Using Multiple High-Count Electrode Arrays in Human Median and Ulnar Nerves to Restore Sensorimotor Function after Previous Transradial Amputation of the Hand

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Abstract—**Peripheral nerve interfaces that can record from and stimulate large numbers of different nerve fibers selectively and independently may help restore intuitive and effective motor and sensory function after hand amputation. To this end, and extending previous work in two subjects, two 100-electrode Utah Slanted Electrode Arrays (USEAs) were implanted for four weeks in the residual ulnar and median nerves of a 50-year-old male whose left, dominant hand had been amputated 21 years previously. Subsequent experiments involved 1) recording from USEAs for real-time control of a virtual prosthetic hand; 2) stimulation to evoke somatosensory percepts; and 3) closed-loop sensorimotor control. Overall, partial motor control and sensation were achieved using USEAs. 1) Isolated action potentials recorded from nerve motor fibers, although sparse at these distal implant sites, were activated during fictive movements of the phantom hand. Unlike in our previous two subjects, electromyographic (EMG) activity contributed to most online recordings and decodes, but was reduced in offline analyses using common average referencing. Online and offline Kalman-filter decodes of thresholded neural or EMG spikes independently controlled different digits of the virtual hand with one or two degrees of freedom. 2) Microstimulation through individual electrodes of the two USEAs evoked up to 106 different percepts, covering much of the phantom hand. The subject discriminated among five perceived stimulus locations, and between two somatosensory submodalities at a single location. 3) USEA-evoked percepts, mimicking contact with either a near or distal virtual target, were used to terminate movements of the virtual hand controlled with USEA recordings comprised wholly or mostly of EMG. These results further indicate that USEAs can help restore sensory and motor function after hand loss.**

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I. Introduction

Limb amputation profoundly affects the activities of daily living (ADL), involving ~1.6 million people in the U.S. alone [1]. Advanced prosthetic arms and hands exist with up to 26 degrees of freedom (DOF) [2], but lack intuitive, dexterous control signals and most sensory feedback.

Peripheral nerve interfaces may help overcome these limitations. The Utah Slanted Electrode Array (USEA) [3] has 100 independent electrodes that penetrate into peripheral nerve fascicles. USEA electrodes allow selective recordings from motor fibers to obtain control signals, and stimulation of sensory nerve fibers to provide cutaneous and proprioceptive feedback. A non-slanted version has been used successfully in human cortex [4]. The flat interface nerve electrode FINE [5], a cuff electrode, provides long-term stimulation, but selectivity at the subfascicular level is limited, and extraneural electrodes are not well suited for recording individual neural discharges. Longitudinal intrafascicular electrodes (LIFEs) [6, 7] and transversal intrafascicular multichannel electrodes (TIMEs) [8] record motor control signals and evoke stimulus percepts, but have relatively few channels. Electromyographic (EMG) activity recorded with surface electrodes or implantable myoelectric sensors (IMES) provides useful control signals, particularly in targeted reinnervation [9], but these sensors do not provide neural stimulation.

We recently demonstrated that single USEAs, implanted in residual arm nerves of two humans after hand loss, can provide offline control of a virtual hand for up to 13 types of digit movements, and activate a greater number of sensory percepts than previously achieved [10]. We now extend this work by using USEAs in two nerves of the same residual arm, so as to provide greater coverage for motor commands and sensory percepts. Further, simultaneous recording and stimulation provided bidirectional sensorimotor control.

II. Methods

A. Subject

The subject was an active 50-year-old male who had his left, dominant hand amputated at the wrist 21 years previously, after a crush injury. The study was approved by the University of Utah Institutional Review Board, the Salt Lake City Veterans Affairs Hospital Research and Development Service Center, and the Department of the Navy Human Research Protection Program.

B. Electrode Arrays

USEAs (Blackrock Microsystems) consisted of 100 silicon electrodes spaced at 400-μm intervals and arranged in a ~ 4-mm by 4-mm, 10 by 10 grid. Electrode lengths ranged from 0.5 to 1.5 mm. Ninety-six electrodes were used for recording and stimulation; four electrodes served as an on-array electrical reference, along with looped double-stranded reference and ground wires [10, 11].

C. Surgical Procedures

Two USEAs were implanted under general anesthesia at the distal ends of the residual ulnar and median arm nerves (one in each nerve), with procedures similar to those used previously [10]. The implanted USEA, reference wire, and the nerve were enclosed within a reconstituted organic nerve wrap (AxoGuard Nerve Wrap, AxoGen Inc.), closed with titanium vascular clips. The ground wires were not placed within the wrap, due to physical constraints. The ZIFClip-96 connector (Tucker Davis Technologies, TDT) to the USEA was sutured to the skin near the percutaneous site. The subject was given dexamethasone and minocycline to reduce the inflammatory response and potentially enhance USEA viability. USEAs were explanted under general anesthesia four weeks later, after experimentation.

C. Experimental Procedures

Two-hour experimental sessions were held twice per day, four to five days per week, for four weeks.

1) Impedances. Electrode impedances (Z) were measured at 1 kHz with a NeuroPort data acquisition system (Blackrock Microsystems), which was also used for collection of all electrophysiological recording data. Electrodes with $Z \geq 500$ kΩ were considered nonfunctional.

2) *USEA recordings and online decodes.* Our system allowed for recording from only one USEA at a given time. Neural and any electromyographic (EMG) activity were filtered and thresholded to yield action potential counts. EMG contributed to many but not all online decodes. Neural/EMG recordings were first obtained during "training" trials, during which the subject attempted fictive movements of his phantom (missing) hand to mirror digit movements displayed by a virtual hand having eight degrees of freedom (DOFs): flexion and extension of the five digits, plus abduction and adduction of the little, ring, and index fingers. During subsequent "testing" trials, the subject attempted to move one or more digits to reach and maintain a virtual target location. A Kalman filter was used to decode thresholded data from selected electrodes and to control virtual hand movements in real time.

3) Stimulus-evoked somatosensory percepts. Percepts evoked by microstimulation through USEA electrodes were systematically mapped across multiple sessions. Standardized stimulation used 0.2-ms constant-current pulses delivered in 200-Hz, 0.2-s trains delivered by a 128-channel TDT stimulator. The subject indicated the percept's location(s); its nominal quality (e.g., "tingle", "vibration," "pressure," "hot," "cold"; or self-defined others, e.g. "sting" or movement, i.e., proprioception); and its intensity on a scale from 1 to 5. In some cases, the subject marked multiple perceived locations when the percept spread, or when it activated adjoining spaces on different digits.

Among additional tasks, the subject was asked to discriminate among five receptive field locations of percepts evoked by stimulation either with one of four individual USEA electrodes, or with the combined set: little finger, tip; little finger, base; ring finger, tip; wrist; or all. The five stimulus conditions were presented in pseudorandom order for seven trials each (35 trials total). In another discrimination task using two USEA electrodes, the subject was asked to discriminate between two different percept qualities ("tingle" or "vibration") evoked at the same perceived location (tip of ring finger). The two stimulus conditions were presented in pseudorandom order for 15 trials each (30 trials total).

4) *Closed-loop sensorimotor control.* Stimulation through the ulnar USEA was used to provide somatosensory feedback to guide virtual hand movements driven by recordings from the median USEA. One of two possible virtual targets was presented on a given trial, which was either close to, or far from, the finger starting positions, representing touching a large- or small-diameter object, respectively. The subject attempted to reach and maintain the target position via flexion of four virtual fingers (as a single DOF) controlled by USEA recordings, which were comprised wholly or mostly of EMG. The computer monitor was turned off, so the subject was unable to see the position of the virtual hand or target. Suprathreshold stimulation was delivered through one USEA electrode when the finger tips were within the target window. The trial terminated when the targeted position was maintained for a predefined period (e.g., 0.5 s). The subject then reported whether the target had been "close" or "far." The trial also terminated if not completed within a period of 60 s. The location of the virtual target was varied pseudorandomly from trial to trial. Two experimental sessions total were conducted on post operation days 26 and 28, with 22 trials and 25 trials, respectively.

5) Offline decodes. Ongoing offline analyses attempt to separate neural activity from EMG activity, in order to perform decodes on neural activity alone. Offline analyses selected electrodes for which neural activity could be discriminated from EMG, and/or performed common average referencing using some or all USEA electrodes as a "virtual reference." Correlations (R values) were computed between the decode output and the target position.

III. RESULTS

Overall, USEAs were functional across the 28-day test period. USEA use provided partial motor control, sensory function, and closed-loop sensorimotor control. There were no detected major adverse consequences post-implantation, during experimental testing, or after explantation.

1) Impedances. The USEA implanted in ulnar nerve had 88, 89, 92, and 91 functioning electrodes (< 500 KΩ) in post-implant weeks 1, 2, 3, and 4, respectively. The median nerve USEA had 80, 67, 60, and 52 functioning electrodes respectively. Electrodes that remained functional had relatively consistent impedances across testing periods. For the ulnar USEA, Z = 133 (60) KΩ, median and (interquartile range, IQR); median USEA, Z = 92 (43) KΩ.

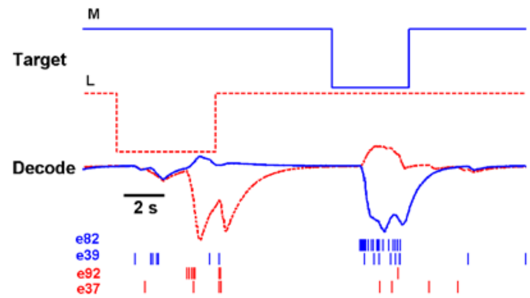

Figure 1. Online real-time Kalman filter-decode (middle traces) using neural spike activity from four USEA electrodes (bottom traces, raster plot of spike times) provides 2 DOF independent control for middle (*M, blue*) and little (*L, red*) finger extension (top traces, arbitrary scalings).

2) *USEA recordings and online decodes.* EMG was often recorded from both USEAs, obscuring neuronal activity. Across sessions, the number of electrodes with identifiable neural activity was small (2-16 electrodes, ulnar USEA; 0-4 electrodes, median USEA). Nonetheless, it was possible to perform decodes using neuronal spikes to control 1-2 DOF movements of the virtual digits (e.g., independent extension of middle or little finger, Figure 1). Online decodes based on EMG activity were also successful. After having undergone multiple unsuccessful surgeries attempting to save his thumb before its amputation, the subject found it emotionally satisfying to be able to move his thumb again, which first occurred 21 years to the day after his initial crush injury.

3) Stimulus-evoked somatosensory percepts. Microstimulation of nerve fibers through individual USEA electrodes frequently evoked somatosensory percepts, and provided a wide distribution of perceived receptive fields with the expected anatomical locations for the ulnar and median nerves (Figure 2). The number of percept-evoking electrodes ranged from 53 to 60, and from 20 to 46, for ulnar and median nerves, respectively. Together, the two USEAs had a combined total of 73 to 106 different electrodes that evoked percepts on a given day across the two USEAs—which may represent the greatest number of individual somatosensory percepts ever evoked at a given time by multiple neural interfaces in an individual.

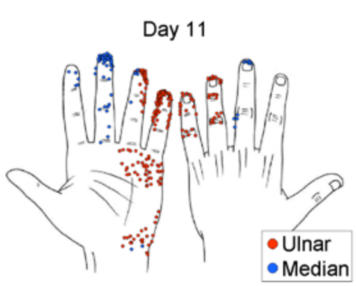

Figure 2. Receptive field distribution for phantom somatosensory percepts evoked by 97 individual USEA electrodes in ulnar nerve (*red dots*) and median nerve (*blue dots*) on day 11 post implantation.

Stimulus thresholds were low: ulnar USEA electrodes, 10.5 (11) μA; median USEA electrodes, 12 (12) μA. Microstimulation evoked a variety of somatosensory submodalities, including "tingle", "vibration," "pressure," "sting," and movement, i.e., proprioception, though the latter was infrequent, perhaps because the USEA implant sites were distal to many motor branch points. "Hot" and "cold" percepts were not evoked, perhaps because these percepts involve small-diameter axons.

The subject successfully discriminated among up to five perceived receptive field locations: four locations on the fingers and palm, plus a combined percept of the four. He indicated the correct location on 35 of 35 trials ($P < 0.0001$). He also discriminated between two qualities of percept ("tingle" or "vibration") evoked at the same perceived location (tip of ring finger) on 30 of 30 trials $P < 0.0001$).

In many cases, the subject found the perceived stimuli to be pleasant and emotionally satisfying, and would sometimes ask for the stimulus to be delivered again. An exception was percepts located at the border of his amputation.

4) Closed-loop sensorimotor control. The subject successfully used percepts evoked by the ulnar USEA to modulate the degree of virtual hand closure—near or far—controlled by recordings with EMG from the median USEA,. The subject was successful on 41 of 47 trials, $P < 0.0001$. These results represent our first use of USEAs in peripheral nerve to provide real-time closed-loop sensorimotor control via simultaneous recording and stimulation.

5) Offline decodes. Offline analyses have begun to separate neural activity from EMG activity, allowing successful two-DOF decodes based on neural activity alone. In one instance (Figure 3), recordings from 51 USEA electrodes included both EMG and neural activity, but the Kalman filter decodes closely tracked the instructed movements, extension of middle or little finger (R between decode and target position: middle finger, 0.82; little finger, 0.77). Isolated neural activity recorded on two of the 51 electrodes yielded comparable R values: middle finger, 0.78; little finger, 0.81. In another instance (Figure 4), common average referencing was used to subtract the EMG and reveal the underlying neural signals, which provided an R of 0.72 between the decode output and thumb flexion.

These results demonstrate proof-of-concept that neural signals can be recaptured and used for motor-control from recordings that also contain EMG activity. Such approaches would need to be implemented in real time online in order to be functionally useful for ADL. The results also demonstrate that decodes based on EMG can provide at least some functional utility.

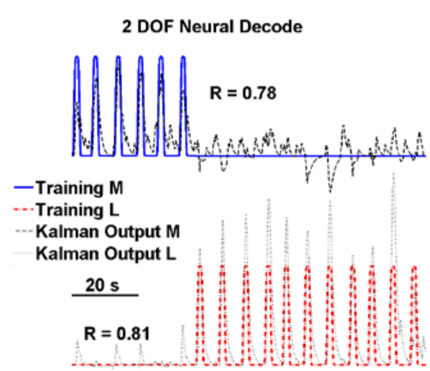

Figure 3. Offline decode (thin dashed or dotted lines) using thresholded neural spikes from two different USEA electrodes produced 2 DOF control for middle (*M*) or little (*L*) finger (blue or red lines, respectively). Correlations R between the Kalman output decode and "training" target movements were 0.78 and 0.81, respectively.

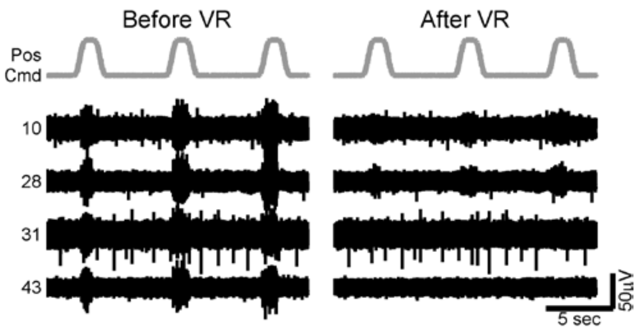

Figure 4. Recordings from same time epoc on four USEA electrode channels (19, 28, 31, 43) before (*left*) and after (*right*) use of offline common average referencing (virtual reference, *VR*) to reduce EMG artifacts. EMG is evident in the activity common to all USEA electrodes in the raw data (*left*). EMG removal (*right*) revealed the neural activity (or lack thereof, electrode 43). Neural firing rate data from channels 10 and 28 predicted thumb-flex position (*top traces*) with an *R* value of 0.72.

IV. DISCUSSION

These results confirm and extend our earlier work using USEAs in two subjects after previous unilateral hand amputation [10]. One novel feature of the present work was the use of two rather than one USEA, which proved to be feasible, and produced no apparent adverse consequences.

Second, stimulation with USEAs in two nerves provided more comprehensive somatosensory coverage of the hand than we [10] or others have previously achieved. As in our previous subjects, the multiple different electrodes provided a rich variety of different somatosensory modalities. The restoration of a sense of "feeling" may provide a psychologically important component of making an individual feel whole again, after limb loss.

Third, stimulation through one USEA while recording with the other USEA provided our first demonstration of closed-loop bidirectional sensorimotor control. Closed-loop control during ADL would make movements more intuitive, reduce the cognitive load associated with relying on visual feedback, and allow operation in circumstances where visual feedback does not suffice, such as modulating grip force for fragile, opaque objects. Bidirectional sensorimotor integration may also enhance the incorporation of a prosthetic limb into the user's body image, and potentially even reduce phantom pain. Future experiments using alternate hardware will attempt simultaneous recording and stimulation through the same array. This capability would allow somatosensory feedback from the digits being moved, which will be important for ADL.

Two factors likely contributed to the relative sparseness of isolated neural motor signals associated with attempted phantom movements. First, the USEA implants sites were at the far ends of the residual nerves, distal to motor nerve branches innervating extrinsic hand muscles in the forearm. Nonfunctional distal sites provided a safe implant location and allowed USEA explantation without risk of function loss. Future investigations will use more proximal USEA implant sites, potentially yielding more control signals.

A second factor contributing to the apparent sparseness of neural units was the presence of EMG, which made it difficult to isolate neural signals online. The reasons that EMG was more prevalent in this subject are unknown. In this subject, the electrical ground wires were not placed in the nerve wrap that contained the USEA, which may have contributed. Nonetheless, successful decodes could be performed on recordings containing substantial EMG. Action potentials in motor nerve fibers correspond in a 1:1 fashion to action potentials in muscle fibers of the same motor unit, so EMG provides a source of useful control signals. However, because EMG typically is picked up from many different motor units simultaneously and is common to many USEA electrodes, the number of independent control signals is likely to be reduced, relative to recording units from nerve fibers on different USEA electrodes. We demonstrated that offline signal processing can isolate neural activity from EMG, but we have not yet incorporated this approach into online decodes, as would be essential for use during ADL. Changes in wire placement and to the USEA containment nerve wrap can also greatly reduce EMG [11].

Taken together, the present and previous study [10] provide support for the use of USEAs in peripheral nerves to restore motor and sensory function after limb loss. By extension, they also provide indirect support for other applications, such as reanimating paralyzed limbs (via stimulation of motor fibers) and obtaining sensory feedback information (via recordings from sensory fibers) after spinal cord injury.

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