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Handcrafted Microwire Regenerative Peripheral Nerve Interfaces with Wireless Neural Recording and Stimulation Capabilities

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Abstract

A scalable microwire peripheral nerve interface was developed, which interacted with regenerated peripheral nerves in microchannel scaffolds. Neural interface technologies are envisioned to facilitate direct connections between the nervous system and external technologies such as limb prosthetics or data acquisition systems for further processing. Presented here is an animal study using a handcrafted microwire regenerative peripheral nerve interface, a novel neural interface device for communicating with peripheral nerves. The neural interface studies using animal models are crucial in the evaluation of efficacy and safety of implantable medical devices before their use in clinical studies. 16-electrode microwire microchannel scaffolds were developed for both peripheral nerve regeneration and peripheral nerve interfacing. The microchannels were used for nerve regeneration pathways as a scaffolding material and the embedded microwires were used as a recording electrode to capture neural signals from the regenerated peripheral nerves. Wireless stimulation and recording capabilities were also incorporated to the developed peripheral nerve interface which gave the freedom of the complex experimental setting of wired data acquisition systems and minimized the potential infection of the animals from the wire connections. A commercially available wireless recording system was efficiently adopted to the peripheral nerve interface. The 32-channel wireless recording system covered 16-electrode microwires in the peripheral nerve interface, two cuff electrodes, and two electromyography electrodes. The 2-channel wireless stimulation system was connected to a cuff electrode on the sciatic nerve branch and was used to make evoked signals which went through the regenerated peripheral nerves and were captured by the wireless recording system at a different location. The successful wireless communication was demonstrated in the result section and the future goals of a wireless neural interface for chronic implants and clinical trials were discussed together.

Keywords: Neural interface; Microchannel scaffold; Nerve regeneration; PDMS

Introduction

Neural interface technologies are envisioned to facilitate direct connections between the nervous system and external technologies such as limb prosthetics or data acquisition systems for further processing. Although cultured *in vitro* neuronal networks have shown a variety of mechanisms of neuronal functionality, the major role of behavioral control by the nervous system cannot be incorporated with the *in vitro* neuronal networks system. Neuronal interface signals captured from awake, freely behaving animals are crucial for the next level of clinical applications. In amputees, such technologies would provide direct neural control of prosthetic movements and restore sensory feedback by functionally reconnecting damaged efferent motor and afferent sensory pathways. The peripheral nerve has been one target for bidirectional interfacing, with renewed interest generated by reports that peripheral nerve tissue is viable for interfacing even years after injury or amputation [1-4]. Several designs, such as cuff electrodes, flat interface nerve electrodes (FINE) [5-7], longitudinal intrafascicular electrodes (LIFE) [5,8-10], Utah Slanted Electrode Arrays (USEA) [11-13], and regenerative sieve and microchannel electrodes [14-20] demonstrated selective recording and stimulation. However, the devices have limited electrode sites and recordings can only be obtained from the limited number of nerve fascicles.

A regenerative peripheral nerve interface, developed here, can be utilized to address these goals and is designed to communicate with the brain through the peripheral nervous system. Previously, we developed 4-electrode and 8-electrode microwire regenerative peripheral nerve interfaces (μPNI) [21-26]. Here we report an advanced generation of the 16-electrode μPNI and even further advanced the μPNI with wireless communication capabilities. The whole implantable microdevice consists of a μPNI for recording placed on the transection site of the sciatic nerve, and three μCuff electrodes, one for stimulation placed on the proximal site of the transection site of the sciatic nerve and the other two for recording placed on the tibial nerve and the common peroneal nerve. Additionally, two electromyography electrode pairs were implanted on the tibialis anterior (TA) and soleus (SOL) muscles on the right hind leg to record the muscle signals during animal's locomotion tests. It gives us the capability of both electrophysiological recording and stimulation to develop a communication pathway from the brain to the endings of peripheral nerves. Peripheral nerve stimulation from one end of the μPNI initiates a neural signal pathway. Animal locomotion on a treadmill was tested in the animal facility at UTRGV and the μPNI has enabled us to analyze any sophisticated behavioral patterns.

There are three fundamental neuroscience backgrounds correlated with the μPNI (Table 1). Independent microchannel neural interfaces will be creatively achieved by microwires embedded inside the microchannel scaffolds which can be occupied by regenerated nerve

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Neuroscience Fundamentals	µPNI
Peripheral nerves regenerate (like hair and nails)	Custom designed Microchannel Scaffolds support nerve regeneration
Action potentials are recordable every 1mm from nodes of Ranvier	1.0 mm length open microwire Electrodes in 3 mm length microchannel scaffolds
CNS-PNS neurons are connected from the brain to peripheral nerves	Peripheral Nerve Interface will collect details of the Brain making the process Noninvasive Brain-Machine Interfaces

Table 1: Supports from fundamental neuroscience.

and develop an isolated neural signal communication. Along with peripheral nerve regeneration, the microwires on the nodes of Ranvier can cover and record neural signals selectively from an isolated neural signal source. The microchannel and microwire are long enough to cover and record neural signals from the isolated nerve branch by structural selectivity during nerve regeneration.

Methods

Fabrication of PDMS scaffolds

Microfluidic channel scaffolds were developed to direct peripheral nerve growth. 50 wires (160 µm in diameter) were tightly packed into Silastic® tubes (OD 1.96 mm, ID 1.47 mm; Cat. No. 508-006, Dow Corning, MI) and then were cast in liquid PDMS (Sylgard® 184, Dow Corning, MI) with a 10:1 base to curing agent ratio. They were placed in a vacuum chamber until all air dissipated and then were placed in an oven for 2 hours at 90°C to allow the liquid PDMS to solidify. The Silastic® tube and Sylgard 184® are composed of the same PDMS material and became a single structure as the liquid PDMS solidified. The solidified PDMS was soaked in chloroform, causing it to expand. The wires were henceforth, removed leaving behind a long, flexible scaffold with an array of microchannels within it. Chloroform is a highly volatile solvent, leaving no residue when it is evaporated. No special process is required for the fabrication process to clean chloroform. Chloroform-swollen PDMS was switched into 70% ethanol to clean the device while shrinking down PDMS and run sterilization process together. Then PDMS scaffolds were placed in an oven at 100°C for 20 minute to make any remaining Chloroform evaporate.

Embedding microwires

The 75 µm diameter microwires (Stablohm 800A, California fine wire, Grover Beach, CA) were inserted in the 160 µm diameter microchannels to record the neural signals from the regenerated nerves inside microchannels. No special micromachining equipment was required and commercially available microwires were efficiently used to implement the µPNI structures. Once the PDMS scaffolds were fabricated, commercially available microwires (75 µm diameter) were embedded within their microchannels. The scaffold was cut 3 mm lengthwise and PDMS tubes, used as suture guides, were placed at both proximal and distal ends of the scaffold, hereafter referred to as proximal and distal tubes, respectively. The proximal tube was cut 3.5 mm long and placed on one end of the scaffold, thereby covering 1.4 mm of the scaffold. It was secured to the scaffold by placing a drop of liquid PDMS solution where they make contact (on the outer surface of the scaffold) and placing in an oven at 90°C for 10 minutes. The distal tube was cut 4 mm long and placed so that it covered 1.4 mm of the other end of the scaffold. To assist in the process of embedding microwires in the scaffold, a small circle with a slit leading to it was made in the distal tube. The gap between the tubes was filled with a dental cement and was subjected to ultraviolet (UV) light for 8 seconds to cause it to harden. The distal tube was opened along the slit to facilitate embedding of microwires into the microchannel.

16 microwires were cut into 8 inch segments and 1 mm of insulation was trimmed off at the tips. They were then folded at 90° angles, 1 mm away from the uninsulated parts. The exposed wires were placed one-by-one into the microchannels through the circle made in the proximal tube and glued to the dental cement previously applied using the same technique. Dental cement was then used to seal the circle in the proximal tube, being careful not to allow any dental cement into the regenerating path of axons. All 16 wires were then braided together to make them as compact as possible and were connected subcutaneously to a head stage connector which was attached to the skull. Microwires are beneficial because they are easy to implant, permit smaller wounds, and create minimal obstruction to the regenerative path.

Animal implantation

Surgical procedures were performed under aseptic conditions at the UTRGV Animal Facility (Figure 1). Prior to implantation, a Lewis rat was placed into an induction chamber and subjected to gas anesthesia (Isoflurane) until unconscious. The surgery locations (right thigh and top of head) were shaved and cleaned using a betadine scrub and isopropyl alcohol. Its maxillary central incisors were hooked into a gas mask through which it continued to receive small doses of anesthesia. It was secured to a surgery table and its body temperature was regulated with a hot pad. Incisions were made along the right thigh to expose the sciatic nerve, tibialis anterior (TA), and soleus (SOL) muscles. The nerve was severed, proximal to the tibial and fibular nerves, and the µPNI was implanted by suturing both the distal and proximal ends of the nerves to the guides of the device (Figure 2). EMG signals were obtained by implanting pairs of microwires (Stablohm 800A, California Fine Wires, CA) (75 µm diameter) into the TA and SOL. All electrodes were guided subcutaneously to an incision made at the top of the head and henceforth attached to a connector (Nano Strip Connector, A79022-001, Omnetics, MN), which was secured to the skull using dental cement and stainless steel screws. All procedures conformed to the Guide for the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council (National Academy Press, Washington, DC, 1996) and were reviewed and approved by the Institutional Animal Care and Use Committee UTRGV.

Figure 1: Surgery setup and implementation. All surgical procedures were done under stringent ethical standards at the UTRGV animal facility.

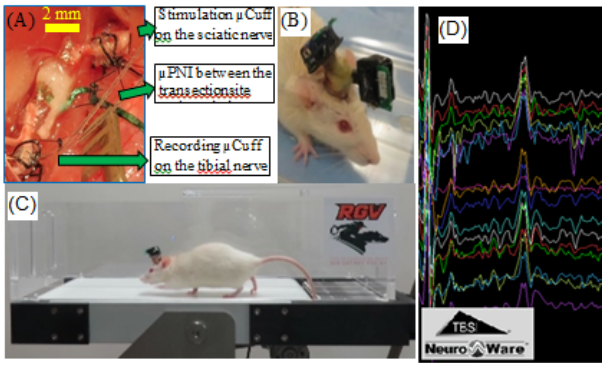

Figure 2: (A) Animal surgery of the sciatic nerve model. Two µCuff electrodes and µPNI are located. (B) Both TBSI stimulation and recording system headstages on a rat. (C) Video monitoring of walking locomotion. 32-channel TBSI wireless recording device is attached on the headplug (D) Neural signals from individual microwires showing different signals from each channel recorded by TBSI 32-channel wireless system. The first picks are the stimulation signals and the second picks are evoked action potentials delayed by the transition speed of the peripheral nerves.

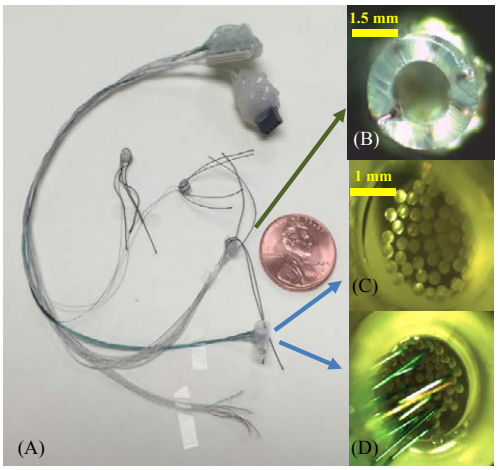

Figure 3: Implantable micro devices (A) whole configuration. (B) 8-electrode µCuff for stimulation. (C) 160µm diameter microchannel scaffold before inserting microwires. 16 out of 50 microchannels were occupied by microwires. (D) 16-electrode µPNI after microwires were inserted inside microchannels.

Results

A manually fabricated implantable micro device ready for the surgery is shown in Figure 3. Both an omnetics connector (Nano Strip Connector, A79022-001, Omnetics, MN) for TBSI neuroware and a sullins connector (S9009E-04-ND, 8 Position 050, Dual Row, Digi-key) for TBSI stimware were placed at one end of the microwire bundle. The other end of the microwire bundle was connected with a µPNI, three µCuffs, and two electromyography electrodes. Peripheral nerve axons were targeted in the µPNI using microchannels that isolate different groups of axons. Since the developed fabrication technique is simple and adjustable, the scaffold parameters (length and microchannel diameter) can be modified to fit different applications. Figure 3C indicates that each microchannel (160 µm diameter) is individually separated and completely sealed. This feature aims to improve the design by reducing the crosstalk between adjacent microchannels and increasing the signal-to-noise ratio. This is a significant advantage of the µPNI because other electrodes that are near each other can create crosstalk due to parasitic capacitances [27].

Figure 2A shows the successful surgery result. The µPNI was implanted between the transected sciatic nerve stumps at the location marked as 'transection' of the schematic design in Figure 4. All embedded electrodes were routed subcutaneously and connected to a head-mounted plug (Figure 2B). The nerve stumps were sutured on each side of the µPNI. The stimulation µCuff was placed on the proximal sciatic nerve from the µPNI. Once the microchannel scaffolds were occupied by the regenerated nerve, the stimulation signal from the µCuff was recorded from the recording µCuff on the tibial and the common peronial nerves. This confirmed the successful nerve regeneration through the µPNI. The µCuff electrodes were used as supplementary recording devices and contributed as a part of neural networks in the sciatic nerve branches. The electrophysiological locomotion data of the sNI was captured by Triangle BioSystems International (TBSI, Durham, NC) wireless system. Figure 2B shows both TBSI w-32 wireless recording system and TBSI S2W stimulator. While an animal was walking on a treadmill for behavioral pattern analysis, TBSI w-32 system recorded the electrophysiological signals from all implanted micro devices (Figure 2C). We used a rodent treadmill system that has the slop angle control capability (760306, Harvard Apparatus, South Natick, Massachusetts), which was installed in a procedure room at the animal facility at UT-RGV. TBSI S2W stimulator was used to generate the evoked signal to analyze the neural pathways and electrophysiological properties of the sciatic nerve branches, SOL, and TA muscles. Neural recording and stimulation signals were forced to flow longitudinally within the microchannel scaffolds which make each microchannel independent from all other microchannels, making it possible to retrieve specific signals. The implantable devices of the µPNI, the µCuff, and the EMG electrodes were implanted in the animal and neural signal recordings were obtained, while the animal was running on a treadmill. The TBSI wireless recording system gave the maximum flexibility for the locomotion studies. Due to the robust nerve regeneration of the sciatic nerve model, all channels were occupied with regenerated nerves. Figure 2D shows the electrophysiological signals captured by the 16-electrode microwire µPNI using TBSI wireless recording system three weeks after implantation. The neural signals through the regenerated nerves in the µPNI were recorded and analyzed to retrieve data corresponding to animal behavior patterns. Electrophysiological signals were recorded from all 16 electrodes. Although some signals showed were identical, these also suggested possible axonal branching from the regenerated nerves. With further analysis in the future work, we could determine if the multiple axons were originated from the same parent neuron to make a same neural signal pattern. It could be confirmed by histology analysis at the end of the procedure after harvesting regenerated nerve tissues. The unique neural signal patterns of the µPNI, depending on the animal behavior patterns, will not only confirm the brain-controlled neural singnals at the µPNI, but also pioneer the delicate neuronal networks in the brain linked to the sensory and motor feedback of peripheral nerves. Action potentials with similar waveforms were identified in the locomotion microelectrode recordings and extracted using a time-amplitude window discriminator routine. The average amplitude of the action potentials extracted from microchannels was about 100 µV with amplitudes ranging from 40~200 µV. Selected and repeated action potentials comparing the µPNI, TA muscle, and cuff data were clearly demonstrating the step cycles. A neural signal combination of all microwires of the µPNI, or part of them, will express a behavioral pattern at a specific temporal moment. A repeatable behavioral pattern

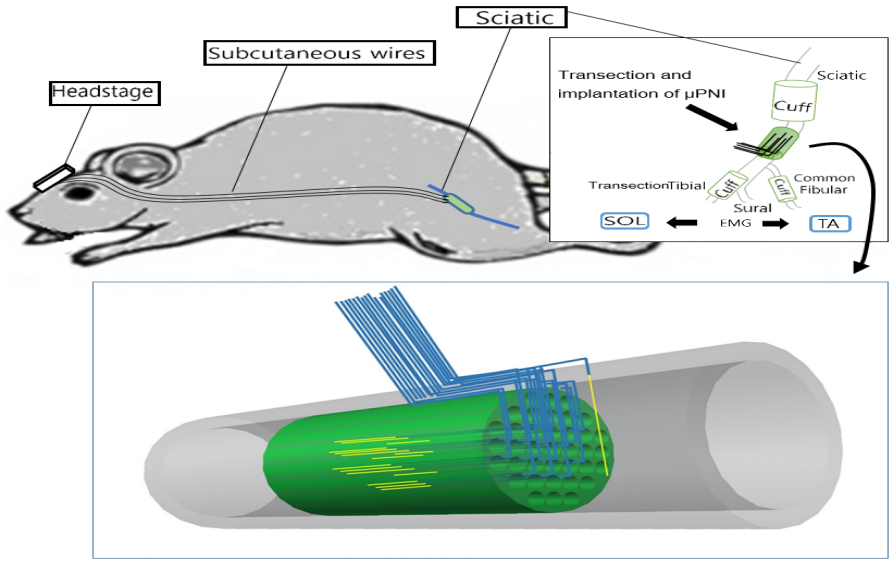

Figure 4: Schematic view of the animal model for μPNI, μCuff, and EMG electrodes on the sciatic nerve braches.

may express a series of temporal neural signal patterns. Thin scar tissue formation covering outside PDMS scaffolds was observed from the harvested μPNI. However, no obstructing inflammation responses was observed inside microchannels with a two-month regeneration period. PDMS is an FDA-approved biomaterial for several clinical applications. As a biocompatible material, PDMS has been used in a wide range of applications, such as a structure itself as part of the device and an insulator. PDMS cuff electrodes have been used on the extradural sacral root to sense the bladder response to stimulation in patients [7].

Discussion

For the chronic animal studies, the microdevices need to be implanted securely inside the animal body without biological rejection and mechanical failure. Moreover, minimally invasive surgery is always required. A biological reaction to foreign materials could be significant in any chronic animal study requiring implantation, especially those that require the implanted device to be kept for more than three months. We recorded electrophysiological signals with the μPNI for two months period, since the axonal reinnervation was achieved after one month and stable muscle signals could be captured afterward. Many implantable devices have been used in the everyday clinical practice and decades of implantation is not a significant issue anymore, which makes us confident about the chronic studies. We used PDMS as a base material for all components of the μPNI. PDMS has been widely used as a major material of the implantable devices for both research and clinical purposes [28-33], due to its easy fabrication technique and biocompatibility. To achieve translational capabilities, PDMS could be replaced by biodegradable materials, such as PCL, PLGA, and PGA [34-39]. After the nerve regeneration, the biodegradable microchannel will be dissolved to give the structures as close to a natural nerve as possible. Each biodegradable material needs to be tested for its own biocompatibility and degradation rate in the peripheral nerve model.

Though we have developed the μPNI targeting the sciatic nerve model with gait analysis of the somatic nervous system, it can be easily adapted for other nerve models including the modulation of the autonomic nervous system. The developed fabrication technique of the μPNI is not dependent on the nerve size as any size of the μPNI components can be developed, ranging from few hundred micrometers to several millimeters in diameter which covers almost all major peripheral nerves and their branches. This allows for flexibility in choosing from a variety of design configurations that target specific nerve fibers.

The μPNI has a significant potential as neuroscience research test beds, if it is combined with biochemical neurotropic factors. The microchannels of the μPNI can be coated with different neurotropic factors to separate the growth of sensory or motor specific axons into the microchannels. They will encapsulate multiple neurotropic factors, such as nerve growth factor (NGF) [40], neurotrophin-3 (NT-3) [41-43], brain-derived neurotrophic factor (BDNF) [44,45], and neurotrophin 4/5 (NT-4/5) [46], ciliary neurotrophic factor (CNTF), and glial cell line-derived neurotrophic factor (GDNF). Inducing the specific axonal growth from a microchannel structure to biochemically infused microchannels could provide data for a more in-depth analysis of axon growth behavior.

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