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A histological analysis of human median and ulnar nerves following implantation of Utah slanted electrode arrays

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ABSTRACT

For decades, epineurial electrodes have been used in clinical therapies involving the stimulation of peripheral nerves. However, next generation peripheral nerve interfaces for applications such as neuroprosthetics would benefit from an increased ability to selectively stimulate and record from nerve tissue. This increased selectivity may require the use of more invasive devices, such as the Utah Slanted Electrode Array (USEA). Previous research with USEAs has described the histological response to the implantation of these devices in cats and rats; however, no such data has been presented in humans. Therefore, we describe here the degree of penetration and foreign body reaction to USEAs after a four-week implantation period in human median and ulnar nerves. We found that current array designs penetrate a relatively small percentage of the available endoneurial tissue in these large nerves. When electrode tips were located within the endoneurial tissue, labels for axons and myelin were found in close proximity to electrodes. Consistent with other reports, we found activated macrophages attached to explanted devices, as well as within the tissue surrounding the implantation site. Despite this inflammatory response, devices were able to successfully record single- or multi-unit action potentials and elicit sensory percepts. However, modifying device design to allow for greater nerve penetration, as well as mitigating the inflammatory response to such devices, would likely increase device performance and should be investigated in future research.

1. Introduction

The use of microelectrodes for the stimulation of peripheral nerves has been studied for nearly a century. Over that time, the use of peripheral nerve electrodes in clinical applications such as respiratory pacing [1–4], sacral nerve stimulation for urinary and fecal management [5–10], and peroneal stimulation for the treatment of foot-drop [11–13], has become routine. Epineurial electrodes, such as book, cuff, or half-cuff electrodes, have typically been used in these treatments. Stimulation by these devices generally results in non-selective stimulation of an entire nerve and/or many thousands of axons within the nerve.

More recently, peripheral nerve electrodes have been investigated in humans for use in applications requiring greater selectivity, such as advanced neuroprosthetics with multiple degrees-of-freedom motion control [14,15]. Microelectrode arrays (MEAs) used for such applications would ideally be highly selective in that they could record from and stimulate single or small groups of axons throughout the nerve. While epineurial electrodes have demonstrated an ability to evoke sensory percepts in subjects over extended periods of time [14], intraneural MEAs may be more suitable as bidirectional interfaces given the close proximity of axons to recording sites and previous research which has demonstrated their potential for high selectivity during stimulation [16,17].

Arrays that axially penetrate the nerve with multiple shanks, such as the Utah Slanted Electrode Array (USEA) are one type of MEA that has been investigated as a neural interface device [17–21]. These arrays contain rows of electrodes that increase in length, which, after implantation into a peripheral nerve, allows for the stimulating and recording sites to be located at multiple depths within the nerve. While these devices have shown promise based on electrophysiological performance, a better understanding of the foreign body reaction (FBR) elicited by these devices, as well as their placement in and integration into the nerve over time, is needed before their widespread clinical use. Previous research of

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similar devices in humans has demonstrated the ability of such devices to work as bidirectional interfaces [22]. Further, previous work has investigated the FBR to these devices when placed within the sciatic nerve of rats and cats [23,24]; however, no information regarding placement, integration, or the FBR over time to these devices in human subjects has yet been reported. Therefore, in this work we investigated the integration of USEAs and the reaction observed around these devices 4 weeks after implantation into the median and ulnar nerves of two subjects.

2. Materials and methods

2.1. Patient population and implantation

This study was approved by the University of Utah Institutional Review Board and all subjects provided their consent to participate in the study. USEAs (Blackrock Microsystems, Salt Lake City, UT), consisted of a 10 × 10 grid of electrodes spaced at 400 μm centers, with each row of electrodes increasing in length to a maximum of 1.5 mm (Fig. 1A). Electrodes were insulated along their shafts with Parylene-C. USEAs were implanted into two volunteers with previous transradial amputations. Subject 1 (1.5 years post-amputation) received an implant in the ulnar nerve (designated hereafter as 1-U), while subject 2 (21 years post-amputation) was implanted into the median and ulnar nerves (hereafter designated as 2-M and 2-U respectively). For all surgeries, the distal nerve end was exposed via blunt dissection near the amputation site. The USEA was then passed transcutaneously via a trocar (7–8 mm diameter) to the implantation site. Array lead wires were sutured (8-0 nylon) to the epineurium, following which the array was pneumatically inserted. All USEAs were implanted just proximal (8–12 mm) to existing neuromas, which varied in size but were always present, in what appeared to be normal nerve tissue. The implanted USEA and associated wires were then wrapped in a reconstituted tissue-derived product (AxoGuard Nerve Wrap, AxoGen Inc., Alachua, FL) in order to maintain the position of the array throughout the implantation period. The nerve wrap was closed using titanium vascular clips while proximal and distal sections of the wrap were sutured to the epineurium using 8-0 nylon sutures. In an effort to reduce implant associated inflammation, subjects were given dexamethasone (0.1 mg/kg IV, Mylan Institutional LLC, Rockford, IL) intraoperatively and minocycline (100 mg BID, Watson Pharmaceuticals, Parsippany, NJ) two days prior to and for five days after surgery.

2.2. Electrophysiology sessions

Two hour experimental sessions were performed an average of three times per week with subject 1 and four to five times per week with subject 2 (sessions were split equally between ulnar and median nerve devices). The time for each session was limited by the availability of the subjects or their willingness to continue testing. For each implanted USEA, alternating sessions of neural recording and stimulation were carried out over the implantation period. For recording, neural signals were amplified and recorded with active head-stage cables (ZIF-Clip 96 channels, Tucker Davis Technologies, Inc., Alachua, FL) and a Neuroport data acquisition system. Neural signals were band-pass filtered with cut-off frequencies of 0.3 Hz (1st order high-pass Butterworth filter) and 7500 Hz (3rd order low-pass Butterworth filter) and sampled at 30 kHz. Offline action

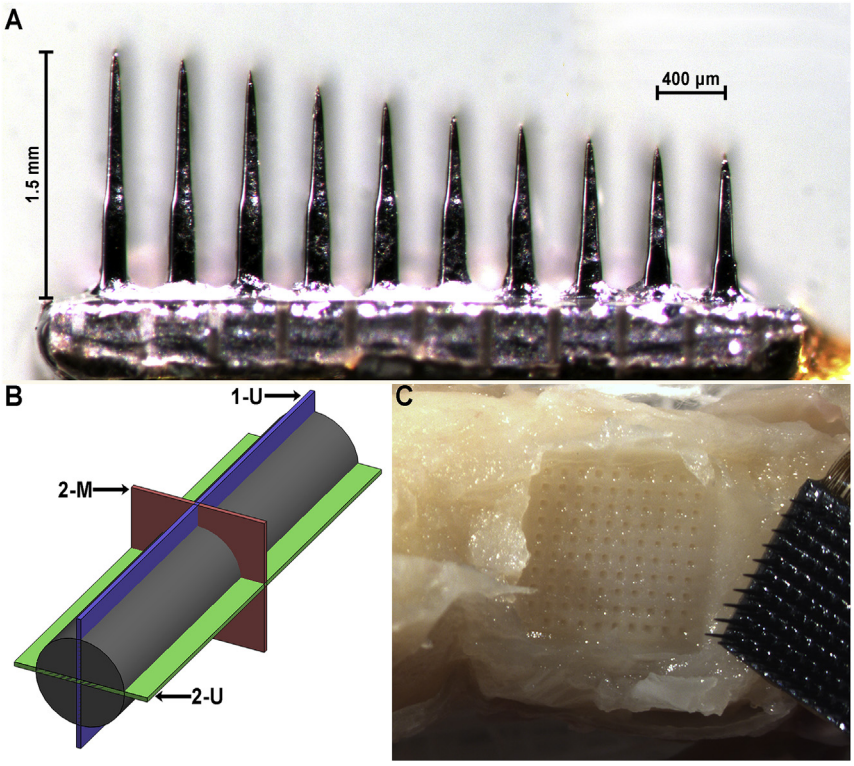

Fig. 1. A) Side view of explanted array. Arrays consisted of a 10 × 10 grid of electrodes spaced at 400 μm centers, with each row of electrodes increasing in length to a maximum of 1.5 mm. B) Representation of imaging planes. Nerve sections were collected laterally (blue plane, nerve 1-U), axially (red plane, nerve 2-M), or longitudinally (green plane, nerve 2-U). C) Representative image of implant location following removal of the array. All implant sites were clearly defined, with visible evidence of electrode penetration into the nerve. Implant sites were also free from discoloration and blood products. Retrieved arrays had minimal amounts of grossly visible adherent tissue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)