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Invasive neural prosthesis for neural signal detection and nerve stimulation

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SUMMARY

This paper specifically examines the implantation of a microelectrode array into the median nerve of the left arm of a healthy male volunteer. The objective was to establish a bi-directional link between the human nervous system and a computer, via a unique interface module. This is the first time that such a device has been used with a healthy human. The aim of the study was to assess the efficacy, compatibility, and long term operability of the neural implant in allowing the subject to perceive feedback stimulation and for neural activity to be detected and processed such that the subject could interact with remote technologies. A case study demonstrating real-time control of an instrumented prosthetic hand by means of the bi-directional link is given.

The implantation did not result in infection, and scanning electron microscope images of the implant post extraction have not indicated significant rejection of the implant by the body. No perceivable loss of hand sensation or motion control was experienced by the subject while the implant was in place, and further testing of the subject following the removal of the implant has not indicated any measurable long term defects. The implant was extracted after 96 days. Copyright © 2004 John Wiley & Sons, Ltd.

1. INTRODUCTION

The concept of interfacing electronically with the human nervous system has been actively pursued since the 1960s. Recent work in this area has pointed towards nerve prosthesis technology that will enhance and augment human capabilities. However, traditionally the driving force behind the integration of technology with humans on a neural level has been restorative; to restore lost functionality in individuals who have suffered trauma such as spinal cord damage, amputation, or who suffer from a debilitating disease, such as lateral amyotrophic sclerosis.

1.1. Restorative neural prostheses

One method of interfacing with the nervous system is to directly record neural activity from the cortex by implanting electrodes into the brain, see Reference [1] for a review. Such invasive

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procedures have already given interesting insights into the neurophysiological functionality of the brain. In terms of work on rats and primates [2, 3], research in this area has supported the hypothesis [4] that the direction and speed of an *intended* movement is predicted in the motor cortex by the activity of populations of neurons. The applications of this technology as a communication aid for patients with conditions such as locked-in syndrome, (who are alert and cognitively intact but cannot move or speak), are clear [5], allowing them to control a computer cursor merely by thought. Progress in this area has, however, been hampered by a lack of understanding of brain functionality.

Interfacing with the peripheral nervous system has shown great promise because, although patients with neural trauma tend to lose sensation and motor function below the level of trauma, the tactile and proprioceptive receptors with associated afferent axons and the muscle fibres with the remaining efferent axon usually remain intact. In essence, neurological damage interrupts the transfer of electrical signals from sensory receptors to the brain causing impaired sensation and from the brain to motor units causing the loss of motor function. By making connections to afferent axons, they can be used as natural transducers for touch, force and position. This sensory information can then be used to restore sensation by bridging the injury or for closed loop control of externally initiated limb movement [6, 7]. Alternatively, functional electrical stimulation (FES) of motor units causes muscular excitation which can allow controlled movement of limbs [8, 9]. FES has proved useful for artificially inducing hand grasp/release and standing/walking functionality in quadriplegic and paraplegic individuals [10, 11], as well as restoring basic body functions, such as bladder and bowel control [12]. However, controlling and co-ordinating muscle movements for complex and generic tasks, such as picking up an arbitrary object, proves to be a difficult challenge.

Sensate prosthetics may also utilize this type of interface, whereby a measure of sensation is restored using signals from small tactile transducers distributed within an artificial limb. FES triggered by these signals can be used to stimulate the afferent axons that remain in the user's stump that are naturally associated with that sensation. This more closely replicates stimuli in the original sensory modality, rather than a form of feedback using neural pathways that are not naturally associated with the information being fed back. As such, the user can employ the lower level reflexes that exist within their Central Nervous System, thus making the control of prosthesis more subconscious. Cole *et al.* [13] have observed that during tele-manipulation with a robot arm, if the motion is appropriate to the command the user can feel that they 'inhabit' the arm. The closer link between the arm and the user created by the neural interface should allow better control by exploiting these phenomena; recent work with monkeys certainly suggests it is possible [14]. Additionally, because the surviving motor axons in the stump of an amputee still receive the neural action potentials used to control the missing body part, these signals can be used to control the prosthetic replacement. This is certainly a more natural alternative to using control commands drawn from unrelated muscular movements, currently a preferred technique [15].

Finally, in some cases it is the sensory receptors themselves that are dysfunctional. Neural prostheses have been used to restore some degree of sensation by direct electrical stimulation of the appropriate nerve fibres in order to mimic the sensory receptor. The most ubiquitous sensory neural prosthesis is by far the cochlea implant [16, 17]. Its modest success is related to the ratio of stimulation channels to active sensor channels in a fully functional ear, with recent devices having up to 24 channels, while the human ear utilizes upwards of 30 000 fibres on the auditory nerve. Certainly with the limitations of the cochlea implant in mind, the retinal implant is a substantially more ambitious sensory prosthesis [18].

2. SILICON/BIOLOGICAL INTERFACE

Peripheral nerve interfaces can be categorized into two distinct types, extraneural or intraneural. Extraneural, or cuff electrodes, generally wrap tightly around the nerve trunk, and allow recording of the sum of the single fibre action potentials, (the compound action potential), [19, 20] in a large region of the nerve trunk, or crudely selective neural stimulation [21, 22].

An ideal nerve interface needs to allow for very selective recording and stimulation, something that is much more suited to intraneural electrodes [23, 24]. Certain types of microelectrode arrays (MEAs) (Figure 1) contain multiple electrodes which become distributed within the fascicle of the mixed peripheral nerve to provide direct access to axons from various sense organs such as muscle spindles, cutaneous receptors or motor axons of specific motor units. This device offers a multichannel nerve interface. The study discussed in this paper utilized such a MEA, implanted in the median nerve of a healthy, able-bodied human.

2.1. Biocompatibility

Applications for chronically implanted neural prostheses are increasing and, as such, the need to ensure the biocompatibility of the physical biological/silicon interface has become prevalent. Problems arise because any foreign object will interact to some degree with the tissue of its host [25]. Essentially this means that there is no truly biocompatible material, indeed 'Biocompatibility is the ability of a material to perform with *an appropriate* host response in a specific application', [26]. In severe toxic reactions, degradation of the foreign body may release cytotoxic chemicals. Motion, orientation or geometry may also trigger an inflammation reaction. Typically, however, following a vital reaction, an implanted foreign body becomes covered with macrophages and 'foreign body giant cells'. This coating may persist, but generally there is granulation tissue and then fibrosis leading to a fibrous encapsulation. If no toxic

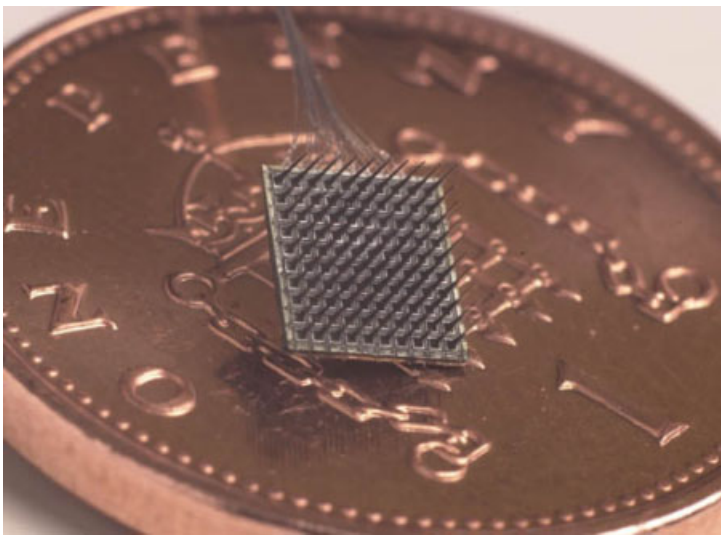

Figure 1. A 100 electrode, 4×4 mm microelectrode array, shown on a UK 1 pence piece for scale.

reaction occurs, it is the fibrous encapsulation of the electrodes that is the worst case scenario, especially for neural signal recording. This encapsulation serves to highly attenuate the small nerve impulses making stable recordings particularly unlikely. Similarly, the impedance of the encapsulation tissue has been shown to affect stimulation pulses [27]; although in applications where large amplitude pulses are applied, such as implanted cardiac defibrillators, this effect is negligible. Encapsulation has, however, been highlighted as a possible cause of the variation in people's speech perception when using cochlea implants where small stimulation currents are utilized [28].

In light of the encapsulation's ability to highly attenuate both neural activity and stimulation pulses, the study reported in this paper is in part to investigate the biocompatible properties of the MEA.

3. NEURAL PROSTHESIS

On March 14th, 2002, at the Radcliffe Infirmary, in Oxford, U.K., a 10×10 electrode MEA (Figure 1) was surgically implanted into the median nerve of the left arm of a healthy, right dominant male subject aged 48. The MEA was made from high purity monocrystalline silicon, measuring 4 mm $\times$ 4 mm, with each of the conical needle electrodes being approximately 80 μm in diameter at the base, 4 μm in diameter at the tip and 1.5 mm in length. Although it may be preferable to have differing length electrodes in order to achieve different penetration depths, all of the electrodes were identical for ease of manufacture. The electrodes were isolated from each other by glass, and individually insulated with silicon–nitrate up to (approximately) the end 55 μm, which was the platinum coated active tip. The first and last rows of the array (20 electrodes) were individually wired via a 20 cm wire bundle to an electrical connector pad. The perineurium of the median nerve was dissected under microscope down to the first available fascicle to facilitate the insertion of electrodes and ensure adequate penetration depth. The nerve fascicle was estimated to be approximately 4 mm in diameter, although at the time of surgery it was not possible to conclusively identify which median nerve fascicle it was. The MEA was pneumatically inserted into the radial side of the nerve with the electrodes penetrating into the fascicle. Penetration was confirmed under the microscope. Two Pt/Ir reference wires were positioned in the fluids surrounding the nerve. In order that the risk of infection in close proximity to the nerve was reduced, the wire bundle was run subcutaneously for 16 cm before exiting percutaneously, distal to the elbow. At the exit point, the wire bundle linked to the electrical connector pad which remained external to the arm. The surgical procedure is described in detail in Reference [29].

3.1. Bi-directional interface module

Ideally, a neural interface will allow bi-directional information flow, that is, perceivable stimulation will allow information to be sent to the user, while control signals are decoded from neural activity in the active regions of the electrodes. As such, a unique bi-directional interface [30] was developed (Figure 2) to interface between the MEA and a remote computing device. In order that the subject was able to interact with their environment without restrictions, the interface module was made compact, wireless and mobile.

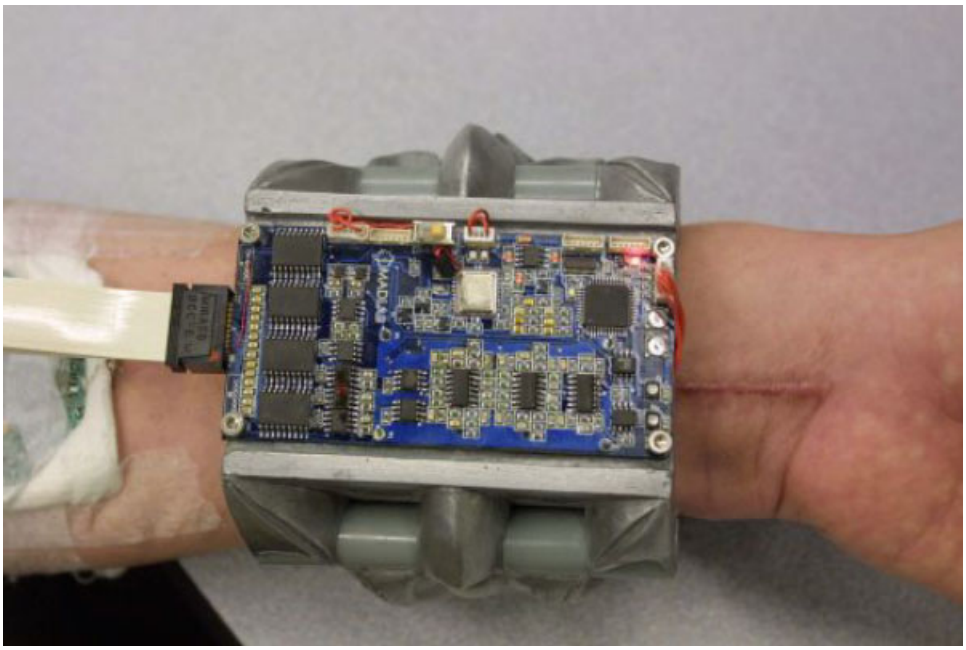

Figure 2. Mobile interface module attached to the subject's wrist.

Each of the 20 electrode channels were multiplexed down to two channels, such that two independent electrodes could be monitored in a quasi-static mode, or a selection/all channels could be switched between and sampled. The bi-directional interface simplified block diagram is shown in Figure 3. Because the active electrode area was of the same order of magnitude as the diameter of a nerve fibre, the microelectrodes allow the action potentials from small subpopulations of axons that surround each of the sensitive tips to be detected. With a typical action potential duration of 1 ms, it is reasonable to assume that the small sub-population extra-cellular neural activity of interest occurs below a frequency of 3.5 kHz. Ideally, only the band of frequencies that contain signals of interest (as specified by the higher and lower cut-off frequency) would be linearly amplified, whilst any frequency outside of this range completely suppressed. However, practical limitations mean that a totally flat cut-off is not realisable. Instead the 'roll-off' is dictated by the order of the filter: the higher the order, the closer to the ideal flat cut-off it becomes. However, there is a trade-off between increasing order of filter and increasing filter complexity with associated filter stability issues. As such, the hardware interface module amplified each channel using an active, fifth order band-limited Butterworth filter stage where gain of the filter = 5000, the lower cut-off frequency (f_l) = 250 Hz and the higher cut off frequency (f_h) = 7.5 kHz. This minimizes the distortion of the extra-cellular action potentials, while aggressively rejecting extraneous noise outside of the pass band. The filtered analogue signal is then made available to both a comparator, whose reference is set by the on-board microcontroller to give a purely temporal description of events (i.e. the inter-spike intervals), and the microcontroller which digitizes the signal to 10-bit resolution. The digitized signal is further processed in software by a leaky integrator of time window 20 ms, the output of which is

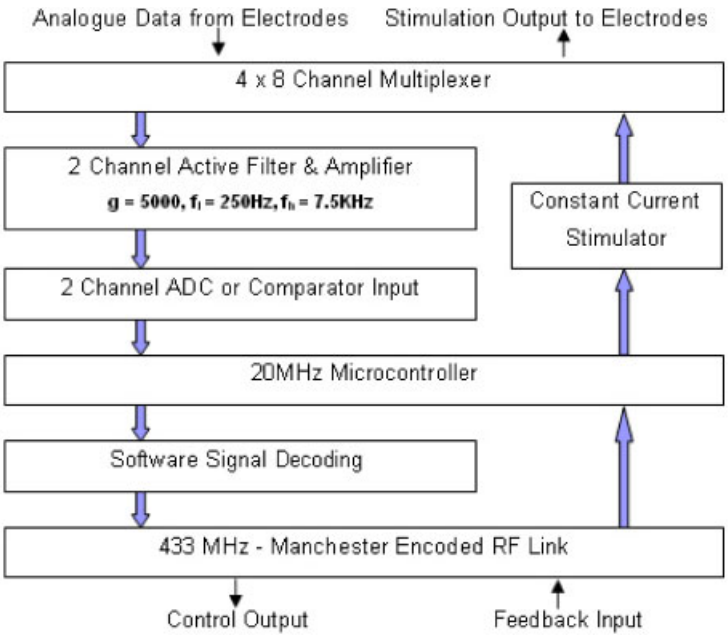

Figure 3. Simplified interface module block diagram.

scaled between 0 (for no activity) and 255 (for maximum activity). Either the scaled figure or inter-spike interval (depending on mode of operation) is then broadcast by the onboard RF transceiver to a remote device whose current action is dependant on the value.

A 'Howland' configuration constant current source was implemented to stimulate the same subpopulations of axons with charge balanced, bi-phasic rectangular pulses with an inter-phase delay of 100 μs and typical pulse duration of 200 μs. Stimulation was applied via the electrode selected by the multiplexers, with one reference wire used as the second current source/sink. It was therefore possible to create artificial sensation, giving the subject feedback information from remote devices.

Stimulation was attempted for the first time 6 weeks after implantation using currents up to 100 μA. During experimentation, it was found that currents below 80 μA had little perceivable effect, although at that magnitude the electrodes showed good electrical characteristics. This implied that current was being passed in the locality of the nerve fibres. A typical stimulation waveform of constant current being applied to one of the array's implanted electrodes is shown in Figure 4.

During initial tests at 80 μA, with the subject blindfolded and the stimulation applied on one electrode at random time intervals; the subject achieved a mean correct identification of stimulation of 70%. By the end of the study, a 95% perception rate was being achieved with a current of 80 μA. The subject was able to distinguish between stimulation via electrodes within two separate regions of the MEA; however, they were not able to distinguish variations in the stimulation pulse. EMG recordings confirmed that stimulation was resulting in muscular excitation of the first lumbrical muscle with the associated sensation of this movement being perceived by the subject. Equally, neural activity associated with voluntary activation of the muscle was detectable by the MEA.

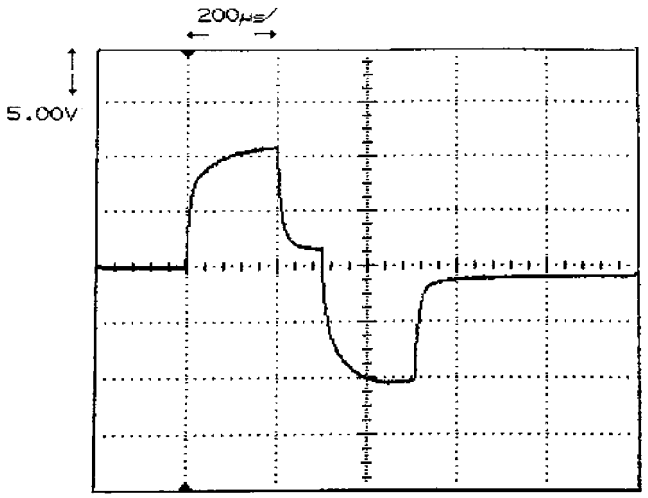

Figure 4. Voltage profile during one bi-phasic stimulation pulse cycle with a constant current of 80 μA.

4. FEEDBACK STUDY: ARTICULATED HAND

The type of articulated hand prosthesis employed in this study [15] has multiple degrees of freedom and can be controlled in a hierarchical manner. Its aim was to mimic the control mechanisms apparent in a human hand. This prosthesis (named 'SNAVE' after its designer, Figure 5) contains force and slip sensors in the fingers and palm and uses a microcontroller to co-ordinate the operation. Joint flexion sensors allow for adaptation of the grip shape and for the force applied to the object to be modified by the microcontroller such that the lightest possible touch is applied.

If the microcontroller detects that the object is slipping, the tension can be automatically adjusted in order to prevent further slippage. As a result, the hand can be controlled by means of voluntary opening involuntary closing (VOIC), whereby the user need only tell the hand to relax for it to grasp the object in the most appropriate manner.

In this study, the integration value from the neural implant was broadcast to the prosthetic hand in order to set the hand flexion. Two thresholds were set such that the hand could achieve three set positions, full closed, 50% open, fully open. The on-board 'intelligence' of the SNAVE hand was used to control the hand grasp function, such that the hand automatically grasped shut, if the activity was below the lowest threshold. The subject's ability to control the hand is shown in Figure 6.

Subsequently, the touch force control in the prosthesis was disabled and the control changed to voluntary opening voluntary closing (VOVC) so the subject had to control the grip force by himself. The sensory data from the hand's fingertips was fed back to the interface module so that as more force was applied to an object, the frequency of neural stimulation was increased. The subject was asked to open and close the hand applying the lightest touch to the object with and without the implant's force feedback and with and without visual feedback.

Over the course of 10 days, (with 5 trials per day) the subject's ability to judge the closing force and stop in a timely manner improved more when he had both force and visual feedback,

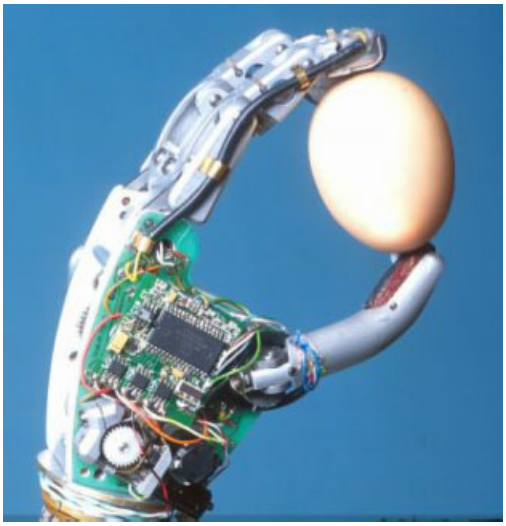

Figure 5. 'SNAVE' intelligent anthropomorphic hand prosthesis.

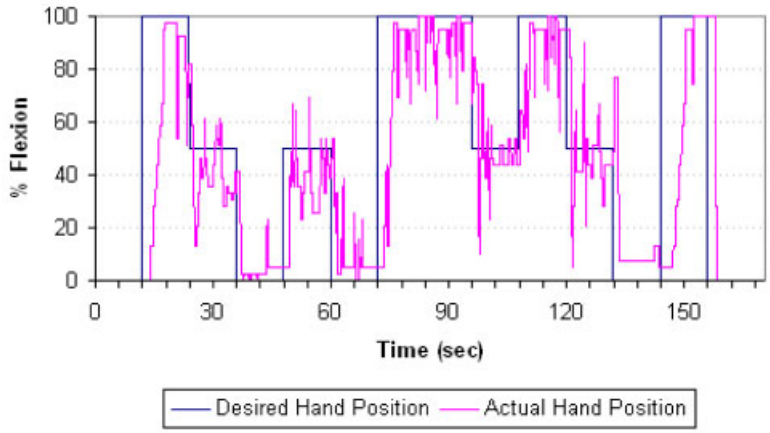

Figure 6. The subject attempts to adjust the prosthetic hand flexion to reach the desired hand position.

than when he had either alone. Figure 7 shows the normalized force, averaged over five trials, when the subject had visual feedback, stimulation feedback and both.

4.1. Post extraction study

The MEA implant was removed on June 18th, 2002, 96 days after implantation. At the time of extraction no signs of rejection were observed; indeed fibrous scar tissue had grown around the implant site holding it in position. Because of the nature of this study, histological examination of the nerve tissue was not possible. However, scanning electron microscope (SEM) examination of the extracted MEA was conducted to look for signs of encapsulation, an indication of

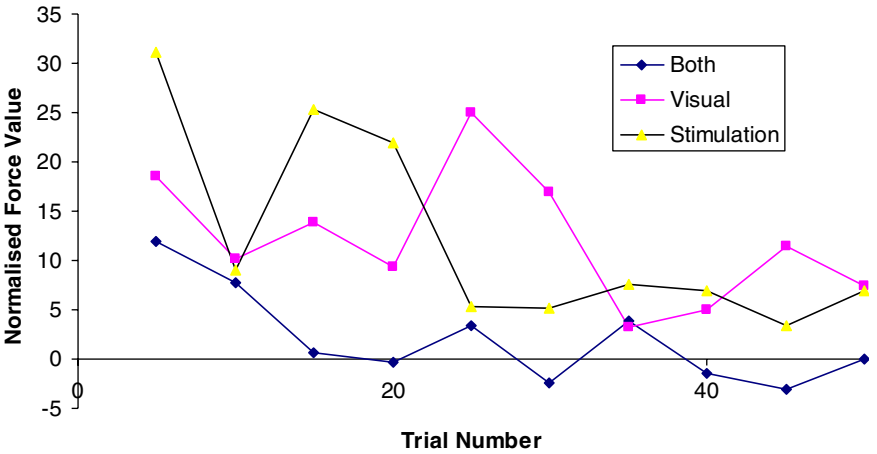

Figure 7. Normalized force, averaged over five trials, applied to an object with visual feedback, stimulation feedback and both.

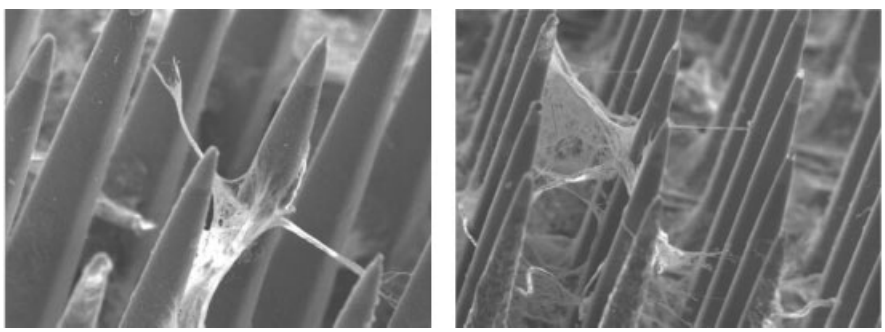

Figure 8. SEM images showing fibrous tissue growth between electrodes of the MEA, 96 days post implantation.

implant rejection by the body. Figure 8 shows two isolated areas of fibrous tissue growth. Although this shows a slight lack of biocompatibility, it does not represent a severe reaction to the implanted MEA.

Throughout the study, the subject was monitored for signs of neural damage using SHAP [31], 2-point discrimination, von Frey hairs and edge discrimination. The final assessment was conducted 9 months following the removal of the device. No loss of sensation or motion control was experienced by the subject while the implant was in place, and the further testing of the subject post-extraction has not indicated any measurable long term defects.

5. CONCLUSION

The use of implant technology for the purpose of both directly measuring neurological signals and stimulating nerve fibres offers opportunities for the treatment of neurological problems and

the amelioration of physical or neurological impairment. In this paper an application study on a healthy individual is described. During this study, it was possible to restore a small measure of sensation, by means of stimulation via the implanted MEA, using signals from tactile transducers on a prosthetic hand. This technique could in practice be employed with an artificial limb to stimulate sensory axons that remain in the remnant stump of an amputee.

Equally, it has been shown that it is possible to decode the neural activity into distinct control commands, such that, in co-operation with the on-board 'intelligence' of a prosthetic hand, the hand flexion can be controlled. This method is more closely associated with the operation of a human hand, as compared to articulated hands controlled by means of surface electromyographic signals, and, as such, should lead to more sub-conscious control.

Issues of biocompatibility and rejection by the body are key points in the design of nerve interfaces because of the high attenuation of both nerve signals and stimulation pulses that fibrous encapsulation can be attributed to. During this study, little encapsulation was observed on the MEA, and the ability of the subject to perceive subtle stimulation pulses at a current of 80 μA throughout the study period certainly support the hypothesis that the MEA is highly biocompatible.

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