RESTORED HAND SENSATION IN HUMAN AMPUTEES VIA UTAH SLANTED ELECTRODE ARRAY STIMULATION ENABLES PERFORMANCE OF FUNCTIONAL TASKS AND MEANINGFUL PROSTHESIS EMBODIMENT

by

David Michael Page

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The dissertation of David Michael Page
has been approved by the following supervisory committee members:

Gregory A. Clark, Chair — August 19, 2016
Date Approved

Douglas T. Hutchinson, Member — August 19, 2016
Date Approved

Richard D. Rabbitt, Member — August 19, 2016
Date Approved

David J. Warren, Member — August 25, 2016
Date Approved

Alan R. Light, Member — August 19, 2016
Date Approved

and by Patrick A. Tresco, Chair of the Department of Bioengineering

David B. Kieda, Dean of The Graduate School

ABSTRACT

Hands are so central to the human experience, yet we often take for granted the capacity to maneuver objects, to form a gesture, or to caress a loved-one's hand. The effects of hand amputation can be severe, including functional disabilities, chronic phantom pain, and a profound sense of loss which can lead to depression and anxiety. In previous studies, peripheral-nerve interfaces, such as the Utah Slanted Electrode Array (USEA), have shown potential for restoring a sense of touch and prosthesis movement control. This dissertation represents a substantial step forward in the use of the USEAs for clinical care—ultimately providing human amputees with widespread hand sensation that is functionally useful and psychologically meaningful.

In completion of this ultimate objective, we report on three major advances. First, we performed the first dual-USEA implantations in human amputees; placing one USEA in the residual median nerve and another USEA in the residual ulnar nerve. Chapter 2 of this dissertation shows that USEAs provided full-hand sensory coverage, and that movement of the implant site to the upper arm in the second subject, proximal to nerve branch-points to extrinsic hand muscles, enabled activation of both proprioceptive sensory percepts and cutaneous percepts.

Second, in Chapter 3, we report on successful use of USEA-evoked sensory percepts for functional discrimination tasks. We provide a comprehensive report of functional discrimination among USEA-evoked sensory percepts from three human subjects, including discrimination among multiple proprioceptive or cutaneous sensory

percepts with different hand locations, sensory qualities, and/or intensities.

Finally, in Chapter 4, we report on the psychological value of multiple degree of freedom prosthesis control, multisensor prosthesis sensation, and closed-loop control. This chapter represents the first report of prosthesis embodiment during closed-loop and open-loop prosthesis control by an amputee, as well as the most sophisticated closed-loop prosthesis control reported in literature to-date, including 5-degree-of-freedom motor control and sensory feedback from 4 hand locations.

Ultimately, we expect that USEA-evoked hand sensations may be used as part of a take-home prosthesis system which will provide users with both advanced functional capabilities and a meaningful sense of embodiment and limb restoration.

I dedicate this dissertation to the many people that
have helped make my life wonderful:

My amazing wife and best friend, Rebecca J. Page; our
two boys, Andrew and Eli; my parents, siblings,
coworkers, and friends; and the volunteer
amputees who donated much of
their time to this research

TABLE OF CONTENTS

LIST OF FIGURES

PREFACE

This dissertation builds on a legacy of peripheral nerve interfacing at the University of Utah, including the development of the globally-recognized Utah Electrode Array and its peripheral-nerve successor, the Utah Slanted Electrode Array. These chapters represent a substantial advance in use of the Utah Slanted Electrode Array in human subjects, and, in particular, human amputees, including a report of widespread proprioceptive and cutaneous sensory restoration, performance of functional tasks, and generation of a meaningful sense of prosthesis embodiment. Enabling engineering advances included hardware and software development for neural interface and muscle array recording and stimulation, development and use of virtual and physical prosthetic hands, and development of experimental and methods and protocols. We anticipate that these developments will serve as a foundation for many additional clinical advances.

This work of this dissertation was sponsored by the Hand Proprioception and Touch Interfaces (HAPTIX) program of the Biological Technologies Office (BTO) of the Defense Advanced Research Projects Agency (DARPA) under the auspices of Dr. Doug Weber, as well as by the DARPA Microsystems Technology Office (MTO) under the auspices of Dr. Jack Judy through the Space and Naval Warfare Systems Center, Pacific Grant/Contract Nos. N66001-15-C-4017 and N66001-12-C-4042. Additional funding was also provided via the National Institutes of Health (NIH NCATS Award No. 1ULTR001067) and the National Science Foundation (NSF ECCS-1533649).

CHAPTER 1

INTRODUCTION

1.1 Abstract

In this introduction, a broad introduction is provided to the field of neuromodulation, including a detailed summary of different approaches that have been used for interfacing with the peripheral nervous system. The unique challenges associated with upper limb loss are also discussed, including loss of functional capabilities and psychological difficulties. These challenges have not been fully overcome with the current prosthetic limbs. Peripheral nerve interfaces have shown promise as an approach for restoring sensory function and dexterous prosthesis motor control to amputees. Utah Slanted Electrode Arrays (USEAs) have been developed by past investigators to allow for activation to subpopulations of peripheral-nerve axons in naturalistic spatiotemporal patterns, which offers many benefits over other neural interfaces. The potential for using USEAs for restoration of broad sensory function for both functional and psychological improvements in human upper arm amputees is presented, as well as an overview of our work toward accomplishment of these goals.

This dissertation details results from three different experimental studies that have either been submitted for publication review or are in final revisions with plans for upcoming submission. The purpose of this introduction is to provide a broad overview of the overall objectives and accomplishments of this combined dissertation as a whole. Detailed introductions for each aim of the dissertation are found in the introductions at the beginning of each subsequent chapter. Finally, an overall conclusion is provided at the end of the dissertation, which summarizes the main outcomes of the dissertation and provides recommendations for ongoing studies with USEAs and peripheral nerve and muscle interfaces to provide sensory feedback and motor control to human amputees.

1.2 Neuromodulation

Neuromodulation has been defined as "the process of inhibition, stimulation, modification, regulation or therapeutic alteration of activity, electrically or chemically, in the central, peripheral or autonomic nervous systems" [1]. Therapeutic neuromodulation was reportedly used as early as the year 15 AD, when a Roman physician, Scribonius, recommended electrical shock from a torpedo fish as a treatment for chronic pain [2]. The first documented use of purposefully interfacing an electrical stimulation device with a nerve was made by Giovanni Aldini in 1804 when he stimulated the facial nerves of fresh cadavers to evoke muscle contractions [3]. Modern neural interfaces are used clinically for treatment of deafness, Parkinson's disease, chronic pain, epilepsy, blindness, depression, incontinence, and chronic pain [1]. The global neuromodulation market is predicted to grow at a compound annual growth rate of 11.2% in coming years, reaching a predicted value of $6.2 billion by the year 2020 [4].

The location of neural interfacing varies depending on the objective of a treatment or research study, with treatment targets including both peripheral nerves, such as nerves of the arms, legs, or bladder, as well as targets in the central nervous system, placed in the brain or spinal cord. Electrical stimulation and recording are the traditional mechanisms for interacting with neurons or nerves via a neural interface, although optical, magnetic, mechanical, thermal, genetic, chemical, and combination methods have also been investigated [1]. In contrast to systemic drug delivery, such as is often used for treatment of epilepsy, Parkinson's disease, and chronic pain, recent neural interface approaches offer selective access to treatment of a subset of tissue with limited side-effects. Neural interfaces are also effective for providing lost motor or sensory function, such as for restoration of movement control in quadriplegics [5]–[8], or restoration of hearing via cochlear implants [9].

This dissertation focuses on the use of electrical stimulation via a peripheral-nerve interface, the Utah Slanted Electrode Array (USEA), for restoration of hand sensation to human subjects with prior upper limb amputations. The Utah Electrode Array (UEA), the precursor of the USEA, has been used for long-term recording in human motor cortex for functional tasks [7], whereas the USEA has been used in only a few limited short-duration studies in human subjects [10], [11]. As will be shown in Chapter 1, when placed in residual arm nerves of human amputees, USEAs offer selective access to numerous sensory axons which, when activated, can create a sense of touch sensation or proprioception on the subject's missing hand. Further, Chapter 2 shows that stimulation-evoked percepts can be functionally discriminable and guide motor behavior; and Chapter 3 presents evidence that stimulation (sometimes with motor control) can promote embodiment and reduce phantom pain.

1.3 Peripheral-nerve interfaces

Peripheral nerves consist of long bundles of nerve axons that extend between receptor organs or neuromuscular synapses and the central nervous system. Multiple fascicles, or segregated bundles of axons, are often present within a single nerve, with each fascicle being surrounded by connective tissue referred to as perineurium. Fascicles and perineurium are bundled together within an outer protective layer of connective tissue, referred to as the epineurium [12]. The objective of peripheral-nerve interfaces is to communicate with the axons in the nerve. One advantage of peripheral nerve interfaces compared to central-nervous-system interfaces is the straightforward information encoding patterns of peripheral nerve axons. Specifically, peripheral motor axons and sensory axons typically encode measureable and simplistic parameters such as joint position, skin pressure, or joint force in their firing rate and/or population activity.

Several different approaches have been used to interface with peripheral nerves. Noninvasive approaches are useful for activating whole-nerve bundles by stimulating through the skin with high voltages, such as for clinical diagnostic purposes. However, noninvasive approaches have not proven useful for functional purposes which require selective activation of different subsets of axons within a peripheral nerve [13]. Invasive approaches include extraneural electrodes positioned within the body but outside the nerve, interfascicular electrodes positioned within the nerve but outside the fascicles, and intrafascicular electrodes positioned at least partially within the fascicles [14]. For electrical stimulation and recording, the currently-accepted dogma is that the level of selectivity of a neural interface is constrained by its level of invasiveness, with less-invasive approaches such as extraneural electrodes providing limited selectivity compared to more invasive approaches as such as intrafascicular electrodes [14].

This dissertation reports on the use of an intrafascicular microelectrode array, the Utah Slanted Electrode Array, to achieve highly selective activation of single axons or subsets of axons in peripheral nerves of human amputees using electrical stimulation.

1.4 Utah Slanted Electrode Arrays

Utah Slanted Electrode Arrays (USEAs), intended for implantation in peripheral nerves, were invented as a modified version of their predecessor invention, the Utah

Electrode Array (UEA), which was designed for implantation in the cerebral cortex of the brain [15]. In addition to offering axon-level, intrafascicular access to the nerve via 100 different silicon microelectrodes, the variable-length electrodes along one dimension of the slanted microelectrode array enable cross-sectional access to axons at different depths within the nerve [16], allowing individual electrode tips to selectively communicate with different axons (Fig. 1.1). Selective communication with many different axons is important for activating a variety of sensory percepts with different hand locations and qualities, as well as communicating with the peripheral nervous system using biofidelic activation patterns. Regenerative neural interfaces, which have only been used in animal models with limited success [17], are the only currently-available peripheral-nerve interfaces that approach the level of intrafascicular cross-sectional coverage of the USEA.

USEAs consist of a square, 4 mm x 4 mm backplane with 100 silicone microelectrodes arranged in a 10 x 10 grid. The electrodes are spaced 400 μm apart, and the electrode lengths vary along a single dimension of the USEA, typically ranging linearly between 0.5 – 1.5 mm in a linear slant (Fig. 1.2). The USEA has been used in a number of animal studies, including control of stance and micturition in anesthetized felines [18], [19], modulation of hand grip in nonhuman primates [20], as well as biocompatibility and behavioral studies in rats [21]. Our prior human studies have demonstrated basic functionality and safety of USEAs in humans, including the ability to restore cutaneous sensations from the phantom hand of human amputees as well as basic motor control of a virtual prosthesis [11], [22], [23].

The work reported in this dissertation represents the first comprehensive use of USEA stimulation in multiple human subjects for performance of functional tasks

(Chapters 2 and 3). Additionally, the work presented here represents the first report on the psychological impact of USEA stimulation in human subjects during closed-loop sensorimotor prosthesis use (Chapter 4). In addition to scientific testing, the work of this dissertation has driven the engineering and development of devices, systems, and methods that we anticipate will enable eventual use of a portable, take-home neural interface system as an assistive device for human subjects with upper limb loss.

1.5 Upper limb loss

In the United States alone, roughly 1.6 million people (one in every 200) suffer from loss-of-limb due to amputation, and the prevalence of upper limb and lower limb amputations is likely to double by 2050, primarily due to increasing rates of divascular disease [24]. The functional deficits experienced due to upper limb amputation are particularly severe. And the psychological impact of limb amputation can be intense, potentially causing depression, anxiety, or suicide [25]. Although sophisticated robotic hand prostheses exist, these have not been used clinically, partially due to a lack of dexterous movement control signals to use for controlling the prosthesis as well as limitations in the ability to provide comprehensive sensory feedback [26].

Several approaches have been used to restore sensory feedback and/or movement control to amputees. Cortical neural interfaces are not a suitable fit for many amputees, due to the higher risks associated with brain surgery [27]. Sensory substitution has been used but is frustrating for subjects to learn [28]. Targeted reinnervation, in which a residual nerve is rerouted to a new patch of skin or a muscle, does not allow for restoration of exogenous proprioceptive feedback and is limited to only a few sensory locations on the hand [29]–[34]. Moderately-dexterous movement control has been achieved using myoelectric recordings from the residual arm muscles of transradial amputees; however, this approach provides no sensory feedback, and likely will not offer full-hand functionality to transhumeral amputees [35]–[37].

Peripheral-nerve interfaces have been used in human amputees to: a) electrically stimulate sensory neurons, creating controllable perception of sensation in the phantom hand, and b) record microvolt level changes associated with intended movement commands to allow decoding of intended joint positions and restored motor control. The restoration of sensation and motor control simultaneously is referred to as closed-loop control.

Despite advances in peripheral nerve interfaces, the extent of closed-loop sensorimotor restoration has previously been limited to only 3 degrees of freedom (DOFs) of movement and 2 sensory percepts [38]. This limitation is primarily due to: a) the use of low-channel-count nerve and muscle interfaces, and b) the use of less selective neural interfaces, such as extraneural cuffs.

In 1974, an amputee was implanted with an extraneural cuff electrode on the residual median nerve, and electrical stimulation produced some limited sensations in the subject's phantom hand via electrical stimulation [39]. In the years 2004 and 2005, recordings via longitudinal intrafascicular electrodes (LIFEs) were used to provide subjects with one-degree-of-freedom (DOF) prosthesis control [40] and electrical stimulation via LIFEs produced some sensations on the phantom hand (Fig. 1.3) [41], [42]. In the years 2010 and 2011, 3-DOF prosthesis control was achieved, including coordinated grips, by use of LIFE electrode recordings [43], [44], and basic object discrimination was demonstrated using two LIFE-evoked sensory percepts [45]. More recently, extraneural cuff electrodes that flatten the nerve to provide improved selectivity (flat interface nerve electrodes, FINEs) were used to evoke 19 sensory percepts which were stable for more than one year [46]. Additionally, a closed-loop system was recently reported in which an amputee achieved 3-DOF prosthesis control using surface electromyography (sEMG) for motor control and transverse intrafascicular multichannel electrodes (TIMEs) implanted in residual arm nerves to provide sensory feedback in two phantom hand locations [47].

One distinct advantage of USEAs compared with other intrafascicular peripheral-nerve interfaces is the ability to quickly implant many electrodes as part of a single device (e.g., LIFEs and TIMEs require manual implantation of only 4-8 stimulating channels at a time). Our recent published studies with USEAs implanted in two residual arm nerves of a human amputee indicates that USEAs can restore up to 131 naturalistic sensations spanning the phantom hand and can also be used to perform motor decodes [22] (see also [11]). However, these prior studies have been limited to rough mappings of cutaneous percepts, with no proprioceptive percepts or encoding of different percept intensities. Furthermore, these previous studies do not fully demonstrate selectivity of USEA-evoked sensory percepts of different locations, qualities, and intensities, such as would be desirable for functional prosthesis use. Furthermore, USEA-evoked sensory feedback was only used in closed-loop control in a simplistic, 1-DOF, single-percept proof-of-concept test.

In this dissertation, we demonstrate an expansion of the use of USEAs in human amputees, in which we have provided human subjects with a rich selection of both proprioceptive and multimodal cutaneous sensory percepts spanning the hand. Additionally, we show that USEA stimulation can be used to encode a broad selection of discriminable locations, intensities, and qualities of sensory percepts. Finally, we demonstrate use of multi-DOF, multipercept closed-loop control of a physical prosthetic hand, which provided a subject with a meaningful sense of prosthesis embodiment. A comparison table of performance results from various peripheral nerve interfaces is provided in Fig. 1.3, including a distinguishment between performance results from USEA use prior to this dissertation, and USEA performance results reported in this dissertation.

1.6 Multichannel, intrafascicular selectivity

Selectivity of a set of neural stimulating electrodes involves their ability to activate unique and distinct subpopulations of neurons. For example, at threshold-level stimulation amplitudes, a population of one or more axons in the vicinity of a USEA electrode tip may be activated. Extraneural electrodes, such as cuffs, are separated from axons in the nerve by the highly-resistive epineurium sheath, requiring use of higher currents for activation of axons. The path of current flow at this high-amplitude stimulation becomes quite broad at the position of the axons in the nerve, causing activation of large subpopulations of axons at perithreshold amplitudes. In contrast, intraneural electrodes such as those on USEAs are capable of activating nearby neurons with low-amplitude stimulation (e.g., 10 μA), with very focal flow of current within the nerve, allowing for selective access to only one or a few axons at perithreshold amplitudes (see Chapters 2 and 3). The low amplitudes of stimulation used with USEAs allow for activation of small subsets of fibers with little overlap between the subsets activated by each electrode tip (see Chapter 3).

The intrafascicular selectivity of USEA electrodes enables activation of many different subsets of axons within the nerve bundle, each with its distinct projected field and quality. The combination of selectivity and cross-sectional nerve coverage provided by the many electrodes of the USEA enables activation of a variety of different axons spanning the nerve. Channel count is important for achieving a larger number of independent percepts with different hand locations and sensory qualities. The skin of the intact hand provides information about sensory location and quality via a population code, making selectivity, channel count, and distribution across the nerve cross-section the primary factors that limit the amount of information that may be exchanged between an external prosthesis and the body via a neural interface. Alternative approaches for sensory encoding, such as targeted reinnervation and sensory substitution have been limited in the number of channels of information they can encode.

Chapter 2 demonstrates that USEAs implanted in the peripheral arm nerves of human amputees are capable of encoding a rich selection of information from the external environment, including sensory percepts of different locations and qualities spanning the phantom hand. Sensory percepts include both proprioceptive and cutaneous submodalities, with implantation in the upper arm, proximal to many nerve branch points to the extrinsic hand muscles, being an important factor in being able to restore proprioceptive percepts.

1.7 Discrimination during functional tasks

Ultimately, we foresee development of a take-home closed-loop prosthetic hand with multiple USEA-coupled sensors for feedback. However, information from the different hand sensors will only be useful if the sensations perceived are distinct for each sensor. This functional discriminability would allow amputees to associate sensor activation with, for example, object contact at a specific location on the prosthesis. Additionally, during closed-loop prosthesis control it is likely that multiple sensors may be activated simultaneously, resulting in simultaneous stimulation on different USEA electrodes or subsets of electrodes. Functional discrimination among combinations of proprioceptive and cutaneous percepts spanning the hand is important for identifying the position of object counterforces or object movement as well as an object's size, shape, weight, and texture.

Chapter 3 demonstrates that percepts evoked by stimulation of different USEA electrodes are perceived as unique by human subjects during functional discrimination tasks. We also show that subjects can discriminate among different intensities of percepts, encoded by changing the stimulation frequency. Intensity encoding is important for providing feedback regarding object compliance by encoding different counterforces for cutaneous pressure and/or vibration frequencies [48]. Intensity encoding for proprioceptive receptors is important for encoding joint position and velocity [49]. Chapter 3 also provides insight into the nature of percepts evoked by multielectrode stimulation, and includes a method for evoking multiple percepts simultaneously via interleaved stimulation of multiple USEA electrodes, such as may be useful during multisensor activation during closed-loop prosthesis control.

1.8 Psychological factors

The long-term objective of this research is not only to provide amputees with functional improvement in prosthesis motor control via USEA-evoked feedback, but also to restore a sense of limb restoration and wholeness. Current prostheses are perceived by their users more as useful tools than as replacement limbs. The ability to embody a prosthetic hand as a replacement limb may resolve many of the psychological struggles associated with limb loss, as well as a possible alleviation of phantom pain [50].

In Chapter 4 we report on the development and use of a low-cost, physical prosthetic hand with integrated motors and sensors. A meaningful sense of limb embodiment was enabled by life-like motor control of the digits of the hand (via recordings from implanted intramuscular electrodes), and touch feedback from multiple locations on the prosthesis (via sensor-coupled USEA stimulation). In this sense, the use of USEA stimulation not only helped the subject to *feel* the world around him again, but will also helped him to *feel whole again*. We also found that the subject experienced a significant effect of phantom pain reduction after experimental sessions compared to before experimental sessions, where sessions included USEA microstimulation, and open-loop and closed-loop virtual prosthesis control in addition to embodiment experiments. We anticipate that this sense of prosthesis embodiment and phantom pain reduction, and the associated psychological benefits, will serve as a major driver for ongoing translational research using neural interfaces for prosthesis sensation.

Ultimately, we foresee development of a take-home, closed-loop prosthesis system which will provide not only functional, but also emotional and psychological improvements to the quality of life for many upper limb amputees.

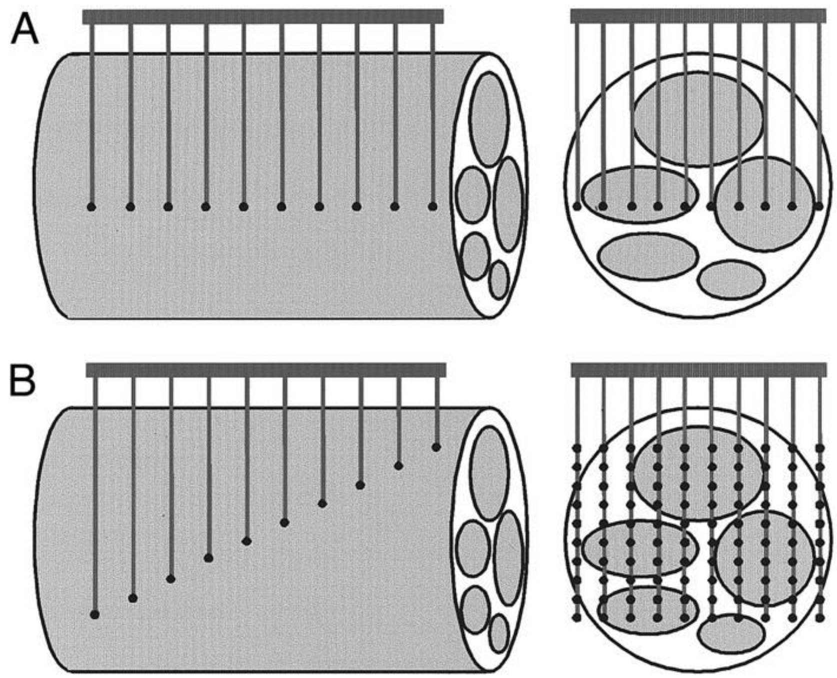


Fig. 1.1. Peripheral nerve anatomy and cross-sectional nerve access. Peripheral nerves consist of an external sheath known as the epineurium, which contains several nerve fascicles (5 fascicles shown here). Each fascicle contains many nerve axons which run along the length of the nerve. Motor axons transmit motor commands from the central nervous system to the muscles, and sensory axons transmit information about touch, muscle position, temperature, etc., from the skin and muscles back toward the brain and spinal cord. Each sensory axon encodes information from a different location, or receptive field (also referred to as a projected field in amputees). Each electrode of a USEA implanted in a peripheral arm nerve can be used to activate a different axon or small subset of axons near the tip of the electrode, generating, for example, sensation of skin pressure or vibration in a specific location on the hand. This ability is enhanced by the varying length of electrodes along the slant (in contrast with the traditional UEA shown in A). In human amputees, the neural pathways and axons that once encoded touch sensation on the hand remain in place long after the amputation. In this dissertation, we use USEA stimulation to restore many hand sensations to human amputees for the performance of functional tasks, and to create a meaningful sense of embodiment of a prosthetic hand. Note that the spacing of electrodes portrayed in this original figure are not fully representative of the actual spacing within a human peripheral arm nerve. Figure courtesy of the *Journal of Neurophysiology* ([16], pg. 1586).

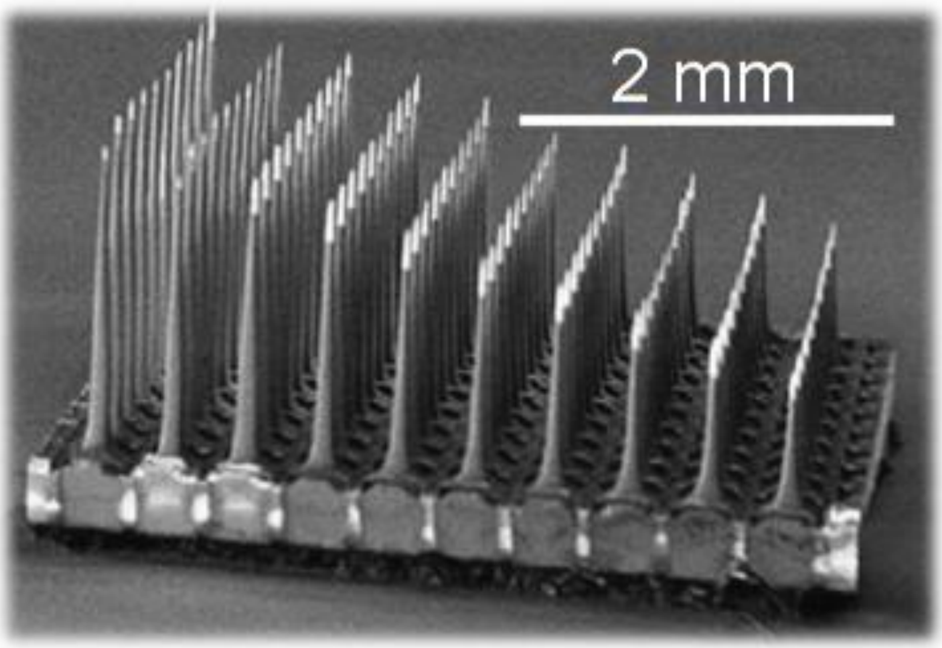
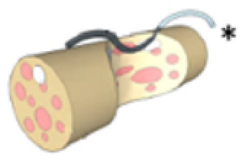
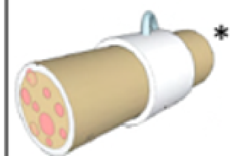
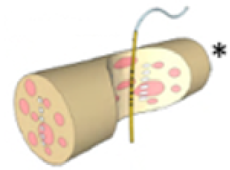
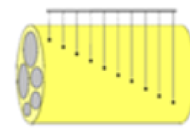
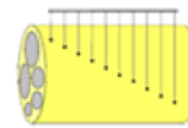


Fig. 1.2. Scanning electron micrograph of a Utah Slanted Electrode Array. The USEA is a 10 x 10 grid of silicon shafts with varying lengths (~0.75 – 1.5 mm for the shafts used in this research, ~0.5-1.5 mm for the shafts shown here) and electrically-conductive electrodes at the tip. The slanted nature of the electrode array allows for cross-sectional nerve access. For functional studies, such as those presented in this dissertation, each electrode of the USEA is wired to a connection pad on a circuit board, which can in turn be connected to stimulation and recording equipment. Stimulation of nerve axons via a USEA electrode involves generating small amounts of current flow in the nerve tissue via the conductive electrode tips. USEAs have previously been used in many animal research studies and a few initial human research studies. The work of this dissertation represents the first comprehensive use of USEAs in humans for performance of functional tasks, including for restoration of sensory feedback during closed-loop prosthesis control. The shafts shown here are platinum-tipped, in contrast to the iridium-oxide tips used in the results reported in this dissertation. Figure courtesy of the *Journal of Neurophysiology* ([16], pg. 1587).

	LIFEs (Hutchinson/ Horch)  *	Nerve Cuffs (Durand/Tyler)  *	TIMEs (Rossini/Micera)  *	USEAs-Past (Hutchinson/ Greger/Clark) 	**USEAs-Current** (Hutchinson/Clark) 
# Percepts	≤ 8	≤ 19	≤ 2	≤ 81 (1 USEA)	≤ 131 (2 USEAs)
Qualities	Cutaneous, proprioceptive	Cutaneous	Cutaneous	Cutaneous	Cutaneous, proprioceptive
Naturalism	Some percepts	Some percepts	NR	Some percepts	Many Percepts
Intensity Gradations	Cutaneous, proprioceptive (resolution NR)	Cutaneous (resolution NR)	Cutaneous (resolution NR)	Cutaneous (resolution NR)	Joint Position, Cutaneous Pressure 4 gradations each
Closed-loop control	2 cut. or 1 cut. + 1 propr., 1 DoF (EMG)	2 cutaneous, 2 DoFs (EMG)	2 cutaneous, 3 DoFs (EMG, class.)	None	4 cutaneous, 3 proprioceptive 5 DoF (EMG/Neural)

* Graphics modified from Boretius et al. (2010)

Fig. 1.3. Performance comparison of different peripheral nerve interface approaches. Several different approaches have been used to interface with peripheral nerves to provide functional prosthesis control and sensation to human amputees, including longitudinal intrafascicular electrodes (LIFEs), nerve cuffs (examples includes spiral nerve cuffs and flat interface nerve electrodes, known as FINEs), transverse intrafascicular multichannel electrodes (TIMEs), and Utah Slanted Electrode Arrays (USEAs). The right-most column of the chart (outlined in bold) represents the work of this dissertation.

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CHAPTER 2

RESTORATION OF MOTOR CONTROL AND PROPRIOCEPTIVE AND CUTANEOUS SENSATION IN HUMANS WITH PRIOR UPPER LIMB AMPUTATION VIA MULTIPLE UTAH SLANTED ELECTRODE ARRAYS (USEAS) IMPLANTED IN RESIDUAL PERIPHERAL ARM NERVES

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David M. Page, Suzanne M. Wendelken, Tyler Davis, Heather A. C. Wark, David T. Kluger, Christopher Duncan, David J. Warren, Douglas T. Hutchinson, Gregory A. Clark

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2.1 Abstract

Despite advances in sophisticated robotic hands, intuitive control of and sensory feedback from functional prostheses has been limited to only 3 degrees-of-freedom with 2 sensory percepts in closed-loop. A Utah Slanted Electrode Array (USEA) has been used in the past to provide up to 81 sensory percepts for human amputees. Here, we report on the advanced capabilities of multiple USEAs implanted in the residual peripheral arm nerves of human amputees for restoring sensation of up to 131 proprioceptive and cutaneous hand sensory percepts in open-loop. We also demonstrate that USEA-restored sensory percepts provide a useful source of feedback during closed-loop virtual prosthetic hand control.

Two 100-channel USEAs were implanted for 4-5 weeks in each of the median and ulnar arm nerves of two human subjects with prior long-duration upper arm amputations. Intended movements were decoded from neuronal firing patterns via a Kalman filter, allowing subjects to control many movements of a virtual prosthetic hand. Additionally, USEA microstimulation was used to evoke numerous sensory percepts spanning the phantom hand. Closed-loop control was achieved by stimulating via an electrode of the ulnar-nerve USEA while recording and decoding movement via the median-nerve USEA.

Subjects experienced up to 131 USEA-evoked proprioceptive and cutaneous sensations spanning the phantom hand. Many USEA-evoked sensory percepts were enjoyable to the subjects, and one subject used a USEA-evoked hand sensation as feedback to successfully complete a closed-loop virtual-hand movement task. Neither subject reported long term functional deficits due to the USEA implants.

Implantation of high-channel-count USEAs enables restoration of a rich selection of both proprioceptive and cutaneous sensory percepts spanning the hand. Future USEA use

in closed-loop may enable restoration of many of the capabilities of an intact hand while contributing to a meaningful embodiment of the prosthesis.

2.2 Background

Amputees using commercially-available mechanical or robotic prostheses do not currently receive cutaneous or proprioceptive sensory feedback from their prosthesis, nor do they have simultaneous, independent, proportional control over all the digits of the prosthetic hand and the wrist. Sensory feedback from, and dexterous control of a prosthetic robotic hand may assist upper limb amputees in activities of daily living (ADL), restore a sense of prosthesis embodiment, and alleviate phantom pain [1], [2].

As early as 1974, amputees were instrumented with a single cuff-like electrode on their residual median nerve, which produced limited sensations in the phantom hand via electrical stimulation [3]. More recently, implanted longitudinal intrafascicular electrodes (LIFEs) were implanted into the peripheral arm nerves of several transradial amputees, and recordings from these electrodes provided subjects with one-degree-of-freedom (DOF) online control of a prosthesis [4]. Additionally, a limited number of sensations were evoked in the phantom hand by electrical stimulation via LIFE electrodes [4]–[6]. LIFE recordings were later used to achieve 3-DOF control of a prosthetic hand, including coordinated grips [7], [8], and basic object discrimination was enhanced by use of two sensory percepts elicited from electrical stimulation of the peripheral nerve via LIFEs [9]. Cuff electrodes (flat interface nerve electrodes, FINEs), implanted around each of the three major residual arm nerves of an amputee, have also been used to evoke 19 sensory percepts, and these percepts have been shown to be stable for up to two years [10]. Finally, a recent closed-loop system has been demonstrated in which an amputee achieved 3-DOF control of a prosthetic hand using surface electromyography (sEMG) for motor control and transverse intrafascicular multichannel electrodes (TIMEs) implanted in residual arm nerves to provide sensory feedback in two phantom-hand locations [11].

Previously, we demonstrated that a single USEA implanted in a residual peripheral arm nerve in human amputees can be used to evoke up to 81 different cutaneous percepts on the hand and provide proportional motor control of up to two DOFs [12]. These past subjects, referred to here as S1 and S2, were each instrumented with only one USEA, implanted at the terminal end of either the residual median or ulnar nerve, respectively. Preliminary results regarding multi-USEA instrumentation in two residual arm nerves of a third subject, S3, have also been presented [13]–[15], demonstrating cutaneous sensory percepts spanning the phantom hand, limited 2-DOF online motor control, and basic closed-loop control.

In expansion of this work, we now present findings from two recent human subjects, S3 and S4. In addition to the use of two USEAs per subject (one in each of the median and ulnar arm nerves) for both S3 and S4, a notable improvement was made by implanting USEAs in subject S4 in the upper arm, proximal to extrinsic-hand-muscle nerve branches. This allowed generation of numerous proprioceptive sensory percepts spanning the hand in addition to many USEA-evoked cutaneous percepts. We also report results regarding electrode and percept stability.

2.3 Methods

2.3.1 Study volunteers

Two transradial amputees, referred to here as subjects S3 and S4, were recruited and evaluated by a physician and psychologist for their willingness and ability to participate in the study (S1 and S2, published previously [12]). Subject S3 was a 50-year-old left-dominant male, whose left arm had been amputated several centimeters proximal to the wrist 21 years prior, following a crush injury. Subject S4 was a 36-year-old ambidextrous male, with bilateral upper limb amputations several centimeters distal to the elbow 16 years prior, due to electrical injury. Baseline phantom limb surveys and medical histories were taken for each subject prior to the study. The surveys included assessment of the subjects' perceived abilities to exert voluntary control over phantom movements, and perceive sensations (both painful and nonpainful) on their phantom limbs. Phantom pain was assessed based on the duration, frequency, and intensity of pain episodes and this assessment continued during the duration of the implant period and for several months afterward.

For the one-month period prior to the study, S3 was given a mirror box in order to practice the phantom-hand movements to be performed in the study [2]. Due to his being a bilateral amputee, S4 was unable use a mirror box and was instead given videos of hand movements to watch and imitate with his phantom hands. Subject S3 continued his use of Gabapentin to relieve back pain throughout the study, which may affect peripheral-nerve activity. The study and consenting of human volunteers was approved by the University of Utah Institutional Review Board, the Salt Lake City Veterans Affairs Hospital Research and Development Service Center, and the Department of the Navy Human Research Protection Program.

2.3.2 Device

Two Utah Slanted Electrode Arrays (USEAs; Blackrock Microsystems, Salt Lake City, UT, USA) were implanted in each subject (one in the median nerve, one in the ulnar nerve). Each USEA consisted of 100 silicon microelectrodes arranged in a 10x10 grid on a 4x4 mm base, spaced at 400 um, and varying in length from ~0.75 – 1.5 mm [16] (Fig. 2.1a). Of the 100 electrodes on each USEA, 96 were used to record from and/or stimulate the nerve. Four of the longer electrodes, near two of the corners of the USEA, were used as an on-array electrical reference [17], and two separate looped platinum wires served as off-array electrical reference and ground leads. All implanted electrodes were wired via a percutaneous incision to a custom-developed printed circuit board designed to allow attachment to data acquisition and stimulation hardware via a ZIF-Clip-96 connector cable (Tucker-Davis Technologies Inc., Alachua, FL, USA).

2.3.3 Surgical procedures

Prior to, and for several days following the implant procedure, subjects were given a prophylactic antibiotic (100 mg minocycline, 7 days, twice per day, starting the day before the implant surgery) which potentially improves the quality of chronic neuronal recordings [18]. Under general anesthesia, two USEAs were surgically implanted into each subject—one in the residual median nerve and one in the residual ulnar nerve (Fig. 2.1b). In S3, both USEAs were placed in the lower arm, approximately 2 cm proximal to the amputation neuroma (Fig. 2.1c). This distal location was used in S3 as an initial precautionary measure, because nerves were not functionally attached at the distal implant locations. Hence, any nerve resection at that point would not compromise essential motor or sensory function. In subject S4, both USEAs were placed in the upper arm, approximately 2 cm proximal to the medial epicondyle. Importantly, the USEAs in subject S4 were proximal to many motor and sensory nerve-branch points, including branches to extrinsic hand muscles, thereby potentially providing a greater richness in motor and proprioceptive nerve fiber access.

For S3, the surgical procedure involved the passage of the unprotected USEAs through a trocar from the percutaneous site to the implant site, which resulted in damage to four of the electrodes on the median nerve implant (and no documented damage to the ulnar nerve implant). A different USEA passage method was devised for S4, which involved securing the arrays inside a plastic tapered carrier for protection before passing them under the skin. There is no indication that any electrodes were damaged using this revised USEA passage method in S4.

In both subjects, the epineurium was dissected from the surface of the nerves prior to pneumatic insertion of the USEAs [19]. The USEA wire bundle, ground, and reference wires were sutured to the epineurium (8-0 or 9-0 nylon suture), and a protective collagen wrap (AxoGen Inc., Alachua, FL, USA) was placed around the nerve, USEAs, and reference/ground wires. The wrap was secured with vascular clips and sutured to the epineurium for stability. After tourniquet removal, subjects were administered 0.1 mg/kg of dexamethasone intravenously to potentially mitigate the foreign body response and improve neural recording capability [20], [21].

Percutaneous wire-passage sites were redressed as needed throughout the study, on at least a weekly basis. Antibiotic wound dressings (Biopatch, Ethicon US LLC, Somerville, NJ, USA) were placed directly over the percutaneous site throughout the study duration to reduce the risk of infection, although subject S4 did experience an infection from which he fully recovered (potentially due to an implant-related hematoma and/or via the percutaneous wire-passage site).

After several weeks (4 weeks for S3, 5 weeks for S4), the USEAs were surgically explanted. In S3, the USEAs and neuromas were removed with the arrays still intact for histological analysis [22]. In S4, only the USEAs were removed due to their placement midway along the nerves in the upper arm.

2.3.4 Experiment setup

Subjects returned for the first experimental session within 4 days of the USEA implant surgery. Experimental sessions were 1-6 h in duration, and were performed 3-5 days per week for 4 weeks for S3 and 5 weeks for S4. Experimental sessions typically included testing impedances of all USEA channels at the beginning of each session, followed by a recording/decoding session, a stimulation session, or both.

2.3.5 Impedance testing

The impedance of each electrode on each USEA was measured in saline prior to implantation via one-week soak testing using a custom-built impedance tester, at 1 kHz [23]. Impedances were also measured shortly before preimplant sterilization using the NeuroPort System (Blackrock Microsystems, Salt Lake City, UT, USA) at 1 kHz. Impedance testing was subsequently performed in vivo at the beginning of each experimental session using the NeuroPort System at 1 kHz.

Impedance measurements were used to identify failed USEA electrodes/channels as well as to monitor the over-time stability of working electrodes. We defined failed channels as those which had an impedance greater than or equal to 500 kΩ. Nonfailed channels were defined as channels which never had an impedance value above 500 kΩ across the implant duration. For each implanted USEA, we tested the null hypothesis that the number of failed USEA electrodes in a session does not change significantly across the implant duration, using a two-tailed Spearman's rank correlation. Additionally, for each implanted USEA, we tested the null hypothesis that the impedance value for nonfailed electrodes does not change over time using a Friedman test and post-hoc two-tailed Wilcoxon's signed-rank test between the first and last post implant impedance testing sessions.

2.3.6 Recording/decode

Neural data collection was performed using the 128-channel NeuroPort System for S3 and either the NeuroPort System or the 512-channel Grapevine System (Ripple LLC, Salt Lake City, UT, USA) for S4. 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 digitally sampled at 30 kHz. A digital high-pass filter was applied to sampled recordings (250 Hz, 4th-order Butterworth filter), and single-unit or multi-unit activity was extracted by detecting threshold crossings of an adaptive, automated threshold, set to approximately negative 6 times the root mean square (RMS) of the signal. Spike-event times from each electrode were binned into 33.3-ms windows and converted into firing rates, which were then used as inputs to train and test a decode algorithm, typically a Kalman filter. Outputs of trained decode algorithms were used to provide the subjects with real-time control of the position of a simulated hand in a virtual environment [24] (Fig. 2.1d).

To train the decode algorithm, the subjects were instructed to imitate with their phantom hands a series of single-DOF virtual-hand movements shown on a computer screen while USEA recordings were collected and saved. Training sets included 5 to 10 trials of each movement, with each movement trial lasting for 1 to 2 s (complete training session generally lasting 5-10 min). The time from training-set completion to online decode testing was typically no longer than 5 to 10 min.

During individual training motions, the experimenters manually selected a subset of electrode channels and movements by viewing electrode maps of spiking activity and selecting the electrode channels with greatest apparent correlation and specificity to a single movement. These electrodes were then used as inputs for training online decodes, whereas electrode channels with little or no firing that was correlated preferentially with single movements were excluded. Further details of the decoding algorithm are discussed elsewhere [25].

2.3.7 Stimulation

Electrical stimulation was performed using the IZ2-128 System (Tucker-Davis Technologies Inc., Alachua, FL, USA) for S3 and either the IZ2-128 System or the Grapevine System (Ripple LLC, Salt Lake City, UT, USA) for S4. For all USEA stimulation, biphasic, cathodic-first pulses were used (typically 200 μs width for each phase, 100 μs interphase interval). When a percept was evoked by USEA stimulation, subjects indicated the perceived location, quality, and intensity or size of the percept on an image of a hand using custom software (Fig. 2.1e). Subjects were instructed to select the percept quality from a list of descriptors (e.g., “tingle,” “vibration,” “pressure,” “movement,” “hot,” “cold”) or to create and use their own descriptors as necessary.

Full-USEA stimulation threshold maps were collected on weeks 1, 2, 3, and 4 for subject S3, and on weeks 2 and 5 for subject S4. For these maps, the threshold current (in μA) required to evoke a sensation via stimulation of each electrode was determined. Thresholds were defined as the minimum current level at which a subject repeatedly perceived stimulation-evoked percepts. For these mappings, biphasic, 200 μs stimulus pulses (with a 100 μs interphase interval) were delivered via single electrodes at 200 Hz for a 200-ms-duration train (the 200 Hz frequency was chosen empirically based on ability of subjects to quickly reach threshold). The stimulation trains were initiated either by the experimenter or self-initiated by the subject via clicking a mouse button.

Full-USEA threshold mapping sessions began by sequentially stimulating each electrode on the USEA individually with a low-amplitude stimulus (e.g., 2 μA), while documenting electrodes for which either a percept was evoked, or for which the voltage between the stimulating electrode and return electrode (looped platinum ground wire) did not return above the safety level of -0.6 V before the end of the interphase interval [26]. These electrodes were excluded from subsequent stimulation, whereas each of the remaining electrodes on the USEA was again sequentially stimulated at an incrementally higher current level. This pattern was repeated at increasing current levels until either there were no remaining unmapped electrodes, or the current reached a maximum threshold amplitude (varied between 35 μA and 120 μA depending on the subject and the session), at which point all remaining electrodes were excluded.

For both subjects, full-USEA threshold mapping routines were performed at multiple times during the study, allowing for temporal stability analysis of the nature of percepts evoked by each electrode. Specifically, we quantified each USEA's percept stability based on the percentage of electrodes on that USEA for which the evoked percept changed either location or quality between two consecutive full-USEA threshold-mapping sessions. For this analysis, a change in percept location was defined as a transition between any of 12 hand location categories (front/back of palm, and front/back of each of the 5 digits). A change in percept quality was defined as a transition between selected percept quality descriptors. For subject S3, we computed the across-week mean of the number of electrodes which had a change in either percept quality or location from week to week. For subject S4, full-USEA threshold maps were collected only on week 2 and week 5 due to time restrictions, and the percentage of electrodes which had a change in either location or quality between these two sessions was quantified.

Additionally, we tested the null hypothesis that stimulation threshold currents for each electrode do not change significantly over time, using either a Friedman test with a post-hoc two-tailed Wilcoxon's signed-rank test between the first and final threshold mapping sessions (for S3), or a two-tailed Wilcoxon's signed-rank test (for S4, since there were only two full-USEA threshold mapping sessions). For each full-USEA threshold mapping session, we calculated the percentage of median- and ulnar-nerve evoked percepts that were within the expected nerve-location distribution (based on muscular and cutaneous innervations documented in intact hands and arms [27], [28]).

2.3.8 Closed-loop control

For S3, stimulation was delivered via a single electrode on the ulnar-nerve USEA during an online, one-DOF decode of simultaneous four-finger flexion produced via recordings on the median-nerve USEA. In a target acquisition task similar to others used for online decode testing, USEA-evoked sensory feedback was delivered whenever the virtual fingers were within virtual spherical targets, producing a basic sense of virtual-object touch. Virtual targets were presented in a pseudorandom order in two different locations: "close" or "far," representing finger contact positions that were either close to, or far from, finger resting positions (equivalent to grasping a large-diameter or small-diameter object, respectively). For a successful trial, the subject had to move the virtual fingers into the boundary of the virtual target and stay within the target zone for 250 ms and then correctly indicate whether the target was "close" or "far." Failed trials were those in which the subject either indicated the wrong distance to target, or failed to maintain 250 ms of consecutive contact with the virtual target before the 30-s time limit. Importantly, these trials were performed in the absence of visual feedback from the computer monitor, presumably limiting feedback regarding virtual object position to that evoked by USEA stimulation. If the probability of attaining the achieved number of successful trials by chance (using binomial test with extreme assumption that chance performance was 50% success) was less than 0.05, we concluded that USEA-evoked sensory feedback significantly assisted the subject to perform the task.

2.4 Results

2.4.1 Subjects enjoyed the experiments

Both subjects enjoyed the experiments, evidenced by their eagerness to volunteer again for future studies. When asked if the USEA stimulation was something he would want to continue simply because it felt good, S3 responded: "Yeah. I would like it if you could keep it stimulated.” Following an online decode, subject S4, whose hands had been amputated 16 years prior, stated, “[…] when I tried to move my thumb and the thumb moved on the screen—that was the coolest thing that’s happened to me in 16 years.”

2.4.2 Electrode impedances were generally low and stable for the implant duration

Implanted USEA electrodes were relatively resistant to failure over time, and nonfailed electrodes/channels did not show significant evidence of increasing impedance levels over time.

Three of the four total USEAs (two for each subject) did not show evidence that the number of failed channels changed over time, whereas the number of failed channels for one USEA (S3 median n. USEA) significantly increased over time ($p < 0.001$; two-tailed Spearman’s rank correlation; Fig. 2.2). The location of failure on a given channel is uncertain. However, failures potentially may occur at the electrode level, the wire-bundle level, or the connector level. Failure rates may be improved in future implants with improved external connectors, additional strain relief for USEA lead wires, and wireless devices.

For all four USEAs, impedances on nonfailed channels (impedance never ≥ 500 kΩ) changed significantly over time ($p < 0.0001$, Friedman test). For S3, the median (and IQR) of the impedance values across nonfailed electrodes on weeks 1-4, respectively, was 96 kΩ (65 kΩ), 81 kΩ (41 kΩ), 89 kΩ (36 kΩ), and 99 kΩ (47 kΩ) for the 41 nonfailed electrodes of the median-nerve USEA, and 171 kΩ (79 kΩ), 141 kΩ (107 kΩ), 110 kΩ (52 kΩ), and 188 kΩ (96 kΩ) for the 81 nonfailed electrodes of the ulnar-nerve USEA. For S4, the median

(IQR) impedance across nonfailed electrodes on weeks 1-4 was 167 kΩ (117 kΩ), 186 kΩ (70 kΩ), 337 kΩ (71 kΩ), and 85 kΩ (69 kΩ) for the 60 nonfailed electrodes of the median-nerve USEA, and 127 kΩ (69 kΩ), 194 kΩ (101 kΩ), 143 kΩ (99 kΩ), and 118 kΩ (96 kΩ) for the 59 nonfailed electrodes of the ulnar-nerve USEA. Post-hoc testing between the first and final postimplant sessions revealed a significant pairwise drop in impedance for electrodes on the median-nerve USEA on subject S4 ($p < 0.0001$; two-tailed Wilcoxon's signed-rank test), but did not reveal a statistically significant pairwise change for the remaining 3 USEAs ($p = 0.82$ S3 ulnar, $p = 0.12$ S3 median, $p = 0.99$ S4 ulnar). These results suggest that USEAs will potentially maintain a low-impedance condition in future long-duration implant studies, potentially allowing for chronic use of multichannel neuronal recordings for decoding movements and intraneural stimulation for providing sensory feedback.

2.4.3 USEA microstimulation produced numerous sensations spanning the hand

For each subject, microstimulation via USEA electrodes produced nearly 100 or more unique proprioceptive and cutaneous percepts that spanned the phantom hand, providing a rich selection of percepts potentially useful as feedback from a prosthetic limb. Importantly, subjects enjoyed many of the evoked sensations and sometimes asked for repeated delivery of pleasurable stimuli.

In S4, 131 of 192 (68%) USEA electrodes produced proprioceptive or cutaneous sensory percepts spanning the hand (Fig. 2.3a), and in S3, 97 of 192 (51%) USEA electrodes produced sensory percepts (primarily cutaneous). Percepts were evoked using different electrodes across the slanted 10x10 USEA. There was no apparent somatotopic arrangement across the nerve cross-section, however we often observed fascicular organization (Fig. 2.3b). Subjects also successfully discriminated among sensory percepts of different locations and qualities (a preliminary report for subject S3 has been provided [13], see also Chapter 3 of this dissertation).

Importantly, proprioceptive percepts were more common in S4 compared with previous subjects, presumably due to implantation of USEAs midway along the upper arm, proximal to many nerve branches to the extrinsic hand-muscles. Proprioceptive percepts for S4 included 17 unique perceived phantom hand movements (i.e., proprioceptive percepts), including flexion and extension of each finger; adduction and abduction of the index, ring, and little fingers; thumb flexion; and wrist extension. In S3, a proprioceptive percept was evoked only once (presumably due to implant location).

Cutaneous percepts were of many qualities, including “pressure,” “vibration,” “tingle,” and “sting” (Fig. 2.3c; “sting” was described only by S3). Many percepts were naturalistic and enjoyable to the subjects (e.g., “vibration” and “pressure”), whereas some percepts were undesirable or nonnaturalistic (e.g., “sting” and “tingle”).

We compared subjects’ perceived percept location distributions for median- and ulnar-nerve percepts with the anatomically-determined median and ulnar innervation distributions of an intact hand reported in literature. For S3, on weeks 1-4, respectively, a total of 84%, 90%, 86%, and 95% of median- and ulnar-USEA percepts were within the expected anatomical innervation regions of the hand (Fig. 2.4). For S4, on week 2 and week 5, respectively, 63% and 75% of median- and ulnar-USEA percepts were within their expected regions (including unique innervations for proprioceptive vs. cutaneous percepts).

For both subjects, the location and quality of percepts evoked by single electrodes was generally stable during 3-4 h experimental sessions. However, single-electrode percepts often changed location and/or quality across weeks. Specifically, for S3, across-week means of 91% and 78% of ulnar- and median-USEA electrodes evoked percepts that changed either location or quality in a one-week period, respectively (percentages are based on the 43 ulnar- and 17 median-nerve USEA electrodes that evoked percepts on all 4 weeks). For S4, 83% of the 12 median-nerve USEA electrodes that evoked percepts both on week 2 and week 5 changed either location or quality across this three-week period. Importantly, no percepts were evoked via ulnar-nerve USEA stimulation on week 5, possibly due to infection-related swelling or USEA movement.

Stimulation thresholds for percept-evoking electrodes were less than 120 µA across the implant duration, but increased significantly slightly over time ($p < 0.01$). For S3, the median stimulation threshold (and interquartile range) on weeks 1-4, respectively, was 10 (6-15.5) µA, 8.5 (6-15) µA, 12 (7-19.25) µA, and 11.5 (8-22) µA for the ulnar-nerve USEA; and 10 (6-16) µA, 11 (7.75-21) µA, 12 (5-30) µA, and 14 (12.5-35) µA for the median-nerve USEA (total of 59, 60, 53, and 56 percept-evoking electrodes each week on the ulnar-nerve USEA and 46, 37, 34, and 20 percept-evoking electrodes each week on the median-nerve USEA). For the 43 ulnar-nerve USEA electrodes that evoked percepts on all four weeks, threshold amplitudes changed significantly over time ($p < 0.01$, Friedman test). A post-hoc contrast test showed that stimulation thresholds generally increased on these electrodes between week 1 and week 4 ($p < 0.01$, two-tailed Wilcoxon's signed-rank test). Similar significant increases were evident for the 17 median-nerve USEA electrodes that evoked percepts on all four weeks ($p < 0.01$, Friedman test, and $p < 0.01$, post-hoc two-tailed Wilcoxon's signed-rank test).

For S4, stimulation thresholds for full USEAs were mapped only on week 2 and week 5, due to limitations on experiment time. Notably, none of the electrodes on the ulnar-nerve USEA evoked percepts on week 5. The median stimulation threshold (and interquartile range) on week 2 was 3 (2-5) µA for the ulnar-nerve USEA and 11 (7-20) µA and 25 (17.5-37.5) µA on weeks 2 and 5 for the median-nerve USEA (total of 87 percept-evoking electrodes on the ulnar-nerve USEA on week 2, and 44 and 16 percept-evoking electrodes on the median-nerve USEA on weeks 2 and 5, respectively). For the 12 median-nerve USEA electrodes that evoked percepts on both week 2 and week 5 there was not significant evidence of changing thresholds over time ($p = 0.11$, two-tailed Wilcoxon's signed-rank test).

2.4.4 USEA-evoked sensations are useful as feedback during closed-loop control

S3 used a cutaneous sensation on his ring fingertip (evoked by stimulation of a single ulnar-nerve USEA electrode) as feedback during an online, 1-DOF decode of 4-finger flexion/extension (decode via median-nerve USEA recording, driven by both neural and EMG). In the absence of visual feedback from the computer monitor, the subject successfully encountered and identified the location ("close" or "far") of virtual targets in 41/47 trials ($p < 0.001$, binomial test), using the USEA-restored sensation as feedback in addition to proprioceptive feedback from intact muscles of the forearm and/or efference copy to determine hand position. Of the 6 failed trials, 2 resulted from timeouts and 4 resulted from misclassifications.

2.4.5 Limited adverse effects

Subject S4 developed an implant-related infection 4-5 weeks postimplant, from which he fully recovered, and from which he suffered no long-term deficits. Both subjects reported no long-term functional deficits due to the procedure, with a full return of phantom hand function to its preimplant state after explantation of USEAs (data not shown).

2.5 Discussion

We used USEAs implanted in peripheral arm nerves to: 1) evoke numerous meaningful proprioceptive and cutaneous percepts across subjects' phantom hands; and 2) provide one subject with limited closed-loop control of a virtual prosthetic hand. These substantial advances are due in part to the increased number and more proximal placement of implanted USEAs, and the additional capability for closed-loop sensory feedback via a virtual environment. No long-term deficits were reported by the subjects after explant, although one subject experienced an implant-related local infection from which he recovered fully.

2.5.1 Stimulation

Microstimulation via USEAs produced a rich selection of up to 131 different proprioceptive and cutaneous percepts spanning the hand. USEA stimulation required no long-term training or reassociation or substitution of sensations. Proprioceptive percepts included flexions and extensions of each finger, flexion of the thumb, several intrinsic finger movements, and wrist extension. The improved ability to produce proprioceptive percepts in S4 compared with past subjects was likely due to placement of USEAs proximal to extrinsic hand muscle motor branches in S4.

In addition to restoring much of the functionality of an intact hand to amputees, quasi-continuous restoration of the sense of proprioception and cutaneous touch may help amputees perceive their prosthesis as an embodied replacement limb rather than a tool [1], which may decrease prosthesis rejection rates and improve amputees' perception of the usability of the device [29]. Our subjects appreciated both the cutaneous and proprioceptive sensations evoked by USEA stimulation.

The high percentages of percepts in expected median and ulnar distributions suggests that cortical boundaries between median- and ulnar-nerve innervation regions for these subjects were still partially intact despite the amputation greater than 16 years prior. However, some projected fields for USEA-evoked cutaneous percepts spanned the edges of two adjacent digits, suggesting the possibility of blurring of digit boundaries in cortex.

We did not perform exhaustive testing of the effect of stimulation frequency on percept quality, location, intensity, and/or size. Future work should be performed to encode percept properties such as pressure gradations, joint angles, or joint velocities, via modulation of stimulation parameters, such as stimulation frequency. Additionally, activation of subpopulations of afferents with stimulation patterns faithful to each respective receptor type (e.g., slowly-adapting I type or II, rapidly-adapting type I or II, or group Ia or II intrafusal muscle fibers) may improve the naturalism, discriminability, and stability of percepts [30]. Naturalistic touch, such as the sensation experienced during motor task phase transitions, activates a diverse subpopulation of axons in distinct patterns, producing a fused population and temporal code [31]. In contrast to cuff electrodes, USEAs offer the opportunity to activate subpopulations of single axons in biofidelic patterns via independent control of stimulation via different electrodes, potentially offering unprecedented naturalism and variety in the nature of evoked percepts.

Instabilities of percepts over time may be due to movement of the USEA electrodes relative to nerve fibers or due to the tissue foreign body response. Both of these potential issues may be ameliorated as improvements are made to the implantation procedure and the USEA materials and structure, and with longer implant times as processes reach asymptote.

2.5.2 Closed loop

This is the first use of USEAs for closed-loop control of a prosthetic or virtual hand. Future closed-loop control with multi-DOF decodes and several unique sensory percepts may allow for dexterous manipulations with a prosthetic hand. Although we did not provide USEA-evoked proprioceptive feedback during closed-loop control for these subjects, we anticipate that this capability may be important in cases where the prosthesis encounters external counterforces, or when velocity control is desired (instead of position control).

Ultimately, we foresee development of a portable, wireless system (i.e., no percutaneous wires) with USEA-enabled closed-loop control of a physical robotic hand that subjects may take home for use in activities of daily living [32]. Closed-loop control of multiple DOFs of a robotic prosthetic hand with graded feedback from multiple cutaneous and proprioceptive sensors via USEAs may allow users to perform activities of daily living while paying little visual attention to their prosthesis, or engage in tasks for which visual feedback is not readily possible (e.g., grasping the back side of an opaque object). In addition to restoring lost function, chronic use of such a device may transform subjects' perception of their prosthesis from simply being a useful tool to being an integral part of their body. We anticipate that embodiment of a prosthesis will not only reduce prosthesis rejection rates, but may also alleviate phantom limb pain and contribute to a restored sense of well-being and completeness.

2.6 Conclusion

We have demonstrated that recording and stimulation via multiple USEAs implanted in the peripheral arm nerves of human amputees can provide subjects with a rich selection of proprioceptive and cutaneous sensations spanning the phantom hand. Furthermore, we restored movement control and sensation via a virtual prosthesis in a one-DOF, single-percept, closed-loop control scenario. No long-term functional deficits reported by our subjects, although the implant did lead to a local infection in S4 that resolved with antibiotic treatment and explant of the devices. The subjects enjoyed feeling sensations on their phantom hand and moving the virtual prosthesis. Future work should include use of biofidelic stimulation patterns and encoding of percept intensity gradations for sensory encodes. Ultimately, we expect USEA-restored sensation and motor control to be used in closed-loop as part of a robotic upper limb prosthesis which amputees may take home for use in activities of daily living.

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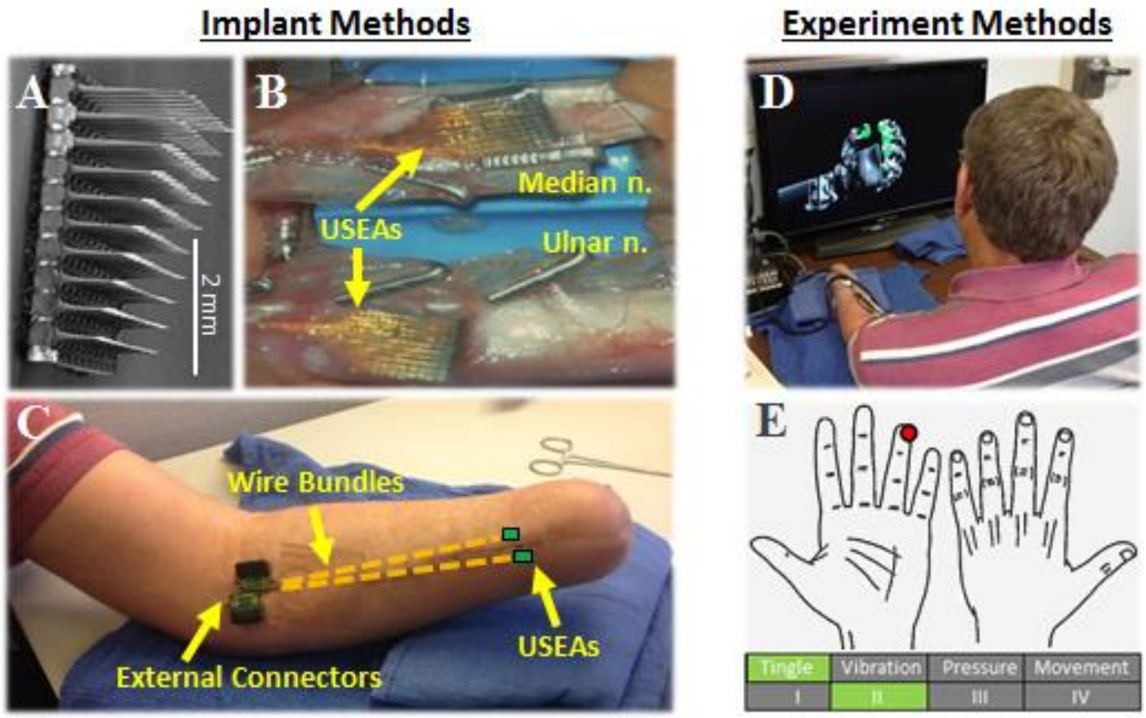

Fig. 2.1. USEA implant and experimental procedures. USEAs implanted in human peripheral arm nerves were used to provide amputees with multi-DOF control of virtual prosthetic hand movement and restore numerous hand sensations. A) Scanning electron microscope image of a USEA. B) Two USEAs were implanted in each subject (subject S4, shown here), one in each of the median and ulnar arm nerves. An organic nerve wrap, fastened with vascular clips, enclosed each USEA. C) USEA lead wires and ground and reference wires were connected to external connectors via a percutaneous incision (subject S3, shown here). D) USEA recordings were used to provide subjects with control of movement of a virtual prosthetic hand (subject S3, shown here). E) USEA stimulation was used to provide subjects with numerous sensations on the phantom hand. Subjects documented the nature of each sensation (location, quality, and intensity/size) using custom software.

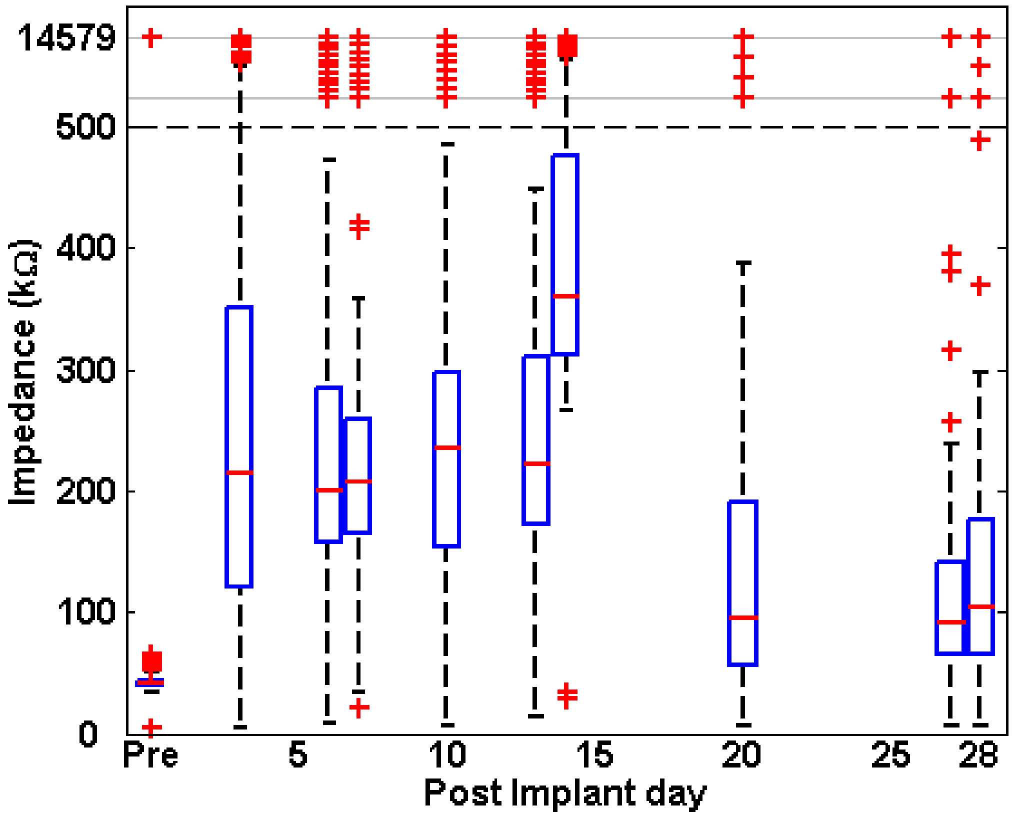

Fig. 2.2. USEA impedances over time. A boxplot of the impedances over time is shown for the 96 electrodes on the median nerve USEA for subject S4. For each day shown, box edges delineate the 25th and 75th percentiles, with a red line midway indicating the median. Outliers are plotted individually as red crosses (outliers are defined as datapoints which are more distant than 1.5*IQR below or above the 25th or 75th percentile, respectively). Whiskers extend to the most extreme datapoints not considered to be outliers.

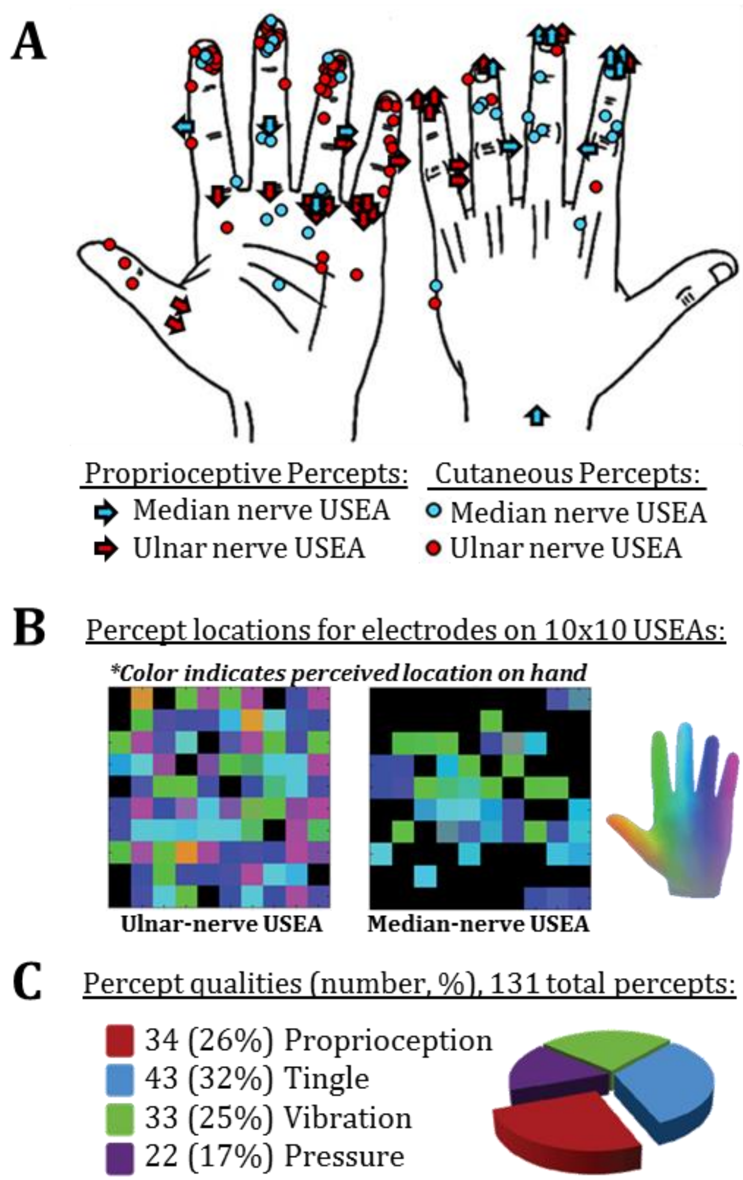

Fig. 2.3. Up to 131 sensory percepts spanning the hand. USEA microstimulation provided a rich selection of percepts of various qualities and locations spanning the phantom hand (subject S4, shown here). A) Stimulation of individual electrodes via two USEAs restored 131 percepts across the phantom hand including both proprioceptive and cutaneous percepts (collected over a 2-day period). Numerous cutaneous percepts were restored on each digit and the palm, and proprioceptive percepts were restored for 17 different movements, including flexion and extension of each finger and flexion of the thumb. For proprioceptive percepts, upward arrows indicate extension, while downward arrows indicate flexion. B) 131 electrodes across the 10x10 USEAs evoked the percepts shown in part A, with no apparent somatotopic arrangement across the nerve cross-section. C) Evoked percepts were of various qualities, with 26% of evoked percepts described as proprioceptive, and 74% of evoked percepts being cutaneous (including “tingle,” “vibration,” and “pressure”).

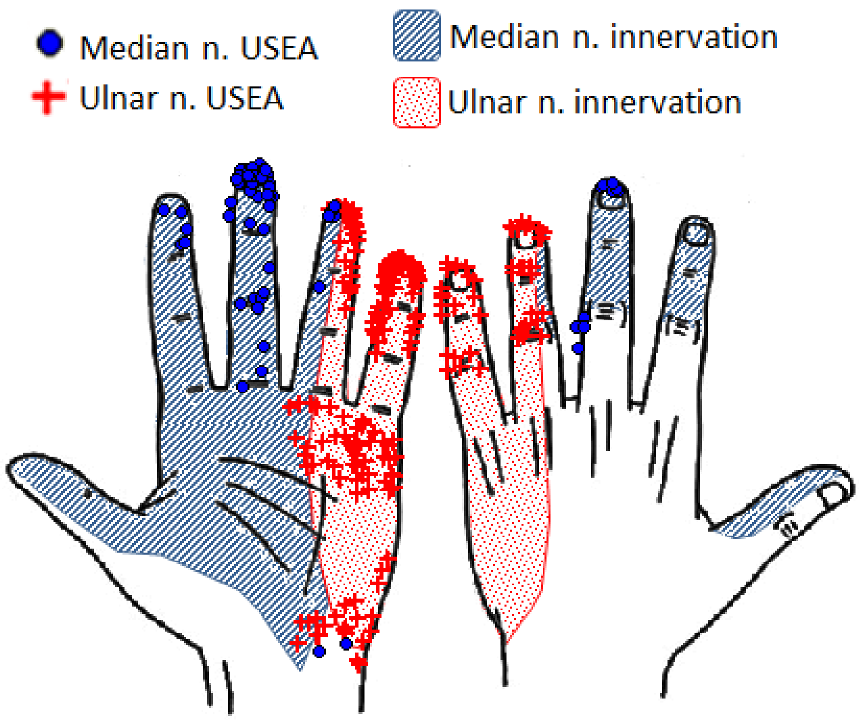

Fig. 2.4. USEA-evoked percepts lie within innervation regions. Percepts evoked by median and ulnar nerve USEAs are generally within the established intact-hand innervation regions for each nerve. For the example shown (subject S3, week 2), 92% and 89% of median-nerve-USEA- and ulnar–nerve-USEA-evoked percepts are within their expected distributions, respectively.

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CHAPTER 3

DISCRIMINATION AMONG MULTIPLE CUTANEOUS AND PROPRIOCEPTIVE HAND PERCEPTS EVOKED BY NERVE STIMULATION WITH UTAH SLANTED ELECTRODE ARRAYS IN HUMAN AMPUTEES

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David M. Page, Suzanne M. Wendelken, Tyler Davis, David T. Kluger, Douglas T. Hutchinson, Gregory A. Clark

Author contributions: DMP, SMW, TD, DTK, and GAC designed and carried out the experiments; DTH performed implant and explant surgeries; DMP wrote the manuscript; other authors edited the manuscript.

3.1 Abstract

Basic hand prosthesis sensation has previously been restored to human amputees using peripheral nerve stimulation; however, functional discriminability among many restored sensations of different hand locations, qualities, and intensities has not been formally reported. The level of information encoded regarding cutaneous percept locations, qualities, and intensities, as well as proprioceptive information regarding joint positions and velocities, varies widely among different neural interface approaches. The Utah Slanted Electrode Array (USEA) has previously been shown to encode many unique sensory percepts of a variety of naturalistic qualities spanning the hand, due to its cross-sectional nerve access via 100 microelectrodes, but formal discrimination among these many percepts has not been shown. We implanted a USEA in each of the median and ulnar residual arm nerves of three transradial human amputees. During subsequent experimental sessions, subjects successfully discriminated among restored sensory percepts of varying cutaneous and proprioceptive locations, qualities, and intensities in blind discrimination trials, including discrimination among up to 10 different location-intensity combinations (15/30 correct trials, $p < 0.0005$). Variations in the site of stimulation within the nerve (via electrode selection) enabled encoding of up to 5 discriminable percept locations and qualities (35/35 correct trials, $p < 0.0001$), whereas variations in the frequency of stimulation enabled encoding of up to 4 different discriminable percept intensities (14/20 correct trials, $p < 0.005$), such as skin pressure intensity, vibration intensity, or joint position. Additionally, simultaneous stimulation of two USEA electrodes that evoked distinct sensory percepts in isolation resulted in an emergent sensation likely due to current summation in the nerve, whereas interleaved

stimulation resulted in simultaneous perception of the two distinct percepts with no additional sensations, such as may be desired during multisensor closed-loop prosthesis use (20/23 correct trials, $p < 0.001$). We conclude that USEA stimulation enables encoding of a diversity of sensory percepts of different locations, qualities, and intensities, and that these percepts are functionally discriminable. We foresee these functionally-discriminable percepts as a potentially rich source of sensory feedback that may enhance performance and embodiment during multisensor, closed-loop prosthesis use.

3.2 Introduction

Clinically available arm prostheses do not currently provide amputees with sensory feedback. Sensation from a prosthesis has been shown to be important for performance of functional tasks and for prosthesis embodiment [1], [2], and many amputees indicate interest in having sensory feedback from their prosthesis [3]–[7]. Peripheral-nerve interface approaches, such as Utah Slanted Electrode Arrays (USEAs), transverse intrafascicular multichannel electrodes (TIMEs), flat interface nerve electrodes (FINEs), and longitudinal intrafascicular electrodes (LIFEs) have demonstrated the ability to evoke sensory percepts of different locations, qualities (e.g., submodalities), and intensities on the missing hand of amputees. However, none of these have formally assessed functional discriminability among sensory percepts of different locations, intensities, and qualities [8]–[12], with the exception of an early, high-level report using USEAs [13]. Basic functional discrimination has been shown for objects of different shapes/sizes and compliances during closed-loop prosthesis control [1], [14].

The USEA provides mid-axon, intrafascicular access to nerve fibers spanning the cross-section of a peripheral nerve via 100 penetrating microelectrodes. In contrast to other peripheral nerve interfaces, USEAs offer cross-sectional nerve access via many channels, enabling activation of numerous sensory percepts spanning the hand [12], [13]. During stimulation of each individual electrode of the USEA, a single axon or small subsets of axons can be activated in isolation, creating perception of a stimulus at distinct projected fields. The selection of different stimulation electrodes enables activation of different axons or subsets of axons with different projected field locations on the hand, and potentially with different sensory qualities. The stimulus intensity at each location can be encoded based on the frequency of stimulation [12], [15]. Despite this understanding, prior publications using USEAs have not fully tested the extent to which human subjects can discriminate among multiple proprioceptive and cutaneous sensory percepts of different locations, qualities, and intensities, such as would be desirable during multisensor closed-loop prosthesis control.

Cutaneous location-discrimination in the intact hand has been performed previously via a 2-point discrimination task, in which functional discriminability was achievable for stimuli as close as 0.55 mm apart [16]. This high level of discriminability is likely attributable to intensity encoding via a population of afferents both close to, and distant from, the site of applied tactile pressure (receptor density is on the order of 1 per square millimeter on the palmar hand [17], [18]). Natural activation patterns in the human hand include activation of several different cutaneous mechanoreceptor subtypes innervating many different locations on the hand. Humans are likely capable of discrimination among hundreds of sensory locations spanning the intact hand.

In microneurography studies, intact subjects have also discriminated among tactile percepts with the same location, but with different intensities. A roughly linear, nearly 3-fold increase in perceived intensity was noted both for normal cutaneous forces between 1-5 N and tangential forces between 1-3 N [19], with an informal indication that subjects are likely capable of discriminating up to ~10 different constant-force levels. Constant-force intensities are generally accepted as being primarily encoded in the firing rates and activation patterns of type I slowly-adapting receptors (e.g., Merkel disk receptors) [20]–[23], although many receptor subtypes are generally activated during naturalistic touch of an intact hand. Type I and type II rapidly-adapting cutaneous mechanoreceptors (i.e., Meissner and Pacinian corpuscles) are generally assumed to be the primary encoders of vibratory intensities via their population activation patterns and firing rates [20]. Human subjects have also been able to differentiate among at least 4 different amplitudes of vibratory tactile stimuli [24].

In previous work, with four subjects referred to as S1-S4, we have shown that USEAs implanted in residual peripheral arm nerves of human amputees provide up to 131 sensations of various qualities and locations spanning the phantom hand of human amputees [12], [13]. However, past reports included only limited details regarding basic location and quality discrimination among cutaneous percepts for three subjects (S1-S3). Furthermore, previous reports did not include cutaneous intensity discrimination trials or discrimination among different proprioceptive digit positions, nor did they include discrimination trials for combinations of percepts with different locations and intensities such as would be presented during closed-loop prosthesis control.

In expansion of our prior work, we now provide additional results from three recent subjects, S3-S5, each of which received implantation of two USEAs, one in the residual median nerve and one in the residual ulnar nerve. These results include successful discrimination among 5 or more cutaneous locations (S3 and S4), 4 levels of cutaneous pressure (S5), 10 cutaneous location-intensity combinations (S5), and 7 proprioceptive digit-position combinations (S5). We also report on a new approach for delivering multielectrode USEA stimulation in a time-shifted manner to avoid current-summation effects, which enabled simultaneous, multipercept sensation in subject S3, such as may be desired during multisensor, closed-loop prosthesis control. This new approach was outlined in brief in a previous short publication [13], and an expanded description is provided here.

3.3 Material and methods

3.3.1 Volunteers

Three transradial amputees participated in this study, referred to as S3, S4, and S5. Subject S3 was a 50-year-old male with a left-arm amputation which had occurred 21 years prior. Subject S4 was a 36-year-old male with bilateral amputations which occurred 16 years prior. Subject S5 was a 43-year-old male with bilateral amputations which occurred 24 years prior. Each subject underwent psychological and medical assessments prior to participating in the study. Preimplant mirror-box or prosthesis-video training materials were provided to the subjects, as reported with previous subjects [12], [13], [25]. The subjects were monitored for medical risks both during and after the implant period, and subjects S4 and S5 were treated for implant-related infections which resolved without issue. The consenting process and experimental procedures were approved by the

University of Utah Institutional Review Board, and the Department of the Navy Human Research Protection Program.

3.3.2 Device

Two USEAs (Blackrock Microsystems, Salt Lake City, UT, USA) were implanted in each subject: one in the median arm-nerve and one in the ulnar arm-nerve. The implant location for subject S3 was in the left forearm, near the end of the residual limb, whereas the implants for subject S4 and S5 were placed midway along the left upper arm, proximal to the medial epicondyle, proximal to many motor branch points. USEAs consisted of 100 silicon microelectrodes spaced 400 μm apart in a 10x10 grid across a 4x4 mm square base. The electrodes varied from ~0.75 – 1.5 mm in length to allow cross-sectional access to the peripheral arm nerves [26]. Separate looped platinum wires were also implanted as stimulation return leads and for use as recording reference and ground leads. Electrical connection to each USEA electrode was available via an external printed circuit board which was coupled transcutaneously to USEAs via a bundle of gold lead wires. Connection of the external circuit board to stimulation and recording hardware was made via a ZIF-Clip-96 connector cable (Tucker-Davis Technologies Inc., Alachua, FL, USA) for S3 and S4, or a 96-channel Gator connector cable (Ripple LLC, Salt Lake City, UT, USA) for S5.

The slanted nature of the USEAs enables cross-sectional nerve access to fibers at different depths, thereby increasing the possibility of activation of different axons or subsets of axons with each electrode [26]. An effort was made during the implant surgery to implant USEAs into the nerves so that the electrodes were positioned squarely perpendicular to the length of the nerve, which maximizes the cross-sectional nerve coverage of the USEA electrodes. The two-dimensional distance between two electrodes on the cross-sectional projection plane is likely the most influential factor on their ability to activate different axons or subsets of axons (Fig. 3.1). The stimulation amplitude on a given electrode influences which axons near the tip of the electrode are activated, whereas the stimulation frequency influences their firing rate. The stimulation amplitude may also influence firing rate when modulated at perithreshold levels, for example, when only a subset of stimulation pulses in a pulse train result in generation of an action potential.

3.3.3 Surgical and experimental procedures

Subjects were given prophylactic antibiotics the day before, the day of, and for several days following the implant surgery (100 mg minocycline, 7 days, twice per day). USEAs were implanted in each subject under general anesthesia, via similar methods to those described in past publications [12], [13]. For subject S5, electromyography leads were also placed in the muscles of the forearm for recording purposes (details regarding motor decodes via electromyography leads and USEAs as well as closed-loop control will be provided in a future publication). After exposure of each nerve implant site, the epineurium was dissected away, and USEAs were inserted into the nerve using a pneumatic insertion tool [27]. USEA lead wires and reference and ground wires were sutured to the epineurium, and a collagen wrap (AxoGen Inc., Alachua, FL, USA) was secured around the USEA, nerve, and reference and ground wires using vascular clips (Fig. 3.2a). For subject S5, the epineurium was sutured around the USEAs and reference and ground wires prior to placement of the collagen wrap. Upon removal of the tourniquet, 0.1 mg/kg of dexamethasone was delivered intravenously to the subjects as a potential means for decreasing the foreign body response [28], [29].

The site of percutaneous wire passage (Fig. 3.2b) was redressed roughly once per week using an antibiotic wound patch (Biopatch, Ethicon US LLC, Somerville, NJ, USA). Subjects S4 and S5 both experienced infections at the USEA implant site with subsequent full recoveries after USEA extraction and antibiotic treatment. Implants were removed after 4 weeks, 5 weeks, and 13 weeks, for S3, S4, and S5, respectively. The USEAs from subject S3 were removed along with the section of implanted neural tissue for histological analysis [30].

Experimental sessions were typically carried out several days per week, for several hours each. In addition to the stimulation-evoked sensory percepts reported here, experiments consisted of impedance testing, decoding of neuronal and myoelectric signals for prosthesis movement control, and closed-loop control of a prosthetic hand.

3.3.4 Microstimulation

Electrical stimulation was delivered using the IZ2-128 System (Tucker-Davis Technologies Inc., Alachua, FL, USA) for S3 and S4, or the Grapevine System (Ripple LLC, Salt Lake City, UT, USA) for S4 and S5. Stimulation pulses were biphasic (cathodic first) with each phase typically having a duration of 200 μs (as well as a 100-μs interphase interval). Subjects used either custom software to indicate the location, quality, and intensity or size of each USEA-evoked sensory percept on the image of a hand, or verbal descriptions. Subjects selected percept qualities from a list or created their own descriptors as necessary. Representations of percept locations and sizes, such as those shown in Figs. 3.3, 3.4, 3.5, 3.6, and 3.7, were created based on the subjects' software markings as well as their verbal descriptions where necessary.

Full-USEA threshold maps were collected periodically for each subject, as described previously [12], [13]. These full-USEA maps provided a basis for selection of the electrodes used in the discrimination trials reported here. During discrimination trials for subjects S3 and S4, a 200-ms train of stimulation was delivered at 200 Hz each time the subject or an experimenter pressed a button. For subject S5, three or four 500-ms trains of 100-Hz stimulation (unless noted otherwise, such as during intensity-encoding sessions) were delivered at a 50% duty cycle after the subject or the experimenters pressed a button. Subject S5 was typically instructed to determine the final percept intensity, quality, and location classification on the basis of the percept evoked by either the initial train in a trial or the final train in a trial for a given session, although practices varied depending on the session. Prior to discrimination trials, the activation threshold amplitude for each electrode (in μA) was determined by incrementally increasing the amplitude until the subject perceived a sensation.

3.3.5 Discrimination trials and data analysis

Discrimination trials were performed by all three subjects during different stimulation sessions. A stimulation session typically included mapping the percept locations, qualities, and intensities associated with several different USEA electrodes, and then down selecting to a subset of locations, qualities, intensities, or combinations for formal discrimination trials. Discrimination trial results reported here were not pooled across sessions or subjects; however, we have included results from similar discrimination trial configurations for different subjects.

Discrimination experiments were performed by delivering randomly-ordered stimulation trials in which the subject was required to classify the location, quality, and/or intensity of the evoked percept for each trial. Stimulation conditions varied across trials, including stimulation via different USEA electrodes or combinations of electrodes, and/or use of different stimulation frequencies. Formal discrimination trials were preceded by informal practice trials in which the subject experienced each different stimulation condition and formulated category labels for the percept associated with the condition. Once the subject felt comfortable identifying the location, quality, and/or intensity of the different stimulation conditions, formal blind trials commenced in which the subject was required to select one of his predetermined percept categories in response to each stimulation trial.

For subject S3 and S4, discrimination trial stimulation conditions included different electrodes and combinations of electrodes. For subject S5, stimulation conditions included different electrodes and/or stimulation frequencies. Importantly, catch trials (no stimulation) were added as a stimulation condition for subjects S4 and S5 to test the hypothesis that sensory percepts were indeed evoked by USEA stimulation (in contrast to pseudesthesia).

Data analysis for discrimination trials was performed using the binomial test, where the probability of guessing the correct classification on a given trial was determined as the inverse of the number of predetermined classification categories. Hypothesis testing was performed with a critical value of $\alpha = 0.05$ A Bonferroni adjustment was made to the critical value for post-hoc tests by dividing the critical value by the number of post-hoc tests performed.

3.4 Results

Our subjects performed functional discrimination trials for percepts of different locations and qualities, percepts with the same location but different qualities, and percepts with the same location and quality but with different intensities. Additionally, subject S5 performed combined location/quality/intensity discrimination trials, including trial sets with cutaneous percepts and trial sets with proprioceptive percepts. Functional discrimination among percepts of different locations, qualities, and intensities will be important for future use of sensory feedback from multiple prosthesis-coupled sensors during closed-loop prosthesis control.

3.4.1 Location discrimination

Subject S3 successfully discriminated among 5 stimulation conditions that evoked sensation at five different hand locations: ring finger tip, little finger tip, little finger base, wrist, and combined perception at all four of these locations. These percepts were evoked by individual stimulation of four ulnar-nerve-USEA electrodes and combined simultaneous stimulation of all four of these electrodes, respectively. Stimulation amplitudes for the four electrodes ranged from 14-30 μA. The subject discriminated among these stimulation conditions by classifying the percept evoked into one of the 5 predetermined classification categories in 35/35 successful trials ($p < 0.0001$, binomial test; Fig. 3.3a). Importantly, the four electrodes selected for these stimulation trials had tip positions as close as ~899 μm within the nerve, yet they each evoked consistently unique sensory percepts, suggesting an exquisite level of selectivity in axon activation. Additionally, the combined stimulation of all four electrodes did not result in emergent sensory percepts (i.e., in addition to the four individual percepts), suggesting that current summation during simultaneous stimulation was limited.

To better study current summation during simultaneous stimulation of multiple electrodes in subject S3, we selected two ulnar-nerve-USEA electrodes with tips placed less than ~899 μm apart within the nerve (~805 μm cross-sectional projection separation assuming USEAs were implanted squarely perpendicular to the nerve) and delivered four stimulation conditions: individual stimulation of each of the two electrodes in isolation, simultaneous stimulation of both electrodes with no time shift, and simultaneous stimulation of both electrodes with a 3-ms time shift relative to each other, which produced an interleaved stimulation pattern between the two electrodes. Stimulation amplitudes for the two electrodes were 23 μA and 20 μA, and stimulation was delivered continuously for 4 s during each trial. The individual stimulation via two different electrodes consistently produced sensations of little-finger-tip sting and lateral-palm tingle, respectively, whereas interleaved stimulation of these electrodes (3 ms time shift difference, 200 Hz) consistently reproduced both of these percepts concurrently with no emergent sensations, and simultaneous stimulation (no time shift difference, 200 Hz) consistently produced both of these percepts concurrently accompanied by an emergent 'massage' feeling bridging between them (20/23 correct discrimination trials, $p < 0.001$, binomial test, Fig 3.3b). One possible explanation for the emergent massage feeling during simultaneous stimulation with no time shift difference is that multiple additional axons may have been activated due to spatiotemporal current summation from the two electrodes [26]. Future use of simultaneous and interleaved multielectrode stimulation may allow for improvements in the number, nature, and stability of restored percepts. This result also provides an important proof-of-concept for a method of interleaving stimulation via different USEA electrodes when current-summation effects are not desired, for example, during closed-loop prosthesis control with simultaneous USEA-evoked sensory feedback from multiple prosthesis sensors.

Subject S4 also performed location-discrimination trials, including discrimination among eight different cutaneous stimulation configurations: individual stimulation of each of 3 ulnar-nerve-USEA electrodes, simultaneous combined stimulation using each combination of subsets of 2 of these 3 electrodes, simultaneous combined stimulation using all 3 electrodes, and no stimulation (11/24 correct trials, $p < 0.006$, binomial test, Fig. 3.3c). Stimulation amplitudes on the three electrodes ranged from 7-13 μA depending on the electrode. Single-electrode percepts included sensation of tingle on the ring finger, touch on the little finger and palm (sometimes with an associated sense of little-finger movement), and tingle on the outer edge of the little finger. The precise nature of combination percepts were not fully documented prior to beginning the formal trials, but informally, the subject indicated that they consisted of a combined sensation of the percepts evoked by the individual electrodes, potentially with fused projected fields or emergent sensations. Importantly, these trials also included a condition of “no stimulation,” which was not included in testing with subject S3. Subject S4 successfully identified when stimulation was delivered compared with when no stimulation was delivered in 24/24 trials ($p < 0.0001$, binomial test), indicating that percepts were indeed evoked by USEA stimulation (in contrast to pseudesthesia).

3.4.2 Quality discrimination

Subject S3 successfully discriminated between two evoked percepts with the same location, but with two distinct qualities, produced via stimulation of two different ulnar-nerve-USEA electrodes (Fig. 3.4). The tips of these electrodes were separated by ~2.1 mm within the nerve (~578 μm cross-sectional projection separation assuming USEAs were implanted squarely perpendicular to the nerve). Stimulation amplitudes for the two electrodes were 11 μA and 12 μA. Prior to formal discrimination trials, the subject identified the percepts evoked by these two different electrodes as having identical intensities and locations near the ring-fingertip ("Right on, exact same space"), but differing qualities of vibration and tingle, respectively. In subsequent formal trials, the subject consistently discriminated between the percepts evoked by the two electrodes (30/30 correct trials, $p < 0.0001$, binomial test). We hypothesize that the different qualities of sensations are due to having activated two different sensory afferent subtypes. This result suggests that subjects may be able to discriminate among activation of different afferent subtypes which have overlapping projected fields. We further hypothesize that future activation of different mechanoreceptors with similar projected fields in biofidelic patterns may evoke a percept with a more naturalistic quality, similar to the sensation experienced via an intact hand.

3.4.3 Intensity discrimination

Subject S5 successfully discriminated among 4 different cutaneous-percept intensities, encoded via stimulation with different frequencies on a single median-nerve-USEA electrode which evoked a sensation of tingle on all four fingertips, although the percept seemed to isolate to the middle-finger only during later stimulation trials (Fig. 3.5). The stimulation amplitude used during trials was 25 μA. During informal practice trials, the subject designated four intensity levels as “high,” “medium,” “light,” or “nothing,” corresponding to stimulation at 100 Hz, 70 Hz, 35 Hz or no stimulation, respectively. During subsequent formal trials, the subject correctly classified these percept intensities in 14/20 trials ($p < 0.005$, binomial test). We anticipate that encoding of discriminable cutaneous percept intensities may provide important enhancements to prosthesis users as contact forces are difficult to gauge using visual feedback.

3.4.3 Combined location and intensity discrimination

Subject S5 performed combined location- and intensity-discrimination trials, similar to what may be used as part of a multisensor closed-loop prosthesis. Trials were performed for both cutaneous and proprioceptive percepts, each with multiple intensity levels encoding either cutaneous pressure/touch, or joint position.

Three cutaneous percepts were encoded in distinct hand locations via median-nerve-USEA stimulation on three different electrodes, with associated percept descriptions of index-fingertip pressure, middle-fingertip touch, and palm pressure. For each of these percepts, stimulation was delivered via at stimulation frequencies of 30 Hz, 70 Hz, or 100 Hz, corresponding to “light,” “medium,” and “heavy” touch or pressure.

The stimulation amplitude used on these three electrodes ranged from 17-64 μA. Sham stimulation was also used (i.e., no stimulation), making a total of 10 classification categories (three intensities at each of three percept locations, plus sham). Subject S5 successfully discriminated among these 10 stimulation conditions in 15/30 trials ($p < 0.0005$, binomial test, Fig. 3.6). In post-hoc analysis, we found that most of the subject's success was attributed to accurate location discrimination (26/30 correct trials, $p < 0.0005$, binomial test for location classification independent of intensity classification, using a corrected critical value of $\alpha = 0.005$), whereas intensity discrimination was successful but seemed challenging (17/30 correct trials, $p = 0.02$, binomial test for intensity classification independent of location classification, using a corrected critical value of $\alpha = 0.005$).

Subject S5 also successfully performed combined location and quality discrimination for two proprioceptive percepts which encoded index-finger and middle-finger flexion positions, respectively, via median-nerve USEA stimulation (Fig. 3.7). Specifically, 17-μA stimulation was delivered at 30 Hz, 80 Hz, or 150 Hz on one median-nerve USEA electrode to encode 10°, 90°, or ~180°/fully-closed flexion on the middle finger (compared to rest position). On a different median-nerve USEA electrode (~1.6 mm away; ~409 μm separation in nerve cross-sectional projection assuming USEAs were implanted squarely perpendicular to the nerve), 40-μA stimulation was delivered at 200 Hz, 50 Hz, or 150 Hz to encode 20°, 50°, or ~180°/fully-closed flexion on the index finger. During practice trials, the subject felt strongly that the nonmonotonic frequency-intensity encoding for the index finger joint position was accurate. However, during formal trials, confusion among the 20°, 50°, and 180° conditions on the index finger was common. A sham condition was also included, creating a total of 7 classification categories (three intensities on each of two digits, plus sham). Subject S5 successfully discriminated among these proprioceptive digit and joint-position combinations in 21/40 trials ($p < 0.0001$, binomial test). The subject performed well in identifying both the location, i.e., the phantom digit moved (32/40 correct trials, $p < 0.0001$, post-hoc binomial test for digit classification independent of joint-position classification, using a corrected critical value of $\alpha = 0.005$), and the joint position (22/40 correct trials, $p < 0.005$, binomial test for joint-position classification independent of joint classification, using a corrected critical value of $\alpha = 0.005$).

3.5 Discussion

We have demonstrated that USEA stimulation can be used to encode sensory percepts with functionally-discriminable locations, qualities, and intensities. Encoding of sensory percepts with different locations and qualities was achieved by stimulation of different USEA electrodes or combinations of electrodes, presumably resulting in activation of different axons or subsets of axons within the nerve. Encoding of sensory percepts with different intensities was achieved by modulation of the stimulation frequency, presumably resulting in an increased firing rate in activated axons. We have also demonstrated that subjects can discriminate among multiple location-intensity combined percepts such as would be desired during closed-loop prosthesis control.

Additionally, we have shown that stimulation on multiple electrodes in an interleaved pattern allows for simultaneous activation of multiple sensory percepts without emergent sensations. Although we have shown that USEA electrodes as close as

800 μm within the nerve cross-section can evoke distinct sensory percepts, simultaneous stimulation via these electrodes often results in current summation and potentially undesired activation of additional axons which evoke additional sensation. Use of interleaved stimulation allows for simultaneous generation of the individual sensory percepts without current-summation effects. During closed-loop prosthesis control, interaction with the external environment may result in simultaneous activation of multiple prosthesis sensors, potentially generating simultaneous stimulation via multiple USEA electrodes. Algorithms may be developed and incorporated to interleave stimulation on different USEA electrodes to prevent current-summation effects. One tradeoff of interleaving stimulation is that a more frequent occurrence of stimulation artifact will likely be produced in USEA electrode recordings, possibly interrupting the ability to perform neural recording decodes for prosthesis movement control. In this case, it may be desirable to develop stimulation artifact blanking approaches or to implant separate recording electrodes in a distant location where stimulation artifact will be minimized (e.g., the residual limb muscles or a distant nerve location).

Sensory feedback from the hand has been shown to be important for identifying when contact events between the hand and the environment occur and for identifying object properties such as curvature, texture, and weight. These complex properties are interpreted using sensory integration across various proprioceptive and cutaneous channels with many receptive fields. Cutaneous information, encoded via multiple different receptors (e.g., slowly-adapting I, slowly-adapting II, rapidly-adapting I, and rapidly-adapting II), provides information regarding contact locations, object texture, object slippage, and gross shape [20], [22], [23], [31]–[34]. Proprioceptive channels provide information regarding hand conformation and position, which, in conjunction with cutaneous information, provides information regarding object shape, weight, and counterforce [35]. Many of these object properties are challenging to deduce using visual feedback alone, particularly when feedback is needed rapidly during motor tasks [36]. The goal of functional discrimination among a variety of sensory channels is ultimately to provide the brain with sufficient information to deduce useful information regarding interactions with the external environment. Our gross encoding of 3 stimulus locations, each with 3 different intensities, may be sufficient to assist subjects in identifying gross object properties such as size and compliance. However, more complex properties such as curvature and skin indentation direction will likely require encoding via sensory percepts of different submodalities (e.g., RAI and SAI) which have nearby projected fields [37]. Restored sensation via multiple axons with adjacent projected fields may be critical for naturalistic sensorimotor hand control since realtime neural encoding of object properties likely involves cortical comparison of spike timings from neurons with adjacent receptive fields [38]. We anticipate that functional prosthesis control will improve with increasing numbers and variety of discriminable sensory feedback channels.

In addition to functional performance benefits of discriminable, multisensor prosthesis feedback, we anticipate that there will be substantial psychological benefits to restoring sensory feedback to amputees, such as prosthesis embodiment [2]. Our subjects enjoyed the variety of sensations evoked by USEA stimulation, including both proprioceptive and cutaneous sensations. After his first stimulation session, subject S3 stated, “My hand is starting to stimulate like it’s starting to wake up or something. It really feels good. […] It's good to know that there's something still there." In response to the proprioceptive percept of middle-finger flexion delivered during proprioception discrimination trials, subject S5 stated that the sensation felt "exactly like movement of the middle finger." When asked to describe one of the sensory percepts evoked during cutaneous location-intensity discrimination trials, subject S5 stated, "It feels like touch. It feels like if I touched that door." We hypothesize that the sense of prosthesis embodiment will increase as a function of the number of discriminable sensory percepts provided for feedback.

The ultimate goal of restored prosthesis sensation is not just to provide subjects with a useful tool, but also to provide subjects with a prosthesis that is perceived by subjects as a replacement hand. Although the results of this report do not begin to approximate the sophistication of an intact hand (hundreds of discriminable cutaneous locations, and ~10 discriminable force levels), this work represents a substantial incremental improvement. Specifically, we have demonstrated that USEA-evoked percepts are repeatable (i.e., not pseudesthesia), and that subjects can discriminate among up to 3 gross-level hand regions such as different digits and the palm, each with 3 different intensities. Ongoing work should focus on discrimination among successively closer projected fields to identify minimum discriminable distances. Additionally, interleaved, multielectrode stimulation strategies may produce surround inhibition effects that could improve functional discrimination. Although USEAs offer the highest channel count of any peripheral nerve interface, the 100 channels likely will not provide the incredibly fine level of resolution that would be required to completely restore sensory hand function. Development of a neural interface that may provide such resolution remains as a substantial challenge to the field.

We have also demonstrated in this report that selective activation of distinct axons or subsets of axons is possible using USEA electrodes as close as ~800 μm within the nerve. Stimulation amplitudes were between 7-64 μA for the trials reported here, which apparently allowed for focal activation of axons within the local area of an electrode tip without activating axons associated with electrodes ~800 μm away. Future testing should be performed using closer electrodes, such as neighboring electrodes that are ~400 μm apart, to see if selectivity is achievable. Additionally, we anticipate that selectivity will decrease primarily as a function of cross-sectional projection distance, suggesting that electrodes that are directly distal/proximal to each other are less likely to evoke selective sensory percepts due to the possibility that the same axon(s) will pass near each electrode tip. Future USEA designs may use a steeper slant to allow for improved selectivity along distal-proximal rows.

Alternative methods for encoding intensity in sensory percepts should also be investigated including the use of stimulation amplitude or activation of multiple neighboring electrodes. Subject S5 often indicated that perithreshold stimulation amplitudes evoked weak percepts compared with the stronger percepts evoked by suprathreshold amplitudes at the same stimulation frequency (comfort-level amplitude was typically 5-10 uA above threshold amplitude). We hypothesize that this intensity change is not due to recruitment of additional nerve fibers at these increasing amplitudes, but rather is due to the increased probability of evoking an action potential with each stimulation pulse at suprathreshold levels (compared with perithreshold levels), effectively increasing the firing frequency of the axon(s). Inherent in this hypothesis is the prediction that an increase in stimulation amplitude may encode increasing intensities until a saturation-point is reached (i.e., when each stimulation pulse produces a single action potential in the nerve fiber). Future intensity-encoding experiments using frequency modulation should use suprathreshold stimulation amplitudes rather than perithreshold amplitudes to decrease stochastic variability in frequency encoding at the axon level.

Although functional discrimination among sensory percepts provides an important metric for demonstrating that percepts are distinct, other assessments may provide additional information. For example, the results presented here do not provide an indication of the theoretical resolution of percept intensities or locations. Future experiments should include mapping of the just-noticeable-difference (JND) between percepts of different locations or intensities, such as is provided via the 2-point discrimination task performed in intact human subjects [16]. JNDs can also be quantified for percepts of different intensities to indicate, for example, the minimum discriminable frequency differences for stimulation on an electrode. JNDs should be mapped at multiple frequency levels to provide a test of Weber's law, which predicts that the JND will scale linearly with stimulation frequency [39].

We observed habituation of sensory percepts during intensity discrimination trials in subject S5. To avoid these effects, we typically allowed for ~30 s of rest between each trial. Despite this, the subject's performance discriminating among intensities typically declined as trials continued, and the subject had a tendency to underestimate the percept intensity in later trials compared with earlier trials in a session. The time constant of habituation in intact subjects in response to tactile stimulation is roughly 62-212 s, with a

2-3 min latency after stimulation for full recovery from habituation [40]–[44]. Future intensity-discrimination trials should allow for adequate time for full recovery from habituation between trials. Use of suprathreshold stimulation intensities, or addition of interpulse variability into stimulation trains (in contrast to constant-frequency stimulation), to produce more biofidelic stimulation patterns, may help reduce the effects of habituation.

Although the sensory percepts restored via USEA stimulation are generally stable within a 2-3 h session, the projected field location, quality, and intensity associated with each electrode often varies across sessions. This instability may be due to a number of factors, including micromechanical shifts of the USEA relative to nerve fibers, the developing foreign body response to implanted USEAs, or degradation or failure of USEA electrodes and/or wire bundles. Ongoing improvements to USEAs should continue, with reliability and longevity as a high priority. Longer-duration implants may also result in improved stability. Additionally, novel stimulation strategies, such as multielectrode stimulation, may decrease the variability in population encoding due to microshifts of USEAs. Also, multielectrode population encoding using biofidelic, receptor-type-specific stimulation patterns may decrease between-session variability in which axon are recruited, while also potentially improving the discriminability and naturalism of some USEA-evoked sensory percepts. USEAs and intraneural electrodes, in contrast to extraneural cuff electrodes, are capable of communicating with the peripheral nervous system on its own terms by independently activating subsets of different populations of specific receptor types with known projected fields in naturalistic, custom-tailored, tunable patterns.

Ultimately, we foresee development of a closed-loop prosthesis system with multiple discriminable sensory percepts coupled to sensors that span a physical prosthetic hand for use in activities of daily living. We anticipate that discriminable sensory feedback via a prosthesis will enhance motor control, particularly in scenarios where visual feedback is limited or undesired. Also, we anticipate that discriminable, multisensor feedback with variable intensity and tunable quality will enhance the level of embodiment of a prosthetic limb, helping amputees to feel as though their prosthesis is a replacement hand, in addition to being a useful tool. Sensory feedback during closed-loop control, and any associated limb embodiment, may also alleviate phantom pain and many of the psychological difficulties associated with losing a hand.

3.6 Conclusion

We have shown that human amputees implanted with Utah Slanted Electrode Arrays in their residual peripheral arm nerves can discriminate among a variety of restored hand sensations in blind trials, including: a) percepts with different hand locations, b) percepts with different qualities, and c) percepts with different intensities. Additionally, we have demonstrated that one subject was able to discriminate among percepts cutaneous or proprioceptive percepts with different combinations of location and intensity, such as may occur during functional prosthesis use with multiple graded sensors for feedback. Furthermore, we have presented a multielectrode stimulation strategy using interleaved stimulation, which may be useful for providing evoking multiple sensory percepts concurrently without the effects of current summation during closed-loop prosthesis control. Our subjects enjoyed most of the sensory percepts and appreciated feeling controlled sensation from their amputated hand. Future work should include investigation of functional discriminability using multielectrode biofidelic stimulation patterns, as well exploration of the limit of functional discriminability resolution with USEAs. We hypothesize that functionally-discriminable sensory percepts with different locations, qualities, and intensities, used during closed-loop prosthesis control, will enable enhanced embodiment and improvements in motor performance for prosthesis users.

3.7 Acknowledgments

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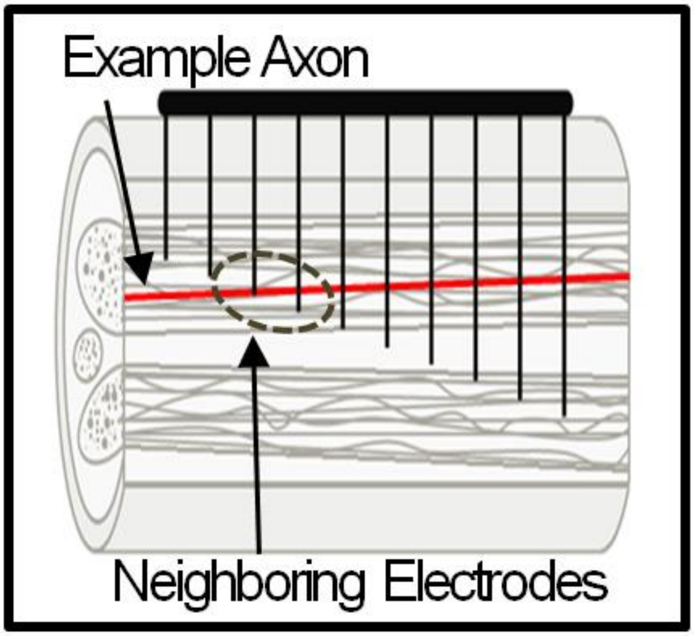


Fig. 3.1. Absolute electrode distance versus cross-sectional projection distance. The 10x10 USEA provides cross-sectional coverage of peripheral nerves, increasing the possibility of activating different axons or subsets of axons with stimulation of each different electrode. Activation of different populations of axons is important for evoking sensory percepts with different locations or qualities. This diagram depicts a USEA implanted in a section of nerve, with an example axon which passes nearby two neighboring electrodes. Although the absolute distance between USEA electrodes is important for assessing stimulation selectivity limits, the cross-sectional distance between electrode tips more precisely indicates the likelihood that electrode tips are close to the same axon(s) (e.g., ~409 μm absolute distance compared with ~83 μm cross-sectional distance for the two example electrodes shown).

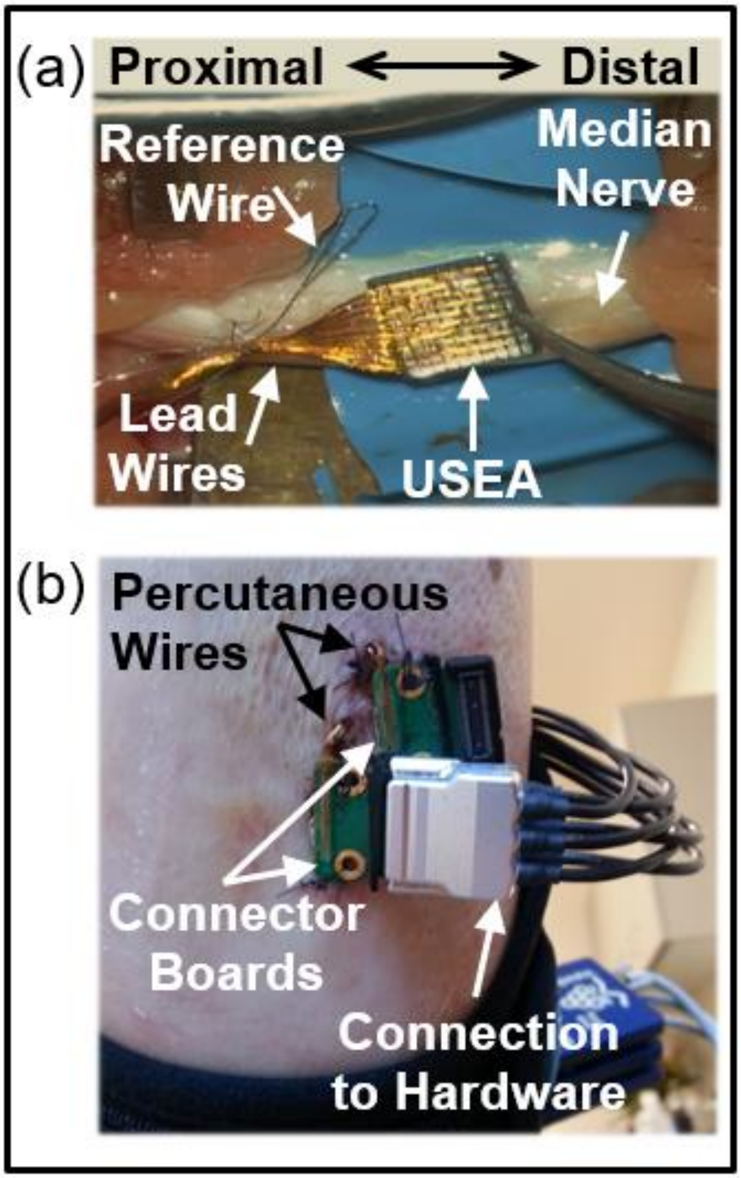
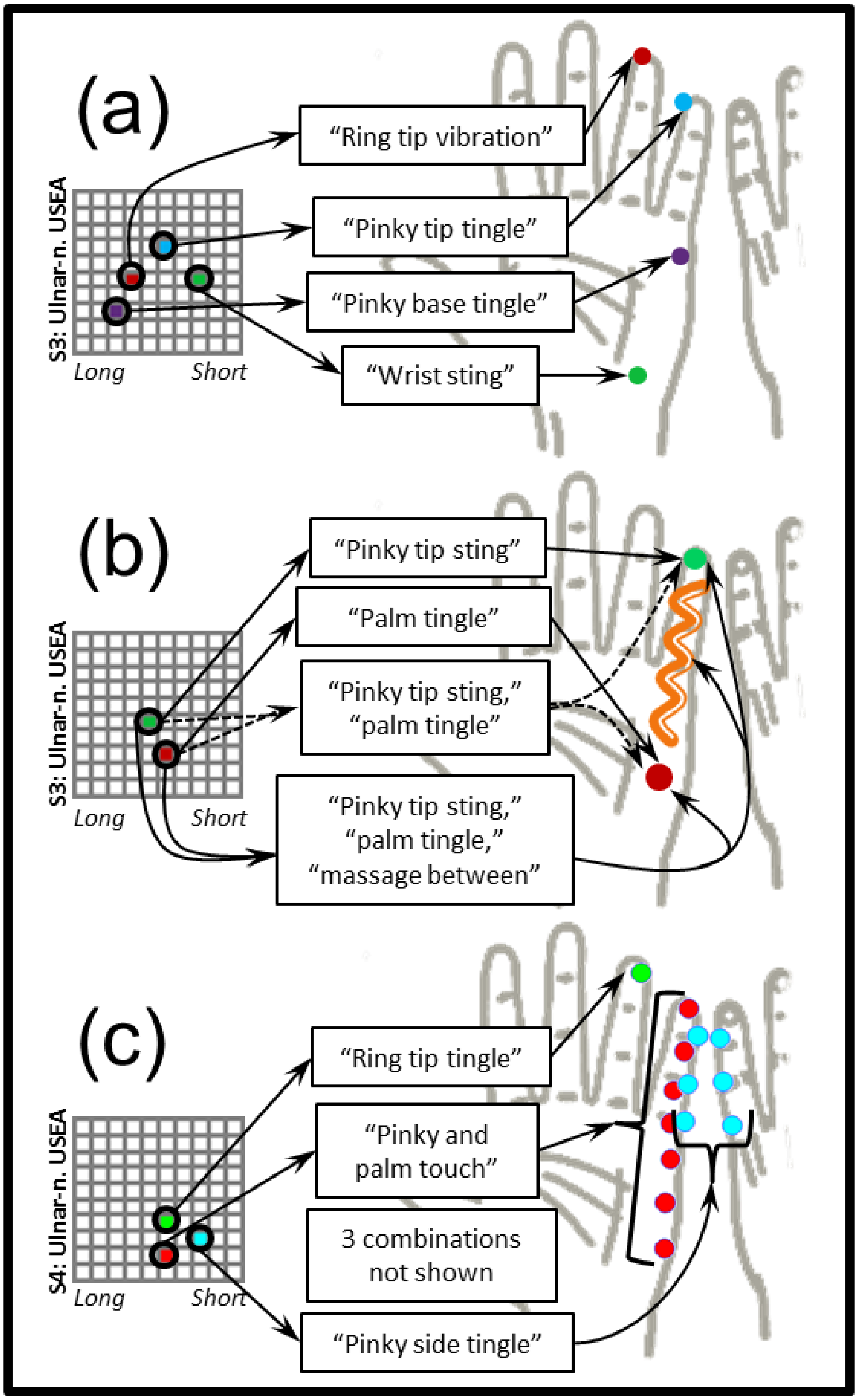


Fig. 3.2. USEA implant methods. (a) Photograph of a USEA in the median nerve of subject S4 taken shortly after pneumatic insertion. The bundle of gold lead wires as well as the separate ground and reference wires were later bundled to the nerve using a collagen nerve wrap. The USEAs were implanted with the long electrodes distally, to avoid damaging axons that may be recruited via stimulation of other USEA electrodes. (b) The USEA lead wires and ground and reference wires for each USEA (one in the median nerve; one in the ulnar nerve) remained attached to external connector boards via percutaneous incisions on either the lower or upper arm (subject S3 lower arm, subjects S4 and S5 upper arm). Stimulation hardware was attached to one or more of these external connectors during experimental sessions.

Fig. 3.3. Location discrimination trials. (a) Subject S3 successfully discriminated among percepts evoked via individual stimulation of 4 different ulnar-nerve-USEA electrodes, as well as simultaneous stimulation of all 4 electrodes (4 categories shown, 5th category was concurrent perception at all four locations; 35/35 successful trials, $p < 0.0001$, binomial test). (b) Subject S3 also discriminated successfully between simultaneous versus interleaved stimulation of two ulnar-nerve-USEA electrodes as well as individual stimulation of the two electrodes. Interleaved stimulation (3 ms time shift difference, 200 Hz) of these electrodes consistently reproduced the original percepts simultaneously with no emergent sensations, whereas simultaneous stimulation (no time shift difference, 200 Hz) consistently produced both of these percepts accompanied by an emergent "massage" feeling bridging between them (20/23 successful trials, $p < 0.001$, binomial test). (c) Subject S4 discriminated among eight different stimulation configurations: individual stimulation of each of 3 ulnar-nerve-USEA electrodes, simultaneous combined stimulation using different subsets of 2 of these 3 electrodes, simultaneous combined stimulation using all 3 electrodes, and no stimulation (11/24 correct trials, $p < 0.006$, binomial test). Importantly, these trials also included a condition of "no stimulation," which was not included in subject S3 testing. Subject S4 successfully identified when no stimulation was delivered with 100% accuracy, indicating that percepts were indeed evoked by USEA stimulation (in contrast to pseudesthesia). These three experiments also demonstrate the exquisite selectivity of USEA-electrode stimulation, with unique percepts being generated by electrodes as close as 800 μm within the nerve.


(a)
S3: Ulnar-n. USEA
Long
Short
"Ring tip vibration"
"Pinky tip tingle"
"Pinky base tingle"
"Wrist sting"
(b)
S3: Ulnar-n. USEA
Long
Short
"Pinky tip sting"
"Palm tingle"
"Pinky tip sting," "palm tingle"
"Pinky tip sting," "palm tingle," "massage between"
(c)
S4: Ulnar-n. USEA
Long
Short
"Ring tip tingle"
"Pinky and palm touch"
3 combinations not shown
"Pinky side tingle"

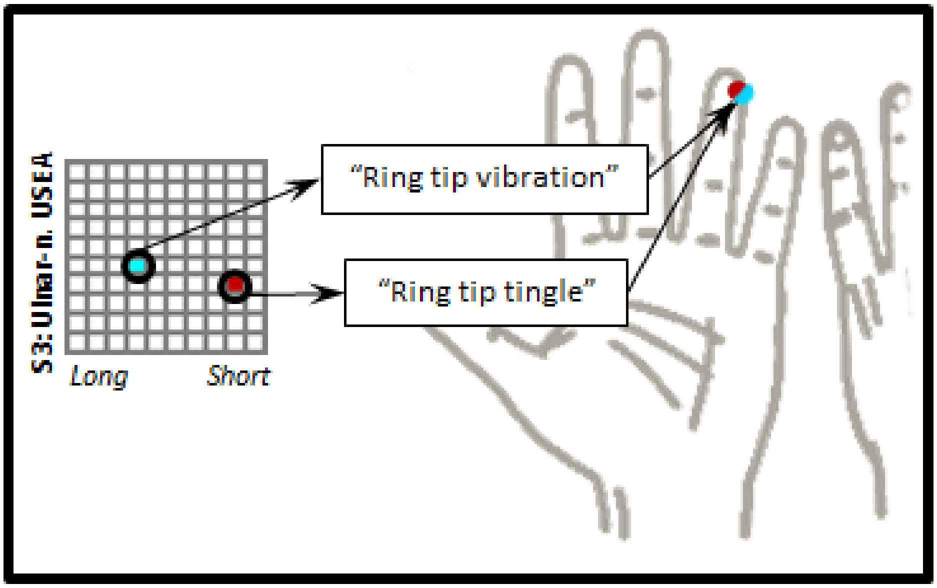


Fig. 3.4. Quality discrimination trials. Subject S3 successfully discriminated between stimulation of two different USEA electrodes that evoked sensation at the same location, but with different qualities (vibration versus tingle). Regarding the locations of the two percepts, the subject said they were “Right on, exact same space.” He also indicated that these sensory percepts were the same intensity level. The subject successfully performed the classification in 30/30 trials ($p < 0.0001$, binomial test).

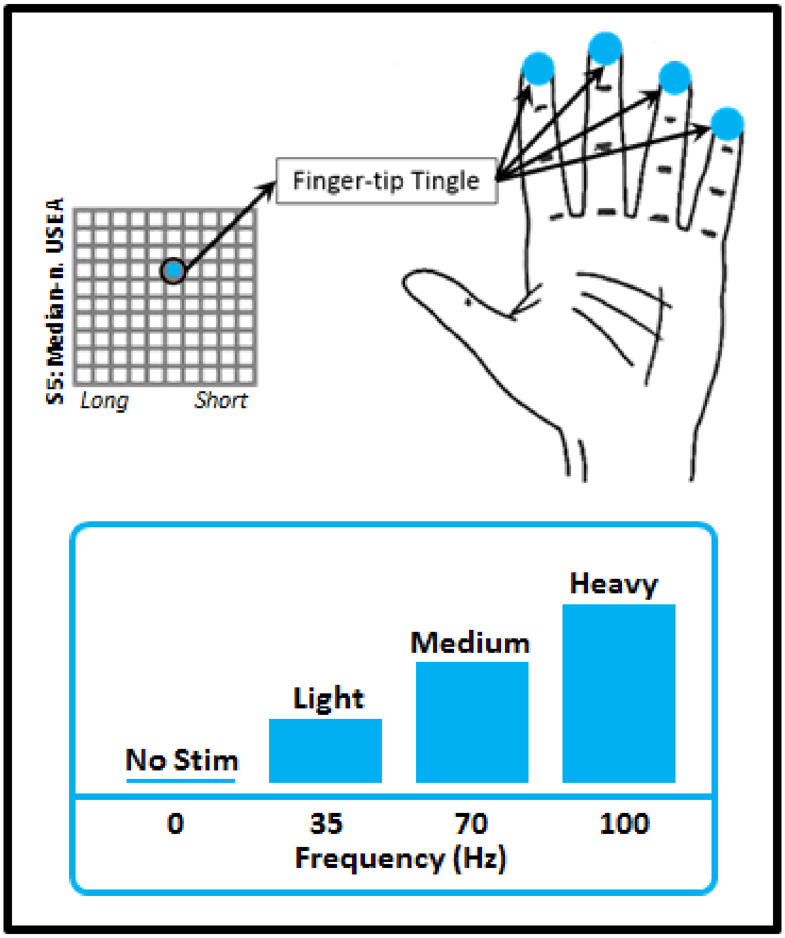


Fig. 3.5. Intensity discrimination trials. Subject S5 discriminated between four percept intensities, evoked by stimulation of a single median-nerve-USEA electrode at three different frequencies (35 Hz, 70 Hz, 100 Hz) or sham (no stimulation). The evoked sensory percept was described as 'tingle' on all four fingertips, although in a later session this percept seemed to consolidate to the middle finger only. The subject successfully classified these different intensities in 14/20 trials ($p < 0.005$, binomial test).

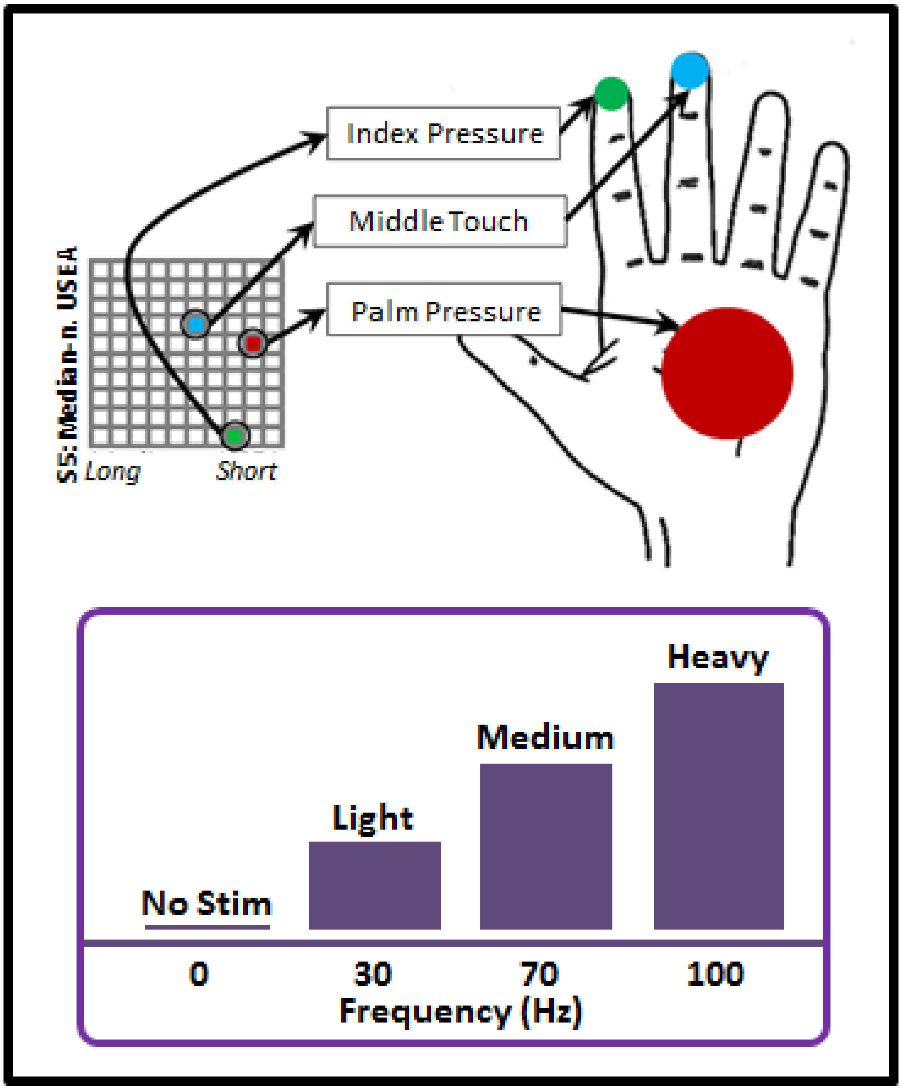


Fig. 3.6. Combined cutaneous location and intensity discrimination. Subject S5 discriminated between combinations of different cutaneous percept locations and intensities. Three median-nerve-USEA electrodes evoked cutaneous "pressure" or "touch" percepts on the index finger, middle finger, and palm, respectively. Three frequencies (30 Hz, 70 Hz, and 100 Hz) were used to encode three different intensities via each electrode. Sham trials were also included (no stimulation) for a total of ten classification categories. The subject correctly classified the combination in 15/30 trials ($p < 0.0005$, binomial test). In post-hoc analysis, we found that most of the subject's success was attributed to accurate location discrimination (26/30 correct trials, $p < 0.0005$, binomial test for location classification independent of intensity classification, using a corrected critical value of $\alpha = 0.005$).

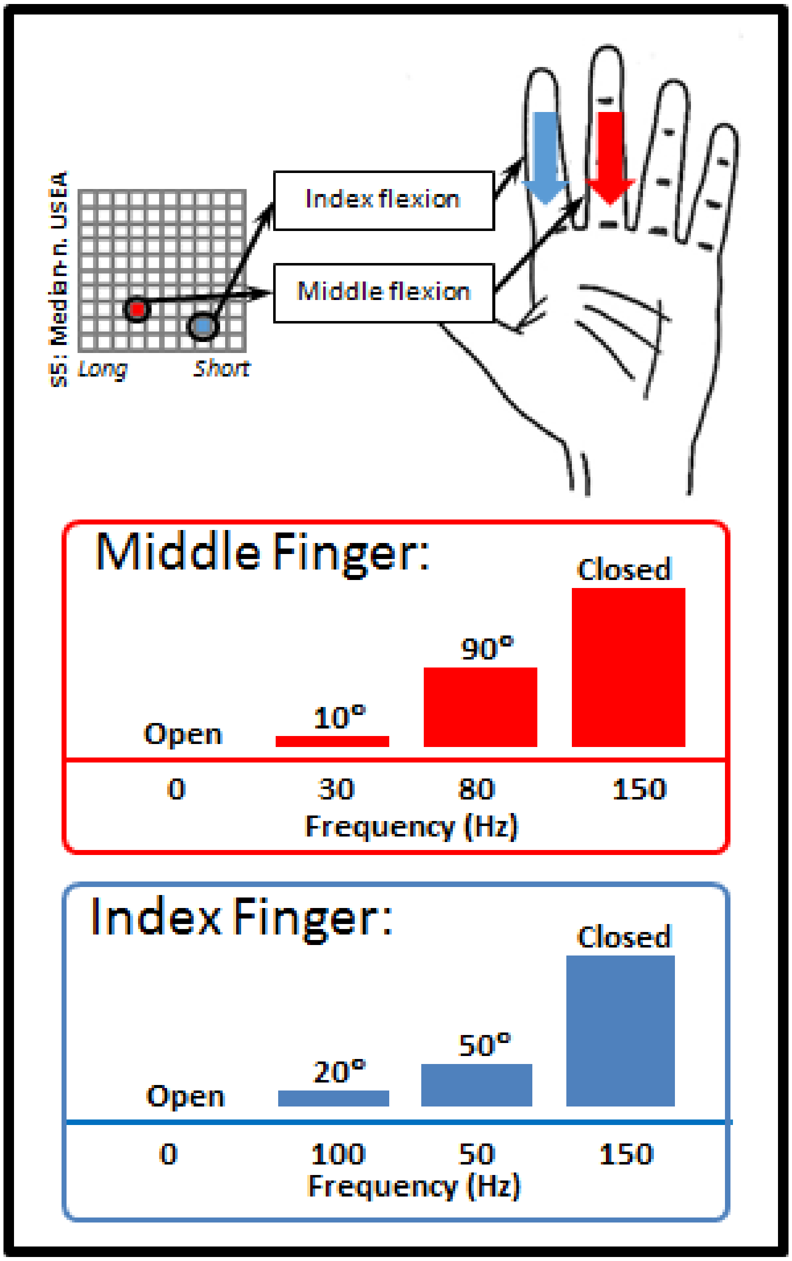


Fig. 3.7. Combined proprioceptive location and quality discrimination. Subject S5 discriminated between combinations of different proprioceptive percept locations and intensities. Two median-nerve-USEA electrodes evoked perception of proprioceptive flexion of the index finger and the middle finger, respectively. Three frequencies were used on each electrode to encode three different joint positions. Sham trials were included (no stimulation) representing a fully-open rest position for a total of seven classification categories. The subject correctly classified 21/40 trials ($p < 0.0001$, binomial test). Note that the subject felt strongly during practice trials that the non-monotonic frequency-position encoding for the index finger was accurate, however we found that confusion between the 20°, 50°, and 180° conditions on the index finger was common during the formal trials.

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CHAPTER 4

PROSTHESIS EMBODIMENT AND PAIN REDUCTION DURING MOTOR CONTROL AND SENSORY FEEDBACK IN AN AMPUTEE

Planned for submission to *Frontiers in Human Neuroscience*

Contributing Authors:

David M. Page, David T. Kluger, Christopher Duncan, Suzanne M. Wendelken, Tyler Davis, Douglas T. Hutchinson, Gregory A. Clark

Author contributions: design of and carrying out the experimental sessions by DMP, DK, CD, SW, TD, GAC; data analysis by DMP, CD, and GAC; surgery and medical care by DTH and CD; writing of the manuscript by DMP; editing of the manuscript by other authors.

4.1 Abstract

We implanted one human amputee with Utah Slanted Electrode Arrays (USEAs) in the residual median and ulnar arm nerves, and intramuscular electromyography (iEMG) recording leads in residual limb muscles, and quantified prosthesis embodiment and phantom pain reduction due to prosthesis movement control and/or sensory restoration. Objective (behavioral) and subjective (survey) measures were used to assess prosthesis embodiment. The subject reported a significant level of embodiment of a physical prosthetic limb during open-loop motor control of the prosthesis (i.e., without sensory feedback), open-loop sensation from the prosthesis (i.e., without motor control), and closed-loop control of the prosthesis (i.e., motor control with sensory feedback). The subject also reported a statistically-significant reduction in phantom pain during experimental sessions that included USEA microstimulation, open-loop prosthesis motor control, and closed-loop prosthesis motor control. To our knowledge, this study represents the first systematic report of phantom pain reduction during neuromuscular prosthesis control and sensation experiments, as well as the first report of prosthesis embodiment during closed-loop prosthesis control.

4.2 Introduction

The emotional, psychological, and functional effects of upper limb amputation can be devastating. Many amputees undergo a period of mourning, a chronic struggle with depression, and endurance of life-long phantom pain [1]–[5], in addition to practical difficulties associated with activities of daily living (ADL) and potential loss of employment. These challenges often result in long-term use of antidepressants and narcotics and ongoing medical costs associated with anxiety and other psychological struggles [6], [7]. We hypothesize that prosthesis embodiment—meaningful integration of the prosthesis into one's body image—as well as sophisticated functional prosthesis use and associated phantom pain reduction, will improve many of these aspects of life for amputees. Additionally, repeatable phantom pain reduction induced via functional prosthesis use may provide a justification for securing insurance payment for advanced prostheses.

The current standard-of-care after upper limb amputation includes four basic options: a) use of a body-powered hook, b) use of a myoelectric hook or hand prosthesis, c) use of a nonfunctional cosmetic prosthesis, or d) use of the residual limb (i.e., no prosthesis) [8]. Most body-powered hooks, myoelectric prostheses, and cosmetic prostheses do not currently provide sensory feedback directly, and motor control of these prostheses is limited to only 1-3 degrees-of-freedom (DOF) which are typically not controllable simultaneously. Many amputees prefer to use their residual limb instead of a prosthesis, which has been proposed to be due to the presence of sensory feedback [9]; however, as for commercially-available prostheses, the residual limb does not provide the sophisticated multi-DOF motor control provided by an intact hand.

Peripheral nerve and muscle interfaces offer an exciting opportunity to provide subjects with improved prosthesis control and sensory feedback. Many different peripheral-nerve interfaces have been used, including transverse intrafascicular multichannel electrodes (TIMEs) [10], flat-interface nerve electrodes (FINEs) [11], and longitudinal intrafascicular electrodes (LIFEs) [12]–[15]; however, none of these approaches have been shown to provide improved prosthesis embodiment or phantom pain reduction when used for motor control and/or sensory feedback. Importantly, each of these neural interfaces is somewhat limited in the number of sensory percepts they are able to produce, due to limited access to the many sensory axons in the peripheral nerve.

Basic motor control has been provided to amputees using implanted myoelectric sensors (IMES) and fine wire muscle electrodes, but outcome measures have focused largely on functional performance [16]–[19], with few reports on psychological and emotional impact metrics such as prosthesis embodiment and/or pain reduction in response to prosthesis motor control [20], [21]. Implants have also been placed in the central nervous system for the purpose of restoring prostheses motor control and sensory feedback [22]–[24]; however, most amputees are unwilling to undergo brain surgery [25]. Targeted nerve reinnervation has also been used to restore basic sensory and motor feedback to human amputees [26]–[29], and prosthesis embodiment was enhanced for two human subjects using sensory feedback alone [30]. However, the study was limited to open-loop sensory-feedback trials (i.e., subjects did not have motor control of the prosthetic hand), in which sensory feedback was provided from only one hand location. The metrics for embodiment in this previous study included survey questions, a temporal order judgment metric using the contralateral intact hand, and monitoring of limb temperature, but did not include quantification of the subjects' perceived phantom hand location. Initial evidence has also been presented that suggests prosthesis sensory feedback can reduce phantom pain [31].

In expansion of the functional performance improvements due to closed-loop prosthesis control we have reported previously using USEAs [32], [33], we here report on the psychological impact of advanced prosthesis control and sensation. We report embodiment of a physical prosthesis during closed-loop, multiple-degree-of-freedom prosthesis control with multiple sensory percepts at different hand locations in a single human amputee. We also report embodiment due to open-loop motor control, as well as embodiment due to multisensor open-loop touch-feedback from the prosthetic hand. This is in contrast to the one past embodiment study with amputees which used only single-sensor, open-loop sensory feedback [30]. Multisensor tactile feedback was provided via intrafascicular stimulation of different electrodes of Utah Slanted Electrode Arrays (USEAs) implanted in the residual peripheral arm nerves. Motor control was provided by decoding intended hand movements from electromyographic recording leads (iEMGs) implanted in the residual extrinsic hand muscles of the residual limb.

This work represents our first use of a physical prosthesis for closed-loop control with USEA-evoked sensory feedback. Additionally, to our knowledge, this is the first publication of prosthesis embodiment during closed-loop prosthesis control, as well as the first report using perceived phantom hand location as a metric for prosthesis embodiment in amputees. This metric has been used extensively in previous studies with intact subjects [34], [35], but never with amputees. We also provide a preliminary report of phantom pain reduction due to participation in experiments including USEA microstimulation, open-loop prosthesis control, and closed-loop prosthesis control.

4.3 Materials and methods

4.3.1 Study volunteer

We implanted Utah Slanted Electrode Arrays (USEAs) and electromyographic recording leads (iEMGs) in one transradial amputee, referred to here as subject S6 (S1-S5 published previously [32], [33]). The subject was recruited by a physician and evaluated by a psychologist prior to participating in the study. The subject was a 57-year-old, left-hand-dominant male, whose left foot and left forearm had been amputated 13 years prior, after an electrocution injury. His unilateral, left-arm amputation was midway along the forearm, leaving many extrinsic hand muscles intact. Notably, the subject had previously received experimental nerve-interface implants on two occasions in his amputated left arm residual nerves. The subject indicated that he generally preferred to use his residual arm instead of a prosthesis, although he occasionally used a body-powered hook for work around his home and a basic rubber-handed myoelectric prosthesis for cosmetic purposes at social gatherings.

Preimplant training included mimicking motor hand movements displayed on a video as well as tactile stimulation training on the skin of his residual limb and his intact hand using a mechanical vibrometer, as outlined previously [33]. The subject routinely used gabapentin (800 mg, typically 1-4 times per day), ibuprofen (800 mg, typically 0-2 times per day), and tramadol (1000 mg, typically 0-2 times per day) both prior to and during the implant period. The subject’s medication use was monitored and documented throughout the study. The consenting process and study procedures were approved by the University of Utah Institutional Review Board, and the Department of the Navy Human Research Protection Program.

4.3.2 Devices

Two Utah Slanted Electrode Arrays (USEAs; Blackrock Microsystems, Salt Lake City, UT, USA) were implanted in the subject’s residual limb: one in the median nerve, and the other in the ulnar nerve. USEAs are silicon microelectrode arrays, with 100 electrode shafts on each USEA, arranged in a 10x10 grid on a 4 mm x 4 mm base. Electrode shafts are spaced 400 μm apart, with lengths of shafts varying along a single dimension from ~0.75 – 1.5 mm [36]. The USEAs used for these experiments had iridium oxide tips and parylene-C insulation. Four looped platinum wires were also implanted—two served as electrical ground and stimulation return, and two served reference wires for recording. Four electrodes from the longest row of electrode shafts on the USEA were also sometimes used as an on-array electrical reference for recordings [37]. The ground and reference wires, as well as the electrodes on the USEAs, were wired to external connectors via a percutaneous incision to allow connection via active or passive Gator Connector Cables (Ripple LLC, Salt Lake City, UT, USA).

Eight intrafascicular electromyographic recording leads (iEMGs; Ripple LLC, Salt Lake City, UT, USA) were implanted in the residual arm muscles, with attempted targeting of each lead to different lower-arm extensor or flexor muscles. Each of the eight leads contained four electrical contacts, totaling 32 recording channels. A separate iEMG was implanted proximal and posterior to the elbow to provide contacts for an electrical reference and ground. The implanted EMG electrodes were also wired via a percutaneous incision to an external Gator Connector Board (Ripple LLC, Salt Lake City, UT, USA).

4.3.3 Surgical implant

Starting the day before the implant surgery, the subject was given an oral prophylactic antibiotic (100 mg minocycline, 7 days, twice per day), which has been reported to improve neuronal recording quality in rats [38]. Under general anesthesia, the

USEAs were placed in the upper arm, several centimeters proximal to the medial epicondyle. The iEMGs were implanted midway along the forearm. After extensive epineural dissection, USEAs were implanted using a pneumatic inserter tool [39]. The epineurium was sutured around each USEA and its ground and reference wires (Fig. 4.1a). A collagen wrap (AxoGen Inc., Alachua, FL, USA) was placed around the median-nerve USEA and secured with vascular clips. Collagen wrap was not placed around the ulnar nerve, due to complications in the implantation of this particular USEA. A 0.1 mg/kg dose of dexamethasone was administered after tourniquet removal, which has been reported to reduce the foreign body response and improve neural recordings [40], [41].

The percutaneous wire sites (Fig. 4.1b) were dressed using an antibiotic wound patch (Biopatch, Ethicon US LLC, Somerville, NJ, USA) at least every 10 days. At the time of this report, the implants had been intact in the subject for 11 weeks and one local infection at the iEMG implant site had been successfully resolved with oral antibiotics (keflex and bactrim) administered for 2-3 weeks. The subject participated in 2-3 h experimental sessions typically 2-4 days per week. Experimental sessions included motor decode training and testing (via iEMG and/or USEA recordings), sensory encode training and testing (via USEA stimulation), and closed-loop control assessments (via simultaneous recording from USEAs and/or iEMGs and stimulation via USEAs) as well as impedance testing of the USEAs and iEMGs at the beginning and end of each session.

4.3.4 Recording/decode

Neural and electromyography recordings were collected using the 512-channel Grapevine System (Ripple LLC, Salt Lake City, UT, USA). A 1st-order high-pass

Butterworth filter (cutoff of 0.3 Hz) and 3rd-order low-pass Butterworth filter (cutoff of 7500 Hz) was applied to neural signals. Threshold detection was performed after application of an additional 750 Hz high-pass filter (threshold was -5 times the 30-s windowed average of the root mean square). Firing-rate activity was computed by binning detected threshold crossings into 60-ms windows. For iEMG recordings, the power of the filtered data was computed by smoothing and rectifying the signal across a 300-ms window. Recordings from iEMGs and USEAs were collected while the subject mimicked a set of preprogrammed virtual hand training movements with his phantom hand, which included individuated movements of different degrees-of-freedom (e.g., flexions/extensions of each digit, wrist flexion/extension, wrist pronation/supination, thumb abduction/adduction). Training sets included 5-10 trails for each training movement.

Firing-rate outputs of selected iEMG electrodes and USEA electrodes, as well as the instructed positions of each DOF from the training, were used to fit the parameters of a Kalman filter. The baseline firing-rate activity for each electrode was subtracted from the overall firing rate prior to training and testing of the Kalman filter. Selection of electrodes for input into the Kalman filter was performed either by: a) selecting all electrodes that displayed a correlation coefficient between the electrode firing rate and the instructed position above a threshold or by using a custom, or b) a stepwise Gram-Schmidt electrode-selection algorithm (this algorithm will be outlined in a future publication). The trained Kalman filter enabled the subject to control movements of either a virtual prosthetic hand or a physical prosthetic hand in real time. The Kalman filter output was either used directly for real-time position control, or was smoothed via a leaky integrator for latched position control (similar to velocity control).

4.3.5 Stimulation/encode

Electrical stimulation was delivered via USEAs using the Grapevine System using Micro2+Stim front ends. All stimulation was delivered as biphasic, cathodic-first pulses, with 200-μs phase durations, and a 100-μs interphase duration. The stimulation frequency typically varied between 10-300 Hz, and stimulation amplitudes were in the range of 1-100 μA. A full report of stimulation amplitude thresholds and the extent of sensory restoration and percept stability via USEAs in this subject will be provided in a separate publication.

Full-USEA stimulation threshold maps were collected roughly every 6-8 weeks, during which each electrode of the USEAs was stimulated in isolation at increasing amplitudes. Electrodes which evoked a sensory percept at less than 100 μA were noted, and the location, quality, and intensity of each percept was documented as well as the threshold amplitude at which the percept was evoked. For these mappings, stimulation was delivered in a pulsed fashion, with a 500-ms train of 100-Hz stimulation being delivered every second. Additional stimulation sessions were carried out in which stimulation was delivered in the same manner on single-electrodes or subsets of electrodes at different frequencies or in different combinations or patterns, for example, to determine which USEA electrodes to assign to prosthesis sensors prior to embodiment experiments.

4.3.6 Closed-loop control

Closed-loop control (i.e., motor control with USEA-coupled sensory feedback) was provided to the subject after performing motor decode and sensory encode training. Sensory encode training consisted of identifying electrodes that evoked percepts which could be associated with sensor locations on the virtual or physical hand. Typically, the assigned electrodes evoked sensory percepts with a very similar hand location as the sensor to which it was assigned, although sensory substitution was occasionally performed. The frequency of stimulation on an assigned electrode was roughly proportional to the indentation force of the sensor in real time, although stochastic variability was added to the stimulation frequency. Closed-loop control sessions included performance of tasks with either the virtual prosthetic hand or the physical prosthetic hand. During virtual prosthesis use, the position of the residual limb was tracked and mapped to the virtual hand using a motion tracking system (OptiTrack, Corvallis, OR, USA). The motor decode during closed-loop sessions was typically performed exclusively using EMG recordings (i.e., not using recordings from USEAs).

4.3.7 Physical and virtual prosthesis

During embodiment experiments the subject used a physical prosthesis. Phantom pain scores were monitored before and after both physical prosthesis sessions and virtual prosthesis sessions. The physical prosthesis (Fig. 4.2) was a 3D-printed ADA Hand (Open Bionics, Bristol, UK) instrumented with PK12 linear actuators on each digit (Firgelli Technologies, Victoria, B.C., Canada) and 0.5-cm-diameter circular, flat, force-sensitive resistors on each digit tip and a 4 cm x 4 cm, square, flat, force-sensitive resistor on the palm (Interlink Electronics, Westlake Village, CA, USA). The physical hand was interfaced with custom software and the Ripple Grapevine System via a digital microcontroller board (Open Bionics, Bristol, UK) that allowed realtime feedback control via all five motors and via four of the six sensors during use. The physical prosthesis was 3D-printed with peach-colored filament, and a translucent, nude-Caucasian-tinted surgeon's glove was placed over it to cover the electronics and sensors, approximating the subject's skin tone.

The virtual prosthesis was simulated and visualized by either the MSMS hand [42] or the MuJoCo virtual reality environment (Roboti LLC, Redmond, WA, USA). The MSMS hand was used only for open-loop motor decode and motor training, and the MuJoCo hand was used for both open-loop and closed-loop-control tasks using integrated virtual sensors.

4.3.8 Embodiment experiments

We assessed the level of embodiment of the physical prosthetic hand via two metrics: a) comparison of the subject's perceived phantom-hand position from before versus after an embodiment training period, and b) collection of survey responses related to prosthesis embodiment.

Quantification of embodiment was performed by assessing a shift in perceived phantom hand position, as has been performed previously with intact human subjects [34]. The physical prosthetic hand was placed palm up on a Plexiglas table, with the index-fingertip being positioned ~13-19 cm to the right of the medial edge of the pronated residual left arm, which was also resting on the Plexiglas table (~13 cm in initial experiments, ~19 cm in later experiments). A barrier was placed between the physical prosthesis and the residual limb so that the residual limb was not in sight. The subject donned a custom lab coat that was attached to the barrier. The coat included a conventional left sleeve for the subject's residual left arm, plus an additional faux left sleeve that was stuffed and positioned in the subject's view, projecting from his left shoulder to the wrist of the physical prosthesis, such that the prosthetic hand appeared to extend from this substitute left arm (Fig. 4.3).

The intact right hand was placed on a lower Plexiglas surface, about 10 cm beneath the physical prosthesis and the residual limb, but was visible to the subject through the upper Plexiglas surface. The barrier between the physical prosthesis and the residual limb was not present beneath the upper surface, so that the intact right hand was free to pass beneath the physical prosthesis, the barrier, and the residual limb without impediment. The starting position of the intact right hand prior to a hand-movement saccade was fixed to be ~49 cm to the right of the position of the prosthesis. A ruler was visible along the lower Plexiglas surface (but not touched by the subject) and a sliding T-square was placed on the ruler to allow for precise measurement of the subject's intact index-finger location during the experiments.

Each embodiment experiment trial began by collecting a baseline assessment of the subject's perceived phantom-hand location by placing his intact right hand at the designated starting position on the lower surface, closing his eyes, and moving his intact right hand along the lower Plexiglas surface until he felt that his right index-fingertip was aligned with his left phantom index-fingertip. The final position of his right-hand index finger was noted. A 4-min embodiment training period then began in which the subject was allowed to view the prosthesis during one of the following four conditions: 1) motor control of the prosthesis, 2) sensory feedback from the prosthesis (experimenter pressed on the prosthesis sensor locations), 3) closed-loop control of the prosthesis (squeezing a ball or other object which allowed activation of the sensors), or 4) a control condition in which there was no motor control of or sensation from the prosthesis (visual fixation on the prosthesis). After the embodiment training period, the subject again placed his intact right hand at the start position on the lower surface, closed his eyes, and moved his right hand until he felt it was aligned with his phantom left hand. The difference between each pretrial and posttrial perceived phantom hand position was used as an objective metric of embodiment. Trials were presented with a 4-min break between them which involved covering the physical prosthesis with a shroud and moving the residual limb and phantom hand as well as massaging, touching, and visualizing the residual limb to invoke disembodiment of the prosthetic hand.

Statistical analysis of the perceived phantom hand position shift involved a two-sided t-test to evaluate the level of embodiment (positive shift toward prosthesis) for each of the four test conditions. Additionally, a pooled comparison of the three noncontrol test conditions (closed-loop, open-loop motor, and open-loop sensory) compared to the visual fixation control condition was performed using a two-sided t-test. If this pooled test was significant, a post-hoc comparison of all six pairwise contrasts with paired two-sided t-tests (paired to account for between-session variability) was performed (i.e., all six possible comparisons of pairs of test conditions), using the Holm-Sidak-Bonferroni method for multiple comparison adjustment of the critical value. Pairing was performed using within-block trails from the same session.

Additionally, we collected subjective responses to survey questions related to embodiment of the limb after each trial. Survey questions were modified from those used in other rubber-hand illusion tasks [30], [43], [44], and included 3 predesignated test questions and 6 additional questions to control for task compliance and suggestibility (Fig. 4.4). The subject indicated responses to the survey questions using a 7-point visual Likert scale. The nine different survey questions were arranged in different random orderings on eight different versions of the questionnaire, and the different versions were delivered in block-random order.

Statistical analysis of the survey question responses for each of the four test conditions included a comparison of responses to the survey question, “I felt as if the prosthetic hand was my hand” to the pooled Likert scores from the six control questions using a two-tailed t-test with a critical value of 0.05. Additionally, a pooled comparison of the responses to this question for the three noncontrol test conditions (closed-loop, open-loop motor, open-loop sensory) compared to the responses for the visual fixation control condition was performed using a two-sided t-test. If this pooled test was significant, six pairwise post-hoc contrasts were performed via two-sided paired t-tests (paired to account for between-session variability), using the Holm-Sidak-Bonferroni method for multiple comparison adjustment of the critical value. Specifically, for the question, “I felt as if the prosthetic hand was my hand,” all six possible pairwise comparisons among the four test conditions (closed-loop, open-loop motor, open-loop sensory, visual fixation) were tested. Additionally, a single pairwise contrast was performed between the closed-loop control and sensory-only conditions for each of the remaining two test questions, “It seemed as though the touch I felt was caused by the object," and "It seemed as though I felt the touch of the object on my hand," using a two-sided paired t-test. Comparisons were only assessed between the closed-loop control and sensory-only conditions for these two test questions since these two questions are irrelevant for the visual fixation and motor-only conditions (no touch was applied to the prosthetic hand during those conditions).

4.3.9 Pain evaluation

An extensive preimplant pain evaluation was performed by a physician. A more concise method was used for routine preimplant and postimplant evaluations, which consisted of asking the subject to rate his pain on a 0-10 scale, where a score of 10 was defined as the most intense pain he had ever experienced. Many different experiments were performed in postimplant sessions in including USEA microstimulation, and motor control and closed-loop control of a virtual prosthesis in addition to embodiment experiments with a physical prosthesis. The results of these other experiments will be provided in later publications. For two separate preimplant sessions, and at the beginning and end of each postimplant experimental session, the subject's pain was documented using the 0-10 rating scale. These questions were posed both for his chronic background pain, which the subject described as being "always there," and for phantom-pain episodes, which occurred periodically and were more intense. For periodic phantom-pain episodes, the duration, frequency, and intensity of episodes was also documented. The subject indicated that he had never had neuromas resected from his residual arm nerves.

The subject's phantom pain was also monitored during and after each experimental session using the 0-10 rating scale. We also monitored the subject's verbal indications of phantom pain changes during the experiments. At the end of each experimental session, the subject was asked to indicate whether his phantom pain was more intense, less intense, or the same as before the session.

Statistical analysis included a paired t-test between the presession and postsession pain ratings across all experimental sessions. Due to ongoing experiments with the subject at the time of the writing of this publication, we used only the available pain scores from the first 10 weeks postimplant.

4.4 Results

The subject experienced embodiment of a physical prosthesis due to a) open-loop visible motor control, b) open-loop visible tactile feedback, and c) closed-loop visible prosthesis control. Additionally, the subject reported a reduction in phantom pain after many of the experimental sessions, which included motor decode (recording), sensory encode (stimulation), and closed-loop control.

4.4.1 Embodiment: shift in perceived hand position

The subject's average (and SEM) perceived shift in hand position toward the prosthesis was 1.5 cm ($^+$/- 1.5 cm) for visual fixation, 5.6 cm ($^+$/- 1.5 cm) for open-loop motor control, 3.6 cm ($^+$/- 1.5 cm) for open-loop sensory feedback, and 6.0 cm ($^+$/- 1.2) for closed-loop control (Fig. 4.5). A statistically-significant shift in the perceived hand position toward the prosthesis was observed for open-loop motor control ($p < 0.01$) and closed-loop control ($p < 0.01$), with evidence toward significance for open-loop sensory feedback ($p = 0.06$). Importantly, there was not substantial evidence of a shift in perceived hand position for the visual fixation condition ($p = 0.32$).

A pooled comparison of the noncontrol test conditions (all trials from sensory-only, motor-only, and closed-loop) revealed a significantly-increased shift in perceived hand position toward the prosthesis in response to these test conditions compared with the visual fixation control condition ($p < 0.02$). A subsequent multiple-comparisons procedure did not reveal significantly-different levels of perceived hand position shift between different pairs of test conditions.

4.4.2 Embodiment: survey results

The test survey question, “I felt as if the prosthetic hand was my hand” yielded average (and SEM) Likert scores of 2.9 ($^+$/- 0.3) for visual fixation, 4.6 ($^+$/- 0.2) for open-loop motor control, 5.1 ($^+$/- 0.3) for open-loop sensory feedback, and 5.0 ($^+$/- 0.3) for closed-loop control (Fig. 4.6). We compared the Likert ratings for this test question to the pooled Likert ratings from the six control questions for each of the four test conditions. Motor-only, sensory-only, and closed-loop test conditions each exhibited a significantly higher response on this test question compared with the control questions ($p < 0.05$ for each of these three conditions), whereas no such difference was found for the visual fixation control condition ($p = 0.30$).

A pooled comparison of the responses to this question for the three noncontrol test conditions (all trials from sensory-only, motor-only, and closed-loop) revealed a significantly-increased level of embodiment compared with the visual fixation condition ($p < 0.001$). A subsequent multiple-comparisons procedure revealed statistically-increased levels of embodiment for each of open-loop motor control, open-loop sensory feedback, and closed-loop control conditions compared to visual fixation ($p < 0.05$ for each comparison, with multiple-comparisons adjustment).

The subject's informal comments were also helpful for assessing embodiment. After a set of embodiment trials, the subject stated, "It does make a difference on the stim [stimulation]. It really feels like you're squeezing my thumb, 'cause where you're squeezing is where the stimulation is." Following one set of embodiment trials, the subject stated, "I want to clasp my hands together," at which point he massaged, touched, and squeezed the prosthetic hand with his intact hand during closed-loop control for about 20 s.

The subject also indicated that although his perceived range-of-motion of movement control of the digits of his phantom hand was normally quite limited, active movement of the digits of the physical prosthetic hand with visual feedback seemed to open his phantom hand. At about 10 weeks postimplant (with experimental sessions several times per week), he reported that the range-of-motion of his phantom digits was beginning to widen at times, allowing him to open and close some digits of his phantom hand, even outside of the experimental sessions.

4.4.3 Phantom pain reduction

The subject described two distinct types of phantom pain: 1) consistent background pain, described as sharp and burning, and 2) sporadic intense pain events which typically lasted several seconds, but which only 1-4 times per day. Sporadic pain episodes rarely occurred during experimental sessions, and so the effect of the experiments on this type of pain was not quantified. The subject's background phantom pain increased to a level of 6 during the first 10 days after the implant and then settled to a relatively stable subjective level of ~4 (Fig. 4.7). The maximum subjective pain score ever reported by the subject was a 7, which occurred while the subject was at home between sessions. The subject's average preimplant phantom pain was a 4.25.

The subject's verbal scoring of his background phantom pain indicates a significant reduction in phantom pain after experimental sessions compared with before experimental sessions, where the 24 experimental sessions included USEA microstimulation, open-loop virtual prosthesis control, closed-loop virtual prosthesis control, and embodiment experiments with a physical prosthesis ($p < 0.005$, Fig. 4.8). Due to the wide variability of experiments and tasks performed across different sessions, we did not formally quantify phantom pain reduction for specific types of experiments. The average (and SEM) presession pain score was 3.79 ($^{+}/-$ 0.18) and the average postsession pain score was 3.17 ($^{+}/-$ 0.14). The average percent of phantom pain reduction across the experiments was 13%. The maximal pain reduction reported by the subject across a session was a decrease from a score of 5 at the beginning of a median-nerve USEA stimulation session to a 2 at the end of the session (~60% reduction).

4.5 Discussion

We used USEAs implanted in residual peripheral arm nerves and iEMGs implanted in residual limb muscles to provide one human subject with touch sensation, motor control, and ultimately closed-loop control of physical and virtual prosthetic hands. The subject embodied the physical prosthetic hand in cases of open-loop motor control, open-loop sensory feedback, and closed-loop motor control with sensory feedback, and the level of prosthesis embodiment was significantly increased compared to a visual fixation condition (e.g., similar to a cosmetic prosthesis). Embodiment experiments were not performed with the virtual hand. The subject also reported a reduction in phantom pain during experimental manipulations which included nerve microstimulation, motor control of a virtual prosthesis, closed-loop control of a virtual prosthesis, and sensory, motor, and closed-loop interaction with a physical prosthesis.

The advances provided in this report are due in part to the development and use of a physical prosthesis for embodiment studies. Also, in contrast to some past subjects who reported little preimplant phantom pain, the current subject reported chronic and intense preimplant phantom pain, which prompted us to monitor pain levels more closely than in previous subjects. Around 79% of amputees report having phantom pain [45].

Embodiment metrics included the objective indication of the subject's perceived location of his phantom hand before and after an embodiment training period, as well as subjective responses to survey responses. Previous studies using persons with intact hands have used perceived hand location extensively as an embodiment metric [34], [35]; however, this report represents the first use of the shift in perceived phantom hand location as a prosthesis embodiment metric for amputees. We found this metric to be both reliable and repeatable in providing an objective measurement of prosthesis embodiment. We anticipate that the embodiment effect is strongly dependent on the extent, naturalism, spatial accuracy, and latency of the restored sensation and motor control. Previous studies with intact hands reported a shift in perceived hand position using sensory feedback alone and using motor control alone [43], [46]. Note also that embodiment of the prosthesis due to open-loop *proprioceptive* sensory feedback was not investigated, but may be more reliable for inducing a sense of shift in perceived limb position.

Additional embodiment metrics may be used for future studies with amputees, including monitoring of the galvanic skin response during a knife threat presented to the prosthesis [47]–[52], or monitoring of residual-limb temperature [30]. These metrics were not included in the present study due to the added time and complication they would present during the experiment. Also, limb temperature may not be a reliable metric for embodiment during motor control or closed-loop control of the prosthesis because the residual limb metabolism and temperature is expected to increase during motor control regardless of whether the prosthesis is embodied.

Embodiment quantification in this study was performed for four cases: 1) open-loop motor control (i.e., without sensory feedback), 2) open-loop sensory restoration, 3) closed-loop motor control (with sensory feedback), and 4) visual fixation (control condition). The sensory feedback for these embodiment experiments was limited to three or four cutaneous sensory percepts evoked via single-electrode stimulation via four different USEA electrodes tied to individual prosthesis sensors. Future experiments should use the rich selection of sensory feedback that can be provided by USEAs to provide extensive sensory feedback via many sensors. Additionally, more biofidelic stimulation patterns using multielectrode, mixed-receptor-type stimulation tied to each sensor may evoke more naturalistic sensations and improved embodiment and/or phantom pain relief [53]. Self-touching of prosthesis sensors may also assist in generating a stronger sense of embodiment via restored tactile feedback.

We hypothesize that the level of prosthesis embodiment will increase with more sophisticated motor control and sensory feedback and ultimately, more extended use in activities of daily living. Future work should include a quantification of the level of embodiment of the prosthetic limb as a function of: a) the number of sensors used for sensory feedback, b) the range of sensation intensity encoded by prosthesis sensors, c) the number of degrees-of-freedom included in the motor decode, d) the precision of proportional motor control, and e) the extent and duration of use. One challenge with these experiments will be blinding the subject to the different test conditions. However, a comparison of phase-shifted versus phase-locked conditions, such as was used in past rubber-hand-illusion studies, may be useful [30], [43]. Fitt's law is a functional performance metric that indicates that the time required to complete a functional motor task is proportional to the task's complexity [54]. We propose that a parallel law exists for psychological or emotional impact metrics, such as embodiment or phantom pain relief, in which the level of embodiment or phantom pain reduction may increase in proportion to the extent of naturalistic sensory feedback and/or motor control provided.

We also anticipate that the nature of the neural interface used for restoration of sensation will influence the extent of prosthesis embodiment by indirectly determining the capabilities for sensory encoding. The multichannel, intrafascicular nature of USEAs enables restoration of many different sensations spanning the phantom hand. In informal preimplant testing using intact hands, we subjectively observed that the rubber hand illusion was more salient when multiple different hand locations were touched in a seemingly unpredictable pattern. During prosthesis embodiment trials, our subject indicated verbally that touch of the prosthesis palm and thumb were particularly meaningful to him and seemed to enhance the sense of embodiment. In future studies, more sensors should be integrated into the prosthetic hand and coupled to additional electrodes of USEAs or multichannel neural interfaces for restoring sensory percepts representing, for example, the tip of each digit, the midsection of each digit, multiple areas of the palm, the lateral edge of the hand, and the back of the hand. The scotoma effect, or the tendency for sensory perception to “fill in” between adjacent sites of sensation, may enable perception of full-hand cutaneous sensation even in locations where tactile sensors are not present.

Additionally, we anticipate that restoration of a variety of sensory qualities, such as light brush stroking and vibration in addition to constant pressure, will create an even stronger sense of embodiment. In contrast to cuff electrodes, USEA stimulation can activate single axons and small subsets of axons independently, potentially including activation of different receptor subtypes with biofidelic patterns faithful to that subtype. Real-world touch is encoded via populations of different receptor subtypes with different receptive fields, each with a stereotypical response characteristic [53]. For example, type I slowly-adapting fibers are the primary encoders of constant pressure [55]–[57], whereas type I rapidly-adapting fibers contribute primarily to encoding tangential motion across the skin [57]–[59], and type II rapidly-adapting fibers contribute primarily to encoding fine textures and sensations of vibration or buzzing [57], [60], [61]. Inclusion of different prosthesis sensors for each of these submodalities, and associated USEA stimulation of appropriate receptor subtypes with corresponding projected fields, may further enhance prosthesis embodiment. Naturalistic stimulation patterns may be incorporated by adding numerous different sensors to the prosthetic hand, with each submodality-specific sensor tied to a single electrode, or by adding a smaller number of gross-level sensors to the prosthetic hand, and using algorithms to produce multichannel biofidelic stimulation in response to activation of each sensor.

One potential limitation of USEAs has been their relative instability during the acute postimplant phase, shown in past reports [32], [33]. Sensory percepts are typically stable during a 2-3 h session, but often change location or quality across days or weeks, at least for the initial period shortly after implant. This instability is potentially due to micromechanical shifts in the USEA electrode positions relative to the nerve fibers, which may be due to movement of tissues and USEAs in the arm during daily tasks, and/or due to an ongoing foreign body response. Failures in USEA lead wires or other areas of the device may also contribute to long-term instability. Ongoing improvements to USEA designs, as well as longer-term implants, may result in improved stability. Also, multielectrode stimulation, such as biofidelic population encoding, may demonstrate improved stability due to the decreased probability of the sensory percepts changing location or quality on all electrodes in a subpopulation compared to just one electrode.

Phantom pain reduction was reported by our subject for many experimental sessions, which included microstimulation, motor control, and closed-loop control of a virtual or physical prosthesis. When we first questioned him about his sensory awareness of his phantom hand, the subject indicated, “Probably the reason that I can feel it’s there is the phantom pain.” He reported that he had previously attempted mirror-box therapy [62], TENS therapy, and magnet therapy for phantom pain relief with no perceived improvement. During his first experimental session, while he was controlling the movements of the virtual hand, he indicated, “That just feels good, actually—seeing it open all the way up.” He later stated, “It’s interesting, ‘cause the mirror [box] didn’t give me that same sensation.”

Although we did not observe full pain relief due to experimental manipulations, the subject indicated that phantom pain reduction is important, helping to keep the pain at a manageable level. For example, the subject stated that although his pain medications do not relieve him of his phantom pain, they keep it at a level which is bearable and which allows him to carry on with activities of daily living.

The mechanisms of phantom pain formulation are not well understood, with evidence suggesting peripheral and/or central mechanisms [63], [64]. Although we did not formally assess the nature of the phantom pain reduction experienced by subject S6, the location of the subject’s phantom pain reduction seemed at times to be related to the anticipated innervation distribution of the nerve being stimulated. For example, median-nerve stimulation sessions often resulted in pain reduction on the 1st, 2nd, and 3rd digits, but not on the 4th and 5th digits.

Visual-motor integration coupled with internal efference copy, such as is generated during dexterous prosthesis motor control, represents the convergence of many rich correlative signals that seem capable of masking perception of background phantom pain. We anticipate that advanced closed-loop control of a sophisticated prosthesis that is attached to the limb and used for daily tasks may represent an even stronger masking signal, potentially providing more substantial pain reduction.

These results extend previous studies by showing that USEA stimulation and iEMG movement decode can provide meaningful psychological benefits to amputees. Psychological and emotional factors may be more important to patients’ overall health and well-being than functional outcomes [65]–[67]. Restoration of sophisticated prosthesis motor control and prosthesis sensation provided a sense of limb-restoration that was meaningful to our subject, and which may assist future amputees to maintain improved emotional health. Ultimately, we envision development of a take-home, wearable, closed-loop prosthesis system that may serve not only as a helpful tool, but also as a limb replacement.

4.6 Conclusion

The challenges associated with limb loss include not only functional deficits, but also the emotional difficulty associated with losing a body part, and in many cases chronic phantom pain. We used peripheral-nerve and muscle interfaces to provide an amputee with simultaneous touch sensation and movement control via many digits of a physical prosthetic hand. The subject embodied the hand, evidenced by a shift in his perceived phantom hand location toward the prosthesis and by his response to survey questions. Additionally, the subject consistently reported a reduction in phantom pain after movement decode and microstimulation sessions. This work represents the first report of the prosthesis embodiment during closed-loop prosthesis use in a human amputee.

4.7 Acknowledgments

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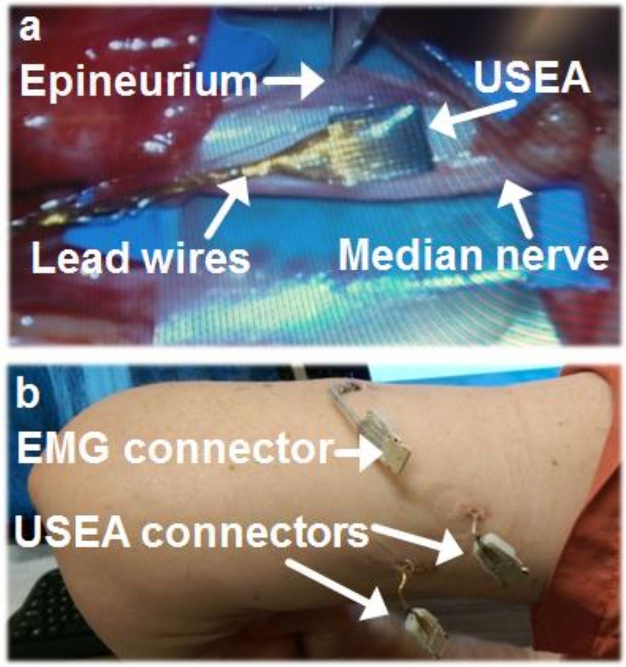

Fig. 4.1. Surgical methods for USEA and iEMG implants. a) The epineurium was separated prior to implantation of a USEA in the median nerve. A USEA was also implanted in the ulnar nerve (not shown). b) USEA and iEMG lead wires were connected to the contact pads of external connector boards via percutaneous incisions. Hardware was attached to these connector boards during experiments to enable stimulation and recording via the USEA and iEMG implants.

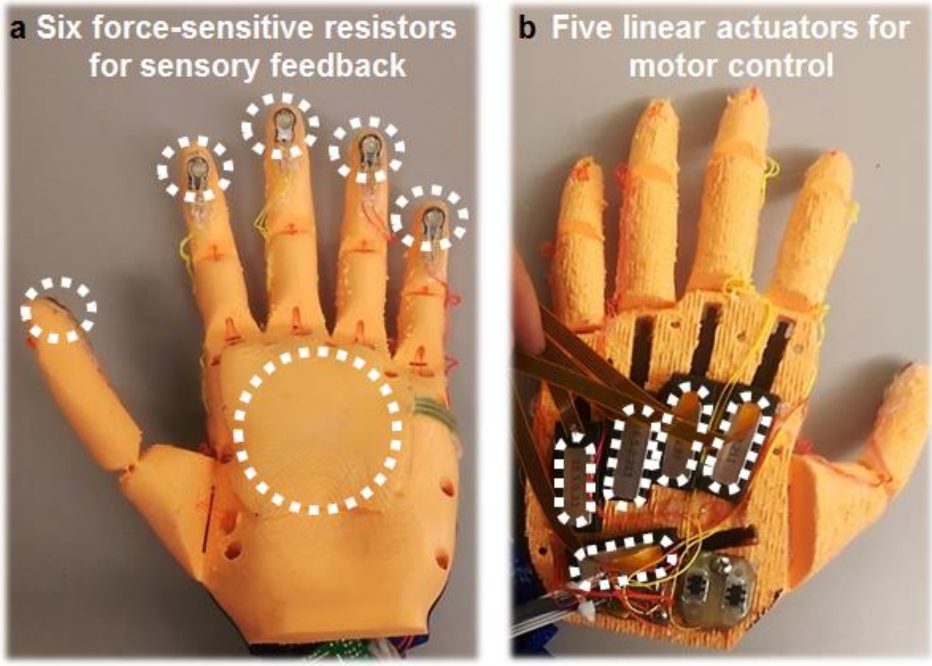

Fig. 4.2. 3D-printed physical prosthetic hand used for embodiment experiments. a) Six force-sensitive resistors were fixed to the prosthetic hand: one sensor on each digit tip, and a larger sensor on the palm. Activation of these sensors produced USEA stimulation and associated sensations on the phantom hand. Typically, the USEA electrode assigned to each sensor evoked a sensory percept that corresponded to the same hand region as the sensor. Due to hardware limitations, a maximum of four prosthesis sensors were used simultaneously. b) On the back of the hand, a linear actuator was attached to the tip of each digit of the prosthetic hand via a plastic cable that acted as an artificial tendon. Motor control signals were generated by decoding recordings from 32 electromyography contacts (8 leads, with 4 contacts each) implanted in the forearm muscles of the residual limb. During most embodiment experiments, the subject was able to control flexion and relaxation of all five digits of the prosthetic hand independently.

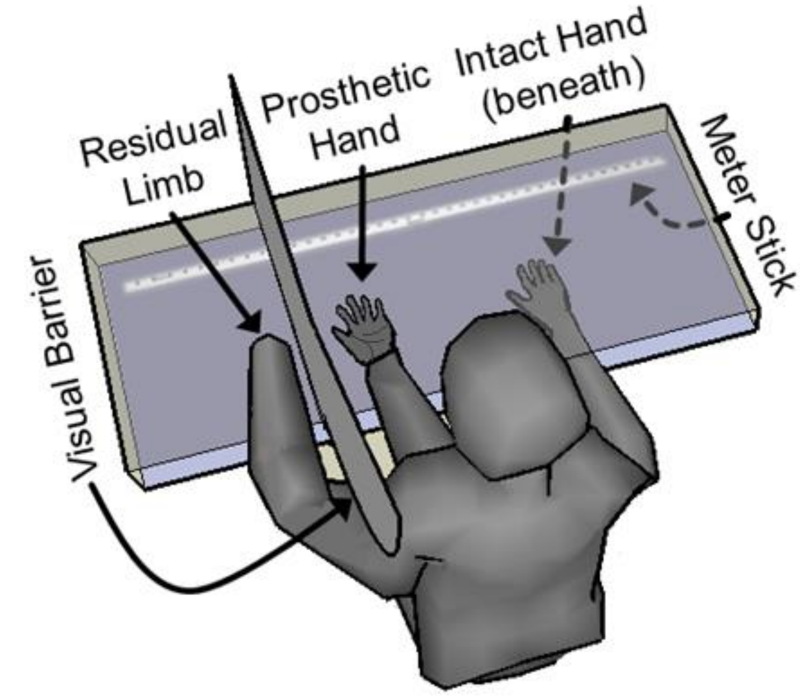

Fig. 4.3. Embodiment quantification via measurement of shift in perceived hand location. The subject was seated facing a two-level plexiglass table. The subject's residual limb was placed on the upper surface of the table and was shielded from his view with a visual barrier. The physical prosthetic hand was also placed on the upper surface in front of the subject along with a stuffed sleeve that was draped over the subject's clothing to give the appearance of an arm extending from the subject's left shoulder to the prosthetic hand. The subject's right intact hand was placed on the lower surface, allowing it to pass beneath the prosthetic hand, the visual barrier and the residual limb. Both before and after each 4-min prosthetic-hand training period, the subject closed his eyes and moved his intact right hand laterally on the lower surface until he subjectively felt that his intact index finger was aligned with the index finger of his phantom hand. The perceived location of his phantom hand was documented using measurements from a meter stick. The shift in perceived phantom hand location during each trial was calculated as a metric of prosthesis embodiment.

	Questions regarding your phantom hand/residual limb:	Disagree Strongly						Agree Strongly
Test Questions	I felt as if the prosthetic hand was my hand	O	O	O	O	O	O	O
	It seemed as though the touch I felt was caused by the object	O	O	O	O	O	O	O
	It seemed as if I felt the touch of the object on my hand	O	O	O	O	O	O	O
Control Questions	The prosthetic hand started to change shape, color, and appearance so that it started to look like my hand	O	O	O	O	O	O	O
	It felt as if my residual limb was drifting towards the prosthetic hand	O	O	O	O	O	O	O
	It seemed as if I might have three arms	O	O	O	O	O	O	O
	It felt as if my hand was beginning to feel 'rubbery'	O	O	O	O	O	O	O
	It almost appeared that I could see the prosthetic hand drifting towards my residual limb	O	O	O	O	O	O	O
	It seemed as if the touch I was feeling came from somewhere between my hand and the prosthetic hand	O	O	O	O	O	O	O

Fig. 4.4. Embodiment survey questions. The subject responded to nine survey questions following each prosthetic-hand training period. Three of the questions served as test questions for to assess the level of prosthesis embodiment for the four different experimental conditions (closed-loop control, open-loop motor, open-loop sensation, visual fixation). The remaining six questions served as controls for task compliance and suggestibility. Eight different orderings of the survey questions were produced, and these different versions were delivered in block-random order. The subject's overall impressions were also noted during the experiments.

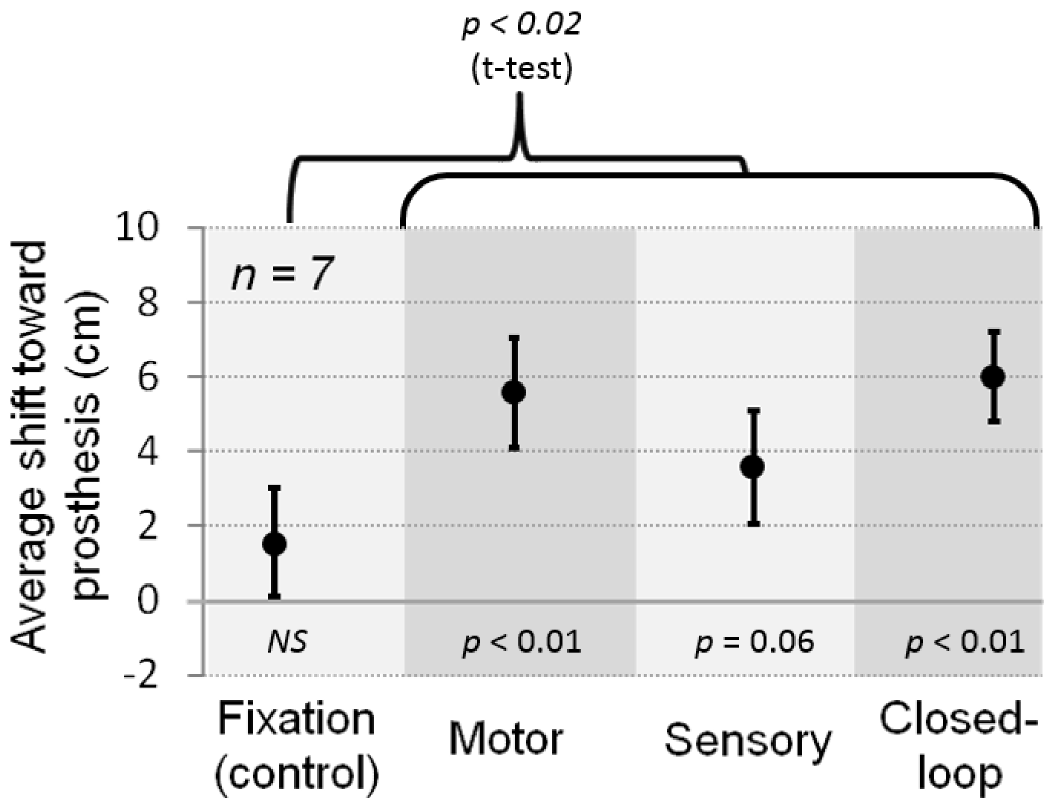

Fig. 4.5. Quantification of perceived shift in limb position for four test conditions. Dots indicate the mean (+/- SEM) shift in perceived phantom limb position between the pretrial and posttrial tests for each of four test conditions. A significant shift toward the prosthesis was observed for each of the motor and closed-loop conditions ($p < 0.01$ for each of these conditions), with evidence toward a shift for the sensory condition ($p = 0.06$), and no significant shift toward the prosthesis for the visual fixation condition ($p = 0.32$). A comparison of the pooled results from sensory-only, motor-only, and closed-loop trials compared with the visual fixation condition suggests that these conditions provide a stronger sense of embodiment than, for example, a cosmetic prosthesis ($p < 0.02$). A subsequent multiple comparisons procedure did not reveal statistically-significant differences between pairs of groups.

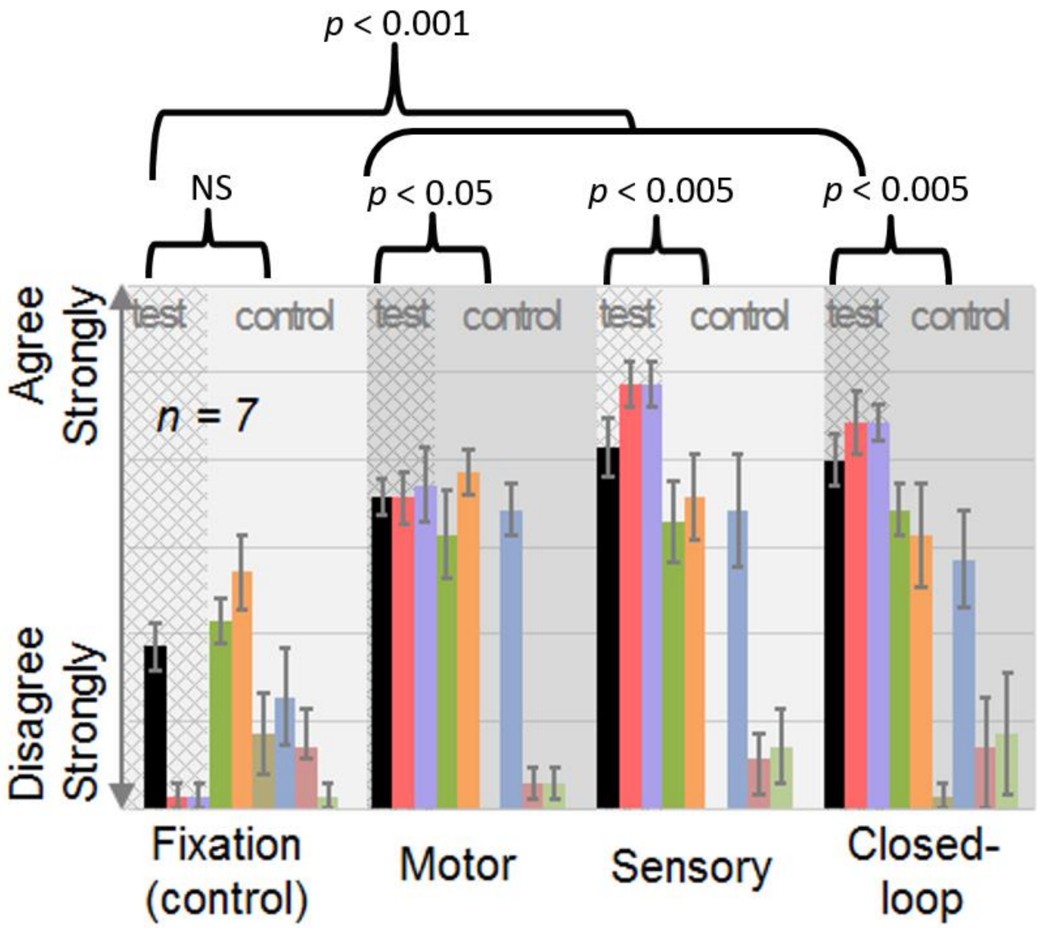

Fig. 4.6. Embodiment survey question responses across four test conditions. Bars indicate the mean (+/- SEM) Likert rating for each of the nine survey questions, across the four test conditions. The survey question ordering from left to right within each of the four test conditions corresponds to the survey question order from top to bottom given in Fig. 4.4, with the left-most three questions being test questions and the right-most six questions being control questions (to control for suggestibility and task compliance). The primary test question, "I felt as if the prosthetic hand was my hand", shown on the far left as a black-filled bar for each test condition, received significantly higher ratings compared with the pooled scores from the control questions within each of the three noncontrol test conditions ($p < 0.05$ for each of open-loop motor control, open-loop sensory feedback, and closed-loop control), whereas no such difference was evident for the visual fixation condition ($p = 0.30$). Additionally, a multiple comparisons procedure revealed significantly higher ratings on this test question for each of the motor-only, sensory-only, and closed-loop control conditions compared with the visual fixation condition.

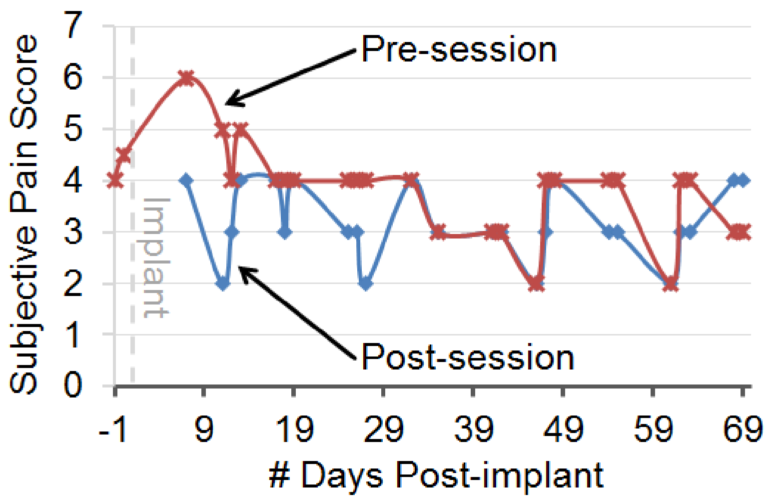

Fig. 4.7. Subjective phantom pain scores across time. We collected subjective ratings of phantom pain across time up to ~10 weeks postimplant for both presession phantom pain and postsession phantom pain. An increase in phantom pain is evident for about the first 20 days after implant, after which the phantom pain settled to levels comparable to preimplant ratings. The subject continued his use of prescription medications for treatment of phantom pain during the duration of the implant (e.g., gabapentin and tramadol).

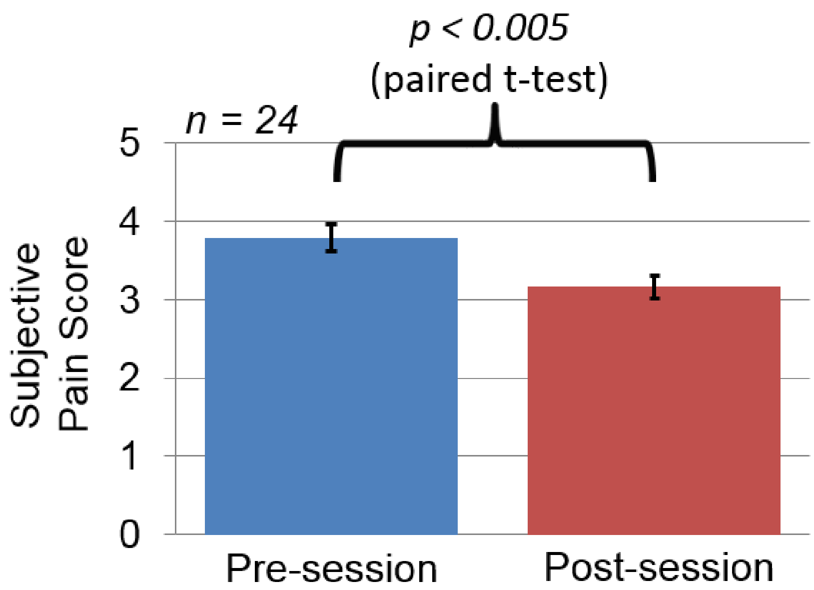

Fig. 4.8. Reduction in phantom limb pain after experimental sessions. A significant reduction in phantom limb pain (*p* < 0.005, paired t-test) was observed between the subject's presession and postsession subjective pain ratings for the 24 experimental sessions leading up to 10 weeks postimplant. These sessions included microstimulation of USEAs, and motor control and/or closed-loop control of a virtual hand in addition to embodiment experiments with the physical prosthetic hand. Although full pain relief was not provided (e.g., an average of 13% pain reduction was observed), the subject indicated that pain reduction is important and helpful for continuing with activities of daily living. Colored bars indicate the mean pain score, with standard errors about each mean also shown.

4.8 References

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CHAPTER 5

CONCLUSIONS AND FUTURE DIRECTIONS

5.1 Neuromodulation

Neuromodulation represents a growing market which, in recent years, has gained traction with regulatory approval and clinical adoption of several new technologies [1]. The challenging transition from research-level devices to clinically-usable devices will require an increased focus on reliability in addition to safety and efficacy. Currently-approved, reliable neuromodulation devices, such as spinal cord and deep-brain stimulators, operate via only few channels on a relatively large volume of target tissue (e.g., ~100 mm^2) [2], whereas USEAs include many channels and very small volumes of target tissue (e.g., ~ 0.5 mm^2). These unique engineering challenges associated with USEAs, as well as the form factor, are likely sources of existing unreliability. Additionally, in contrast to multichannel cochlear implants, which undergo very little movement due to their placement in the head, USEAs in the peripheral arm nerves undergo extensive movement during tasks of daily living.

An additional challenge in development of the neuromodulation market is the establishment of market and clinical needs and development of sustainable companies. For example, establishment of prosthesis embodiment as a substantial clinical need will be important for justifying insurance reimbursement for neural prosthetic implants. The impact of prosthesis embodiment on the overall mental and emotional health of amputees must be demonstrated to provide substantial improvements to patient quality of life and cost savings to healthcare payers. Additionally, companies that produce neural interface implants and the associated prosthesis system must be formulated in a manner that promotes business sustainability and ongoing care to patients, despite the relatively small size of the market.

Despite these challenges, neuromodulation devices have the potential to produce a substantial impact on many patients in treatment of many disorders. Neurostimulation devices seek to mediate disease states in a selective, nonsystemic manner, directly at the level of the human body that is most impactful on quality of life—the nervous system. The human experience is deeply rooted in our multisensory perception of self [3]. Modulation of neural function is the most direct method for modulating this and other related fundamental aspects of the human experience for the better, either in the treatment of disorders directly or in the alleviation of symptoms.

5.2 Peripheral-nerve interfaces

Selectivity of peripheral-nerve interfaces is important because it allows a neural interface to communicate with the nervous system on its own terms, in an axon-by-axon manner, or by activating small subpopulations of axons. The selectivity of USEA stimulation enabled full-hand coverage of sensory percepts with many locations and qualities. Selective stimulation of different axons will also be important for naturalistic population encoding. We anticipate that all these factors will impact embodiment of the prosthesis as well as improve functional use of the prosthesis.

Although selectivity is key, gaining selectivity with electrical stimulation requires increased invasiveness [4], which in turn, often results in decreased reliability possibly due to either the delicacy of smaller, more invasive devices, or due to the relatively small size of the devices compared with the size of location shifts relative to the nerve fibers. Less invasive approaches, such as cuff electrodes, have demonstrated long-term stability in human amputees [5]. We have proposed use of multielectrode population encoding using USEAs may invoke more stable sensory percepts because micromovements of nerve fibers relative to USEAs may not occur near all electrodes in an electrode subset. Also, long-duration implants of USEAs should be carried out to see if stability is achieved beyond several months. The longest-reported USEA implant in any in-vivo experiment to date is 7 months in cats using early-generation USEAs [6]. The improved USEAs used in our recent experiments may provide better performance over time. Finally, local diffusion of dexamethasone, or use of hydrogel matrix coatings may improve USEA longevity and stability [7]–[10].

Alternative approaches for nerve activation are being investigated, including magnetic stimulation and optical stimulation [11]–[13]. These approaches may prove capable of providing selective nerve stimulation with a minimized tradeoff in invasiveness. For example, infrared beams projected from outside the epineurium can be used to activate some axons within the nerve, potentially in a selective manner [14]. Penetrating optrode arrays, similar to USEAs but designed for passage of light, have also been developed [15], [16]. Additionally, genetic modifications to different types of nerve fibers can allow them to be selectively activated by different wavelengths of light [17], although it is unclear how these approaches could be safely and ethically applied in human subjects. Nerve regeneration via a neural interface may yet show promise for providing selective activation, as axonal regeneration can be controlled and even steered using mechanical scaffolds and nerve stimulation [18]–[20]. However, an approach for reconnecting nerve fibers with their appropriate targets has not been developed.

Central nervous system stimulation in the cortex has also been used to encode tactile sensory information in nonhuman primates [21], rats [22], and more recently, in a human with spinal cord injury [23]. These evoked sensations are reported to be naturalistic and stable for months. Although cortical stimulation may be suitable for many patients with spinal cord injuries, it may not be a suitable option for amputees, many of whom are unwilling to undergo brain surgery [24].

5.3 Upper limb loss

Many amputees indicate that the prostheses that are currently available do not meet their needs [25]. Neural and muscle interfaces in the residual limbs of amputees have proven useful for restoring movement control of, and sensory feedback from, a sophisticated virtual prosthesis. In this dissertation, we have demonstrated 5-degree-of-freedom motor control of a physical prosthetic hand with simultaneous sensory feedback from 4 hand locations. However, many challenges remain for promoting full-adoption of such a prosthesis system for take-home use.

Specifically, whereas some amputees are willing to undergo implantation of neural and muscle interfaces for improved prosthesis sensation and control, many are unwilling to take these risks in exchange for the proposed benefits [26]. Opinions may change if either a) the risk level can be reduced, or b) the proposed benefit can be increased. Risk levels may be decreased by development of a wireless transmitter/receiver system which would eliminate percutaneous routing of lead wires, which present a risk for infection [27]. Additionally, for motor decodes, surface electromyography recordings from multiple electrodes may prove sufficient for multi-DOF prosthesis control, potentially eliminating the need for implanted muscle electrodes. Sensory restoration via stimulation, on the other hand, will likely require implantation of one or more devices, to allow for sufficient selectivity. Patients may also be more willing to adopt an implanted prosthesis sensation and control system after becoming better informed of the extent of the benefits, including the potential sense of embodiment and alleviation of phantom pain in addition to functional outcomes.

Another remaining challenge in development of a take-home closed-loop prosthesis system is reliability. Several of our human subjects reported that they rarely use their myoelectric prostheses due to unreliability (e.g., battery limitations, power limitations, broken parts, etc.). Civil-war-era body-powered mechanical hooks have continued to be the standard-of-care for many. Our amputee subjects have each indicated that a usable system would need to work in a simplistic way, and would need to consistently work well for full adoption. We anticipate that retraining or reassignment of electrodes to prosthesis sensors would need to be performed at most once every several weeks. The user interface to the prosthesis, including the sensory and motor calibration routine, would need to be simplistic and straightforward, but still offer full configurability.

5.4 Expanding use scenarios in peripheral nerves

The work presented in this dissertation represents not only a substantial step forward for treatment for humans suffering from limb loss, but also an important precursor for USEA implantation and use in other human subject scenarios. USEAs may be useful for treatment of several different disorders or disabilities.

Movement disorders such as spinal cord injury and stroke affect many young adults and can be an enduring, lifelong struggle [28]. USEAs implanted in peripheral nerves of quadriplegic patients may be used in concert with a control signal from a brain or spinal cord implant to selectively stimulate motor fibers and restore some movement control [29]–[31]. Additionally, USEAs have been shown to be capable of recording sensory information from intact sensory neurons, and sensory information could be transmitted to a cortical implant to restore intuitive sensation of touch or proprioception [32], [33].

USEA stimulation has also been shown to be useful for controlling urination in an animal model, and may also be useful for controlling defecation and reflex erection selectively as well [34]–[36]. Selective modulation of pain may be achievable using USEAs, which may allow for elimination of chronic pain without affecting motor control or sensory feedback from a limb. USEAs implanted in the vagus nerve may be used for treatment of epilepsy or depression [37], [38]. Occipital nerve stimulation via USEAs may also prove useful for alleviating chronic migraine headaches [39]. Neuromodulation methods such as USEA stimulation and recording, may also prove useful for rehabilitation purposes, such as the use of selective neural stimulation for assisting with nerve or spinal cord regeneration following injury [40].

5.5 Final remarks

Prior to this dissertation, two reports had been provided regarding implantation of USEAs in peripheral nerves of human amputees [41], [42]. These previous reports outlined the basic functional capabilities of single and dual USEA implants placed in the forearm, near the amputation neuroma. In this dissertation, we have expanded upon prior work by demonstrating that USEAs implanted in two peripheral arm nerves in the upper arm, proximal to many motor branch points, can provide broad sensory coverage spanning the hand, including proprioceptive and cutaneous sensory percepts. We have also reported in this dissertation the largest number of somatic sensory percepts restored to date by neural interfaces, and we have demonstrated functional discriminability among USEA-evoked sensory percepts as well as their usefulness in a basic closed-loop functional task. Finally, this dissertation provides the first report of prosthesis embodiment during closed-loop prosthesis control as well as open-loop motor control, as well as systematic, albeit moderate, phantom pain relief after advanced sensorimotor prosthesis use.

In accomplishment of the results provided in this dissertation, we have developed surgical, experimental, and engineering methods that have enabled amputees to have realtime, closed-loop prosthesis control via either a virtual or physical prosthesis. Future work should include efforts to improve the chronic stability of indwelling microelectrode arrays such as the USEA as well as the stability of USEA-evoked sensory percepts over time. Biofidelic activation patterns should also be explored systematically to see if improvements are made to the quality and stability of sensory percepts. Additionally, habituation of USEA-evoked sensory percepts needs to be studied and better understood to determine the source (e.g., biological or via the electrode-tissue interface) and the extent, and, if necessary, to develop methods for reducing habituation. Ultimately, we expect that ongoing research with amputees will work toward production of a reliable, closed-loop, take-home neuroprosthesis system which may enhance the quality of life of many patients.

5.6 References

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