
13. Woo SL, Kung TA, Brown DL, Leonard JA, Kelly BM, Cederna PS. Regenerative peripheral nerve interfaces for the treatment of postamputation neuroma pain: A pilot study. *Plast Reconstr Surg Glob Open* 2016;4:e1038.
14. Santosa KB, Oliver JD, Cederna PS, Kung TA. Regenerative peripheral nerve interfaces for prevention and management of neuromas. *Clin Plast Surg.* 2020;47:311–321.
15. Kubiak CA, Kemp SWP, Cederna PS. Regenerative peripheral nerve interface for management of postamputation neuroma. *JAMA Surg.* 2018;153:681–682.
16. Kubiak CA, Kemp SWP, Cederna PS, Kung TA. Prophylactic regenerative peripheral nerve interfaces to prevent postamputation pain. *Plast Reconstr Surg.* 2019;144:421e–430e.
17. George JA, Kluger DT, Davis TS, et al. Biomimetic sensory feedback through peripheral nerve stimulation improves dexterous use of a bionic hand. *Sci Robot* 2019;4:eaax2352.