In Vivo Evaluation of a µECoG Array for Chronic Stimulation

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***Abstract*— Advancements in neural interfaces capable of neural stimulation have shown that neural implants may potentially target the central nervous system to treat neurological disorders. Unfortunately, many of the current technologies used to stimulate and record from the brain do not suffice for this purpose; those that provide a sufficient channel density, which is required for interfacing and chronic functionality *in vivo*, fail quickly, while others that last for an extended period of time *in vivo* are limited in recording and stimulation capabilities. Of the current methodologies available, electrocorticography (ECoG) based implants show promise for providing both high channel density interfaces as well as chronic functionality after implantation. This study evaluates the performance of a µECoG for the purpose of chronic stimulation.**

I. Introduction

In recent years the advances in neural electrode design and stimulation parameters have shown promise for treating many neural diseases and disorders. Regrettably, many of these advances are still limited by the inability of neural interfaces to function chronically *in vivo*. In order to develop clinically-relevant neural interfaces that can treat disorders such as sensory loss or limb loss, chronically functional high channel density devices are needed to record neural activity and stimulate the brain. Many of the highest channel density neural implants are penetrating devices such as microwire arrays, 2 dimensional silicon penetrating arrays, and linear silicon arrays. The current hypotheses suggest that these penetrating devices become non-functional after implantation due to the brain's chronic immune response [1-3]. The immune response is characterized by an acute stage, where there is cell response to the initial brain trauma, and a chronic stage, where the brain enters a state of device rejection producing the signature glial sheaths believed to be the primary cause behind device failure [4]. But, there is one type of neural interface that can avoid this chronic immune response and enough channel density to effectively interface with the brain: electrocorticography (ECoG) arrays. Placed on the surface of the brain, ECoG arrays avoid evoking the same immune response as seen with penetrating electrodes while still offering high channel density. ECoG arrays have also been shown to work well in human subjects as they are used in the treatment of seizures, control of remote prostheses, and have been used to successfully evoke somatosensory sensations in human patients [5-8]. In this study we evaluated a µECoG array, an ECoG scaled down to increase site density and sensitivity along with a control penetrating electrode. We monitored the degree which these devices were affected by the immune response and gauge their ability to evoke behavioral responses over time.

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II. Materials & Methods

A. Animals

For this study, 3 male Sprague-Dawley rats (350-400 g) approximately 5 months of age were implanted with µECoGs arrays (2 rats) and penetrating electrodes (1 rat). The laboratory animal protocol for this work was approved through the Institutional Animal Care and Use Committee of Purdue University (West Lafayette, IN, USA), and conforms to the guidelines of the US National Institutes of Health.

B. Electrodes

Two types of electrodes were used for this study, a µECoG array and a penetrating Michigan array. The µECoG arrays in this study were developed by the NITRO Lab of University of Wisconsin and are similar to a previous rat ECoG arrays developed by the same lab [9]. The electrode consisted of 16 contact sites coated with a layering of 10 nm of Cr, 200 nm Au, and 20 nm of Pt measuring 200 µm in diameter and arranged in a 4 by 4 array with rows spaced on a 750 µm pitch on a flexible Paralyne substrate. The penetrating electrode used in this study was a 16 channel four shank silicon microelectrode array with iridium oxide sites of 1250 μm^2 spaced on a 200 µm pitch (NeuroNexus Technologies, Ann Arbor, MI). All sites on the penetrating array were located at depth between 800 µm and 1600 µm.

C. Surgery

The implantation surgeries performed in this study were similar to procedures performed in previous publications by our lab with modification made for the implantation of the µECoG arrays [10]. In brief, animals were anesthetized using 1% to 5% isoflurane/oxygen mix at a flow of 1.5 to 2 liters/minute and monitored throughout the surgery to maintain an areflexive state as monitored by toe pinch tests. The µECoG craniotomies in this study were made by drilling away the skull over the primary auditory cortex of the right hemisphere so that a square 3 mm by 3 mm flap of bone remained. This was accomplished by drilling through the bone on 3 sides of the square and thinning the last side (lower edge of craniotomy). Once a bone-flap was made, the µECoG was placed epidurally onto the auditory cortex by hand and secured by pushing the skull back into position and then applying dental acrylic over the bone-flap. To secure the implant and connector, 4 titanium bone screws (size 2-56, United Titanium, Ohio, US) were inserted into the skull, 2 anterior and 2 posterior to craniotomy and additional dental acrylic applied. A small wire was connected to one of these bone screws prior to dental acrylic application to serve as the electrical ground.

D. Electrical Monitoring

Complex impedance spectra and cyclic voltammograms were taken every day for the first two months of implantation and then twice a week after until the animal was sacrificed. The impedance magnitude and charge carrying capacity were measured using an Autolab potentiostat/galvanostat (Metrohm Autolab, Netherlands) with techniques previously published by our lab [11]. In brief, impedance spectra were taken with frequency sweeps from 100 Hz to 10 kHz logarithmically spaced, repeated 3 times and averaged to calculate site impedance magnitude. Charge carrying capacity was recorded by performing cyclic voltammetry sweeps on each of the electrodes sites, using 3 sweeps and averaging for each site.

E. Behavioral Task

The behavioral task performed in this study was a conditioned avoidance task previously performed by our lab in studies examining signal detection and discrimination [10, 12]. In brief, the animals were placed on a water deprived regime and then presented a water spout during testing. Trials began once rat licking was detected. Two types of randomly ordered trials were presented to the animals: safe, where no stimulus was presented, and warning, where a 650 ms warning tone (acoustic training) or pulse train (implanted electrode) was presented. A "hit", or successful detection of the stimuli, was recorded for warning trials when animals did not lick the spout during the last 200 ms of the trial. A "miss", or unsuccessful detection of the stimuli, was recorded for warning trials when animals continued to lick the spout during the last 200 ms of the trial and the animal was given a 1.6 mA shock via the spout. Animals were trained on auditory stimuli before surgery then tested using electrical stimulation after device implantation.

Stimulation to the electrodes was delivered via a MS16 stimulus isolator (Tucker-Davis Technologies, Alachua, FL) and consisted of a 650 ms cathode leading pulse train of symmetric biphasic pulses with 205 µs pulse duration and variable current level (approximately 20-300 µA).

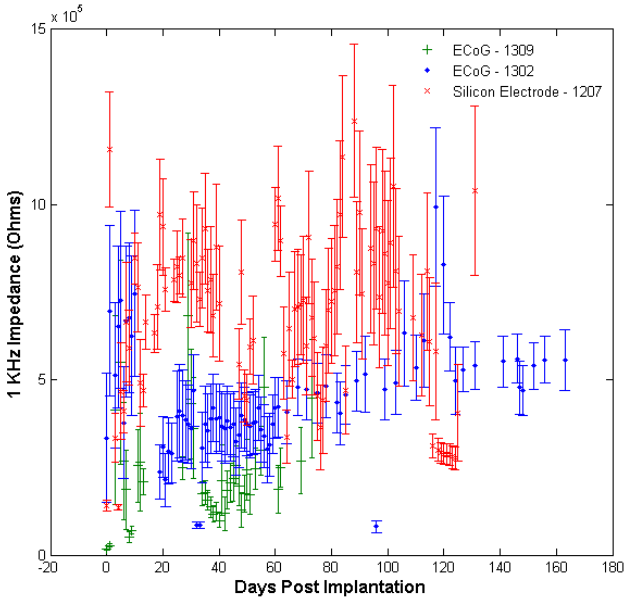
To determine the behavioral detection threshold to a stimulus an adaptive paradigm was used where the stimulus amplitude was modulated based on the detection performance of the animal. When the animal successfully detected a warning stimulus the stimulus amplitude was lowered and when a warning stimulus was not detected the stimulus amplitude was raised. After 5 reversals the trial was concluded and the average level of the last 5 reversal stimuli was taken to give a 50% detection threshold.

III. Results

A. Chronic Impedance and Charge Carrying Capacity

One method of evaluating the performance of a device *in vivo* is to measure the impedance over time. This impedance measure indicated whether the device is functioning normally, partially isolated from the brain, or broken. The higher the impedance, the more isolated from the brain the device is by glial cells [13]. A chronic analysis of the µECoGs' impedance compared to a representative penetrating electrode [14] is shown in Fig. 1. From this figure we can see the impedance for the µECoGs rises shortly after implantation, indicating immune response acting upon the electrode, but returns to approximately baseline after 3 weeks indicating a cessation of the initial immune response. After 1 month, the µECoG devices maintain stable impedance with smallerincrease over time relative to the penetrating electrode. Comparing the average µECoG impedances against those of the penetrating electrode we saw a significantly lower impedances over time with µECoG (Student's t, $p<0.0001$).

Figure 1. Chronic Impedance Magnitude. The 1 kHz impedance of contact



sites for µECoGs (Blue, Green) and a penetrating electrode (Red) over time post implantation. Error bars show standard error.

Another method of evaluating the performance of the device is by measuring the charge carrying capacity of the electrode sites. The charge carrying capacity describes the amount of charge that an electrode can store which is important for performing stimulation as it is the charge on the electrode that stimulates neurons rather than just the current passing through the electrode [15]. Thus the lower the charge carrying capacity the less effective the device is at stimulating the local environment. The chronic charge carrying capacity of the devices is shown in Fig 2.

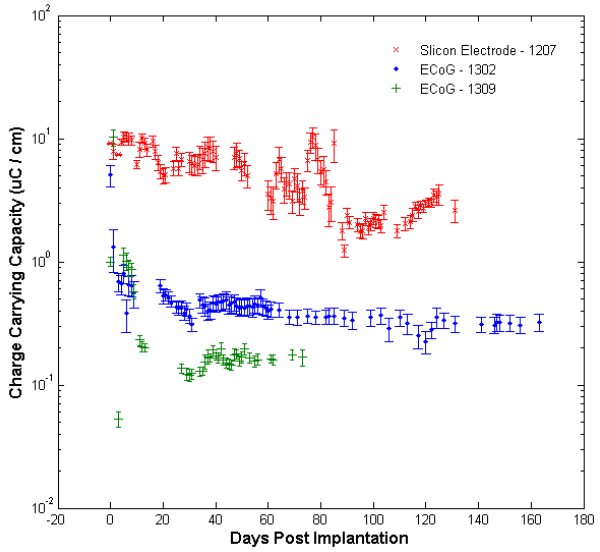


Figure 2. Chronic charge carrying capacity of µECoG arrays (Blue, Green) and a penetrating electrode (Red) over time post implantation. Error bars show standard error.

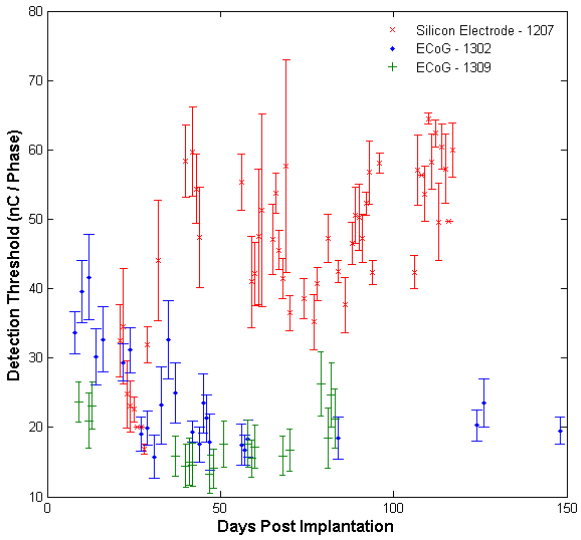
From Fig. 2 we observe a sharp and significant decrease in charge carrying capacity of the electrodes immediately post implantation. This decrease, though substantial, appears only once and the charge carrying capacity does not decrease further after extended time implanted. Statistically analyzing the dataset we find that the ECoG rats have significantly lower charge carrying capacity compared to the penetrating electrode (TukeyHSD, $p<0.0001$).

B. Behavioral Detection Thresholds

A third measure used to evaluate the functionality of the devices was the animals' performance on a behavioral task. The behavioral thresholds obtained from this task describe the lowest stimulation threshold the animal was able to detect 50% of the time. Fig. 3 shows the trend of the behavioral thresholds over time.

Initially, the µECoG detection thresholds are similar to those for penetrating electrodes, but over time we observe that the thresholds decrease indicating increased sensitivity to the stimuli. The detection thresholds also appear to be stable at extended time points post implantation with no significant increase in detection threshold observed after 2 months implanted (TukeyHSD, $p>0.05$). Additionally, µECoGs show significantly lower in detection threshold over time than penetrating electrode ($p<0.0001$), and no significant changes in detection thresholds post 2 weeks implanted ($p>0.05$), suggesting chronic stimulation stability.

Figure 3. Chronic behavioral detection thresholds – Behavioral threholds measured in nC/phase over implantation period for two µECoGs (Blue, Green) and a representative penetrating electrode (red). Error bars show standard error.



IV. Discussion

Our analysis of the impedance, charge carrying capacity, and behavioral detection thresholds over time indicate that the µECoG developed by the NITRO Lab is a stable platform for stimulating the cortex of a behaving rat. The impedance of the µECoGs was significantly lower than our representative penetrating electrode and showed little variation over time. Though the charge carrying capacity did decrease faster and significantly more than our penetrating electrodes, the µECoGs were able to still effectively stimulate the animals chronically with a detection threshold comparable or lower than that of penetrating devices [10]. Overall, the µECoG devices showed functionality and high stability over time.

This stability is likely due to the ability of the µECoG array to avoid evoking the same immune response as penetrating electrodes. Since, for this study, the dura was never compromised the most probable cause for device impairment comes from sources outside the brain's immune system [16, 17]. This is supported by the time-line of the changes observed in the electrical properties which suggest that the implant is not affected by a chronic inflammatory response, but rather the acute immune response. First, the spike in 1 kHz impedance occurs shortly after surgery and returns to approximately baseline 2-3 weeks later; this mirrors the acute immune response's timeline for wound healing and restoration of the dura. This suggests that the spike in impedance is due to transient effects related to the surgical injury rather than an effect of chronic device

rejection/chronic inflammation as we would expect to see a progressive decrease in implant function over time if the chronic immune response was active.

The drop in charge carrying capacity also supports this view as it is likely not due to device failure or glial coatings, but likely due to a quick buildup of collagen fibers on the surface of the μECoG device. If the change was due to the chronic immune response we would expect to see a continual degradation of function as we saw with the penetrating electrode, but rather the changes occur immediately and do not worsen after approximately a week *in vivo*.

Even though the electrical data is promising, the clinical efficacy of the device is best evaluated in the ability to chronically evoke behavioral responses. We see that over time post implantation the device continues to evoke behavioral responses from stimulation and does not appear to have any significant increases in the threshold current, contrasting what is usually observed with many penetrating electrodes.

One aspect of this study which surprised the authors was the generally low stimulation threshold required to evoke behavioral responses. Based on the theoretical volume-conductor hypothesis, the empirical results of the stimulation reported here are in conflict with studies indicating lower thresholds for deep stimulation targets compared to shallow targets [10]. However, this may be due to the larger electrode contact sites being able to affect a large colony of neurons thus obtain similar absolute numbers of responding neurons from that pool or other effects based on the dynamics of the stimulation field. Future research with this device will focus on quantifying and understanding the mechanisms by which these low thresholds are obtained and how stimulation can be improved.

V. Conclusion

The goal of this study was to characterize the performance of a μECoG implanted for chronic stimulation. Our study shows that the μECoG maintains low impedance over chronic implantation with lower variability than penetrating devices, though the charge carrying capacity of the contact sites drop significantly more than penetrating devices. But this does not negatively affect the ability to stimulate as the ability to evoke behavioral responses is stable after the first month, and can produce these responses with stimulation levels comparable to penetrating devices.

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