Flexible Neural Clip (FNC) for Neuromodulation of Small Peripheral Nerves

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***Abstract*— Modulation of neural activity with implantable bioelectronics is a potentially powerful way to regulate physiological function and restore health. Interventions based on bioelectronic neuromodulation rely on reliable neural interfaces to record and discriminate nerve signals and/or stimulate or block nerve signals of small nerves without neural damage. Here, we propose a flexible neural clip (FNC) to be a reliable way interfacing diversified peripheral nerves for bioelectronic medicine applications. To show comprehensive demonstration of our FNC technology, we stimulate sciatic nerve branches and pelvic nerves to evaluate the feasibility of the design in modulating the function of each of these nerves. Our results demonstrate that this novel FNC allows conformal and reliable implantation on the peripheral nerves. More importantly the active FNC successfully achieves wireless stimulation of visceral nerves located deep in the body. We anticipate our interface to be useful for bioelectronic medicine that requires reliable modulation of different sizes and locations of small peripheral and visceral nerves.**

Keywords- Bioelectronic medicine; Bladder modulation; Pelvic nerve; Neural clip; Sciatic Nerve Branches; Wireless

I. INTRODUCTION

The growing field of neurotechnology involves modulating neural impulses to control artificial prostheses [1-3] or physiological function [4-6]. This enormous progress, which has been opening up promising possibilities of implantable bioelectronics [7-11], can be attributed to the development of flexible and implantable devices, which enables more sensitive and accurate biosignal recording or stimulation as well as the integration of bio-sensors, actuators and active components. By combining these cutting-edge technologies with neuroscience, we have new ways of enabling bioelectronic medicines [12, 13]. Regarding bioelectronic medicine applications, precise targeting and modulation of neural signals in small peripheral nerves still remains as a grand challenge due to many physiological and anatomical difficulties in accessing deep nerves associated with the autonomic nervous system. These challenges include i) for the autonomic nervous system, complex innervation of the organs or muscles, renders precise control of specific functions challenging; ii) quick and mechanically secure implantation is an important consideration in the presence of physiological motion such as respiratory and cardiovascular movements; and iii) nerves are highly compliant and associated with moving organs and demand considerable compliance and flexibility from neural interfaces. Recently, a tiny wireless neural dust integrated neural recording electrodes, active components and ultrasound power delivering chip was reported, indicating a promising direction of making neural dust for future bioelectronic medicine [12]. Nevertheless, a general purpose neural interface, which can establish close and rapid implantation on visceral nerves without neural damage, is still required to make implantable devices more accessible [14].

Here, we propose a flexible neural clip (FNC) implant that enables not only easy and conformal implantation on a variety of small peripheral nerves but remote modulation. To demonstrate potential bioelectronic medicine applications, we targeted two nerves that required small neural electrodes for modulating the specific physiological functions of organs or tissues. Furthermore, active FNC as a form of wireless neural dust was also developed to provide remote modulation of bladder function.

II. DEVICE DESIGN

A. Neural Clip Interface

Our novel neural interface was inspired by the design of a paper clip for quick and reliable implantation on very small

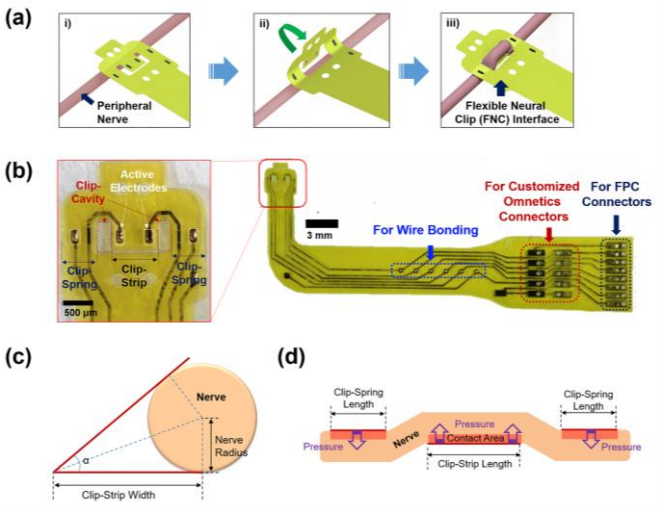

Figure 1. (a) Schematic diagram of the steps involved in implanting flexible neural clip (FNC) on a peripheral nerve (i-iii). (b) Photomicrographs of the fabricated FNC. Schematic diagrams of (c) opening clip head for implantation of a nerve and (d) cross-section view after the implantation.

nerves located inside the body in narrow and deep spaces with continuous movement. This design allows us to clip active electrodes to the nerve after slightly bending the clip-head in a manner analogous to clipping a paper clip (Fig. 1a). The flexible and biocompatible polyimide is used as a scaffold for the electrode (Fig. 1b). The thickness of the device is largely a tradeoff between flexibility and rigidity of the clip interface. To reliably perform the clipping function, while maintaining conformal contact with the nerve, a total thickness of 16 μm was experimentally selected [15]. Based on mechanical stress tests, an optimal angle (α) between the clip-strip and the clip-spring is around 33 ~ 34° for reliable and repetitive opening of the clip. The width of the clip-strip takes the radius of the nerve into account while maintaining the optimal angle (Fig. 1c). Gentle pressure is applied to three different parts of the nerve after implantation on the nerve (Fig. 1d). There is no compressive pressure due to the unique clip structure, which applies sufficient pressure to clip the nerve while still making good contact.

III. Experimental

A. Fabrication Device

The flexible clip interface consists of a polyimide (9 μm)-Au (300 nm)-polyimide (9 μm) sandwiched structure fabricated by micro-electro-mechanical systems (MEMS) technology. Photosensitive polyimide (Durimide 7505, Fujifilm, USA) was used as an insulating material, as well as the body of the neural electrodes. The fabrication procedure of the polyimide can be found in previous papers [15, 16].

B. Iridium Oxide Coating

Iridium oxide is widely used for neural recording and stimulation due to its good stability and large charge storage capacity (CSC). Electrodeposited iridium oxide film (EIROF) shows the largest CSC and lowest impedance [17]. To improve stimulation, the released electrodes were coated with EIROF.

To characterize electrochemical performance of the coated electrodes, electrochemical impedance spectroscopy for measuring impedance, as well as cyclic voltammetry for measuring CSC, were conducted using a three-electrode setup in phosphate buffered saline.

The coated IrO_2 on the Au sensing electrodes showed a good impedance value (1.9 ± 0.09 kΩ at 1 kHz, n=10), and a high cathodic charge storage capacity (56.4 ± 2.42 mC/cm^2, n=10). These values are comparable to, or even better than, materials used previously in the literature for neural stimulation [17-19]. This result demonstrates that the IrO_2 coated electrodes can be used for *in vivo* stimulation experiments.

C. Surgical Implantation

Adult female Sprague-Dawley rats (200-300g) were used for acute *in vivo* experiments in this study. All procedures were performed in accordance with protocols approved by the Institutional Animal Care and Use Committee of the National University of Singapore. The surgery was carried out in accordance with the 143/12 protocol. For each experiment, the rat was anesthetized with a mixture (0.2 ml/100 g) of ketamine (37.5 mg/ml) and xylazine (5 mg/ml) intraperitoneally (I.P.), and supplementary doses of 0.1 ml/ 100 g were injected for maintenance. For the sciatic nerve branch experiment (N = 2 rats), after an adequate depth of anesthesia was attained, the right sciatic nerves were exposed through a gluteal-splitting incision. The FNCs were implanted on the branches. For the bladder experiment (N = 1 rat), the animal was placed in the supine position, and a ventral midline incision of the lower abdomen was first made to expose the bladder and then extended laterally to expose the pelvic nerve. The underlying muscles were cut, and adipose and connective tissues were removed or pushed aside to expose about 2 mm of the nerve for the electrode implantation.

D. Physiological Characterization of Bladder Functions

Intra-bladder pressure was measured via a saline-filled catheter (Instech Laboratories Inc.), inserted into the bladder while connected to a pressure sensor (Transpac IV). An infusion pump for refilling the bladder was used when necessary. A pair of wires (part of a voltage divider circuit) was placed outside the urethral meatus to detect voiding or urine outflow. A data acquisition board (PicoScope 4424) was used to acquire amplified pressure signals, sync pulses from the stimulator, and voltage changes from the urine detection wires at a sampling frequency of 20 kHz. All acquired data were then analyzed using custom MATLAB code. Pressure data were low-pass filtered at 30 Hz, and a 5 second window prior to each electrical stimulation was taken as the baseline to calculate changes in pressure.

E. Wireless Active Neural Clip Interface

This wireless active FNC (70 mg) consisted of a receiving coil, a rectifier, and an LED. All of them were constructed on a Gold Phoenix printed circuit board (PCB). The coil was wound on top of the PCB with an inner diameter of 2 mm using copper wire (Belden, 36-gauge magnet wire, 200 μm diameter), with 3 turns depending on the design frequency (~1.6GHz). For the rectifier circuit, two Schottky diodes (Skyworks SMS7630-061) and two 10-pF capacitors were arranged in a one stage rectifier configuration, in which the output voltage is twice the input peak voltage. A LED (Bivar, SM0603UV-400) was placed after the rectifier to ensure a constant 2.8 voltage necessary to drive the electrode. The electrode was connected in parallel with the LED. The entire FNC was encapsulated in a silicone elastomer (World Precision Instruments, Kwik-Sil Adhesive) except the active electrodes of the FNC. The power used to operate the device was around ~0.1 mW.

IV. Result

A. Stimulation of Sciatic Nerve Branch for Muscle Activation

This work was funded by the National Research Foundation in Singapore (NRF-CRP10-2012-01).

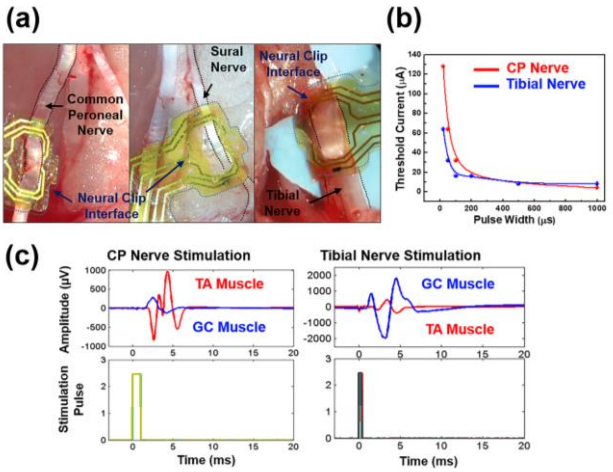

Figure 2. (a) Photomicrographs of sciatic nerve branches. (b) Threshold currents versus pulse widths when stimulating the common peroneal (CP) and tibial nerves. (c) The recorded electromyogram (EMG) signals and stimulation pulses of the CP and tibial nerve stimulation.

We tested the FNC on various sciatic branches as a means to interrogate the peripheral limb system: the common peroneal (CP) nerve, tibial nerve, and sural nerve in rats (Fig. 2a) while recording compound muscle action potentials (CMAPs) from the gastrocnemius muscle (GC) and the tibialis anterior (TA) muscles. The size of the smaller sciatic branches is also comparable to visceral nerves. In addition, the specificity of these branches [20, 21], makes them ideal for showcasing the function of the FNC. To optimize the effectiveness of stimulation, we sought to determine the chronxie (T_{ch}), which is the shortest pulse width at a current amplitude about twice of the rheobase current (I_{rh}) [22]. We measured the threshold current needed to evoke the CMAPs as a function of pulse width for the CP nerve and the tibial nerve (Fig. 2b). The biphasic pulse widths were varied between 20 to 1000 μs. The I_{rh} of the CP nerve was 4 μA, and the calculated T_{ch} from the curve was 470 μs. For the tibial nerve, the I_{rh} was 8 μA, and the T_{ch} was 180 μs. After that, we demonstrated the CP nerve and tibial nerve stimulation using pulse widths close to their respective T_{ch}, (CP nerve: 500 μs; tibial nerve: 170 μs) but at current amplitudes higher than the respective thresholds (Fig. 2c). The TA muscle was activated more than the GC muscle during CP nerve stimulation, and ankle dorsiflexion was clearly observed. During tibial nerve stimulation, the GC muscle was activated more than the TA muscle, and ankle extension (plantar-flexion) with leg stretch was visible. We also conducted the sural nerve stimulation. However, only small twitch of the middle toe in the rat was observed and there were no muscle signals of the TA and the GC, a result that is consistent with previous literature showing that sural nerve mainly includes sensory fibers instead of motor fibers that activate the muscle [24]. These results indicate that the FNC work well on sciatic nerve branches with different sizes, and consequently can be used to evoke different patterns of muscle activation. Furthermore, we stimulated the sciatic branches with corresponding T_{ch} that provides the most energy-efficiency stimulation [23]. This possibly indicates a paradigm-shift approach of restoring signals for bionic limb using wireless and multiple FNCs implanted on smaller nerve branches, in contrast to bulky multichannel cuff-types electrodes required for precise selective stimulation techniques [1].

B. Stimulation of pelvic nerve for modulation of bladder function

Bladder dysfunction, which remains a major healthcare challenge and can impair daily life of patients, is a widely studied area in the field of neuromodulation [25]. The pelvic nerve is a promising stimulation target for the control of bladder function as it provides autonomic efferent inputs to contract the bladder detrusor muscle, and is anatomically and functionally more specific for bladder neuromodulation [25-29]. However, the pelvic nerve is a small visceral nerve located deep within the body, which leads to difficulties in implantation, as well as maintaining contact for reliable stimulation if current neural electrodes are used [1, 30-32]. We successfully performed stimulation of the pelvic nerves using a miniature FNC to control bladder function while monitoring bladder pressure (Fig. 3a). The FNC interfaced successfully with the pelvic nerve in two different implantation configurations: either 400 μm **(**Fig. 3b) or 1600 μm (Fig. 3c) inter-electrode site distances. Bladder contractions corresponding to increased positive bladder pressure changes were observed for both implantation configurations at increasing simulation currents (range: 25-200 μA, n=3 trials). Lower 'subthreshold' stimulation amplitudes increased bladder pressures without micturition, while higher 'supra-threshold' amplitude (100 and 200 μA) caused larger pressure changes and led to graded and repeatable micturition of urine. It indicates that functional, consistent electrode-nerve interfaces were achieved. The results suggest that 1) the FNC can reliably be implanted onto small pelvic nerves while maintaining effective electrical contact with the nerve for reliable and repeatable stimulation in *in vivo* anesthetized situations, and 2) the FNC is mechanically robust to withstand handling across different experiments. The present findings indicate that the pelvic nerve was stimulated in a graded

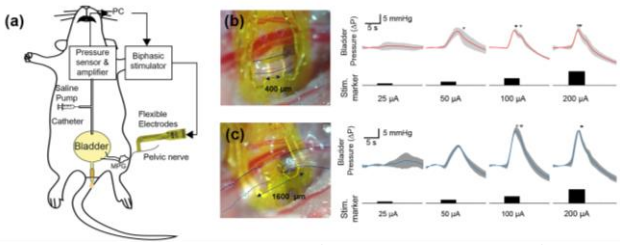

Figure 3. (a) Schematic diagram of pelvic nerve stimulation for the modulation of bladder function. Evoked intra-bladder pressure changes and micturition outcome with increasing stimulation amplitudes for (b) short (400 μm) and (c) long inter-lead distances (1600 μm). Photomicrographs of implanted flexible neural clip (FNC) electrodes on the same nerve in two different configurations are shown in (b) and (c). Inverted triangles denote the onset of voiding events.

manner to control bladder contractions, leading to reproducible micturition events comparable with other published techniques that use large size electrodes with high possibility of damaging nerves along the usage process [33, 34].

C. *Wireless Stimulation of pelvic nerve for modulation of bladder function*

Many visceral nerves reside deep in the body close to critical organs. Reaching and stimulating these nerves requires excess wiring as well as powering scheme. To avoid implanting a power source, we performed wireless remote neuromodulation of pelvic nerves using the FNC integrated with a tiny coil (Fig. 4a) for the midfield powering scheme which allows the transfer of mW levels of power to FNC in deep tissue (>5 cm) [35-37]. Fig. 4b shows the assembled active FNC on a pelvic nerve. We observed large intra-bladder pressure with bladder contractions when applying pulse widths of 1 ms. We repeated the stimulation with this parameter, and observed micturition of urine (Fig. 4c). The expected stimulation current was 400 μA based on the calculation. However, the impedance of the electrode after implantation on the nerve was higher than that in phosphate buffered saline. This might cause lower current, which requires the wider pulse width for the stimulation. In addition, this wide pulse width might be the reason for the slight instability in bladder pressure changes even though we observed micturition of urine. The result indicates that more experiments need to be conducted, but the efficacy of the wireless clip implant for remote modulation of bladder function via visceral pelvic nerves was demonstrated.

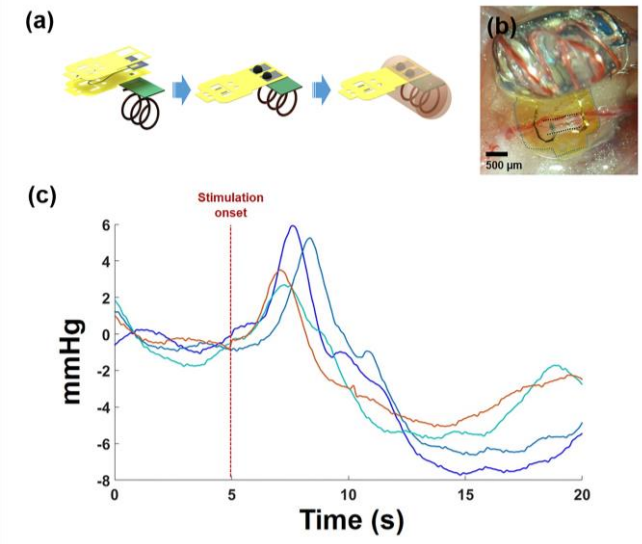

Figure 4. (a) Schematic diagram of the assembly of the active FNC. (b) A photomicrograph of the implanted active FNC on a pelvic nerve in a rat. (c) Results of the pelvic nerve stimulation on bladder pressure changes.

V. Conclusion

The proposed novel FNC shows great potential for use in neuromodulation of small peripheral nerves. With future chronic FNC implantation experiments, we can assess nerve health and functionality over time to validate long-term efficacy and reliability of the FNC. This FNC does not only provide sciatic nerves interfacing in a paradigm-shift manner, but pave a way of doing neural modulation for bioelectronic medicine in visceral organs affected by disease or injury, as well.

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