Residual Motor Signal in Long-Term Human Severed Peripheral Nerves and Feasibility of Neural Signal-Controlled Artificial Limb

Xiaofeng Jia, MD, PhD, Matthew A. Koenig, MD, Xiaowen Zhang, PhD, Jian Zhang, MD, PhD, Tongyi Chen, MD, Zhongwei Chen, MD

From the Department of Orthopedic Surgery, Zhong Shan Hospital, Fudan University, Shanghai, People's Republic of China; Biomedical Engineering Department, Johns Hopkins University School of Medicine, Baltimore, MD; Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD; and Institute of Rehabilitation Engineering, Shanghai Jiao Tong University, Shanghai, People's Republic of China.

Purpose: The residual motor pathways after amputation have not been fully elucidated. We sampled potentials from peripheral nerve stumps with intrafascicular electrodes to study residual motor transmission and explore the feasibility of nerve signal-controlled artificial limbs.

Methods: Six intrafascicular electrodes were inserted into the ulnar, radial, and median nerves in the stump of an amputee. An electrode was placed outside the fascicle as a reference. Potentials from 4 of the 6 electrodes per trial were monitored using a 4-channel electromyogram machine, and 32 groups of electrophysiologic tests were conducted under volitional control. Actions included finger extension and flexion, forearm pronation and supination, and wrist extension and flexion. Each action was carried out with light, intermediate, and full efforts. Then, 2 of 6 electrodes randomly chosen per trial were interfaced to a nerve signal-controlled artificial limb. Finger extension and flexion of the prosthesis were tested under volitional control.

Results: The volitional motor nerve potentials uniquely associated with the missing limb were recorded successfully with intrafascicular electrodes. The signal amplitude from the radial nerve was 5.5 μV $\pm$ 0.8 (mean $\pm$ SD), which was greater than the amplitudes from the ulnar (2.5 μV $\pm$ 0.4) and median (2.2 μV $\pm$ 0.3) nerves. Under volitional control of the subject, finger extension of the artificial limb was triggered by the radial nerve signal, but the remaining actions were unsuccessful.

Conclusions: The long-term amputee was able to generate motor neuron activity related to phantom limb movement. Intrafascicular electrodes can be used to monitor residual motor nerve activity in the stump, and the amplitude may predict successful control of artificial limbs. (J Hand Surg 2007;32A:657–666. Copyright © 2007 by the American Society for Surgery of the Hand.)

Key words: Artificial limb, human, intrafascicular electrode, motor signal, peripheral nerve.

People with upper extremity traumatic amputations tend to reject prostheses. Although some patients consider the prosthesis beneficial for driving, employment, and recreational activities, the vast majority use the prosthesis primarily for appearance.[1] With use of myoelectric prostheses and modern techniques of rehabilitation,[2,3] the acceptance of upper-extremity prostheses has improved,[2] but recently the rate of rejection of prostheses still remains unsatisfactory (22%–50%).[1,2,4–8] The relevant reasons given for rejection include lack of functional gain, pain, poor appearance, proximal level of amputation, weight of the prosthesis, and the timing of the first prescription of the prosthesis.[1,2,5–9] Control accuracy is not great enough because of the signal source's poor duplication and sensitivity to environmental interference.[10] The above deficiencies pose a challenge to improving prosthesis design; however,

research into possible signal sources for limb control has been scarce.[10] To seek new control sources, researchers are directing attention toward nerve-signal control for upper extremity prostheses.[11–13]

The nervous system has plasticity, rendering it capable of adaptation and functional recovery.[10,14] Nerve signals accurately reflect the motor nerve commands from the brain. Moreover, neural signals are also highly stable, reproducible, and can be exported.[11–13] Interfacing peripheral nerve electrical signals from the nerve stump is becoming the focus of research into the control of prostheses.[11–13,15–17] Researchers[18–23] have contributed much to preparing and developing intrafascicular electrodes and many related animal models. However, the special volitional control, which constitutes the most critical part in developing a nerve signal–controlled prosthesis, is difficult to simulate in an animal experiment.

After long-term limb amputation, neural pathways undergo degeneration or differential atrophy, including decreased conduction velocity, amplitude, and integrated area of action potentials, and loss of effective neuromuscular contact or central connections.[24–29] It is unknown whether the contact between the artificial limb and severed nerve stump would be a functional pathway allowing residual motor signal efficiently to control the artificial limb. The volitional motor control of nerve activity has not been completely elucidated. Interfacing intrafascicular electrodes with severed fascicule of proximal nerve stumps in radial, ulnar, and median nerves is an important way to explore residual motor signaling and intrinsic relationship.

In previous research, the implantation of longitudinal intrafascicular electrodes was guided with the aid of a 50-μm-diameter tungsten needle, which was chemically bonded to the leading end of the intrafascicular electrode using cyanoacrylate adhesive, through the perineurium along within the endoneurium for 6–10 mm, back out of the perineurium and then subsequently cut off and removed.[23] We developed intrafascicular electrodes with a spring-like structure fashioned 8 mm from the proximal end, using a direct microsurgical implantation, and completed successful animal experiments[30–33] in preparation for our human experiment. Our previous study shows that our intrafascicular electrodes recorded the electrical signal of the peripheral nerves stably and reproducibly and they were suitable for long-term implantation. To study residual volitional motor transmission and explore the feasibility of nerve signal-controlled artificial limbs, we sampled and analyzed potentials from peripheral nerve stumps of an amputee with intrafascicular electrodes.

Materials and Methods

Clinical Data and Experimental Materials

In November 2002, a 31-year-old man was admitted 2 years, 5 months after a severe injury. The patient's left hand and wrist were crushed by an industrial machine. Salvage was not possible, and his hand was amputated 8 cm proximal to the wrist. He was given a 1 degree of freedom (DOF) myoelectric artificial hand 1 month after the amputation. After written consent and approval by the institutional review board, he took part in this study as a volunteer. On physical examination, he was healthy and had no other abnormalities. The amputation stump exhibited perfect healing with no pain and a normal sense of touch; however, the skin temperature was slightly decreased. The activity of the left elbow and shoulder was normal. The muscles in the left forearm were slightly atrophied. Function of the electric prosthesis was normal.

To guarantee the stability and reliability of the firing model of nerve activity in the experiment, the subject implemented a 2-week program of nerve rehabilitation training before the operation. The subject was told to consciously make the same volitional actions associated with the missing limb as he performed finger-extension, finger-flexion, wrist-extension, wrist-flexion, pronation and supination in the healthy side. The contraction of muscles in the left forearm could be seen at the time.

The Nerve Signal-Controlled Prosthesis Simulation Instrument (NSPSI) was developed in China by Shanghai Jiao Tong University and Dalian University of Technology. Four-channel Haishenhao type 1 nerve-muscle information recording equipment (Paseidon NDI-500 Electromyogram (EMG) instrument) was developed by the Navy Medical Institute (People's Republic of China).

Electrode Fabrication

The intrafascicular electrodes were made from 100-mm, 5-μm Teflon-insulated 95% platinum/5% iridium alloy wires with diameters of 60 μm. The spring-like structure was fashioned 8 mm from the proximal end[32] (diameter 0.5 mm and 10 cycles) (Fig. 1) to ensure firm fixation with microsutures during the operation. For all of the 6 intrafascicular electrodes, approximately 1 mm of insulation at the proximal end was removed by controlled heating to

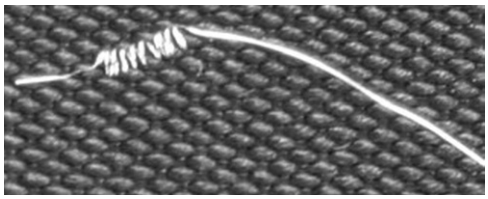

Figure 1. Intrafascicular electrodes with spring-like structure 8 mm from the proximal end.

prepare for implantation in the fascicle, and 10 mm of insulation at the distal end was removed for future attachment to the NSPSI.[30,33] A similar 120-mm alloy wire was made as a conference electrode after removing the insulation at the proximal and distal ends in the same way.

Surgical Procedure for Implantation of Electrodes

The subject was anesthetized with routine gas anesthesia and local anesthesia and kept in a supine position. A 4-cm vertical incision, 5 cm superior above the elbow, was made to the anterior-lateral side of the left upper arm. The radial nerve was exposed over a length of 3–4 cm at the lateral side of the biceps brachii muscle. The radial nerve was carefully separated from the surrounding connective tissue for about 3 cm and kept moist with sterile saline. Two large fascicles were chosen at the posterior and lateral main aspect of the radial nerve.[34] Under a surgical microscope (Leica MC-1, Leica Microsystems, Ltd., Heerbrugg, Switzerland), approximately 2 mm of the epineurium was carefully teased open longitudinally with microsurgery equipment. Special attention was paid to ensure that the perineurium remained intact. A nerve retractor was used to keep the nerves under moderate tension. Unlike other studies,[11–13,23] our electrodes were inserted only by microsurgical technique and were not attached with an extra hard tungsten needle to lessen the damage to the surrounding nerve tissue. Without separating the fascicle, an intrafascicular electrode, held by a microneedle holder near the proximal end, was carefully inserted under microscopy at 60° oblique to the fascicle until the tip pierced through the perineurium. The proximal end was threaded into the fascicle for about 4 mm, then changing to the longitudinal direction parallel with the nerve fascicle. Another intrafascicular electrode was implanted in the same way (2 intrafascicular electrodes implanted in the radial nerve as shown in Fig. 2). Electrodes were fixed at the point of spring-like structure with the epineurium using a 9-0 silk suture along the nerve 2–3 times.

Another 4-cm vertical incision was made to the anterior-medial side of the upper left arm, 5 cm above the elbow. After the target nerves were extricated, 2 fascicles at the anterior and inferior main aspect of the median nerve and 2 fasciculi at the radial aspect of the ulnar nerve were chosen. Every chosen fascicle was implanted with an intrafascicular electrode and fixed to the epineurium in the same way. The position and serial number of the intrafascicular electrodes implanted in 6 fascicles of 3 nerves is shown in Figure 3.

Another wire was placed outside the epineurium of the median nerve and parallel to the longitudinal direction of the nerve as a reference electrode, with its recording area aligned to that of the intrafascicular electrode. It was fixed to the epineurium by microsutures. All distal ends of the electrodes were fixed to the skin by medical adhesive tape.

Real-Time Nerve Signal Clinical Detection

We chose 4 of 6 intrafascicular electrodes of the 3 major nerves in the upper left arm, beginning with 2 in the radial nerve, 1 in the ulnar nerve, and 1 in the median nerve. After connecting all distal ends with the 4-channel Paseidon NDI-500 EMG instrument, the subject was aroused. When the effects of anesthesia wore off, the conscious subject was directed to make various limb movements associated with the missing portion of the amputated limb as he performed the same action on the healthy side. Actions included finger extension, finger flexion, pronation, supination, wrist extension, wrist flexion, and relaxation, and actions were applied with mild, normal, and full strength.

Then, switching 1 channel from the radial nerve to another intrafascicular electrode in the ulnar nerve and then to the median nerve, electrophysiologic tests were conducted in the same way using different

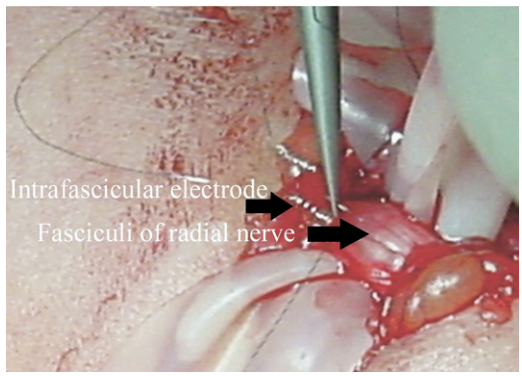

Figure 2. Two intrafascicular electrodes surgically implanted in the radial nerve.

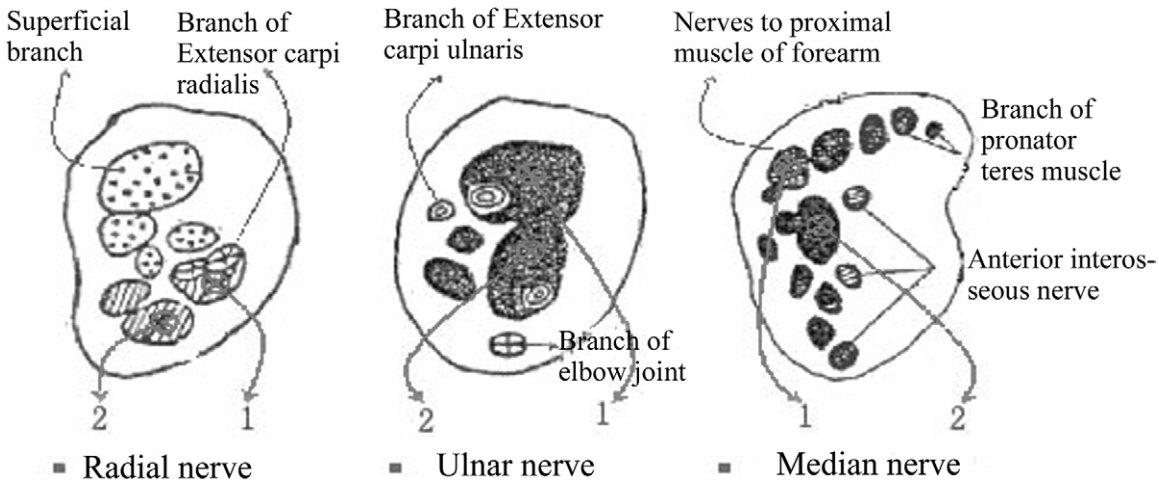

Figure 3. The positions where intrafascicular electrodes were implanted in the 3 major nerves (1 and 2 are the serial numbers of intrafascicular electrodes).

combinations of 4 among 6 recording electrodes. Real-time motor signal was recorded by an EMG instrument in different modes between the reference electrode and the intrafascicular electrodes. Surrounding muscle tissue around the intrafascicular electrode was grounded.

After 32 groups of data were recorded with sample frequency of 5 kHz and duration of 10 milliseconds, we investigated and analyzed the wave pattern of the electrical signal in time domain by each group. Then, we saved the recording information by 500 points per 10 milliseconds for program frequency analysis with MATLAB software.[10,35]

First Experimental Study on an Electric Prosthesis Controlled by Signals of Nerves in an Amputation Stump

The gain of the NSPSI was adjusted to 30,000 and input impedance was adjusted to 430 kOhm. After real-time nerve signal clinical detection was completed, interfacing 1 intrafascicular electrode of the radial nerve and reference electrode with the signal input system of the NSPSI, the conscious subject made volitional finger extension and finger flexion actions associated with the missing hand as he performed the same action on the healthy side. To verify that the NSPSI would recapitulate the intended action, the real-time nerve output information was used to control the NSPSI after amplifying the difference between the 2 electrodes. Next, we switched intrafascicular electrodes to the ulnar nerve and then to the median nerve in sequence, interfacing to the NSPSI together with the reference electrode. The conscious subject was directed to make the same actions using the phantom limb.

Finally, the electrodes were removed, and the incision was closed by layers.

Results

Real electric nerve signaling was recorded by intrafascicular electrodes when volitional actions associated with the missing limb were made. Related muscle groups contracted simultaneously proximal to the amputation site. A total of 32 groups of 6 actions (ie, finger extension, finger flexion, wrist extension, wrist flexion, forearm pronation, forearm supination) were successfully recorded. Stable nerve signal harvested by intrafascicular electrodes was displayed on the EMG instrument (Fig. 4).

When the input signal came from 1 intrafascicular electrode in the radial nerve and another reference electrode, as the subject imagined finger extension and finger-flexion of the lost hand, finger-extension of the NSPSI was triggered successfully (Fig. 5) while finger flexion was not. Electrical signals conducted from the ulnar nerve and median nerve did not trigger any action of the prosthesis.

Time Domain Analysis

During finger extension (Fig. 4a), active neural potentials were elicited from the radial nerve with high amplitude, low frequency, and mixed high/low components, whereas the action potentials from median and ulnar nerves were predominately low amplitude and high frequency. The amplitude of action potentials from median and ulnar nerves increased when finger flexion was undertaken (Fig. 4b). As wrist extension was performed (Fig. 4c), the amplitude of the action potential from the radial nerve was high, whereas the amplitude was low from median and

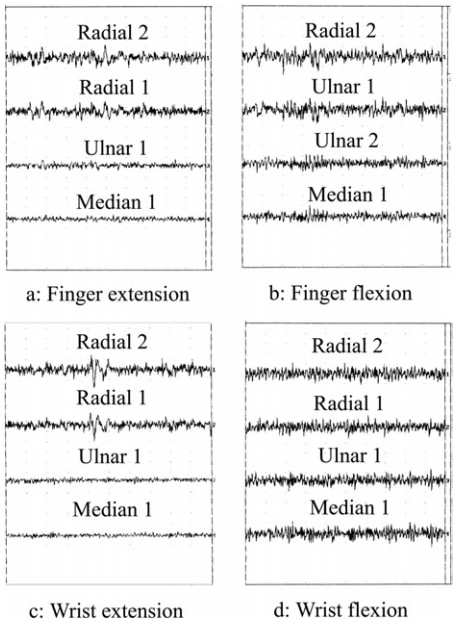

Figure 4. Representative raw electrical signals of the 3 major nerves as various actions were made show the nerve controlling agonistic muscles firing more actively than the nerve controlling the antagonistic muscles when the motor command was carried out.

ulnar nerves. The maximal amplitude from radial nerve was more than 6-fold greater than from median and ulnar nerves. High-frequency firing activity was seen in all 4 channels of the nerves as wrist flexion was made (Fig. 4d), and slightly higher frequency was observed with median and ulnar nerves.

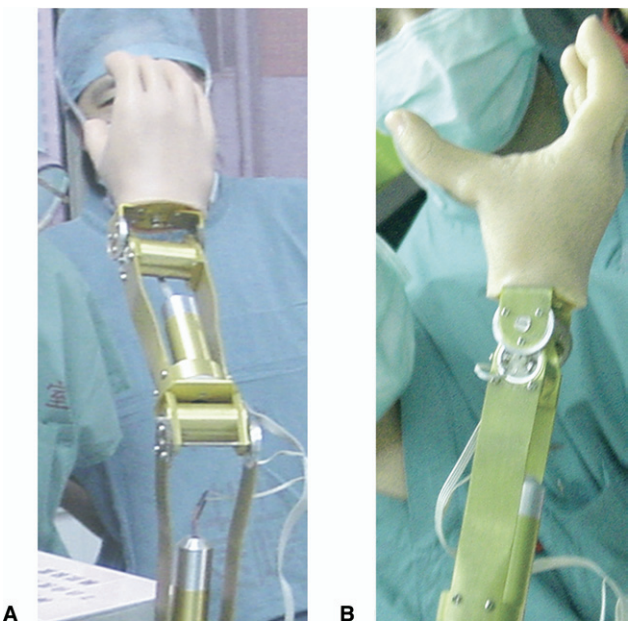

Figure 5. (a) The original position of the neural signal-controlled prosthesis. (b) Finger extension of the NSPSI was triggered during the operation.

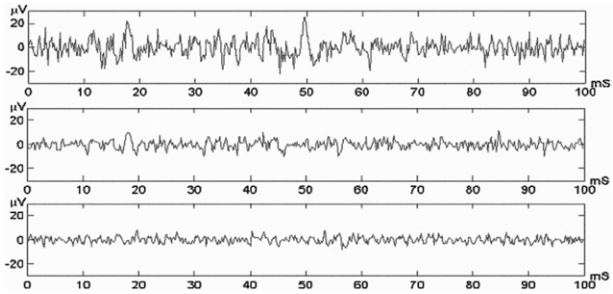

Figure 6. Time domain analysis of representative raw electrical signal as finger extension in the phantom hand was made. Category (x) axis is time and value (y) axis is amplitude. The illustration shows the signal firing from the radial nerve (upper) is stronger than the ulnar (middle) and median nerves (lower). The average absolute amplitude of the signals from the radial nerve in all data was greater than the amplitude of signals from the ulnar nerve and median nerve.

The average absolute amplitude of the signals from the radial nerve in all 32 actions with time domain analysis was 5.5 μV $\pm$ 0.8 (mean $\pm$ SD), which was greater than the amplitude of signals from the ulnar nerve (2.5 μV $\pm$ 0.4) and medium nerve (2.2 μV $\pm$ 0.3) (Fig. 6). Anatomical review[34] showed that at the implanted position, there were almost pure motor fascicule of the radial nerve, whereas there were mixed motor and sensory fascicule in the ulnar and median nerves.

Frequency Domain Analysis

Pattern difference of neural activity was not observable with time domain analysis but became more conspicuous with frequency domain analysis (Fig. 7a). The nerve signal was elicited in 2 different intrafascicular electrodes in the radial nerve when finger extension was volitionally controlled (Fig. 7b). These data imply that the same information was transmitted in different fascicule in the same nerve and combined at the nerve terminal to form the motor nerve commands to target muscles. By this mechanism, the safety factor for transmission of motor signaling is enhanced, even in the presence of unhealthy fascicule in the pathway. The nerve signal was elicited in the intrafascicular electrode from the radial nerve when the repeated action of wrist extension with full force was volitionally controlled (Fig. 7c). This implies that the information in the frequency domain in the same functional fascicule has stability when repeated actions with a similar force were undertaken. The nerve signal was elicited in an intrafascicular electrode in the radial nerve when wrist extension was volitionally controlled with normal and full strength (Fig. 7d). Unlike predominating

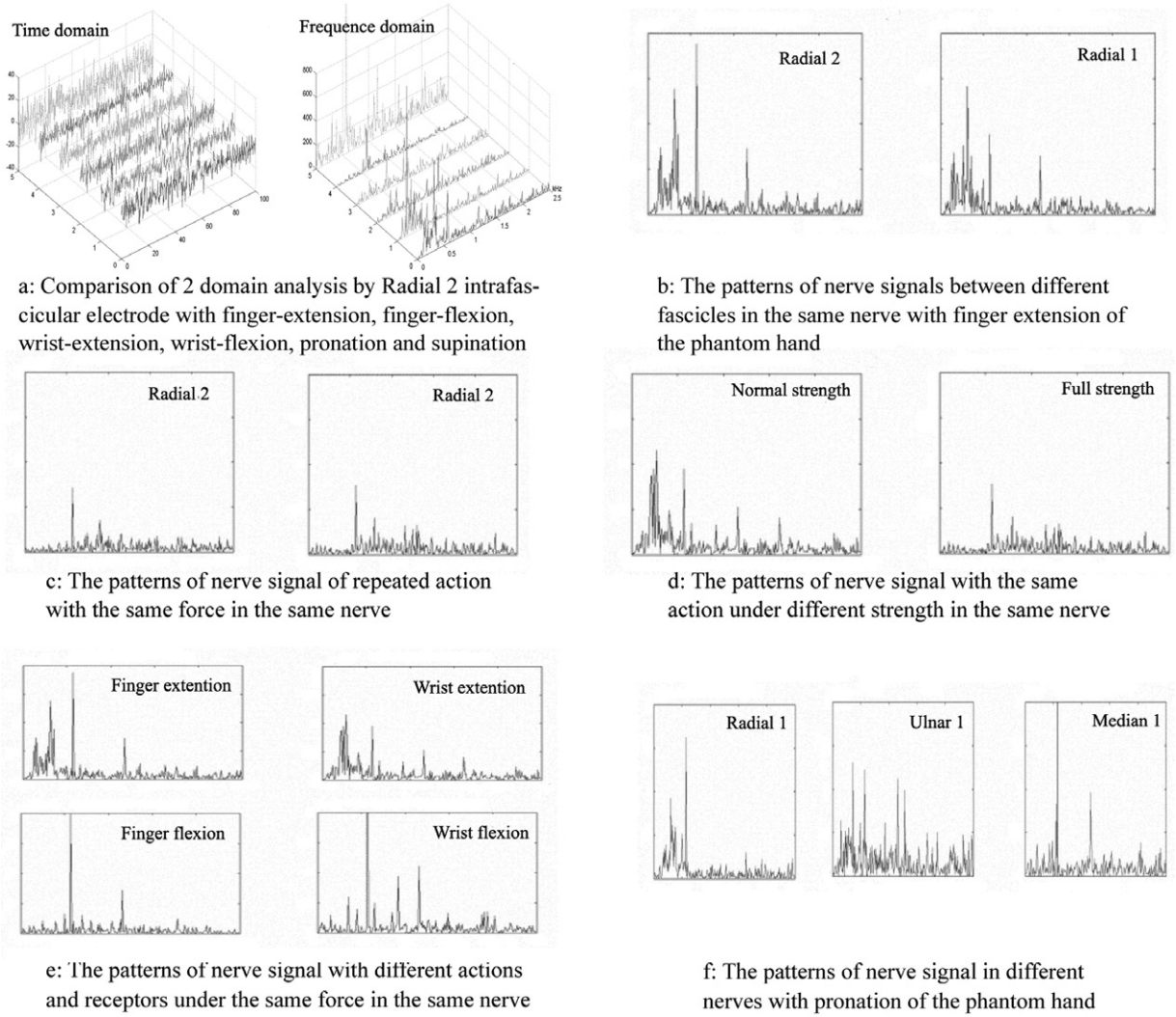

Figure 7. Frequency patterns of nerve signals recorded by intrafascicular electrodes using frequency domain analysis.

by increasing the amplitude in myoelectrical signal with increased strength, the low-frequency component of the nerve signal decreased and the high-frequency component increased as the applied force increased. Time domain analysis, on the other hand, was unable to detect changes in signaling characteristics with changes in applied force. The nerve signal was elicited in the intrafascicular electrode in the radial nerve when different actions were volitionally controlled with the same force (Fig. 7e). There was a great difference in frequency pattern from the radial nerve between extension and flexion action, but no difference was found between different wrist extension and finger extension. Advanced analysis showed that the frequency pattern from the median and ulnar nerves lacked these characteristics. These findings imply that the pure motor fascicles of the radial nerve elicit better signaling characteristics than mixed motor and sensory fascicles from the ulnar and median nerves. The nerve signals with different frequency spectra were also elicited in different intrafascicular electrodes in the radial, ulnar, and median nerves when pronation was volitionally controlled (Fig 7f).

Discussion

The key issue of motor control in bionic prosthesis research, especially for prostheses with multiple DOF, is reliably and reproducibly recording and transmitting neural signals. Collecting information from peripheral nerves for prosthesis control may be preferred over myoelectric sources for reasons including a lack of stable open-loop or essential closed-loop feedback,[36] muscle fatigue,[3] and control limited to one movement at a time.[37]

Potential impediments to interfacing artificial limbs to the peripheral nervous system of long-term (>3 months) amputees include axotomy-induced loss of central connections, questionable viability of

the proximal nerve stump, and reorganization of CNS areas related to the missing limb regions.[13] Our current experiments show the subject was able to generate motor neuron activity related to phantom limb movement, and intrafascicular electrodes were able to export the real-time electrical signal of nerves 29 months after amputation without any nerve rehabilitation training before this clinical trial. It also confirms that either the neural pathways for control of missing limb motions remain intact or dynamic and adaptive motor cortical plasticity quickly comes into play.[12,38,39]

Although rapid plasticity of cortical movement representation has been reported by simple movement training repeated over a short period of time[40] in human subjects, our data imply that the native pathway remained intact for 29 months after limb amputation or reorganization reversed rapidly after a 2-week program of nerve rehabilitation training by the amputee bringing back the muscles' actions related to the phantom limb. This implies that cortical plasticity either did not occur in this patient or did not completely disrupt the native pathways because imagined finger extension still caused activation of the radial nerve or the native pathways still controlled the original limb movement. It also implies that the possible reorganization of the cortical regions after limb amputation may be through unmasking of existing but functionally inactive pathways, redundancy of CNS circuitry allowing alternative pathways to take over functions, or modulation of synaptic efficacy rather than neuronal sprouting or retraction.[13,38,41] The central and peripheral pathways remain largely intact from the functional point of view[12] even in the subsequent absence of effectors for years.

During finger extension, the dominant agonistic muscles controlled by the posterior interosseous nerve, as the common extensor muscle of fingers, fired with high amplitude, while the median- and ulnar-innervated antagonist muscles displayed low amplitude potentials. The median and ulnar nerves changed from controlling the antagonistic muscles to agonistic muscles and the amplitude of their action potential increased during finger flexion. During wrist extension, the amplitude of the action potential from the median nerve and ulnar nerve was low whereas that of the radial nerve was high as the radial nerve controlled the agonistic muscles and the median nerve and ulnar nerve controlled the dominant antagonistic muscles. Although high-amplitude firing was found in all 4 channels of the 3 major nerves during wrist flexion with strong efforts, the firing frequency from the median nerve (controlling the flexor carpi radialis) and the ulnar nerve (flexor carpi ulnaris) was higher than it was from the radial-innervated antagonistic muscles.

When the signal came from an intrafascicular electrode and a reference electrode of the radial nerve, successful finger extension was triggered, but nerve signals exported from the ulnar and median nerves were unable to trigger finger movements of the prosthesis (ie, the median and ulnar nerves were not activated during movements like finger flexion that are controlled by median and ulnar innervated muscles). This may be due to the ineffectively recognized information patterns[12] of finger-flexion actions recorded by the prosthesis or limited sampling provided by implanting only a few electrodes[12] or greatly diminished motor cortical representation of the truncated limb and nerves after amputation and axotomy.[13,42,43] Improving the gain of the prosthesis may be beneficial for finer control with signal exported from the ulnar and median nerves. However, there is no clear answer if certain actions can be triggered by electrical signals only from a single nerve, which limits the benefit for better control by increasing the gain from median and ulnar intrafascicular electrodes. Increasing the signal-to-noise ratio of nerve signals (eg, implanting the electrodes more precisely in closer proximity to motor fascicles and increasing the filter ability with intelligent control strategies by feature extraction and neural network classification[10]) and obtaining control commands by establishing mapping between the movement intentions and the patterns of neural signals from intrafascicular electrodes would be a better choice, which may lead to better pattern analysis of signal character to improve the ability of signal identification, movement recognition, and motor control of neurally controlled prostheses.

According to Sunderland's nerve anatomy atlas, motor fascicule predominate at the radial nerve implantation sites, but mixed motor and sensory fascicule were present at the implantation site of the ulnar and median nerves. Simple motor fascicule are ideal for signal exportation as controlling information sources and produce obvious action characteristics with better signal-to-noise ratios. The data presented here also show low amplitude of signal in the median and ulnar nerves versus high amplitude in the radial nerve in volitional phantom limb motor control, which demonstrates that at least in this detection site, motor signals are more intense than those of sensory

or mixed signals. The intensity of signal from the ulnar and median nerves may not be strong enough to efficiently drive the prosthesis. It implies that the amplitude of the signal may be predictive of the success of neural control from these nerves. More experiments are needed to confirm that the amplitude of signal from the nerve stump will predict which patients have enough residual nerve function to actually control the prosthesis.

A 2-week program of nerve rehabilitation training was implemented for the subject before the operation to optimize the firing pattern of electrical signals in the amputee stump. The inability of nerve signals exported from the ulnar and median nerves to trigger finger movements of the prosthesis may imply that the rehabilitation training was not rigorous enough for the ulnar and median nerve. After amputation, the volunteer subject was given a 1 DOF myoelectric artificial hand with open-loop control for 28 months and may have been using the radial nerve-finger extension/wrist extension pathway regularly when using this prosthesis. Use of the single DOF myoelectric prosthesis for more than 2 years might have affected the subject's outcome—the 28-month radial nerve experience might affect the radial nerve amplitude by strengthening the control pathway and affect the subject's ability to cause finger extension of the prosthesis. Longer rehabilitation training may be needed for future nerve signal research in long-term amputees. Further research is needed to answer whether use of a prosthesis with more DOF (to control opening and rotation) might affect the amplitude of signal of the median and ulnar nerves.

For implantation, instead of 90% platinum–10% iridium wire, we used a more flexible 95% platinum–5% iridium wire and made spring-like structures near the end of the intrafascicular electrodes to avoid shearing or stretching forces during limb movements.[32] The longitudinal intrafascicular electrodes are difficult to keep in good position, easily dislodged during surgery, and are not good for long-term implantation. This modified spring-like structure prevented the activity of surrounding soft tissue from breaking the wire and was able to decrease injury to the fascicle. Instead of implantation guided with an extra tungsten needle, which would have doubled the effective diameter of electrodes, made another hole throughout the perineurium and epineurium, and added the naked exposure of the distal end besides its original recording area of the electrode,[11–13,22,23] we used direct microsurgical implantation. This technique decreased injury to fascicles, avoided possible external interference, provided relatively better insulation,[30–33] and showed benefit for long-term implantation in an animal model.[14]

Because of subject preference, we did not implant intrafascicular electrodes for a long term or attempt a longer clinical study. Therefore, it led to the paucity of clinical sampled data, and we cannot ensure that the electrical signal from the nerve is suitable for chronic limb control. The exact duplication of limb actions by the NSPSI were imperfect in this subject, possibly because of the long interval after amputation (29 months), even though nerve rehabilitation training was undertaken for 2 weeks prior to the experiment. Disuse and unfamiliarity with the experimental tasks likely contributed to the failure of movement of median- and ulnar-innervated muscles, which adds to the uncertainty of the experimental results. For a more suitable subject, less time after amputation and more rehabilitation time will likely benefit future clinical trials.

The clinical data we obtained from this feasibility study may be useful for future neurally controlled prosthetic limb research. Our previous animal research, including short-term and up to 9-month implantation of intrafascicular electrodes, showed excellent biocompatibility with only minor injury to the peripheral nerve with rapid healing. The implantation of intrafascicular electrodes and harvesting of nerve electrical activity to drive neural signal-controlled prostheses remain experimental, but this experiment demonstrates feasibility. Future goals include identifying the electrical signal through pattern analysis,[35,44–46] discovering a locomotion pattern rule, harvesting sensory neural signals[12,13] (ie, proprioception) from the stump fascicule as a feedback to boost prosthesis control,[36] and exploring intradermal embedded intrafascicular electrodes with telemetry systems.

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Corresponding author: Xiaofeng Jia, MD, PhD, Biomedical Engineering Department, Johns Hopkins University School of Medicine, Traylor 710B, 720 Rutland Avenue, Baltimore, MD 21205; e-mail: xjia1@jhmi.edu

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