Proceedings of the 25th Annual International Conference of the IEEE EMBS
Cancun, Mexico • September 17-21, 2003

Microfabricated Ceramic Sensor Arrays for Direct Interfacing to Deep Brain Structures in Primates.

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Abstract - **In this article we demonstrate the use of microfabricated ceramic based multisite microelectrodes for electrophysiological recordings from primate hippocampus. These electrodes possess superior strength and signal-to-noise characteristics than previous micro-array designs fabricated on silicon substrates. Because of their superior strength long probes can be fashioned which are capable of penetrating into deep brain structures. Additionally, the ceramic substrate eliminates several problems including cross-talk between microelectrodes and high background currents that have plagued prior silicon substrate based designs.**

Keywords - **Electrochemistry, Electrophysiology, Microelectrodes, Sensors, Brain-Computer Interface**

I. Introduction

Much of the recent work in Direct Neural Interfacing (DNI) to the brain has focused on building interfaces to cortical regions. The reason for this is two fold. First, the cortex is easily accessed both surgically and functionally. Second, due to technological limitations the arrays fabricated thus far have been short and as such only able to penetrate about a centimeter into the brain. The cortex is a logical place to begin developing a DNI since sensory and motor systems have distinct functional maps in these brain areas. However, deep structures such as the thalamus, putamen, globus pallidus, and others have important roles in pre-processing information destined for the cortex. The hippocampus, another deep structure, plays a critical role in memory. It is these deep structures that are often the targets of neurological disease processes such as epilepsy and Parkinson's disease. Interfaces to these and other deep structures may permit us to elucidate the role(s) these structures play in the normal functioning of the brain. Such knowledge may provide valuable insight into the treatment of movement, memory, or cognitive disorders.

Microfabricated arrays of in vivo microelectrodes constructed from silicon substrates have been in use since the mid 1970's [1][2] for recording from the central nervous system but have suffered from a number of problems including mechanical fragility, limited recording depth, and poor signal-to-noise ratio. Initial studies [3]-[5] indicated that the high background current and poor signal-to-noise characteristics of silicon multisite microelectrodes were likely due to cross-talk between the recording sites and a shunt capacitance between the metalization layer and the silicon substrate [6][7]. This shunt capacitance is due to the fact that the silicon substrate is a good conductor and must first be insulated with silicon nitride to protect it from the saline environment of a solution or brain environment before the metalization step. The cross talk between the lines may be due to a similar capacitance created by the poor insulating quality of the silicon nitride. Thus, the silicon substrates themselves may not be the optimal material to use as a substrate for the fabrication of microarrays for use in the high salt environment of the brain. Recent work in our lab [8]-[10] and another [11] utilizing new materials, fabrication techniques, and custom electronics have resulted in durable, microfabricated sensor arrays which are capable of recording from superficial as well as deep brain regions. In this article we report on the use of a long sensor design for electrophysiological recording from the hippocampus in non-human primates.

II. Methodology

A. Fabrication

The tips of our Deep-brain Electrochemical / Electrophysiological Probes (DEEP) contain platinum circuitry patterned on polished Superstrate 996 ceramic substrates (Coors Ceramics Company, Golden, Colorado). The recording tips were mass produced using micro-photolithographic techniques and bonded to ceramic shafts. The shafts contained gold interconnect circuitry insulated by several layers of glass. The tip and shaft were bonded using an industrial grade epoxy, then the circuitry of the recording tip and shaft were connected using gold wire bonding (Fig. 1, Inset A). The resulting junction was insulated using several thin coats of epoxy. The finished product was a dart-like long probe (Fig. 1). The tip and shaft both have a nominal thickness of 120 microns. In addition to the 4S1 recording tip shown in Figure 1, 14 other types of recording tips with various geometries and layouts of microelectrodes have been produced. Each of the microelectrode tip configurations represents optimized designs for different intended uses and can be mounted on either the long shaft shown in Figure 1 or on short holders (not shown) for use in smaller animals.

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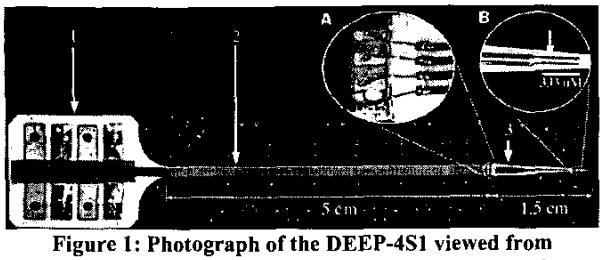

Figure 1: Photograph of the DEEP-4S1 viewed from above. Two piece construction permits a variety of different mass produced microelectrode tip configurations to be fitted to a single mass produced shaft. The finished unit consists of 3 major sections: the connection area (1) where the sensor inserts into a head stage amplifier socket, the shaft (2) and the microelectrode tip (3). Inset A shows the wire bonding site where the connection is made between the circuitry of the microelectrode tip and shaft. Inset B shows the four recording sites at the microelectrode tip, one of which is indicated by the arrow. The design designation 4S1 indicates a tip design with 4 microelectrodes each measuring 333 microns long x 15 microns wide in a pair-wise, side-by-side layout.

B. Cleaning

Prior to use for electrophysiological recordings the active surface area of the microelectrodes was assessed using electrochemical testing. This provides a direct measure of the electrically viable surface area of a microelectrode and thus is a reliable indicator of microelectrode patency. In preparation for testing, the sensors were cleaned by immersing the microelectrode containing portion of the tips (Fig. 1, Inset B) in a 40% solution of acetone in EtOH in a low intensity ultrasonic bath for 1 minute. The microelectrodes were then rinsed with a 70% EtOH in ddH_2O solution.

C. Electrochemical Testing

Electrochemical testing was conducted using a FAST 16 voltammetry system (Quanteon, L.L.C.). A beaker containing 40 mL of phosphate buffered saline (PBS) was prepared into which a Ag/AgCl reference electrode (RE-5, Bioanalytical Systems) was placed. The FAST system was started and a +0.7 V potential was applied vs. the Ag/AgCl reference electrode. The sensor was allowed to equilibrate approximately 10 minutes prior to beginning the calibration/testing procedure. Once the sensor had equilibrated (i.e. baseline became relatively flat) the first value for the test was computed by taking the mean of 10 points from the flat region. Then three 40 microlitre aliquots of 8.8 micromolar H_2O_2 were sequentially added to the PBS. Each addition resulted in a shift in the sensor's baseline and was proportional to the concentration of H_2O_2 in solution. With each addition the baseline was allowed to stabilize and the mean of 10 data points from the stable region was taken. Following the computation of the fourth mean, the regression line through the four points was computed. The value of the slope of the regression line is proportional to the oxidation current and an indicator of the functional surface area of the electrode.

D. In vivo testing

One rhesus monkey (*Macaca mulatta*) was anesthetized with ketamine (100 mg/kg) and maintained on isoflurane throughout the procedure. A DEEP-4S1 was stereotaxically positioned using a Kopf stereotaxic frame and micromanipulator, such that the recording sites were located in the CA1 layer of hippocampus (4 mm anterior to interaural line, 10 mm lateral to midline, 32mm ventral to surface of brain). The microelectrode was connected to a preamplifier and spike sorter (Plexon, Inc) for recording and analysis of neural activity. Single neuron activity was monitored during electrode positioning to ensure placement in the cell layer. Action potentials (spikes) from individual cells were sorted by waveform characteristics to identify all spikes originating from a single neuron, then waveforms and firing records were stored on disk for later analysis.

III. Results

Sensors mass produced using micro-photolithographic techniques had good feature definition (< 5 microns), tight platinum/polyimide junctions (Figure 2), and uniform construction between sensors. All 39 sensors passed leak testing of the tip, tip/shaft junction, and shaft. In earlier prototypes, leakage through gaps in the epoxy impacted the

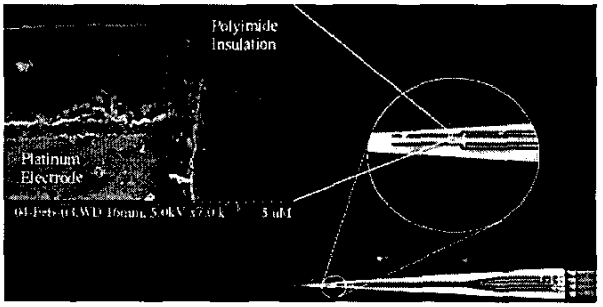

Figure 2: Detail of a microelectrode site on a DEEP-4S1 sensor taken at the junction of the platinum (Pt) electrode surface and the polyimide (PI) insulating layer. The microelectrode sites are visible in the micrograph (inset at the top right) as widened areas in the circuitry. The borders of the PI are sharply defined at the microwell containing the microelectrode sites. The PI forms a tight junction around the Pt circuitry where it emerges in the microwell and widens to form the microelectrode (SEM, top left).

signal-to-noise ratio of the microelectrodes. This problem has been alleviated in the current designs by using a high grade epoxy for the tip/shaft junction, increasing the insulation thickness on the shaft, and general tightening of the manufacturing specifications.

The results of electrochemical testing for 39 sensors are given in Figure 3. Oxidation current values of approximately -50 pA/uM H_2O_2 were considered adequate; values less than -60 pA/uM H_2O_2 were preferred. Measurements for sensors 11 and 32 are absent due to

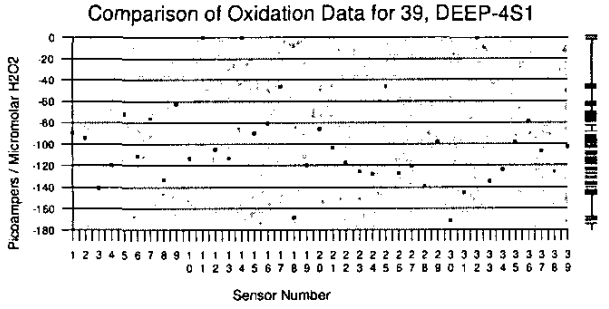

Figure 3: Scatter plot of the oxidation current data for 39, DEEP-4S1. Each point represents the mean of 4 values since there are 4 microelectrodes on a sensor. The data points shown on the large graph are also shown on the smaller whisker plot at the right. Note that most of the sensors have values less than -60 pA/uM H_2O_2.

damage incurred following leak testing. Sensor 14 contained structural defects, which impacted signal strength. Sensors 17 and 25 had mean values just above -50 pA/uM H_2O_2 but were still usable. Figure 4 illustrates electrophysiological data obtained from a DEEP-4S1 in the CA1 layer of the hippocampus in a non-human primate.

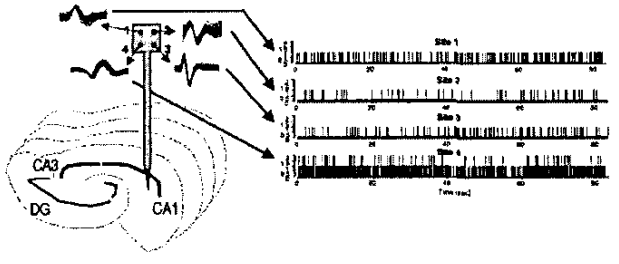

Figure 4: Illustration of single neuron isolation and recording via a DEEP-4S1 positioned in layer CA1 of the hippocampus of a nonhuman primate. Waveforms at top show isolated single neuron action potentials recorded from each microelectrode site (1-4). Scale bar: 500 ms, 50 uV. Arrows indicate the respective stripcharts of single neuron activity recorded from those same microelectrode sites. Each bar indicates an action potential occurrence (once or twice in 100 msec bins) across an 80 sec recording period.

IV. Discussion

The formation of a direct brain-computer interface depends on the maturation of a number of technologies including microfabricated electrochemical (e-chem) and electrophysiological (e-phys) sensors. Since electrical activity is only one aspect of brain function it is desirable to develop sensor technologies capable of detecting chemical, and/or other brain-function correlated events. Near real-time, in vivo detection of the neurochemistry of brain function using microfabricated sensor arrays is an emerging technology. Previous research [10] has demonstrated the use of ceramic-based multisite microelectrodes for the in vivo electrochemical detection of the neurotransmitters L-glutamate and dopamine [8][9]. In addition to the electrophysiological results presented above, the tips used on the DEEP-4S1 are regularly used in our lab for the electrochemical detection of different neurotransmitters.

In this article we have demonstrated electrophysiological recording using the DEEP-4S1. One of the goals for this research is the implementation of a hybrid probe containing both e-chem and e-phys sensors on the same substrate. Such a sensor would be capable of near real time recording of correlated electrophysiological and neurochemical activity; thus providing a robust sensor technology for DNI. The DEEP-4S1 probes described above have been used successfully to record electrical activity from deep brain regions in primate. In use the probes exhibit excellent signal-to-noise characteristics and mechanical strength. However, work is underway to fully characterize both the electrical and mechanical properties of our long probes. Of particular interest are impedance, capacitance, lateral shear, and axial compression.

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