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A floating metal microelectrode array for chronic implantation

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Abstract

Implantation of multi-electrode arrays is becoming increasingly more prevalent within the neuroscience research community and has become important for clinical applications. Many of these studies have been directed towards the development of sensory and motor prosthesis. Here, we present a multi-electrode system made from biocompatible material that is electrically and mechanically stable, and employs design features allowing flexibility in the geometric layout and length of the individual electrodes within the array. We also employ recent advances in laser machining of thin ceramic substrates, application of ultra-fine line gold conductors to ceramic, fabrication of extremely flexible cables, and fine wire management techniques associated with juxtaposing metal microelectrodes within a few hundred microns of each other in the development of a floating multi-electrode array (FMA). We implanted the FMA in rats and show that the FMA is capable of recording both spikes and local field potentials.

Keywords: Multi-electrode arrays; Neural prosthesis; Brain–machine interface; Rats

1. Introduction

For over 40 years, metal microelectrodes have been used to record and stimulate neural tissue (Green, 1958; Mortimer et al., 1970). Many electrode designs ranging from single and bundled microwires to sophisticated silicon probes have been used with various success in acute and chronic applications (Campbell et al., 1991; Hoogerwerf and Wise, 1994; Kipke et al., 2003; Nicolelis et al., 1997; Schmidt et al., 1976). Multi-electrode arrays that can record from and stimulate neurons without causing tissue damage or deterioration of the electrodes are becoming essential tools for many neuroscience investigators. Current research on neural prosthesis applications including cortical stimulation for a visual prosthesis and cortical recording for motor prosthesis require the use of arrays of electrodes maintained in a stable mechanical position relative to the associated neuronal structures for prolonged time periods (Bradley et al., 2005; Carmena et al., 2003; Musallam et al., 2004; Schmidt et al., 1996; Taylor et al., 2002). Given the highly convoluted structure of the human brain and our experimental need to access a variety of surface and deep areas, we set out to develop arrays made with electrodes of arbitrary lengths that can record from neurons that lie deep in sulci and neurons that lie on the surface of the brain. Here, we present a microelectrode array that 'floats' (is not anchored to the skull) on the brain that meets all the above requirements.

The concept behind the development of the floating multi-electrode arrays (FMA) used in this study is a light-weight superstructure platform populated with rigid microelectrodes and tethered to a connector by a thin, flexible and light-weight cable (Fig. 1). The concept of using a "floating" intra-cortical microelectrode as opposed to an electrode fixed rigidly to the skull had its origins with Gualtierotti and Bailey (1968) in which they describe a "neutral buoyancy" electrode incorporating a rigid shaft for penetration into the brain that was attached to a flexible lead wire. The interface between the rigid electrode shaft and the flexible lead wire consisted of a hollow plastic "bubble", which presumably floated on the surface of the brain. These electrodes were originally designed for NASA to be used in frogs that would be undergoing extreme gravitational forces. The idea was to design an electrode system that approximated the same specific gravity of the brain and therefore would move

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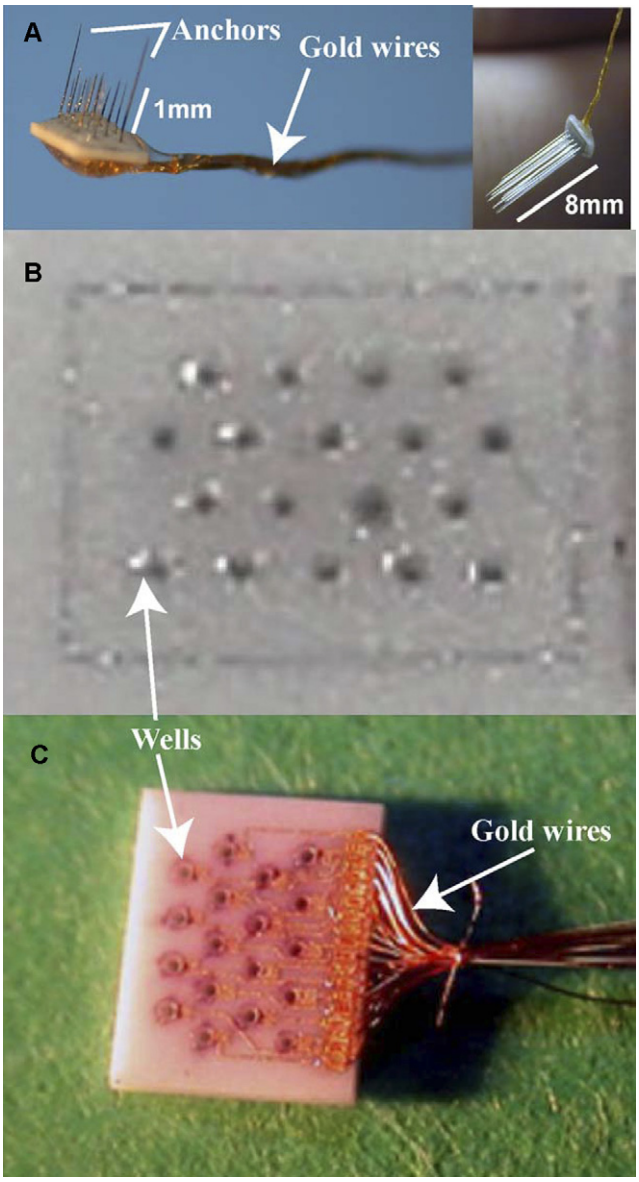

Fig. 1. (A) FMAs with short and long electrodes. The two anchors on the short arrays are there to ensure that the arrays stay in the brain. (B) Laminated well structure. The electrodes are oriented perpendicular to the wafer (into the page) and (C) FMA substrate, 1.95 mm × 2.45 mm, with attached 0.001 in. Parylene-C insulated gold wires. Note that for the FMAs used in this study, the substrate's gold circuit lines were not used.

with the brain as the brain moved relative to the skull during acceleration. A commercially available multi-electrode array (Cyberkinetics, Inc.) that floats on the brain differs markedly from the array presented here as it is based upon the Utah silicon array (Maynard et al., 1997). These arrays are not long enough to access deep sulci and other deep neural structures. The Utah array is manufactured by using a saw to cut slices through a solid block of silicon. Selective etching of the block produces a dense multi-electrode array. The shanks are then coated with platinum using a sputtering process. Arrays based upon this technology are useful for surface recordings as shown by their success in recordings related to a brain–machine interface (Serruya et al., 2002; Santhanam et al., 2006; Hochberg et al., 2006). However, because the Utah array is cut out of a solid piece of silicon, it does not lend itself to the fabrication of arrays that have long electrode lengths or varieties of tip geometries, and electrode material types. Currently, the technology is geared towards uniform-sized platinum-tipped microelectrodes that are not well-suited to high-charge injection electrical stimulation. Coating of the Utah array electrodes with activated iridium oxide for stimulation has not yet been demonstrated, and the current technology results in electrodes that have uniform exposed surface areas precluding the mixing of impedance values.

Floating arrays have been manufactured by Huntington Medical Research Institute that were effective for over 1 year presents the most convincing demonstration of the effectiveness of this design (Bradley et al., 2005). The array we present here is a more cost effective and reproducible way of making these same arrays at about 1/10th the cost. In addition, many attributes of the arrays (electrode length and type) make this a more useful array for a wider range of applications. Here, we present the design, manufacturing methods and results for a multielectrode floating array that allows the mixing of electrode types, impedances, irregular electrode spacing, arbitrary electrode lengths, and the mixing of electrode materials such as tungsten, platinum, platinum–iridium, and activated iridium oxide, within the same multielectrode array.

2. Materials and methods

2.1. Array manufacturing

Two arrays used in this study are shown in Fig. 1. The platform, which houses the individual microelectrodes, is fabricated from 250 μm thick alumina ceramic (Fig. 1B). It has been laser machined to have 18 holes distributed with 400-μm separation although other separation distances are possible. The overall dimensions of the ceramic substrate are 1.95 mm × 2.45 mm. The holes (wells) are laser drilled to any diameter specified by the user's choice of electrode diameter. In our case, the diameter of the holes was 90 μm in order to accommodate electrodes having a diameter of 80 μm. Gold was applied to the ceramic plate using RF sputtering techniques (Fig. 1C). A CO_2 laser was used to drill the holes and cut out the individual ceramic platforms.

The electrodes used in this study are platinum/iridium 70%/30%. The selection of this metal type was chosen for stiffness, biocompatibility and relatively low concomitant tip impedance for optimum signal to noise ratio. Current fabrication techniques allow individual electrodes to have lengths between 0.5 and 10 mm. The results presented in this paper were obtained from arrays with electrode lengths of 1 mm (surface arrays) or 5–6 mm (deep arrays). The electrode lengths of the deep arrays were staggered between 5 and 6 mm in order to minimize dimpling. The array with the short electrodes has two additional longer electrodes for stability, which were also used for ground and reference (anchors in Fig. 1). The Pt/Ir microelectrodes are electrochemically sharpened in a salt solution (Fig. 2). The electrodes are then micro-welded, using a Unitek model UB25 micro-welder, to a 25-μm diameter gold wire at a distance from the tip necessary to yield the predetermined depth of electrode

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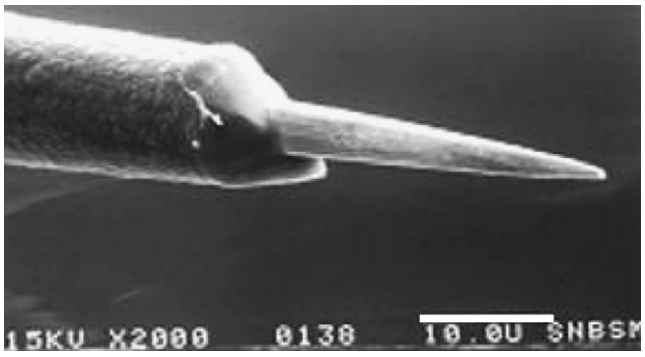

Fig. 2. An SEM of an electrode used in the FMA. This electrode was pre-treated with A-174 Silane before being insulated with 3 μm of Parylene-C. The tip was exposed by a non-thermal ablation technique using a dual beam Eximer Laser System having a wave length of 248 nm. This is an image of an arbitrary electrode that may not have been used in this study. Reprinted from Journal of Neuroscience Methods, 62, Schmidt, Bak and Christensen, Laser Ablation Paralyne-C insulated, 89–92, 1995, with permission from Elsevier.

insertion into the brain. The electrodes are pre-treated with a monolayer of the Silane adhesion promoter A-174 by boiling off the Silane in a vacuum chamber to enhance the bond between the insulation and the Pt/Ir metal surface. The electrodes are then insulated with Parylene-C in a vacuum chamber to yield a thickness of 3 μm. Note that the gold circuit lines shown in Fig. 1C were not used in this study but will be used in the next generation of FMAs.

The electrode tips are exposed using a dual beam Eximer laser system having a wave length of 248 nm (Fig. 2). This process allows for precise non-destructive removal of the Parylene-C from the Pt/Ir microelectrode tip (Schmidt et al., 1995). The microelectrode tips are then inspected under a higher power light microscope to ensure that complete ablation of the Parylene-C has occurred from the tip. Continuity and tip impedance are determined for each electrode before incorporating them into the array. The target impedance for microelectrodes used in this study was 500 KΩ.

The ceramic substrate and a specially designed gold plated surface mount Omnetics connector are mounted on a custom fixture designed to be integrated to a Hybond, Model #572, sonic bonder. The ceramic substrate is positioned on top of another larger ceramic piece that has holes, which are also laser drilled to be coincident with holes on the small substrate. This ceramic fixture will act as guide ensuring that the microelectrode shafts are perfectly aligned to be parallel to each other and perpendicular to the bottom surface of the ceramic substrate. The Pt/Ir shaft distal to the tip, and close to the micro-weld joint, is cut off using flush cut diagonal cutters leaving the gold wire and Pt/Ir electrode assembly free to be mounted to the substrate. A polished pair of #5 Dumont forceps is used to position the Pt/Ir microelectrode-gold wire assembly by grabbing the gold wire a few millimeters above the micro-weld joint so that the microelectrode tip is just above one of the 90-μm holes. The tip of Pt/Ir microelectrode is slowly lowered through one of the holes in the ceramic substrate until it is completely seated with the weld joint flush against the ceramic substrate surface. Depending on the length of the electrode shaft the gold wire may be fixed in place with a very small amount of cyanoacrylate glue to ensure that the microelectrode does not come out of the hole while the remaining microelectrode assemblies are positioned in the holes.

The gold wire is positioned over one of the gold plated connector pads of the Omnetics connector and the Parylene-C insulation is removed where the gold wire is to be bonded to the connector pad using a micro-heating element. The gold wire is sonically bonded to the connector pad and the bond site secured and strain relieved using a small amount of cyanoacrylate glue. After all the microelectrodes have been inserted into the substrate and the gold wires bonded to the Omnetics connector, a sufficient amount of Medical Grade Epoxy glue, Loctite #M-121HP is applied to totally encapsulate the connector contacts.

The same epoxy is used to encapsulate the ceramic substrate. A thin ceramic disk is positioned on top of the epoxy and positioned to be centered and parallel to the surface of the ceramic substrate. This is to ensure that when the FMA is held by the insertion tool, which is used to lower the microelectrodes into the brain, the electrodes will be lowered perpendicular to the brain's surface to minimize any potential tissue damage (see Section 2.2 below for additional compensatory mechanisms to ensure perpendicular electrode entry). After the epoxy has cured, MDX4-4210 silicone elastomer is applied over the substrate assembly and over the gold wires, which have been gathered to form a tight cable and onto the epoxy encapsulated Omnetics connector where the gold wires enter the epoxy to provide strain relief.

Once the silicone elastomer has cured, the ceramic substrate is carefully lifted from the ceramic mold using a micromanipulator. A fire polished sharpened micro-pipette is used to make slight adjustments if necessary to insure that all the electrodes are properly aligned. A small amount of the silicone MDX4-4210 elastomer is applied to the bottom surface of the substrate, along the sides of the substrate and over the top in order to ensure complete encapsulation with the silicone elastomer. The electrodes are individually inspected under a light microscope and the impedance values measured and cataloged for each electrode position in the substrate relative to the Omnetics connector.

2.2. Inserter

A simple device was used to insert two of the four arrays. The device is a pair of forceps that have been modified so that they are remotely opened by a handle located 30 cm away. The forceps sit on a joint that allows the forceps to rotate so that the arrays enter the brain perpendicular to the surface. Pressure applied to the handle will open the forceps (which are otherwise closed) and allow the forceps to latch onto the arrays. The forceps at the end of the inserter are drilled with a groove so that the FMA sits firmly in the forceps and does not move once upward pressure by the brain occurs during insertion (Fig. 3B). Once in the appropriate position, pressure is again applied to the handle squeezing the forceps open and releasing the arrays without vibrating the forceps. Other methods of holding the array for insertion, such as vacuum suction, are currently under investigation.

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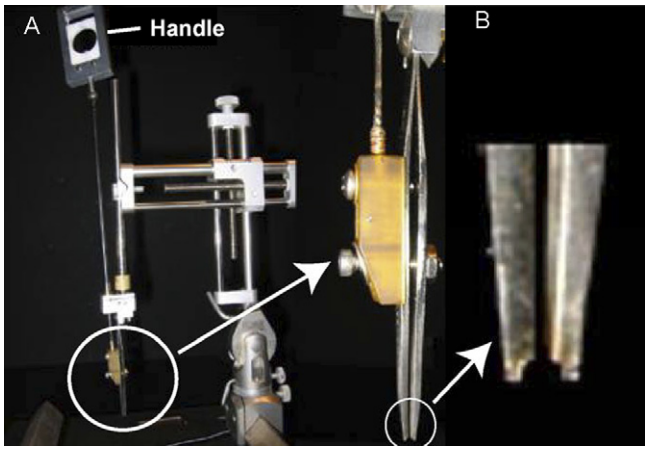

Fig. 3. The FMA holder that was used to insert some of the arrays into the cortex. Tweezers shown in (B) are attached to the handle. Without any pressure, the tweezers are closed. Squeezing the handle pulls the yellow plastic brake upwards (note that the screws do not move. They penetrate the brake and sit in a longitudinal groove that is not a part of the break). The tweezers have been drilled to accommodate the FMA. Once in the brain, squeezing the depressor will release the FMA.

2.3. Animal surgery and recordings

All surgical and animal care procedures were in accordance with the National Institute of Health guidelines and were approved by the California Institute of Technology Institutional Animal Care and Use Committee.

Sprague–Dawley rats were handled for several days before the surgery in order to accustom them to handling by the investigators. Before surgery, the rats were placed in an induction box and exposed to isolfurane (3–4%). Once general anesthesia was reached, the animals were transferred to a face mask to continue delivering the anesthetic (1–3%). Heart rate, oxygen saturation and rectal temperature were continually monitored and recorded. The surgical procedure was performed under sterile conditions.

An incision was made along the rostro-caudal line along the sagittal suture and the Bregma visually identified. A craniotomy measuring 5 mm in diameter was then made centered around Bregma posterior 1.0 mm which corresponds to the barrel fields of the animals. The craniotomy did cross the coronal suture but never crossed the sagittal suture. In one animal, an FMA with 5–6 mm long electrodes was inserted from this location. We assume that these electrodes were in the caudate or in the external globus pallidus. In two of the rats, the arrays were inserted by hand. For the third and fourth rat, the arrays were placed in an inserter (Fig. 3) and lowered using the stereotaxic arm until they were fully inserted. In order to prevent dimpling, the dura of the rats was dissected prior to array insertion. The arrays placed using the inserter shown in Fig. 3 were inserted at a speed of approximately 1 mm/min. Fig. 1 depicts two of the arrays used. Duragen was then placed over the arrays and the connector was cemented onto the skull using dental acrylic. Four titanium skull screws were inserted around the craniotomy. For the surface arrays in one rat, a bridge made from acrylic was build over the arrays to ensure that the arrays are not pushed out of the brain. (Note also that anchors were added to the arrays for the same purpose (Fig. 1A).) The opening was then covered with dental acrylic. A thin silver wire was placed under the skin and attached to a screw embedded in the acrylic for use as an additional ground. The rats were given Baytril (antibiotic) and Ketoprofen (analgesic) daily for 5 days post surgery and Bupronorphine when necessary to alleviate pain. The rats were allowed to recover for at least 1 week before recordings were performed. All recordings were performed with the rats awake and mobile. Spiking activity and local field potentials (LFP) were recorded simultaneously from 16-electrodes using a multi-channel acquisition processor (MAP, Plexon Inc., Dallas, TX, USA): single units were isolated online using time–voltage windows and their timing and spike waveforms stored on disk.

3. Results

The first rat had single unit activity in 4/8 channels and additional multi-unit activity in 1 channel. No spikes or LFPs were recorded in the second rat, however this was due to the arrays (with 1 mm electrodes) drifting outside the brain due to a cavity that developed above the arrays post surgery. To ensure that the arrays remained in the brain, we added anchors to the arrays manufactured for surface implantation and built a bridge made from acrylic over the arrays (Fig 1, see Section 2). (In the primate, we plan to suture the dura over the arrays, something that cannot be done in the rat due to the fragility of the dura.) Activity from the third and fourth implantations are depicted in Fig. 4. Fig. 4A shows a recording from the array inserted 1 mm into the cortex of one rat 3 weeks after array insertion. In this recording, a minimum of 10 single units (red and blue traces) were sorted using template matching techniques while an additional 2 channels exhibited multi-unit activity that were clearly modulated with sensory input. Fig. 4B shows a 16 channel array implanted deep in the brain 3 months after surgery. Even after 3 months, the array has multi-unit and single unit activity on 13/16 channels. In this plot, the mean of all the waveforms is also shown (thick red line in Fig. 4B). Fig. 5 shows the local field potentials (Fig. 5 A) and their power spectrum (Fig. 5B) of the LFPs from the same recording as that shown in Fig. 4A. Prominent in these plots is the increase in power at frequencies between 7 and 10 Hz. Oscillations at these frequencies are consistent with exploratory rat behaviour (Buzsaki, 2002). These plots show that these arrays can be used to record high frequency spikes and low frequency LFPs.

4. Discussion

We present a new type of multi-electrode array that can be made from different electrode types and impedance values, can have irregular electrode spacing, arbitrary electrode lengths and is designed to float on the brain. Two rats implanted on the surface and one rat implanted in the caudate yielded single and multiunit activity from most electrodes.

The success of the FMA was in part due to the development of several new manufacturing technologies: the use of solid core platinum/iridium microelectrodes having unique fabrication processes, a unique design concept based on an array

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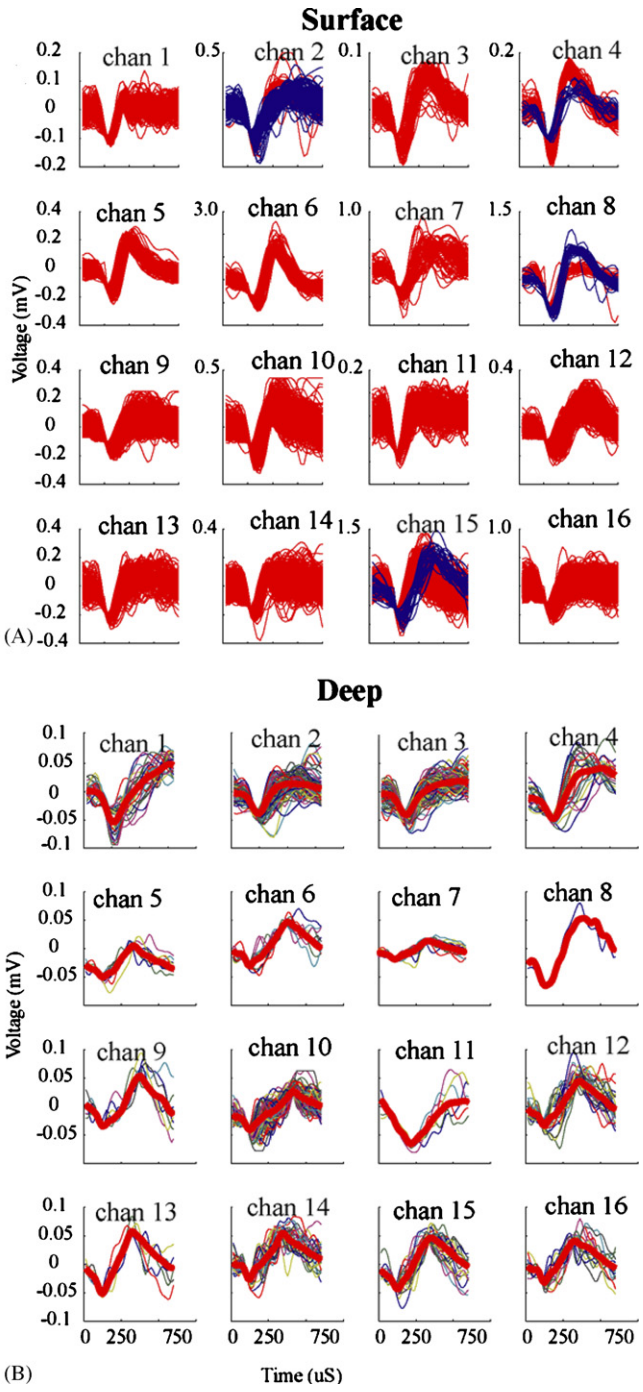

Fig. 4. Spike channels showing single and multi-unit activity from arrays implanted on the surface (A) and deep into the caudate (B) of two separate rats. The red and blue traces in (A) depict different neurons while the thick red traces in (B) are the mean of all the waveforms on that particular channel.

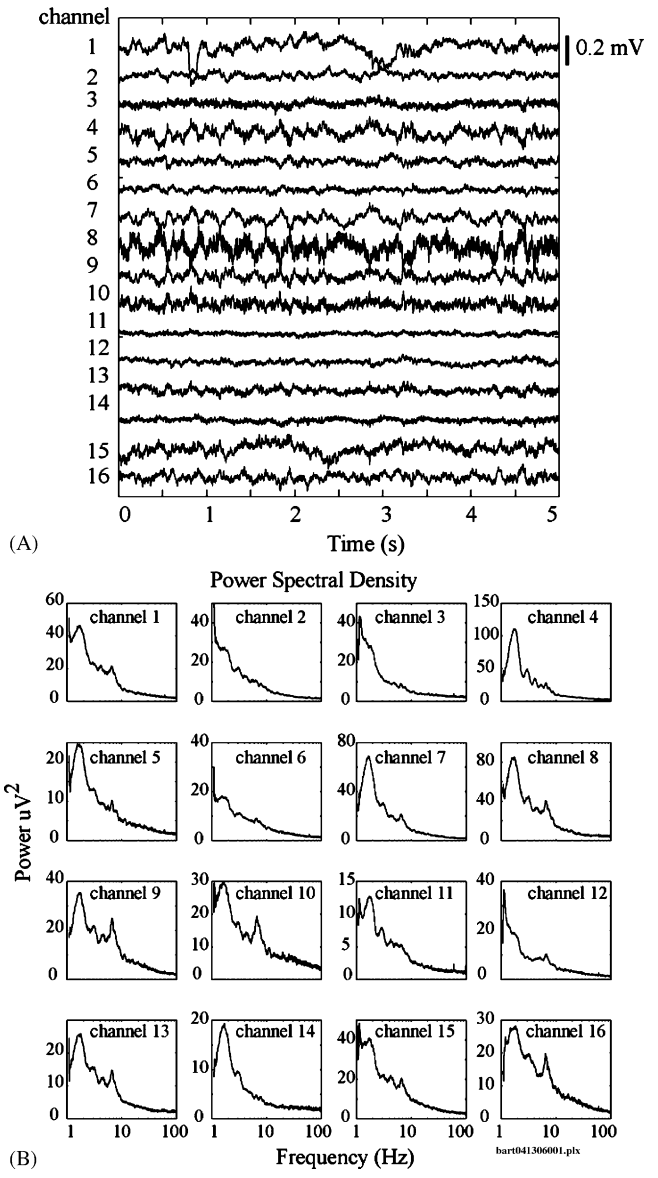

Fig. 5. (A) Local field potentials of 16 channels recorded from the FMA. (B) Power spectrum of the local field potentials recorded on the same day as the activity shown in Fig. 4A. The recordings were 2 min long and the traces were smoothed with a moving window of 0.3 Hz.

of microelectrodes mounted to a ceramic substrate which is attached to an ultra-flexible lightweight gold wire cable, and specialized fabrication procedures utilizing sophisticated micro and sonic wire bonding techniques.

Another and equally important reason for using a "floating" electrode system is the requirement associated with developing a fully implantable system for human neuro-prosthetic applications. Although the need to strain relieve the cabling to the skull in order to establish a stabilizing point between the electrode arrays and the connector/electronics is mechanically obvious, the problems associated with having to fix hundreds or even thousands of electrodes to the skull would likely compromise the normal healing processes associated with such an implant. In addition, employing floating platforms to support the electrodes lends itself to the ideal design in which the platform may also incorporate the necessary electronics for stimulation/recording and communication to external RF control circuitry, thus completely eliminating the need for lead wires.

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