The Effect of Site Placement within Silicon Microelectrodes on the Long-term Electrophysiological Recordings

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Abstract— **Intracortical microelectrodes can be used to treat various neurological disorders given their capabilities to interface with single or multiple populations of neurons. However, most of these penetrating devices have been reported to fail over time, within weeks to months, putatively due to the foreign body response (FBR) which persistently aggravates the surrounding brain tissues. A number of studies have confirmed that various electrode properties, such as size, shape, and surface area, may play a role in the biological responses to the microelectrode. Further experimental data is needed to determine the effect of these properties on the FBR and the recording performance. In this paper, we evaluate the effect of site placement using Michigan arrays with sites on the center, edge, and tip of the shank. The results show that there is significant performance variance between the center, edge, and tip sites.**

I. Introduction

Penetrating microelectrodes that can specifically target single neurons have provided us a deeper understanding of the central nervous system (CNS), as well as opened up possibilities for treating various neurological disorders. However, for successful clinical application, there are several obstacles that must be addressed, one being the functional longevity of the electrodes [1,2]. While there are studies demonstrating the feasibility of using microelectrodes on a long term basis [3,4], the general consensus is they lose their functionality over time and eventually fail within weeks to months [5-8]. Studies have investigated both biotic and abiotic aspects of chronic implant failure. While abiotic aspects also play an important role and need further study, biotic aspects, which are characterized by the formation of an astrogliotic sheath around the device and loss of nearby neurons, are likely the critical failure mechanism.

This work was sponsored by the Defense Advanced Research Projects Agency (DARPA) Microsystems Technology Office (MTO), under the auspices of Dr. Jack W. Judy (jack.judy@darpa.mil) and Dr. Doug Weber (Douglas.Weber@darpa.mil) as part of the Reliable Neural Technology Program, through the Space and Naval Warfare Systems Command (SPAWAR) Systems Center (SSC) Pacific grant No. N66001-11-1-4013.

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Previous studies have suggested device design parameters such as size, shape, and flexibility greatly influence the degree of FBR and the functional longevity of the implant [9,10]. However, individual effects of those parameters were yet to be evaluated. A number of studies have compared the performance of different types of electrodes and concluded the difference between these devices was statistically significant. Seymour et al., demonstrated sites on the flexible lateral edge outperform sites on the probe shank with histological assessment [11]. Karumbaiah et al., showed that microwires outperform Michigan arrays both in histological and cytokine gene expression aspects and recording performance aspects [10]. While these results were meaningful, the dominant factor that made the improvements and if there was an interactive effect between different parameters were not properly answered. In this study, we evaluate the chronic recording performance of silicon microelectrodes whose site layouts are modified from standard devices; specifically, sites are located on the center, on the edge, and at the tip. With this design, we seek to elucidate the effects of site placement within the device on the long-term recording performance. Our electrophysiological data suggest edge sites outperform center sites in terms of detectability and longevity, while tip sites lack statistical power to make a discernable observation.

II. Methods

A. Surgical Procedures

All surgeries and animal experimentation were performed under the guidance of the Institutional Purdue University Animal Care and Use Committee. A total of eight (8) adult male Long Evans rats (300-360g, Charles River, Chicago, IL) were implanted bilaterally (16 channels in each hemisphere) with silicon-substrate microelectrode arrays (GP1x16_249 - see Fig. 1 for details, NeuroNexus Technologies, Ann Arbor, MI). Animals were injected with a cocktail of ketamine (75-95mg/kg) and xylazine (5mg/kg) for anesthesia and maintained with oxygen throughout the surgery. The electrodes were implanted in the primary motor cortex (M1) targeted at 2mm anterior to and 2mm lateral to the bregma. After a dural incision was made, the device shank was attached to an insertion rod using heated poly(ethylene-glycol) (PEG) [12] and inserted into the cortex to a depth of 1.8mm at a rate of 20 mm/s with an automatic inserter. Both hemispheres received the same procedure and were implanted symmetrically. Craniotomies were covered with wetted Gelfoam (Pfizer Inc., USA) followed by Kwik-Sil (World Precision Instruments, Sarasota, FL) and dental acrylic.

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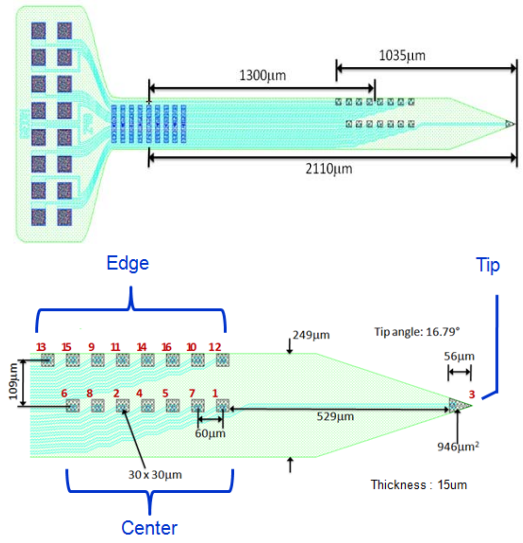

Fig. 1. Schematic of the device structure used in the study.

B. *Electrophysiological Measurements*

Single-unit extracellular recordings were taken using a 16-channel data acquisition system (RZ5, Tucker-Davis Technologies, Alachua, FL). Electrophysiological recordings (Ephys) were sampled at 24 kHz and band pass filtered at 300Hz – 3kHz. Spikes were extracted using a custom built MATLAB (MathWorks, Natick, MA) software using an amplitude threshold of 4 times the noise standard deviation (= median(abs(noise))/0.6745) [13]) followed by appropriate artifacts removal. Electrochemical impedance spectroscopy (EIS) were taken with PGSTAT128N (Metrohm Autolab, The Netherlands) paired with Ephys. Multi sinusoidal inputs ranging from 10 Hz to 30 kHz were applied, and corresponding resistive and reactive impedance values were measured. Both Ephys and impedances were collected daily during the first week after implantation and 3 times a week afterwards. Animals were sacrificed between 2-6 months post-implantation when the Ephys activities were completely lost.

III. Results

The study included bilateral implantation of eight rats, but implants that are not presented in this paper were excluded from analysis mostly due to surgical complications. Animals were numbered from HIST031 to HIST044 for ease of description. R/L denotes right/left hemisphere.

Fig. 2 (a) shows representative Ephys recordings from HIST044 at 1 day post implant (DPI) and 9 DPI. A large number of single unit spikes were detected at 1 DPI whereas only a few spikes were detected with decreased amplitude at 9 DPI. This shows a typical degradation of Ephys involves loss of discernable spikes as well as a decrease in signal-to-noise ratio (SNR). As nearest sites were only 60 um apart, we see that single units also appeared at the neighboring sites. Fig. 2 (b) shows a typical Nyquist plot of complex impedance. The progression of spectrum closely resembles that of previous findings [4,7].

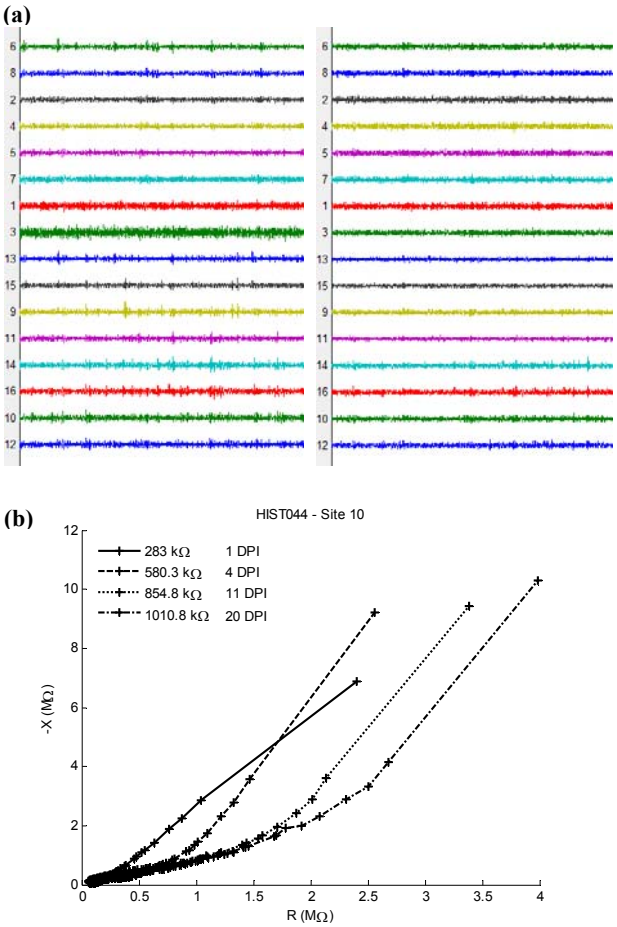

Fig. 2. Progression of Ephys & Nyquist plot of impedance. (a) shows 0.25 second Ephys of HIST044 at 1 DIP and 9 DPI. (b) shows a typical transition of impedance spectra from Ch 10 of HIST044.

Fig. 3 shows the number of channels that detected units (a discernable single unit action potential or multi-unit cluster) for the given week since DPI. The data suggest there was qualitative variance specifically between center and edge sites. Edge sites had a larger number of channels that detected spikes and were functionally active for a longer period of time. HIST041R was the only implant that had more spiking channels on the center sites. As we see from the average across animals, most of the center sites failed within a week, while edge sites lasted up to 3-4 weeks. Due to the sparseness of the data, it was hard to determine whether tip sites performed better or worse than other sites.

The average 1 kHz impedances of each site type are shown in Fig. 4 (a). Statistical test was performed using unbalanced two-way analysis of variance (ANOVA), treating devices and site types as blocks. We confirmed there was statistically significant ($p<0.05$) variability among devices but no interaction effect between devices and site types. Tip sites generally had lower impedances than the center and edge sites, and the statistical significance became apparent from 14 DPI. The significance of the difference did not last throughout the lifetime of the implant due to the decrease in number of rats.

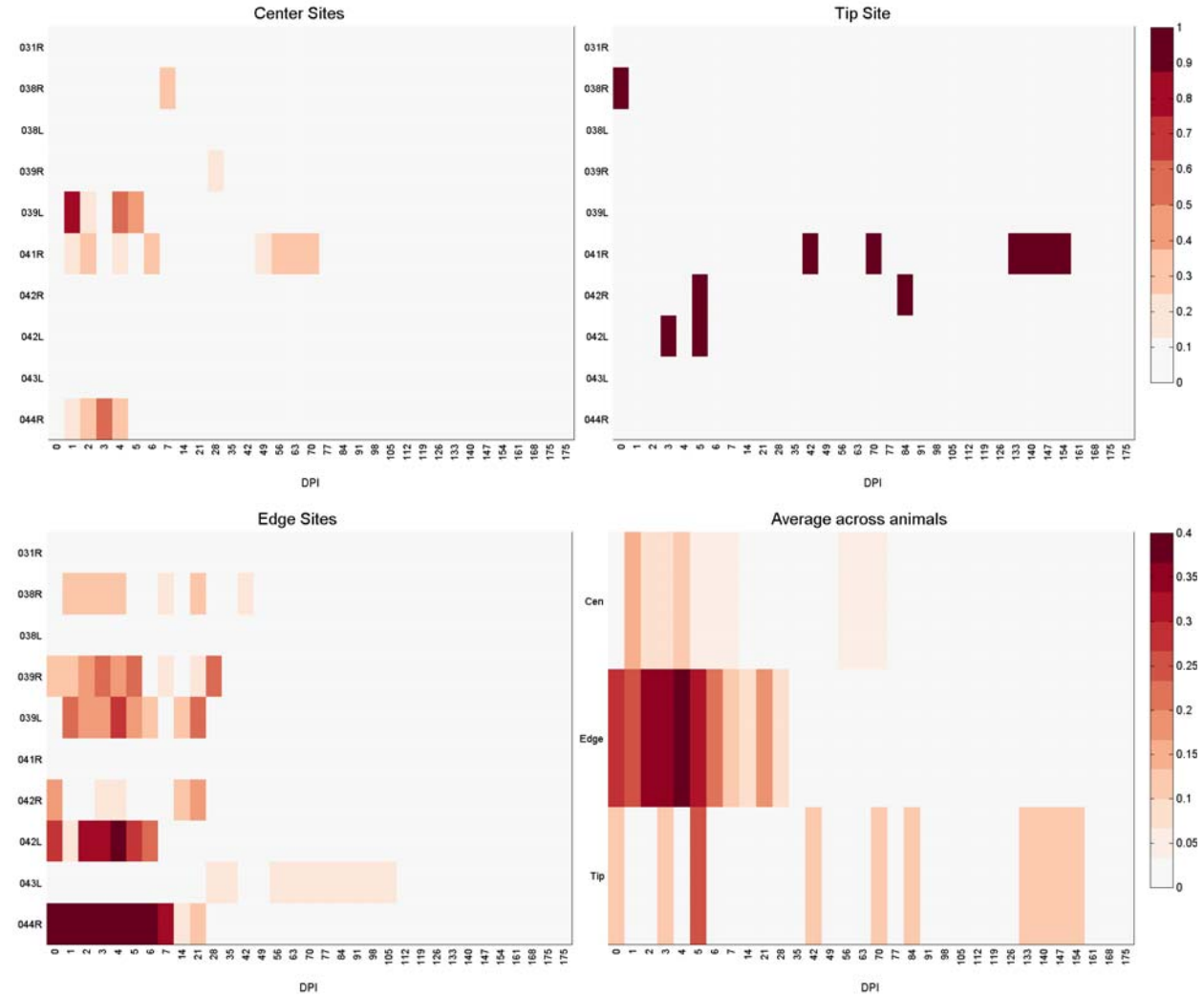

Fig. 3. Percent activity of spiking channels over days post implant (DPI). The numbers in Y axis represent animal index. Center, edge, and tip site activities were scaled from 0 to 1, where 1 corresponds to all the sites detecting single unit spikes and 0 corresponds to none of the sites detecting spikes. Average activity was scaled from 0 to 0.4. 031R and 038L were disregarded when calculating the average activity since they detected no activities throughout the study.

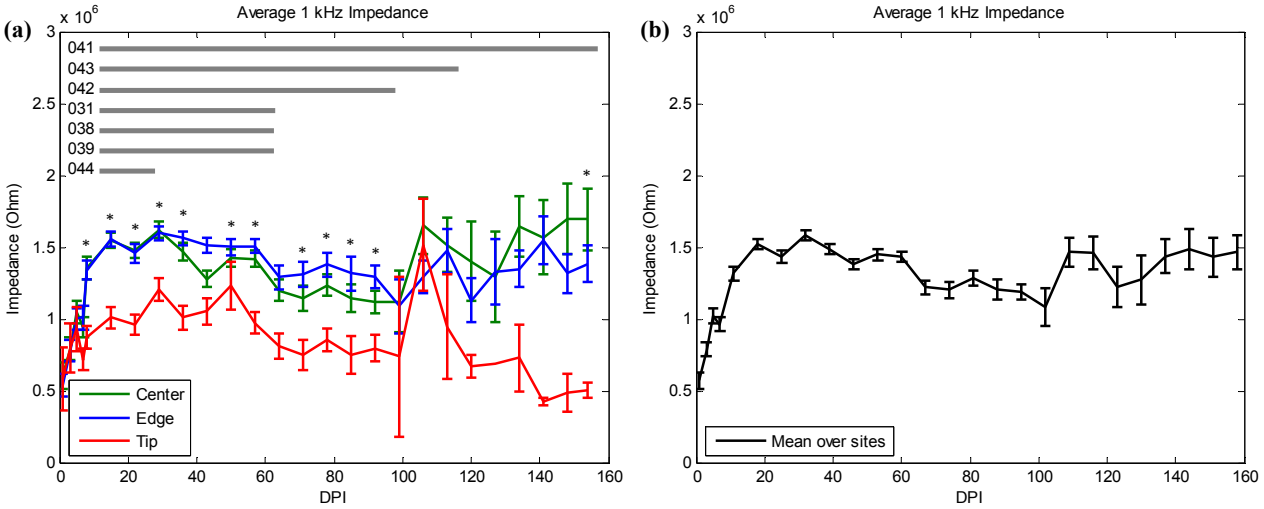

Fig. 4. Average 1 kHz impedance magnitude of (a) center/edge/tip sites and (b) entire sites. Data points were collected on a weekly basis. Error bars represent standard error. Asterisks represent the differences between site types were statistically significant ($p<0.05$) for the given week. Bars on the top of (a) shows the life span of each animals (044 is still being recorded).

The total average impedance from Fig. 4 (b) indicates that electrodes typically experienced the acute rising phase until the first 2-3 weeks and the chronic phase afterwards.

IV. Discussion

The differences in recording performance between center and edge sites were assessed with Ephys. As we see from Fig. 3, the edge sites had higher chance of detecting spikes than center sites. Better accessibility of the edge sites to neurons in the acute phase indicates that the physical structure, where there is no shank area on the edge that blocks signal conduction, enables the sites to hear from more neurons. In addition, the edge sites tended to remain functional longer than the center sites. One possible explanation is that neurons near the edge sites were healthier due to being less affected by the FBR compared to neurons near the center sites. There was no significant variability of 1 kHz impedance magnitudes between the center and edge sites, as well as between weeks for both site types after 21 DPI. This further support the idea that the degradation of Ephys has more to do with loss of neurons rather than glial sheath formation that increases impedance, as evidenced by other literatures [14,15].

We were not able to draw the conclusion that tip sites performed the best, which was expected as tip sites would have been only minimally affected by the presence of the bulky shank due to the tapered width. Although the EIS data suggest that the tip sites had the lowest impedances, it did not appear as better Ephys performance. We concluded that due to having the tip site ~500 um apart from the other sites, it was not a fair comparison as the tip site would have landed at deeper layers of the cortex. Additionally, the fact that there was only one tip site per device as opposed to seven and eight for center and edge sites, respectively, made it harder to examine the performance of the tip sites thoroughly due to the lack of statistical power.

Nonetheless, the low impedance profile at tip sites indicates that our electrophysiological results coincide with histological studies [16,17], as well as stimulation studies [18] performed previously. Low tip site impedance may not be solely due to the reduction of FBR induced by tapered probe shank but may also be due to the reduced presence of meningeally derived cells along the shank. Balanced experimental design of implantation depth and number of sites may reveal that tip is the most preferred location to put sites on. Microwires' high performance among commercially available electrodes may be attributed to the placement of sites at the tip [10].

V. Conclusion

We validated the effects of site placement on the long term electrophysiological performance of cortical microelectrodes by comparing the center, edge, and tip sites of Michigan arrays. Edge sites outperformed center sites in terms of recording capability. Tip sites had the lowest impedances, but this was not correlated with the recording performance. Identifying the biological cause of these findings with histology will be the main focus of our future work.

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