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TITLE: Using Arrays of Microelectrodes Implanted in Residual Peripheral Nerves to Provide Dextrous Control of, and Modulated Sensory Feedback from, a Hand Prosthesis

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14. ABSTRACT
The proposed research is focused on restoration of hand motor and sensory functions by utilizing a direct electrical interface with residual peripheral nerves. The direct connection with the residual nerves will enable the patient to have intuitive control over and receive touch sensation from a prosthetic hand that are not provided by current forearm prostheses. The improvement in intuitive control and the providing of sensory feedback will allow patients to use highly articulate prosthetic hands with improved long-term functional outcomes for military personnel and civilians with a forearm amputation. Based on preliminary studies in peripheral nerves it is possible to decode finger movements from electrophysiological signals recorded from peripheral nerves, and to evoke somatosensory perceptions through micro-stimulation of peripheral nerves. The proposed research will determine the type and complexity of movements that can be controlled by a direction connection to arm nerves, and will also determine the type and range touch sensations that can be provide through a direct connection to residual nerves.

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1. **INTRODUCTION:** The proposed research is focused on restoration of hand motor and sensory functions by utilizing a direct electrical interface with residual peripheral nerves. The direct connection with the residual nerves will enable the patient to have intuitive control over and receive touch sensation from a prosthetic hand that are not provided by current forearm prostheses. The improvement in intuitive control and the providing of sensory feedback will allow patients to use highly articulate prosthetic hands with improved long-term functional outcomes for military personnel and civilians with a forearm amputation. Based on preliminary studies in peripheral nerves it is possible to decode finger movements from electrophysiological signals recorded from peripheral nerves, and to evoke somatosensory perceptions through micro-stimulation of peripheral nerves. The proposed research will determine the type and complexity of movements that can be controlled by a direction connection to arm nerves, and will also determine the type and range touch sensations that can be provide through a direct connection to residual nerves.

2. **KEYWORDS:** Peripheral Nerve Interface, Prosthetic Hand, Neural Prosthesis, Sensory Feedback, Micro-stimulation, Electrophysiology, Action Potentials, Micro-electrode, poly-Longitudinal Intrafascicular Electrode (poly-LIFE)

3. **ACCOMPLISHMENTS:** Provided in italics in appropriate sections.

   What were the major goals of the project?

   Specific Aim 1: Dexterous control of, and sensory feedback from, an advanced prosthetic hand will be provided using micro-electrode arrays implanted in residual peripheral nerves

   Major Goal 1: Preparation for Studies

   Subtask 1.1: Regulatory Approvals (Months 1 – 4)

   - UU: Dr. Hutchinson, Nousheen Alasti; oversee writing and submission of protocol and associated documents for IRB and HRPO.

     Will no longer be collaborating with University of Utah and will be formally requesting cancelation of University of Utah subcontract.

   - Mayo: Dr. Smith and Mayo Study Coordinator oversee writing and submission of protocol and associated documents for IRB and HRPO.
   - Dr. Greger; assist in writing and submission of IRB and HRPO documents.

     80% complete. Draft of IRB protocol written and will be submitted to Mayo Clinic IRB and HRPO by 30-November-2015.

   Subtask 1.2: Micro-electrode Arrays. (Months 4 – 30)

   - Production of 9 human-ready Sputtered Iridium-Oxide (SIROF) micro-electrode arrays consisting of 100 electrodes.

     25% complete. Design and drawings of micro-electrode arrays complete.

- Measure impedances on all electrodes in each array prior to sterilization, and if possible after explantation at the end of the study.

  50% complete. Instrumentation to obtain impedances on micro-electrode arrays at multiple frequencies currently in place and validated.

- Obtain light microscope images of the arrays prior to implantation and after explantation.

  30% complete. Contract in place to perform light and electron microscopy on the micro-electrode arrays with the Aberration Corrected Electron Microscopy core facility at ASU. Have obtained test images.

Major Task 2: Implantation and explantation of micro-electrode arrays in a residual nerve of patients with trans-humeral, trans-radial, or elbow disarticulation amputations

Subtask 2.1: Patient Recruitment (Months 4 – 30)

- Volunteers will be recruited and informed consent obtained at the Mayo Clinic using the procedure in the approved IRB protocol.
- We expect to recruit 5 patients (~2/year) for participation in the study.

  0% complete. We cannot begin patient recruitment until protocol is approved by Mayo Clinic IRB and HRPO.

Subtask 2.2: Micro-electrode array implantation (Months 4 – 30)

- Implantation of one micro-electrode array in either the median, radial, or ulnar nerve of each patient will be performed.

Milestone #1: Implantation of first patient. (Months 6)

Subtask 2.3: Micro-electrode array explantation (Months 9 – 36)

- Explantation of the micro-electrode array will be performed at the completion of the study (30 – 90 days post-implantation).

  0% complete. We cannot implant or explant first patient until protocol is approved by Mayo Clinic IRB and HRPO.

Major Task 3: Recording of isolated action potentials or multi-action potential activity from residual peripheral nerve while patient intends movements of amputated hand/arm

Subtask 3.1: Mapping of neural activity (Months 4 – 36)

- Patients will be asked to intend a number of individual finger and multiple finger flexion, extension, adduction, and abduction movements of their amputated hand

by mimicking computer controlled movements of the virtual prosthetic hand. Similarly, they will be asked to make pronation-supination forearm movements; and flexion, extension, adduction, and abduction movements of their wrist.

- The spatio-temporal patterns of action potential firing evoked in the efferent fibers of the nerve will be recorded with the micro-electrode array during these intended movements. We will map the different intended movements onto the neural activity recorded on the electrodes of the micro-electrode array.

Milestone #2: chronic electrophysiological recording from first patient (Month 6)

25% complete. The infrastructure for performing the electrophysiological recordings and nerve mappings is in place and validated.

Subtask 3.2: Offline analysis and decoding of movements (Months 6 – 36)

- Analyze the data recorded during sub-task 3.1 to determine if the neural activity can accurately predict the movements being intended.

50% complete. The workstation computer and data server have been setup in the Goldwater Computing Center, and the offline analysis code have been implemented.

Subtask 3.3: Online (real-time) decoding of movements (Months 6 – 36)

- Using data collected during subtask 3.1 we will train an online decode algorithm and then provide the patient real-time control over the virtual prosthetic hand.

Milestone #3: real-time control of multiple degree of freedom virtual prosthetic had in first patient (Month 9)

50% complete. Computers for real-time computer analysis and control of the virtural prosthetic hand have been implemented in the patient cart. Real-time data acquisition, analysis, and control of the virtual prosthetic hand have be validated.

Major Task 4: Evaluation of somatosensory perceptions evoked by electrical micro-stimulation of the implanted nerve via the micro-electrode array

Subtask 4.1: Topographical mapping and subjective description of evoked perceptions (Months 6 – 36)

- We will perform electrical micro-stimulation at various currents on each electrode in the micro-electrode array in order to determine the minimum current needed to consistently evoke a sensory perception.

Subtask 4.2: Spatial two-point discrimination (Months 6 – 36)

- Using super-threshold micro-stimulation levels obtained in subtask 4.1, we will determine if micro-stimulation on pairs of electrodes with differing inter-electrode spacing evoke a single perception or two spatially distinct perceptions.

Subtask 4.3: Modulation of evoked perceptions (Months 6 – 36)

- We will determine if changes in micro-stimulation parameters result in modulation of the evoked sensory perceptions. We will provide modulation of micro-stimulation frequency using input from tactile sensors such as would be used in a prosthetic hand, i.e. micro-stimulation frequency would be modulated by the amount of pressure on a fingertip tactile sensor.

Milestone #4: Completion of studies and longitudinal analysis in all 6 patients. Preparation of manuscript for publication in scientific literature (Month 36)

25% complete. The infrastructure for performing micro-stimulation to perform electrophysiological recordings and nerve mappings is in place and validated.

What was accomplished under these goals?

We have been making progress on activities and objectives related to 1) protocol preparation, 2) improving the micro-electrode neural interface, 3) installing and validating the human patient care for data acquisition and micro-stimulation, and 4) improving the virtual reality prosthetic hand and patient environment and decoding algorithms.

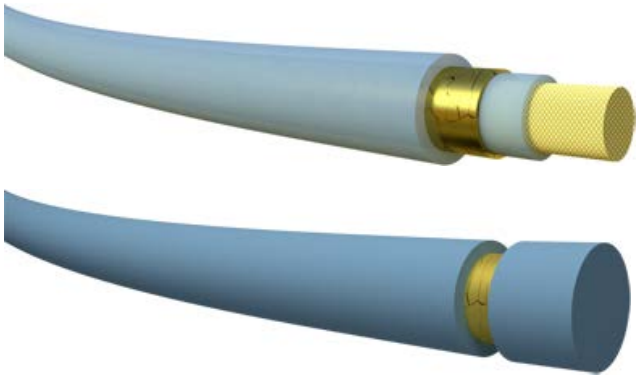

Figure 1 – CAD drawings of the poly-LIFE. Top panel: A schematic representation of a poly-LIFE, consisting of a Kevlar filament core, clad with metal layers (Ti/Au) and insulated with silicone. Bottom panel: finished single electrode with exposed Au electrode site (outer diameter 100 – 200 µM). Multiple poly-LIFE fibers can be formed into an array with individual electrodes implanted into multiple individual nerve fascicles.

Data from an earlier human study reveal challenges with using rigid silicon arrays in an active human patient population. The rigid silicon arrays were capable of making good electrophysiological recordings and performing micro-stimulation, however, they are susceptible to crush damage. We have designed a compliant poly-LIFE micro-electrode array using Kevlar-fiber and cracked-gold materials that are similar to electrode arrays used successfully in previous human and animal studies that is resistant to crush damage (Figure 1). In contrast to the rigid silicon based electrode arrays, the materials used in the poly-LIFE electrode arrays allow them to compliantly move with the peripheral nerves and resist mechanical damage.

This information on the electrode array device design impacted the Mayo Clinic IRB and HRPO applications. Both the original rigid silicon based electrodes arrays and the newer compliant Kevlar and cracked gold based electrode array designs needed to be finalized prior to inclusion in the protocol. With the micro-electrodes array designs finalized and their surgical implantation techniques addressed, I can complete and submit the protocol application to the Mayo Clinic IRB and HRPO. In parallel we will make a formal request to CDMRP to incorporate the poly-LIFE arrays into the study.

Figure 2 - patient cart. Recordings and stimulation systems, and computers for real-time experimental control and decoding of finger position.

We have implemented the human patient cart for performing electrophysiological recordings and micro-stimulation stimulation. The patient cart has been assembled and we have performed the systems integration on the computers and equipment needed for performing the recording and stimulation experiments (Figure 2). The patient cart contains all the hardware needed to perform the proposed real-time virtual reality prosthetic hand control and sensory feedback experiments. The cart has been inspected and approved by the Biomedical Engineering department at the Mayo Clinic for recordings.

We have implemented and improved the virtual reality environment for patient training and real-time control of the virtual prosthetic hand. Patients in an earlier study reported a mismatch between the perceived position of their phantom hand and the visual position of the virtual reality prosthetic hand. This interfered with their ability to control the virtual reality hand and their embodiment of the prosthetic hand. In order to improve patient control during real-time decoding of neural signals and patient embodiment of the prosthetic hand we have improved the virtual reality interface. We have made the virtual reality prosthetic hand environment fully immersive using Occulus Rift goggles. This immersive environment allows the patients to control a virtual reality hand mapped onto their residual arm. During training the control of the virtual prosthetic hand is provided by tracking movement of the patient's intact hand. The movements of the intact hand can be

monitored by an infra-red tracker that is used in a portable system that can be taken home by the patients from practice prior to array implantation. By using tracking of the patients' intact hand prior to implantation of the electrode array we will be able to establish an accurate mapping of the visual input of the position of the prosthetic hand onto the felt position of the patient's phantom hand. Additionally, practice with the virtual prosthetic hand immersive virtual reality environmental will enable patients to "re-activate" their phantom limb prior to array implantation and therefor increase the likelihood or recording neural activity correlated with hand control. After the micro-electrode arrays have been implanted and during real-time decoding experiments, hand position will be monitored using a high-speed and high-resolution motion capture system, which will allow precise mapping of the neural signals onto finger and hand position (Figure 3).

We have improved on past decoding efforts using machine learning algorithms based on multivariate time and frequency domain features. Patients and rehabilitation specialists have informed us that very high performing decoding algorithms are critical as even a few percent error translates into an unacceptable failure rate in object manipulation, e.g. dropping a utensil 5% of the time. The machine learning algorithms are being implemented on the patient cart for use in the real-time control of the virtual prosthetic hand experiments.

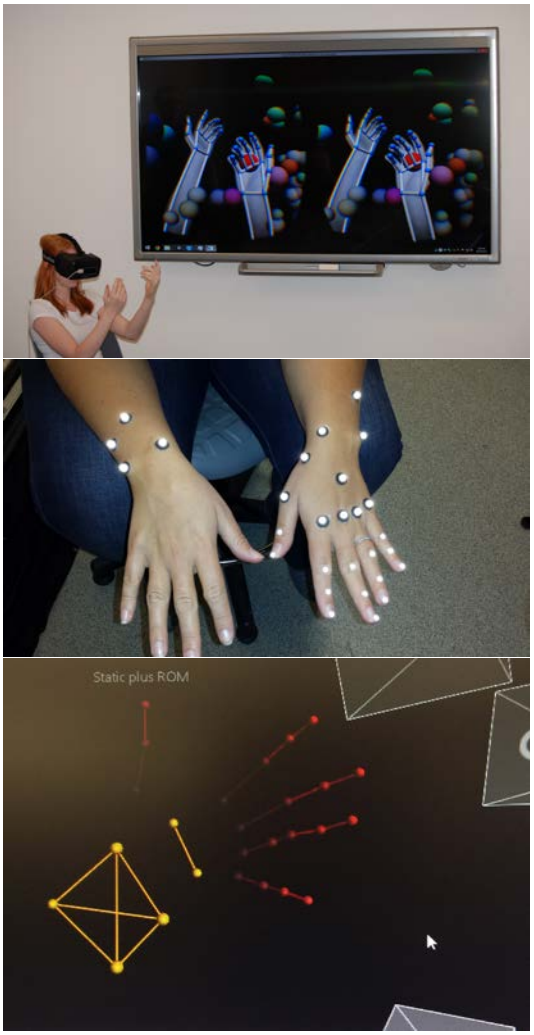

Figure 3 – Top panel) A student is shown wearing the Occulus Rift goggles and infrared hand tracking system. The screen shows the position of the students hand's captured by tracking systems and displayed to her by the googles. Patients will be able to take this system home in order to practice the tasks and improve the "re-activation" of their phantom limb. Middle panel) Reflective markers are placed on the hand to allow precis tracking of hand movements. Bottom pannel) The position of the wrist and finger joints as captured by the high-reolution motion capture system. system.

The Goals that have been delayed are predicated on electrode array design and fabrication. Due to the device failures with the rigid silicon based electrodes used in previous studies we have been very carefully considering the path forward in consultation with device fabrication and our clinical partners. Although the rigid silicon arrays appear to have a very challenging design issued due to their rigidity and brittleness, they may be appropriate for use in acute studies in a few patients in order to establish important prosthetic control and sensory feedback design parameters. The use of compliant micro-electrode arrays will likely address this issue and provide path forward to long-term patient peripheral nerve interfaces.

What opportunities for training and professional development has the project provided?

Nothing to Report

How were the results disseminated to communities of interest?

The development of the improved virtual reality environment for patient training and improved decoding algorithms have been disseminated through presentations at scientific meetings, invited seminars, and television news programs.

What do you plan to do during the next reporting period to accomplish the goals?

Early in the next reporting period we will obtain Mayo Clinic IRB and HRPO approvals and implant the first patient. If the poly-LIFE arrays cannot be fabricated by the time the protocol is approved the first patient(s) will be implanted with the rigid silicon based electrode arrays. As the compliant ploy-LIFE arrays are available we will switch implanting them. All of the infrastructure for performing the proposed work is in place, so once protocol approval is obtained all of the goals and milestones should occurred at the projected intervals.

4. **IMPACT:**

What was the impact on the development of the principal discipline(s) of the project?

The development of the immersive virtual reality environment will enable new techniques and measurements of patient rehabilitation. We will be able to have patient practice with their virtual reality prosthetic hand prior electrode implantation. This will likely increase and improve the quality of the neural signals present in the residual nerve and thus improve the control over the prosthetic hand once the electrode array is implanted.

By using machine learning algorithms that utilize both time and frequency domain features we have improved the performance prosthetic control. To date control of advanced prosthetic hands have utilized linear decoding algorithms that do not incorporate the knowledge the most neural signals encode information in a nonlinear manner. These improved algorithms will likely increase patient acceptance of advance prosthetic hands, as

even a few percent improvement in control translates into fewer unwanted movements, e.g. dropping a help object.

What was the impact on other disciplines?

The development and use of compliant poly-LIFE arrays may enable multiple applications that necessitate long-term peripheral nerve interfaces: bowel/bladder control in paralyzed patients, regulated hypertension, and treatment of epilepsy. The machine learning algorithms we have developed for decoding neural signal in residual peripheral nerves can also be applied to neural signals recorded from the central nervous system for application to provide control for severely paralyzed patients.

What was the impact on technology transfer?

An invention disclosure on the use and surgical placement of the compliant electrode arrays was filed with Arizona Technology Enterprises (AzTE).

What was the impact on society beyond science and technology?

Nothing to Report

5. **CHANGES/PROBLEMS:**

Changes in approach and reasons for change

Since the inception of the current project I have learned of failure modes of the rigid silicon electrode arrays originally planned on using for the project and encountered difficulties with my surgical collaborator. Most of these issues only came to light as the CDMRP funded current project was starting up.

Surgical and electrode array Issues: Dr. Hutchinson the surgeon I had originally planned on collaborating with for this project, was also the surgeon on a DARPA funded project of which I was involved. As part of the DARPA funded work he implanted an array in NHP. This surgery resulted in the nerve in NHP being destroyed and the animal having to be sacrificed. During the DARPA funded project he also harvested tissue from a patient without first obtaining consent. Given the surgical failures and what I perceive as questionable ethical behavior, I cannot in good conscience collaborate further with Dr. Hutchinson and will be collaborating only at the Mayo Clinic in Scottsdale. We will be formally requesting a cancelation of the University of Utah subcontract. In a previous DARPA funded project four patients were implanted at the Univ. of Utah with the electrode arrays I was originally planning on using for the current project. I would categorize two of these patient implantations as failures. One electrode array failed after a week of implantation due to the array/wire being crushed/broken by the patient likely during performance of their job. The second array failure occurred a few day after implantation likely due to reference and/or ground wire breakage and/or improper surgical placement of reference/ground leads. Given the high failure rate observed, we are planning on switching to a more compliant electrode array technology that has a better chance of serving as platform for the long-term control of a prosthetic hand. We

will be making a formal request to include the compliant electrode array in the proposed work.

Actual or anticipated problems or delays and actions or plans to resolve them

Actual delays:

Electrode array failures.

Resolution - Transition from rigid silicon arrays to compliant Kevlar-fiber and cracked-gold poly-LIFE arrays.

Surgical issues and challenges.

Resolution: Perform all patient work at the Mayo Clinic.

Failure in communicating well with CDMRP:

Resolution: This has primarily be due to a significant health issue with my wife (I can provide details and documentation if required). She has been undergoing treatment for the past few months and is improving significantly. I am confident that, barring and major setbacks, I'll be able to be responsive in a timely manner in the future.

Anticipated delays: None

Changes that had a significant impact on expenditures

No to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

None to report.

Significant changes in use or care of human subjects

None to report.

Significant changes in use or care of vertebrate animals.

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

Publications, conference papers, and presentations

Greger B, Decoding finger movements from peripheral nerve signals. 2015 4th ASU Rehabilitation Robotics Workshop

Greger B, Evoking sensory percepts using electrical micro-stimulation of the nervous system. 2015 invited seminar SUNY Upstate Medical University

Greger B, Evoking sensory percepts using electrical micro-stimulation of the nervous system. 2015 invited seminar Rice University

Barton C, Padmanaban S, Kellis S, House P, GREGER B, Extracting high-frequency features of neural activity from µECoG surface electrodes. 2015 Society for Neuroscience Abstract 522.17

Oswalt D, Kellis S, House P, Greger B, Multiclass support vector machine decoding of spoken words from micro-electrocorticography recordings over Wernicke's area and face motor cortex. 2015 Society for Neuroscience Abstract 522.18

Inventions, patent applications, and/or licenses

Invention disclosure: TUFT peripheral nerve interface: a compliant micro-electrode array for recording electrophysiological signals and micro-stimulating neural tissue. 5/30/2014

Other Products

None to report.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

What individuals have worked on the project?

Name:	*Bradley Greger*
Project Role:	*PI*
ORCID ID):	*0000-0002-6702-7596*
Nearest person month worked:	*2*
Contribution to Project:	*Dr. Greger has been overseeing as aspects of the project*
Funding Support:	*ASU startup, DARPA, CDMRP*
Name:	*Kevin O'Neil III*
Project Role:	*Graduate Student*
Researcher Identifier	
Nearest person month worked:	*6*
Contribution to Project:	*Kevin O'Neil III has been developing the VR prosthetic hand and immersive environment, and programing the patient cart*

Funding Support:	*ASU Dean's Fellowship, CDMRP*
Name:	*Subash Padmanaban*
Project Role:	*Graduate Student*
Researcher Identifier	
Nearest person month worked:	*2*
Contribution to Project:	*Subash Padmanaban has been developing machine learning algorithms*
Funding Support:	*CDMRP*
Name:	*Cody Barton*
Project Role:	*Graduate Student*
Researcher Identifier	
Nearest person month worked:	*1*
Contribution to Project:	*Cody Barton has been investigating the use of high-frequency power as an adjunct to action potential recordings for controlling prosthetic hands*
Funding Support:	*DARPA*
Name:	*Denise Oswalt*
Project Role:	*Graduate Student*
Researcher Identifier	
Nearest person month worked:	*1*
Contribution to Project:	*Denise Oswalt had been developing and testing nonlinear support vector machines for decoding neural signals*

Funding Support:	*ASU Dean's Fellowship*
Name:	*Kari Ashmont*
Project Role:	*Graduate Student*
Researcher Identifier	
Nearest person month worked:	*1*
Contribution to Project:	*Kari Ashmont had been building the patient cart and getting it approved for use at the Mayo Clinic Hospital*
Funding Support:	*ASU/Mayo Clinic seed grant*
Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award).*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

Nothing to Report.

8. **SPECIAL REPORTING REQUIREMENTS**

Not applicable.

9. **APPENDICES:**

Davis T, Wark HAC, Hutchinson DT, Warren DJ, O'Neill III K, Scheinblum T, Clark GA, Normann RA, Greger B, Restoring motor control and sensory feedback in people with upper extremity

amputations using arrays of 96 microelectrodes implanted in the median and ulnar nerves. Paper accepted with minor revision at Journal of Neural engineering.

Paper provides information on earlier study and support for proposed changes to current work.

Restoring motor control and sensory feedback in people with upper extremity amputations using arrays of 96 microelectrodes implanted in the median and ulnar nerves

T S Davis[1,2]*, H A C Wark[1]*, D T Hutchinson[3], D J Warren[1], K O'Neill III[1], T Scheinblum[1], G A Clark[1], R A Normann[1], and B Greger[1,4]

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Abstract

Objective: An important goal of neuroprosthetic research is to establish bidirectional communication between the user and new prosthetic limbs that are capable of controlling > 20 different movements. One strategy for achieving this goal is to interface the prosthetic limb directly with efferent and afferent fibres in the peripheral nervous system using an array of intrafascicular microelectrodes. This approach would provide access to a large number of independent neural pathways for controlling high degree-of-freedom prosthetic limbs, as well as evoking multiple-complex sensory percepts.

Approach: Utah Slanted Electrode Arrays (USEAs, 96 recording/stimulating electrodes) were implanted for 30 days into the median (subject 1-M, 31 years post-amputation) or ulnar (subject 2-U, 1.5 years post-amputation) nerves of two amputees. Neural activity was recorded during intended movements of the subject's phantom fingers and a linear Kalman filter was used to decode the neural data. Microelectrode stimulation of varying amplitudes and frequencies was delivered via single or multiple electrodes to investigate the number, size and quality of sensory percepts that could be evoked. Device performance over time was assessed by measuring: electrode impedances, signal-to-noise ratios, stimulation thresholds, number and stability of evoked percepts.

Main results: The subjects were able to proportionally, control individual fingers of a virtual robotic hand, with 13 different movements decoded offline (r=0.48) and two movements decoded online. Electrical stimulation across one USEA evoked >80 sensory percepts. Varying the stimulation parameters modulated percept quality. Devices remained intrafascicularly implanted for the duration of the study with no significant changes in the signal-to-noise ratios or percept thresholds.

Significance: This study demonstrated that an array of 96 microelectrodes can be implanted into the human peripheral nervous system for up to 1 month durations. Such an array could provide intuitive control of a virtual prosthetic hand with broad sensory feedback.

1. Introduction

The volitional control of movement involves a complex and integrated hierarchy of sensory-motor neural systems. Arrays of microelectrodes implanted at various levels in this hierarchy have been used to record spatiotemporal patterns of neural activity and for correlation of these patterns with sensory stimulation and motor behaviours. Early efforts to obtain volitional control signals from the nervous system were conducted in non-human primates by decoding neural activity patterns recorded with microelectrodes implanted in the motor cortex [1, 2, 3, 4, 5, 6]. Researchers have begun translating these efforts to human subjects, and

electrode arrays implanted into the motor cortex of people with paralysis have provided the unidirectional communication needed for the volitional control of external devices such as the two-dimensional movements of computer cursors [7, 8, 9] and the robotic manipulation of objects in three-dimensional space [10]. Although the central nervous system is an effective implantation site for people with paralysis, less invasive approaches are warranted for people with amputations, such as peripheral nerve targeted reinnervation [11, 12] or peripheral nerve electrode implantation [13, 14, 15, 16, 17, 18, 19, 20, 21, 22].

The current state-of-the-art for people with upper-limb amputations are mechanically or myoelectrically controlled prosthetic arms with few degrees-of-freedom (DOF) that do not provide sensory feedback [23]. Next generation prosthetic arms are being developed with upwards of 26 DOF [24, 25] and with embedded sensors intended to be used to provide sensory feedback to the user [14, 21, 26]. Several strategies are being investigated for providing sensory feedback from these new prosthetic limbs including surface vibrators [26], and extraneural [18, 19, 22, 27] or intraneural [21, 28, 29, 30, 31] electrodes. The number of extra/intraneural electrodes (or 'contacts') implanted into each human peripheral nerve has been increasing, with previous studies having used: one [14, 17], six [32], eight [22, 33], sixteen [21], or twenty [30] electrodes to established bidirectional communication with a subject's peripheral nervous system.

Modern, high-DOF bidirectional prosthetic arms and hands may require numerous microelectrodes to obtain sufficiently independent control and feedback signals. Motor intent has been decoded online and offline [14, 20, 21, 32] with control of up to three different movements from offline decodes [14, 20, 21], and sensory feedback has been provided via electrical stimulation [14, 15, 17, 21, 22, 26, 33, 34] with the evocation of a maximum of nine different percepts for a single neural implant [21].

We report herein an approach for the control of prosthetic limbs using an array of 96 microelectrodes, the Utah Slanted Electrode Array (USEA) [29], which increases the number of electrodes that have been used to interface with a peripheral nerve by 80 more electrodes per nerve over previously investigated neural interfaces [21, 22]. This work was conducted in two subjects who had previously undergone transradial amputations. Each subject had a microelectrode array implanted in one of their transected peripheral nerves in order to selectively access individual or small groups of motor and/or sensory fibres. Selective spatiotemporal neural activity patterns were recorded when subjects were asked to make volitional movements of their phantom fingers. Closed-loop neural control of multiple cursors or virtual robotic fingers was achieved in each subject with two DOF control achieved online for both subjects.

To our knowledge, this is the first peer-reviewed publication that investigates both stimulation and recording of human peripheral nerves with high-count (96 electrodes) intraneural electrodes. The work presented in this manuscript increases the number of movements that were decoded from human peripheral nerve from 3 different grasp movements, equivalent of 1 DOF [20, 21] to 13 different movements, equivalent to 8 DOF. The maximum number of sensory percepts evoked by a single peripheral neural interface was previously eight [22] and in this study we increase that number to a maximum of 86 percepts (number of percepts in a single stimulation session) with an average of 81 percepts over the study duration. This work demonstrates that an array of microelectrodes implanted into residual nerves of patients with a forearm amputation allows for selective access of both sensory and motor nerve fibres. These results further suggest that intuitive and dexterous control of prosthetic fingers with sensory feedback can be provided for future bidirectional prosthetic limbs using an array of intrafascicularly implanted microelectrodes.

2. Methods

This study was approved by the University of Utah Institutional Review Board, the Salt Lake City Veterans Affairs Hospital Research and Development Service Center and the U.S. Federal Defense Advanced Research Projects Agency.

2.1. Pre-study enrolment period

Two volunteers with previous transradial amputations participated in this study and underwent implantation for a one month period with a USEA into their median nerve (Subject 1-M, Median nerve implant, 31 years post-amputation) or ulnar nerve (Subject 2-U, Ulnar nerve implant, 1.5 years post-amputation). Potential volunteers were evaluated for the extent by which they perceived that they were able to make specific movements with their phantom fingers. The duration, frequency, and intensity of phantom limb sensations, including pain, were documented in the patient's journal throughout the study. Multiple phantom movements mediated by median and ulnar nerve activity were evaluated in each volunteer, and the extent of their ability to move their fingers was noted from their descriptions (e.g. Subject 1-M had 'a very fluid hand' but Subject 2-U's phantom fingers were often 'clenched tight'). After selection for inclusion in the study, volunteers were then given a mirror box and specific exercises to perform in order to strengthen their perceived ability to move the digits on their phantom hands. Volunteers were asked to document any changes in the perceived control of their phantom hand, and if any decreased control or unpleasant sensation was experienced, the volunteers would have been asked to discontinue use of the mirror box (none of the volunteers experienced such changes). Prior to enrolment, volunteers underwent a psychosocial evaluation in order to determine if any underlying psychological conditions were present which would have excluded them from the study.

2.2. Nerve electrode arrays

The USEA (Blackrock Microsystems, Salt Lake City, UT, USA) has been described elsewhere [29] and will only be briefly described herein. The array consists of 100 electrodes (96 recording/stimulating electrodes, 4 electrodes wired as unused backup reference electrode) with lengths ranging from 0.5 to 1.5 mm (10 by 10 grid with 400 μm spacing) that project out from a 4 x 4 x 0.3 mm^3 substrate. Lead wire lengths from the connector (custom-built item compatible with the ZIF Clip 96, Tucker Davis Technologies, Inc., Alachua, FL, USA) to the array were configured for implantation into the upper limb nerves at a transradial location. Lead wires included: 1) 100 lead wires (~9 cm long) with 96 of the wires bonded to electrodes used for recording and 4 bonded to backup reference electrodes, 2) two low-impedance platinum reference wires (~8.5 cm long) connected to the reference channel, and 3) two low-impedance platinum ground wires (~7.5 cm long) connected to the recording amplifier ground and stimulation return. Approximately 10 mm of the distal ends of the reference and ground wires were twisted and looped back, with distal ends secured onto the proximal reference or ground wires by coating with silicone (MED-4211, NuSil Technology LLC, Carpinteria, CA, USA). Thus, each loop consisted of two wires (two reference or two ground wires), and the distal ends of these loops were de-insulated to reduce their impedance. The lengths of the reference and ground wires were measured from the base of the connector to the end of the distal loop. The reference and ground wires were placed inside the nerve wrap (see section 2.3 surgical procedures) near the electrode array.

A Neuroport data acquisition system (Blackrock Microsystems, Salt Lake City, UT, USA) was used to measure the electrode impedances. A sinusoidal current at 1 kHz was passed through a reference electrode,

and impedance was simultaneously computed on all electrodes. Before implantation, the electrodes on each device had an average (mean ± std) impedance of 75 ± 57 kΩ (Subject 1-M) and 90 ± 28 kΩ (Subject 2-U). Working electrodes were defined as electrodes with an impedance < 500 kΩ.

2.3. Surgical procedures

The distal nerve end was exposed and the implant site was selected such that it was distal to any branching points and proximal to the transitional zone adjacent to the neuroma (approximately 5-10 mm from the neuroma). The USEA was then passed transcutaneously via a trocar (7-8 mm diameter) down to the exposed implantation site. A metal platform was placed underneath the nerve, along with a high visibility background and a reconstituted organic nerve wrap (AxoGuard Nerve Wrap, AxoGen Inc., Alachua, FL, USA). The lead wires were then sutured (8-0 nylon) to the epineurium (~5 mm from the base of the electrode array). The USEAs were inserted with a pneumatic insertion device [31] that was hand-held by the surgeon. The implanted USEA, reference wires, ground wires, and nerve were contained within the organic nerve wrap, which was closed snuggly around the implant site with titanium vascular clips (Supplementary Figure 1). The organic nerve wrap was sutured (8-0 nylon) to the epineurium proximal and distal to the array site to prevent movement of the wrap along the nerve.

The percutaneous site was dressed with a 1" diameter, clorohexadine antibacterial patch (Biopatch, Ethicon Inc., Johnson & Johnson, New Brunswick, NJ, USA). In Subject 2-U, the connector was sutured down to the skin to prevent stress on the lead wires due to movement of the connector. The entire percutaneous site was layered with gauze and covered with a breathable and waterproof transparent dressing (Tegaderm, 3M Healthcare, St. Paul MN, USA). The gauze and film dressing was changed during each experimental session and antibacterial patches were replaced every 7-10 days. To decrease the inflammatory process and potentially assist in enhanced signal quality over time, subjects were given dexamethasone (0.1 mg/kg IV, Mylan Institutional LLC, Rockford, IL) intraoperatively after removal of the tourniquet and minocycline (100 mg BID, Watson Pharmaceuticals, Parsippany, NJ) 2 days prior and for 5 days after surgery [35, 36].

At the end of the one month experimental period, each subject underwent explantation of the USEAs under general anaesthesia. The percutaneous wires were cut at the level of the skin and the entire limb was then prepared for surgery. The implant side was exposed and the lead, reference, and ground wires were cut adjacent to the organic nerve wrap containment system and all wires were removed. The entire implant site and neuroma was excised. The new nerve end was then sutured deep in the surrounding musculature according to standard surgical procedures for neuroma excisions.

2.4. Experimental sessions

Two hour experimental sessions were performed on an average of three times per week. The time was limited by subject availability or their willingness to continue testing (Subject 1-M underwent 12 total experimental sessions: 6 electrophysiological recording sessions and 8 microstimulation sessions; Subject 2-U underwent a total of 14 experimental sessions: 13 electrophysiological recording sessions and 8 microstimulation sessions). All experimental sessions were recorded with a video camera, which was time-stamped to the neural recording or stimulation data.

2.5. Neural recordings, decoding and instrumentation

Neural signals were amplified and recorded using active head-stage cables (ZIF-Clip 96, Tucker Davis Technologies, Inc., Alachua, FL, USA) that connected to a custom-built interconnect board used to interface

the ZIF-Clip cable with the Neuroport data acquisition system. The continuous neural signals were band-pass filtered with cutoff frequencies of 0.3 Hz (1st-order high-pass Butterworth filter) and 7500 Hz (3rd-order low-pass Butterworth filter) and sampled at 30 kHz. Online multi-unit activity was extracted from high-pass filtered recording data (250 Hz 4th-order Butterworth filter) by setting a threshold using the auto threshold setting in the Neuroport data acquisition software (multiplier = 3, threshold = multiplier × noise estimate of the signal). For each of the 96 neural recording channels, multi-unit neural firing rates were calculated using unsorted spikes and a moving box-car average of 300 ms with an update period of 33 ms. Offline, action potentials were isolated from the high-pass filtered data using commercially available software (Offline Sorter version 3, Plexon Inc., Dallas, Texas, USA). Signal-to-noise ratios (SNR) were calculated by dividing the mean peak-to-peak action potential amplitude by two times the standard deviation of the recorded noise [37].

2.5.1. Decoding neural signals and control of virtual robotic fingers or computer indicators. A standard Kalman filter was implemented to perform the continuous neural decodes [38]. This algorithm assumes a linear relationship between the kinematics (finger position) and the neural data. For this study, it was used to provide continuous estimates of finger position based on the firing rates of multiple neurons. Sessions began by cueing the subjects to perform multiple flexions, extensions or abductions of their individual phantom fingers. A total of 4 movements were performed for Subject 1-M (Thumb-Flex, Index-Flex, Middle-Flex, and Ring-Flex) and 13 movements for Subject 2-U (Thumb-Flex, Thumb-Extend, Index-Flex, Index-Extend, Index-Abduct, Middle-Flex, Middle-Extend, Ring-Flex, Ring-Extend, Ring-Abduct, Little-Flex, Little-Extend, Little-Abduct). These movements are given acronyms based on the first one or two letters of each word, which are used in subsequent figures (e.g., Thumb-Flex = TF). The subjects were instructed to make finger movements by either a computer controlled display of indicators (Subject 1-M) or by movement of virtual robotic fingers [39] (Subject 2-U) (Supplementary Figure 1). Subject 1-M held a small manipulandum consisting of individual, movable pads that could be depressed by each finger with the subject's intact hand. The subject was asked to mirror the movements made with the subject's phantom fingers by pressing on the manipulandum pads with the subject's intact fingers. The instructed finger position (instruction variable) for Subject 1-M was measured as the continuous voltage signal from pressure sensors on the pads of the manipulandum. Subject 2-U was instructed to duplicate the movements of the virtual prosthetic hand using the subject's phantom hand. The instructed finger position (instruction variable) for Subject 2-U was taken as the software-generated position of the virtual prosthetic finger. The positions of the virtual prosthetic fingers were generated using a cosine function, which was normalized from -1 (full extension/adduction) to +1 (full flexion/abduction). Multi-unit firing rates from selected electrodes and the movement instruction variables were then used to train and test the decode algorithm for both online and offline control. During online neural control the subjects made finger movements to computer generated targets while simultaneously controlling multiple fingers with continuous modulation of finger position, i.e. proportional control. A trial would start when the subject placed all prosthetic fingers under neural control at a hand-at-rest position indicated by the computer generated targets. After a few hundred milliseconds, the computer generated targets would shift positions and the subjects were required to match finger positions of all prosthetic fingers under neural control to the positions of all the computer generated targets for at least 300 ms and up to 3000 ms. The targets would then return to the hand-at-rest position and the subject would have to match the fingers to the targets in order to begin a new trial. For example a finger would be required to move from the hand-at-rest position to a target by flexing or extending the finger, while simultaneously the other fingers would be required to maintain the hand-at-rest position. The finger required to move the target and the position of the target would be changed for different

trials. This produced individuated proportional finger movements during simultaneous neural control of multiple fingers (See Supplemental Video 2).

2.5.2. Online neural decodes. For online decoding, electrodes were selected based on their ability to record movement-correlated action potentials. This selection process was made using two methods: 1) the experimenters viewed a map of correlation coefficients between the instruction variables and the firing rates on each electrode and 2) the experimenters' subjective observations of the high-pass filtered neural data on each electrode during the cued movements. Following electrode selection, the decode algorithm was trained on a set of 10 trials for each movement type. For testing, subjects were asked to control a computer display of indicators (Subject 1-M) or virtual prosthetic fingers (Subject 2-U) and acquire targets in a trial-based format. Subjects began a trial by moving the fingers of their phantom hand to a neutral, at-rest position, which moved the indicators or virtual prosthetic fingers to a start position. Once all fingers were at the start position for a specified hold period, subjects would be shown the target(s) to which they were to move their finger(s). Targets were presented of varying diameters (30% to 36% of full-range movement) and distances (40% to 100% of full-range movement) from the starting point. In order to correctly complete a trial, the subjects had to acquire and hold the target(s) while maintaining the fingers that were not being instructed to move at their start positions. Start and target hold periods varied from 300 to 5000 ms. This task paradigm assessed the ability of subjects to move the virtual fingers/cursors independently. Targets were placed at various distances to assess the ability of the subjects to proportionally control the indicators or virtual fingers.

2.5.3. Offline neural decodes. For offline decoding, an average of 22 (range of 13 to 37) trials of each movement type recorded during a typical experimental session were analysed. Electrodes were chosen on the basis of the results of a Wilcoxon signed-rank test. First, a 'baseline-period' was defined as the 2 s period prior to the onset of the movement cue, and a 'movement-period' was defined as the 2 s period after the onset of the cue. Then, the difference in median firing rates was calculated between the 'movement-period' and the 'baseline-period' for all movement types and trials recorded on each electrode. The null hypothesis was that the data came from a continuous, symmetric distribution with a median difference equal to zero (i.e., the electrode did not record increased firing rates in the movement-period compared with the baseline-period). All electrodes for which the null hypothesis was rejected ($p < 0.001$) with a positive median difference from baseline were kept. These electrodes were then sorted in order of increasing median difference and the top 90% of electrodes were used in the offline decode. After electrode selection, the decode algorithm was trained on the first 10 trials for each movement and tested on the remaining 3 to 27 trials. A Pearson's correlation coefficient (r) between the instruction variable and the Kalman filter estimate of finger positions, calculated for the entire continuous sampling of data corresponding with the trained movements for the remaining 3-27 testing trials, was used to quantify the decode performance.

2.6. Neural stimulation and instrumentation

Current-controlled, biphasic, cathodic-first (without anodic bias) stimulation [40] (IZ2, 128-channel Tucker-Davis Technologies Stimulator, Inc., Alachua, FL, USA) was delivered to individual or subsets of electrodes using custom LabVIEW software (National Instruments Corp., Austin, TX, USA), using the platinum ground wires as a return. The stimulator had a compliance voltage of ± 15V (LZ48-400, Tucker-Davis Technologies Stimulator, Inc., Alachua, FL, USA). Maximum stimulation was limited by either: 1) the comfort level of the subject, 2) a perceived change in the quality of the percept or 3) if the maximum safety limit for delivering electricity to tissue was reached [41]. The safety limit for injecting charge into

the tissue was determined by measuring the maximum cathodic voltage excursion (with a safety limit of -0.6 V) across the electrode and ground during stimulation [42, 43, 44]. The voltage drop due to tissue impedance was not subtracted in our calculations, resulting in a conservative estimate of safe stimulation parameters. Stimulation parameters varied depending on the objective of the experimental session. Pulse amplitude, frequency, and train duration ranged from 1-100 μA, 1-320 Hz, and 0.2-60 s, respectively. Pulse width and inter-phase interval were held fixed at 200 μs and 100 μs.

2.6.1. Stimulation across different amplitudes and frequencies (Subject 1-M). In Subject 1-M, stimulation experiments were focused on a subset of electrodes to investigate the subject's ability to detect and discriminate single and multiple sensory percepts and the effects of modulating stimulation frequency on sensory percepts. A custom-built software interface (LabVIEW software, National Instruments Corp., Austin, TX, USA) was used to allow Subject 1-M to control the amplitude of stimulation (1-100 μA in steps of 1 μA) at a constant frequency (200 Hz) and train duration (0.2 s) in order to determine the threshold of a sensory percept (sessions 1-8, post-implantation days 5-26). Control of frequency (1-320 Hz in 1 Hz steps, threshold amplitudes, 0-60 s durations) was provided to the subject by pressing down on a pressure sensor mounted on the manipulandum with a finger from the subject's intact hand (sessions 4-8, post-implantation days 14-26).

2.6.2. Simultaneous multielectrode stimulation (Subject 1-M). Stimulation was delivered via multiple electrodes simultaneously to investigate if the subject could discern multiple electrically evoked percepts simultaneously. Stimulation sessions were performed where the subject was cued that a trial began, but did not know whether stimulation was delivered via either of two electrodes, both electrodes simultaneously, or no-stimulation was delivered. Such blinded-trial data was collected during three different experimental sessions on post-implantation days 13, 19, and 26. Electrodes with different inter-electrode distances were chosen, and supra-threshold stimulation amplitudes were used (day 13 - electrodes 16 and 19, 1200 μm distance, 19 μA and 25 μA thresholds; day 19 - electrodes 19 and 20, 400 μm distance, 47 μA and 18 μA thresholds; day 26 - electrodes 20 and 46, 1442 μm distance, 18 μA and 10 μA thresholds). For each trial, the subject had to record the size, location and intensity of the evoked percept on anterior and/or posterior maps of a hand. If no percept was evoked, the subject reported no sensation.

2.6.3. Stimulation thresholds for all 96 electrodes over 30 days (Subject 2-U). All 96 USEA microelectrodes were individually stimulated (six sessions at 200 Hz on post-implantation days 6-25; two sessions at 20 Hz post-implantation days 26-27) and the threshold, location, size, quality and intensity of each evoked percept was mapped using custom built software (LabVIEW software, National Instruments Corp., Austin, TX, USA). Subject 2-U controlled when stimulation was delivered, but the experimenter controlled the amplitude (1-100 μA in steps of 1-5 μA) and pulse train duration (0.2 or 2 s). The quality of the percept was designated from a list (tingle, pressure, vibration, hot, cold) or could be defined using their own words. When a percept was faint or the subject was unsure of the sensation, stimulation could be repeated until they were sure the percept was electrically evoked (as opposed to a phantom limb sensation).

2.6.4. Stability of percept location over 30 days (Subject 2-U). All of the electrodes that evoked a percept during each stimulation session when each electrode in the entire array was stimulated at 200 Hz were analysed (post-implantation days 10-25; Subject 2-U). A percept was considered stable if it remained in a localized anatomical region of the phantom hand, defined as one of the following: anterior or posterior of a particular finger, the palm, or the back of the hand. If a portion of an evoked percept was located on the

border separating two anatomical locations (e.g., over the metacarpophalangeal joint), the percept was considered within the location where the majority of the sensation occurred; however, if the size of the percept spread beyond the border then the percept was not considered stable. The first stimulation session (post-implantation day 6; Subject 2-U) resulted in an incomplete mapping of the array where maximum stimulation was not delivered to all 96 electrodes. The last two sessions (post-implantation days 26 and 27; Subject 2-U) were mapped using a different frequency (20 Hz). These three stimulation sessions were not included in the spatial stability analysis.

3. Results

The results presented herein demonstrate that, using a 100 microelectrode array implanted into human peripheral nerves, up to 13 different movements, equivalent to 8 DOF, could be decoded and a maximum of 86 percepts could be evoked.

3.1. Electrode impedances

For Subject 1-M, the mean *in vivo* impedance for working electrodes over the 29-day implant was 222 ± 133 kΩ (mean ± std, n = 7 sessions; Figure 1(a)). Due to mechanical failure of the lead wires, the number of working electrodes dropped from 93 to 20 by the end of week 2, and then to 4 by the end of week 4. In Subject 2-U, the percutaneous connector was sutured to the skin to minimize strain applied to the wires, and no systematic failures indicating wire breakages occurred. The mean impedances for the working electrodes over the 31-day implant for this subject was 143 ± 76 kΩ (mean ± std, n=13 sessions; Figure 1(b)), and the number of working electrodes was 87 ± 5 (mean ± std). Impedances were found to vary significantly over the course of the study ($p < 0.0001$, Kruskal-Wallis test, Subject 2-U), with an increase from post-implantation days 3 to 10.

3.2. Recording and decoding of motor intent with high-count electrode arrays

Neural recordings were made while the subjects were asked to make volitional flexion, extension or abduction movements of their phantom fingers throughout the study period. Examples of action potentials recorded from the same electrodes over time are shown in Figure 1(c-d) for each subject. In Subject 1-M, an average of 7 ± 9 electrodes recorded action potentials for the 6 recording sessions with a maximum of 20 electrodes recording action potentials on post-implantation day 3 (Figure 1(e)). In Subject 2-U, an average of 22 ± 7 electrodes recorded action potentials for the 13 recording sessions with a maximum of 40 electrodes recording action potentials on post-implantation day 7 (Figure 1(f)). The mean SNR of the action potentials recorded during all sessions for each subject were 5.2 ± 2.3 for Subject 1-M and 5.1 ± 2.8 for Subject 2-U (Figure 1(e-f)). For Subject 2-U, after post-implantation day 10, there was no significant change in the SNR of the action potentials for the remainder of the study ($p = 0.24$, Kruskal-Wallis test).

3.2.1. Recording neural activity during different intended phantom finger movements. Subjects were cued to make different finger movements either by a computer cursor or by movement of virtual robotic fingers. The intent to flex or extend individual phantom digits produced spatiotemporal neural firing patterns that were visible in the high-pass filtered recording data (Figure 2(a-b)). The patterns of neural activity varied across electrodes and movement types. Some electrodes recorded action potentials that were correlated with a single movement type (Figure 2(a), middle finger flexion (MF), electrode 44, Subject 1-M) or movement of a single digit (Figure 2(b), thumb, electrode 88, Subject 2-U); however, other electrodes recorded action potentials that correlated with multiple different fingers and movement types (Figure 2(b), electrodes 13 & 44).

3.2.2. Multiple movements could be decoded offline. Predicted finger positions showed high correlations (r=0.9) with the instruction variables for the best two movements (IF and MF) achieved in Subject 1-M and the best four movements (TF, IAb, IE, TE) achieved in Subject 2-U (Figure 2(c-d)). Prediction accuracy decreased as the number of predicted movements or DOF increased, with a value of r=0.48 at 13 different finger movements for Subject 2-U (Figure 2(f)). To validate the decode results, the electrode order was randomly shuffled between the training and testing sets, and the firing rate data was decoded again. Using this shuffled data, the prediction accuracy dropped to r=0.14 for 13 different movements (Subject 2-U). For Subject 2-U, the median decode performance for seven sessions spanning 23 days for the same eight movements was r=0.62 ± 0.07 (the 5 finger extension movements were added on post-implantation day 13 and were not included in this analysis).

3.2.3. Multiple movements could be decoded online. Data recorded from the median nerve was decoded online for middle and index phantom finger flexion, and the subject was able to move the cursor to targets specific to each finger individually with a median time to trial completion of 9 ± 6 s (16 trials, 5 electrodes; Figure 2 (g)) (see Supplemental Video 1). Data recorded from the ulnar nerve was decoded online for thumb and little phantom finger flexions, and the subject was able to independently and proportionally control each of the virtual robotic fingers with a median time to trial completion of 2 ± 5 s (79 trials, 4 electrodes; Figure 2(h)) (Supplemental Video 2). For both subjects, online decodes were successful in obtaining 2 DOF control. However, some crosstalk existed between these DOF, making independent control more difficult.

3.3. Intrafascicular microstimulation evoked sensory percepts

In Subject 1-M, single electrode stimulation on 17 electrodes over the course of the study evoked sensory percepts with an average threshold of 27 ± 20 μA (mean ± std) (Figure 3(a)) that were approximately located in an expected median nerve distribution (Figure 3(c)). In Subject 2-U, when all 96 electrodes were stimulated individually, an average of 81 electrodes evoked sensory percepts with a mean threshold of 12 ± 11 μA (mean ± std) (Figure 3(b)) that were approximately located in an expected ulnar nerve distribution (Figure 3(d)). For this subject, no significant changes in the thresholds occurred after post-implantation day 10 (p=0.46, Kruskal-Wallis test). Further, a comparison of all 96 electrodes demonstrated that the mean percept threshold for an electrode over the duration of the study (8 stimulation sessions) was negatively correlated (r=-0.46, p<0.0001) with the number of days that an electrode recorded an action potential (13 recording sessions) (Figure 4(a-b)).

3.3.1. Detection of multiple percepts simultaneously (Subject 1-M). For Subject 1-M, blind trial data was collected during three different experimental sessions on post-implantation days 13, 19, and 26 that included stimulation delivered via one electrode, a different electrode, both electrodes, or no electrodes. The following electrode-pair combinations were chosen to include varying inter-electrode distances using supra-threshold stimulation amplitudes: day 13 - electrodes 16 (19 μA) and 19 (25 μA) with a 1200 μm distance; day 19 - electrodes 19 (47 μA) and 20 (18 μA) at 400 μm distance; day 26 - electrodes 20 (18μA) and 46 (10 μA) at 1442 μm distance. Subject 1-M correctly discriminated between any-stimulation (stimulation on either electrode individually or both electrodes simultaneously) versus no-stimulation with 98% accuracy (58/59 total trials; day 13 - 19/19 trials; day 19 - 20/20 trails; day 26 - 19/20 trials). Subject 1-M correctly discriminated between spatially distinct percepts evoked by microstimulation delivered via one of two electrodes (n = 5 for each electrode per session) with 87% accuracy (26/30 total trials; day 13 - 9/10 trials; day 19 - 8/10 trials; day 26 - 9/10 trials). Spatial discrimination was accurately reported with

electrodes separated by 400 μm (day 19) (Figure 3(e)). Subject 1-M was also able to discriminate between simple patterns of stimulation, i.e., stimulation via either electrode individually versus simultaneous stimulation via both electrodes, with 84% accuracy (38/45 total trials; day 13 - 11/14 trials; day 19 - 13/15 trials; and day 26 - 14/16 trials).

3.3.2. Frequency and duration of stimulation modulated the quality of percepts (Subject 1-M). Subject 1-M was allowed to self-modulate the stimulation frequency from 1-100 Hz by pushing down on the manipulandum pressure sensor with the subject's intact hand with stimulation being delivered to a single electrode at 30 μA (post-implantation day 14). High frequencies (100-320 Hz) evoked an 'electric shock' like quality, and lower frequencies (1-25 Hz) and longer stimulation times (up to 60 s) could evoke more physiological percepts (e.g., pressure).

3.3.3. Location stability of percepts for all 96 electrodes over time (Subject 2-U). Five of the total eight stimulation sessions (post-implantation days 10-25) resulted in a complete mapping of all 96 electrodes at fixed parameters of 200 Hz, 0.2 ms durations, 200 μs pulse widths, and amplitudes that varied from 1-100 μA. Figure 3(f) shows examples of percepts evoked by two different electrodes over these five sessions. One of the electrodes (electrode 63) evoked a stable percept across all five sessions. The other electrode (electrode 88) was stable for two consecutive sessions. A total of 61 electrodes evoked percepts across all five sessions. Out of these 61 electrodes, 18 electrodes produced percepts that were considered stable within a defined region (see Methods 2.6) of the phantom hand for two consecutive sessions (separated by 1-3 days). A total of eight electrodes evoked stable percepts for three consecutive sessions, four electrodes evoked stable percepts for four consecutive sessions, and three electrodes evoked stable percepts across all five stimulation sessions.

3.3.4. Number and quality of percepts for all 96 electrodes (Subject 2-U). The quality of evoked percepts in Subject 2-U combined across all five complete mapping sessions at 200 Hz included: 76 'tingle' percepts; 7 'pressure' percepts; and 216 'vibration' percepts. For the last two stimulation sessions, separated by one day, where the array was mapped at 20 Hz, a total of 76 electrodes evoked percepts on both days, with 17 electrodes evoking stable percepts. The percept quality evoked during these sessions included: 21 'tingle' percepts; 19 'pressure' or 'hair brush' percepts; 17 'vibration' percepts; and 96 'cold' or 'air brush' percepts. The subject noted that the 'tingle' and 'vibration' percepts evoked during each session were of a 'painful' quality.

3.4. Phantom limb sensations occurred post-stimulation in both subjects

Both subjects differentiated between phantom limb sensations (the normal feelings from their phantom hand) and phantom limb pains (percepts that were considered uncomfortable). Subjects reported an increase in the occurrence of phantom limb sensations that took on the characteristics of the sensory percepts evoked by electrical stimulation. At times, the post-stimulation sensations included percepts such as 'pressure' or 'hair brushing on the skin.' At other times, the subjects reported an increased occurrence of post-stimulation evoked phantom limb sensations that were painful, and the quality of such percepts included: 'electric shock,' 'stinging,' or 'tingling.' For each subject, percepts (duration ≈ 1-2 s) began after the first day of stimulation, and had peak occurrences of 10/hr for subject 1-M and 2-9/hr for Subject 2-U. By 30 days post-explantation of the electrode array, both subjects no longer reported phantom sensations that were of the quality of stimulation-evoked percepts.

4. Discussion

In 2003, a human volunteer had a Utah microelectrode array (with all electrodes of the same length) implanted in his median nerve for 96 days. Although this study provided new data for the field of peripheral nerve interfaces, it also had several limitations including the following: stimulation and recording were carried out through 20 electrodes (out of the 100 electrodes that were implanted); no action potential data were presented to support that the devices were implanted intraneurally; no longitudinal data was presented to show the stability of the device capabilities (stimulating percepts and recording neural activity); and finally, decoding multiple DOF was not investigated [30, 45]. Here, we extended that work by investigating multiple aspects important for developing future bidirectional neural prostheses based on high-count microelectrode arrays, including: the quality of percepts evoked by microelectrode stimulation, frequency modulation of percept quality, the number of different movements that can be decoded using action potential data, and the overall recording and stimulation capabilities of microelectrode array devices over a 30 day period.

4.1. Stability of USEAs implanted for 30 days and potential for longer duration implants

In Subject 1-M, the impedances for the majority of the electrodes went out of specification at the end of the first week due to lead wire breakage; however, four electrodes remained viable for the duration of the implant. Suturing the percutaneous connector to the skin appeared to have reduced the chance of wire breakage in Subject 2-U (no observed wire breakages). The SNR was stable after day ten of implantation for Subject 2-U, and we hypothesize this may be due to the stabilization in the surrounding tissue as the acute inflammatory response begins to resolve [46]. Impedances varied significantly over the duration of the study with an increase during post-implantation days 3 to 10. This variability may reflect either changes in the electrode itself (surface chemistry of the iridium oxide) or changes in the electrode-tissue interface (cellular milieu). Furthermore, impedances may stabilize after 30 days as shown in previous studies of USEAs implanted in the feline sciatic nerve [47].

A robust percutaneous connector or a telemetry system will be needed before applications using microelectrode arrays achieve clinical utility. Also, the generation of microelectrode arrays used in this study have maximum electrode shank lengths of 1.5 mm, which limits the cross-sectional access to the deeper regions of the relatively large human peripheral nerves that are greater than 3 mm in diameter. Longer electrodes and/or multiple arrays may be needed to expand electrophysiological access across the entire diameter of the nerves.

A more robust containment system, an anchoring system, or a more compliant microelectrode array design may be required to achieve the very long functional lifetimes necessary for clinical applications. The tissue response to indwelling intrafascicular electrodes has shown that, although implantation of intraneural electrodes results in tissue damage, viable neurons are found within distances (<150 μm) needed for safe stimulation of and selective recording from neurons after >30 days of implantation [47, 48, 49]. Additionally, Utah microelectrode arrays have been implanted for >5 year durations in motor cortex and continue to record neural signals that can be used to control external devices, suggesting the viability of this type of interface for longer duration implant times [10]. Both subjects were given dexamethasone and minocycline doses in order to potentially increase the quality of action potential recordings over time [35, 36]. However, additional control studies are needed to investigate whether administration of these drugs can improve neural signal longevity over long-term electrode array implantations.

In this study, action potentials were recorded across multiple microelectrodes for the duration of the 30 day implant, which validates that the devices remained intrafascicularly implanted for the duration of the study. Moreover, electrodes that reliably recorded action potentials throughout the study generally evoked percepts at lower stimulation amplitudes, suggesting that these electrodes were intrafascicularly implanted, while other electrodes that did not record action potentials may have been implanted between fascicles.

4.2. Neural recordings and decoding independent and proportional phantom finger movements

An important aspect of any decoded signal for controlling a prosthetic hand is that it can mediate proportional control. This was investigated in two ways. First, we used a linear Kalman Filter to decode the neural data, which provided a continuous estimate of finger position that was proportional to some linear combination of the neural signals. Second, we placed targets at various positions located between full extension and full flexion. This required that the subjects proportionally modulate the neural signals in order to acquire the targets and complete the task. The advantage of using a virtual prosthetic hand as opposed to an actual robotic hand was programmatic control of target size and distance. With a virtual hand, we were better able to quantify the accuracy and timing of neurally-controlled movements. For both subjects, the decoded neural activity patterns provided proportional control of finger position and, importantly, such control was achieved during the first recording session with each subject. Some crosstalk existed between the DOF, which sometimes made it difficult for the subjects to independently control different digits during the online experimentation.

The relationship between the central representation of motor control and the kinematics of movement is complex, with activity in single neural units correlated with the movements of multiple finger muscles [50, 51]. The central and peripheral nervous systems control the synergistic biomechanics of the human hand [52]; however, current high-DOF prosthetic hands do not implement mechanical synergies [24, 25]. These synergies require co-activation of multiple muscles innervated by multiple nerves. The relationship between neural encoding and the hand biomechanics is further complicated by the possibility of post-amputation neural plasticity and the specific location of the array implantation along the proximal-distal nerve axis. Future work is needed to develop efficient mapping of these synergistic neural signals onto the non-synergistic mechanics of high-DOF prosthetic hands, or to develop prosthetic hands that accurately model the biomechanics of the human hand. Additional work will also be required to develop new algorithms or strategies that optimally decode the spatial-temporal neural activity patterns recorded with intrafascicularly implanted electrode arrays for independent and noise-free control of each DOF.

4.3. Stimulation-evoked sensory percepts

We explored the ability to evoke sensory percepts by injecting currents into the peripheral nerves via many of the electrodes in the implanted arrays. In both subjects spatially discrete somatosensory percepts were evoked using low levels of current. These spatially discrete percepts could be used for registering contact of the fingers in a prosthetic hand with an object with high spatial fidelity. Translations of non-physiological percepts into more physiological percepts was achieved by varying the frequency and the duration of microstimulation, i.e., the percept changed from an ‘electric shock-like tingle’ to pressure, indicating that modulation of microstimulation parameters may be used to address sub-modalities of somatosensation. Subject 1-M was able to detect and discriminate simple patterns of microstimulation, suggesting the more complex spatio-temporal patterns of stimulation could provide more complex sensation such as brushing or sliding across the skin. Subject 1-M noted:

(1) "As I'm pressing that down there [on the manipulandum pressure sensor] on that intensity and moving the finger a little bit…this [the sensory percept] stayed on that finger as I was moving it."
(2) "As they speed up [the stimulation frequency increasing from 1 to 100 Hz] I can feel more of the finger. … It applies pressure on the index and this finger [of the phantom hand, indicated by pointing to the tip of the ring finger on the subject's intact hand]."
(3) Question from the experimenter: "Could you use this stimulation to recreate touch?" Answer from Subject 1-M: "Definitely…The more you press it [subject pressed on manipulandum pressure sensor changing the frequency from 1 to 100 Hz] you can sense it [the phantom finger] more. … And you'll get the sense of touch, 'cause that's what you did for me."

This subject was also very accurate at reporting the absence of any sensation when no microstimulation was provided. The stability of the stimulation-evoked percepts was assessed, and indicated that while evoked percepts were grossly stable they did change over time. The changes in evoked percepts likely results from micro-motion of the electrode array relative to the nerve, and perceptual stability could be increased by improving the systems used to contain the array and anchor it to the nerve. The results presented here indicated that implantations of microelectrode arrays into the peripheral nerves of amputees could provide sensory feedback that would improve the manipulation of objects using highly dexterous prosthetic hands.

Future studies are warranted to investigate the stimulation parameters that evoke other sensations, such as proprioception, as well as, long-duration stimulation to evoke long-lasting sensations. Recent studies have shown modulation of stimulation intensity with a time-variant pulse width results in more natural evoked perceptions [22] and employing these methods may improve the quality of percepts produced by microelectrodes. Moreover, Tan et al. have also demonstrated stability of percept location may stabilize after 27 weeks post implantation[33], and thus, longer duration USEA studies are warranted to assess such time periods.

4.4. Post-stimulation evoked sensory percepts

The subjects experienced post-stimulation percepts that occasionally had the uncomfortable or painful qualities of the percepts evoked by some electrical stimulation. Importantly, neither of the subjects experienced these qualities of percepts prior to participating in the study. Future work should address optimizing microstimulation parameters to produce only physiologically relevant sensory percepts, and investigate plasticity in the central motor and sensory neural representations resulting from long-term microstimulation of the peripheral nerves [53, 54, 55, 56, 57]. Subject 2-U noted the feeling of the non-painful post-stimulation percepts in the subject's phantom limb sensation diary:

"I've had the kind of fluttering or breath-on-the-skin or hair-pressure that I had often in the lab session today. (Located in the web area between my PIF [phantom index finger] and PMF [phantom middle finger].) It's as if now that the sensation has been awakened, it keeps registering, regardless of context – a little like a kid using a new vocabulary word liberally or a cook using a favourite spice or herb in all kinds of meals…"

These “awakened” phantom limb sensations may have implications for embodiment of neural prostheses. Consistent stimulation of the nerve may engage or reactivate central neural circuits that encode the representation of the phantom or prosthetic limb. This embodiment of a prosthetic limb could be enhanced by coupling the nerve stimulation with simultaneous input from other sensory modalities, e.g. vision of the limb being touch.

5. Conclusion

Numerous electrodes on the arrays recorded neural activity patterns from residual nerves that were volitionally generated by the intention to flex, extend or abduct individual digits in the subjects’ missing hand. Up to thirteen movement types could be decoded offline (r=0.48), and proportional control of multiple digits on a virtual prosthetic hand was achieved. Stimulation of up to 96 electrodes, either one-at-a-time or via small groups simultaneously, evoked multiple percepts that were spatially distributed across the phantom hands in anatomically appropriate distributions. The relatively large number of channels of motor and sensory information provided by the microelectrode arrays indicate that such arrays can serve as a neural interface for controlling high-DOF prosthetic limbs. The subtle verbal descriptions of evoked perceptions from the subjects indicated an attempt to integrate the sensations, either cognitively or perhaps due to neural plasticity, into their subjective bodily representation. Patients outfitted with a highly dexterous prosthetic limb controlled through such a bi-directional peripheral nerve interface might begin to think of the prosthesis not as a piece of hardware attached to their arm, but rather, as an integral extension of themselves.

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Figures

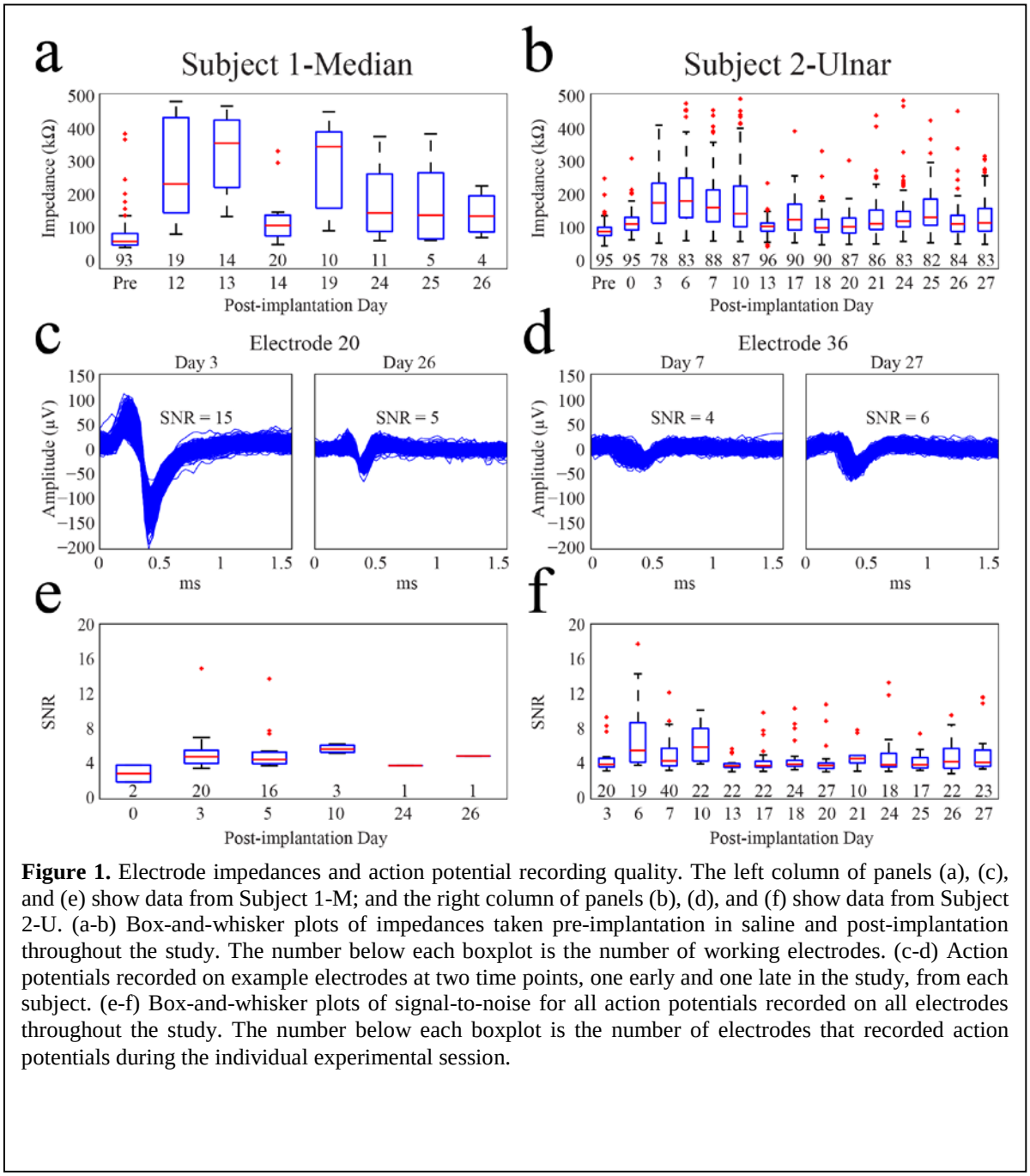


Figure 1. Electrode impedances and action potential recording quality. The left column of panels (a), (c), and (e) show data from Subject 1-M; and the right column of panels (b), (d), and (f) show data from Subject 2-U. (a-b) Box-and-whisker plots of impedances taken pre-implantation in saline and post-implantation throughout the study. The number below each boxplot is the number of working electrodes. (c-d) Action potentials recorded on example electrodes at two time points, one early and one late in the study, from each subject. (e-f) Box-and-whisker plots of signal-to-noise for all action potentials recorded on all electrodes throughout the study. The number below each boxplot is the number of electrodes that recorded action potentials during the individual experimental session.

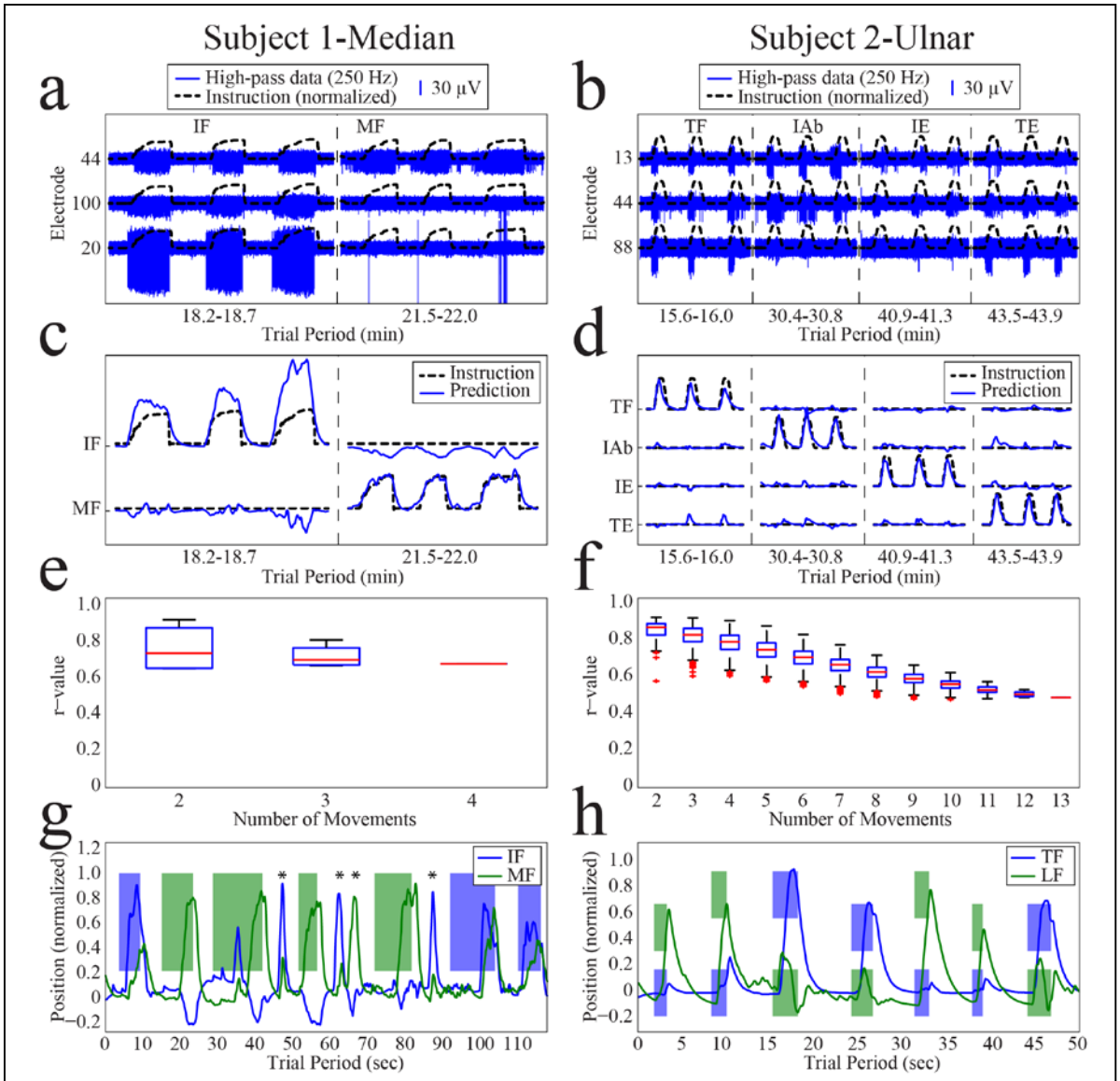


Figure 2. Decoding volitional phantom finger movements from peripheral nerve action potentials. The left column of panels (a), (c), (e), and (g) show data from Subject 1-M; and the right column of panels (b), (d), (f), and (h) show data from Subject 2-U. (a-b) High-pass filtered neural recordings (solid blue) made by three electrodes during phantom finger movements for Subject 1-M (post-implantation day 3) and Subject 2-U (post-implantation day 24). Superimposed is the instructed finger movement (dashed black). Action potentials can be seen in the high-pass filtered data extending out of the noise during the instruction period. (c-d) Kalman filter predictions for the best two movements for Subject 1-M and the best four movements for Subject 2-U. Only a subset of trials is shown. Prediction correlations of 0.9 were achieved using multi-unit firing rates calculated from unsorted spike events on 18 electrodes (Subject 1-M, post-implantation day 3) and 55 electrodes (Subject 2-U, post-implantation day 24). (e-f) Box-and-whisker plots of offline Kalman filter performance for all combinations of available movements using the same electrodes as in (c-d). (g-h) Examples of Kalman filter performance during real-time decode sessions for each subject. Boxes represent trial-by-trial target locations and the traces represent the Kalman filter predictions for the intended finger movement. To successfully complete a trial, the predicted finger movement must enter and remain in the target box for a specified hold duration (3000 (g) and 300 (h) ms). Asterisks highlight verbally-stated volitional movements made by the subject in the absence of a target.

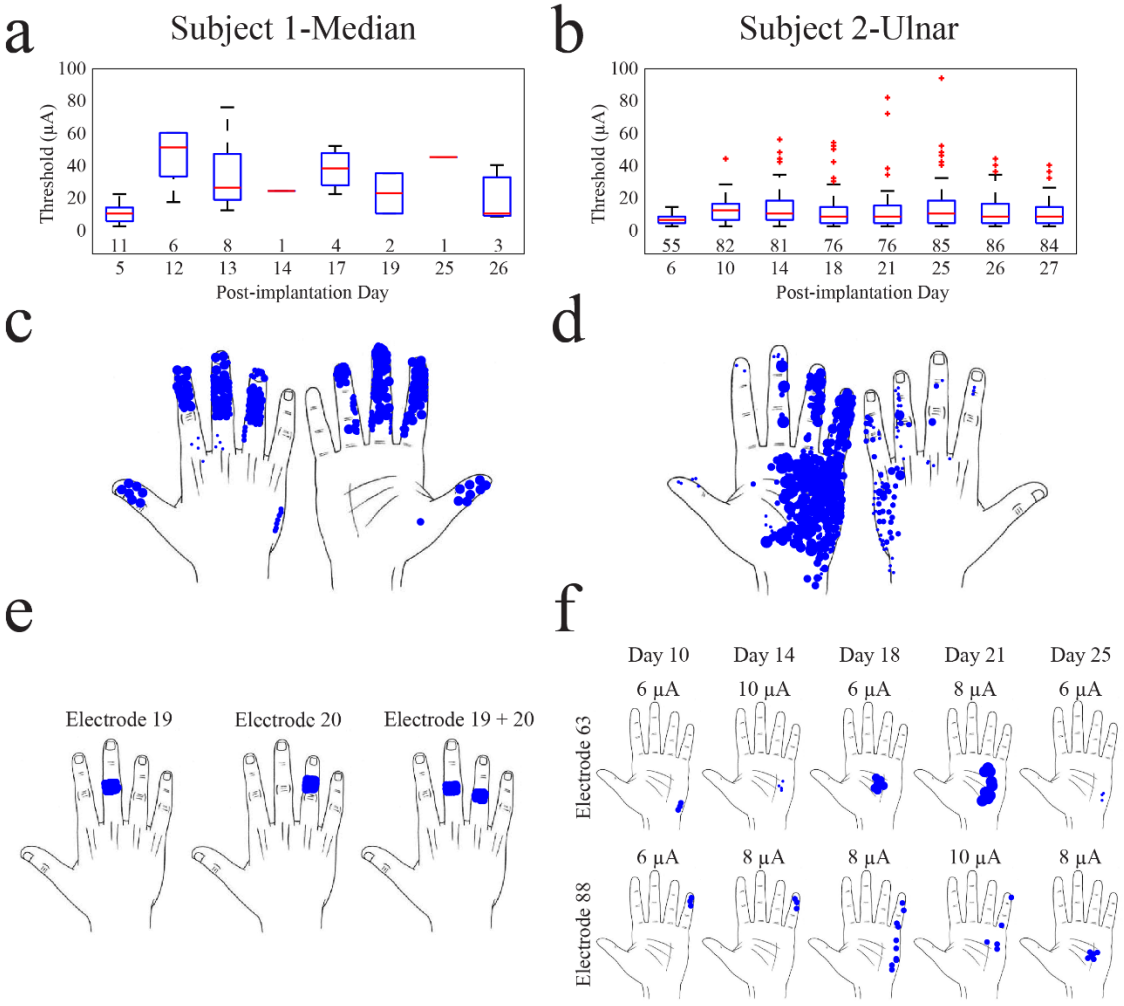


Figure 3. Electrical stimulation can evoke spatially distinct and stable sensory percepts. The left column of panels (a), (c) and (e) show data from Subject 1-M; and the right panels (b), (d), and (f) show data from Subject 2-U. (a-b) Sensory percept thresholds over the duration of the experimental period for both subjects. For subject 1-M, only a subset of electrodes was stimulated each session. For subject 2-U, except on post-implantation day 6, all 96 electrodes were stimulated each session. The number below each boxplot is the number of electrodes that evoked a sensory percept. (c-d) Results from intrafascicular stimulation of human median and ulnar nerves show evoked sensations in the phantom hand that approximately followed the expected spatial distributions for each nerve. The cumulative data from all microstimulation sessions is shown. (e) Single electrode stimulation (electrode 19 at 47μA; electrode 20 at 15μA) produced discrete sensory percepts, and when the same electrodes were stimulated simultaneously the two discrete percepts could be perceived simultaneously (Subject 1-M). The inter-electrode distance in this example was 400 μm. (f) Examples of percepts that were evoked by two different electrodes with one percept that was considered stable across all five sessions (electrode 63; top row of hands) and another that was stable for two consecutive sessions (electrode 88; bottom row of hands). Marked locations were felt simultaneously (Subject 2-U).

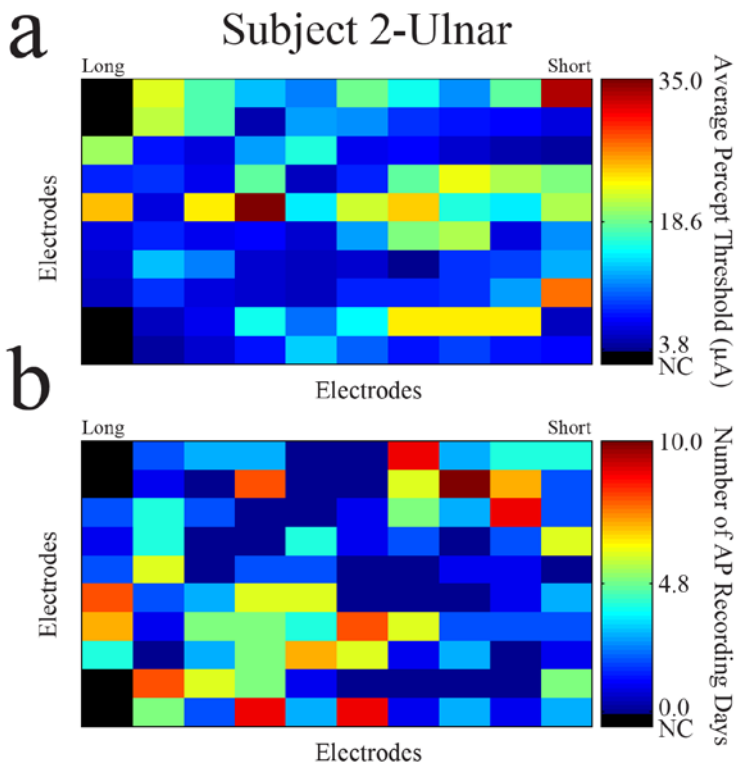
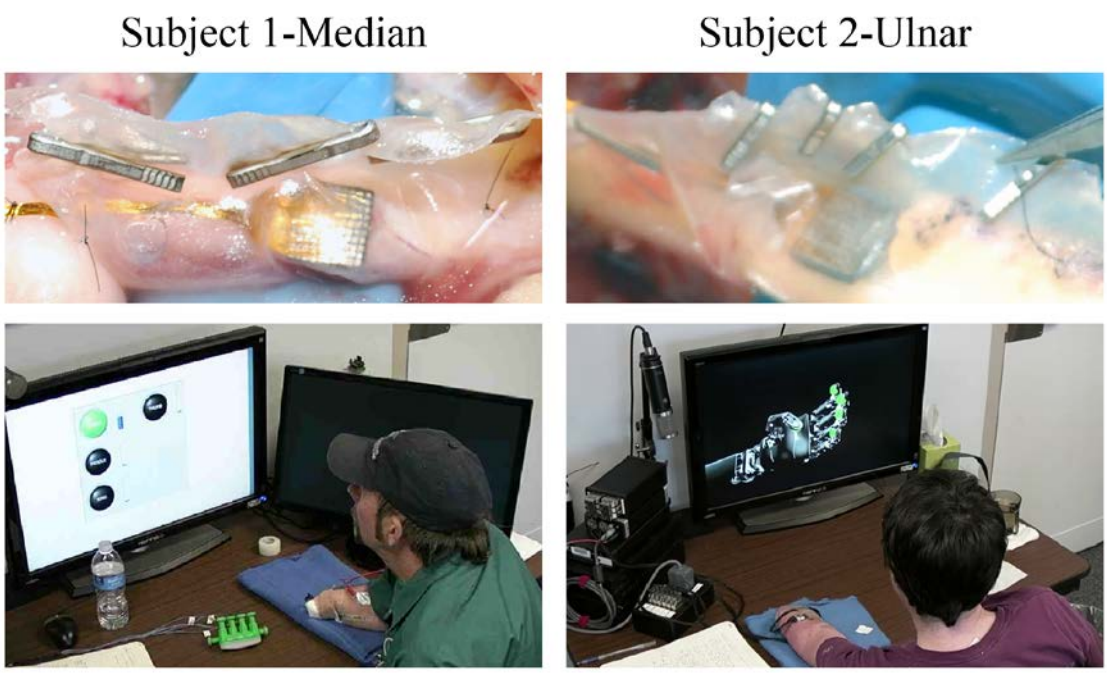


Figure 4. Spatial distributions of percept thresholds and action potential recordings for all 96 electrodes over 30 days. (a) Mean threshold needed to evoke a sensory percept via stimulation on each individual electrode over the duration of the study (8 total stimulation sessions, last stimulation session on day 27 post-implantation). (b) Number of days that each electrode recorded at an action potential over the duration of the study (13 total recording sessions, last session on day 27 post-implantation).



Supplementary Figure 1. Upper panels show photographs of intrafascicular USEA implantation into the median (Subject 1-M) and ulnar (Subject 2-U) peripheral nerves. The device-nerve interfaces were contained within an organic nerve wrap (clear material surrounding the implant) and secured with vascular clips (3-5 clips are seen in each photo) to minimize movement of the device and allow containment of the reference wires proximal to the arrays. Lower panels show the experimental setup primarily used by each subject for volitionally controlling either a computer controlled display (Subject 1-M) or the digit of a virtual hand (Subject 2-U). In the images shown, the neural information corresponding to the phantom movement was decoded in real-time and used to control the virtual movement.

Supplementary Video 1. Real-time decode of index finger position in Subject 1-M on post-implantation day 10. The subject achieved proportional control of the finger position on his first attempt of controlling the virtual prosthetic hand. The subject was able to position the finger at halfway flexed and fully flexed following verbal instructions.

Supplementary Video 2. Real-time decode of thumb and little finger positions in Subject 2-U on post-implantation day 24. The subject was able to simultaneously control the thumb and little finger and move them to visual targets presented at two different locations.

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