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Micro-field evoked potentials recorded from the porcine sub-dural cortical surface utilizing a microelectrode array

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Abstract

A sub-dural surface microelectrode array designed to detect micro-field evoked potentials has been developed. The device is comprised of an array of 350- μm square gold contacts, with bidirectional spacing of 150 μm, contained within a polyimide Kapton material. Cytotoxicity testing suggests that the device is suitable for use with animal and human patients. Implementation of the device in animal studies revealed that reliable evoked potentials could be acquired. Further work will be needed to determine how these micro-field potentials, which demonstrate selectivity for one eye, relate to the distribution of the ocular dominance columns of the occipital cortex.
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1. Introduction

Single-unit research in animal models has revealed highly detailed knowledge of how information is processed in a number of settings. For example, research has revealed that there are particular neurons in the motor cortex that, through their connections with other neurons in the motor cortex, fire in correlation with arm reach in a particular direction in primates (Georgopoulos, 1996). Other researchers have shown that neurons in the dorsolateral prefrontal cortex are activated in association with the task of directing attentional resources at keeping something actively held in memory (working memory) in primates (Goldman-Rakic, 1987). Although these lines of research have facilitated our understanding of the cortical areas responsible for processes such as motor control and working memory, similar details regarding how information is processed in areas of cortex specific to humans, such as those responsible for human language, have eluded us. There are three reasons for this lack of detailed understanding: (1) the studies involving these areas are largely limited to the macroscopic studies utilizing functional neuroimaging and lesion approaches; (2) the lack of specifically analogous areas in animal models and (3) the limited ability to use penetrating microelectrodes with human subjects due to the inherent invasive nature of the penetrating electrodes. One approach that some researchers have used to acquire a more detailed understanding of information processing within the cortex has been examining neural processing at the level of the cortical columns. Throughout the cortex, neurons are organized into functional units called columns. The cortical columns of the mammalian cortex are typically 300–500 μm in transverse diameter, and do not differ significantly in size between mammalian brains that vary in size over three orders of magnitude (Bugbee and Goldmann-Rakic, 1983). The details of this columnar neuronal circuitry have been particularly well described for the primary visual cortex. Within the visual cortex, each cortical column receives information from each eye

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in an alternating (left eye, right eye) pattern (Gurshumov and Yinon, 2005; Mountcastle, 1997). Additionally, detailed studies are widely available for the somatosensory cortex, auditory cortex, and motor cortex (Mountcastle, 1997). Investigations regarding the processing of more complex information have also been performed. For example, the columnar organization of motion detection in the middle temporal area and visual object discrimination in the inferior temporal cortex have been well described (Mountcastle, 1997). However, as with the research previously discussed involving investigation at the level of the single-unit, the research directed at examining neural processing at the level of the cortical columns is also limited in the relatively human-specific areas of cortex. Therefore, development of a nonpenetrating microelectrode array that is suitable for use with human patients would provide a relatively non-invasive method for investigating these cortical areas for which such detailed information is quite limited.

In order to understand how information is processed in the brain using nonpenetrating electrodes, we have developed an array of nonpenetrating electrodes designed to detect micro-field potentials from the surface of the cortex. The size and arrangement of these electrodes are similar to those of the cortical columns. Previous research in a rodent model using a similar single-contact surface electrode has demonstrated the ability, using signal averaging, to detect highly anatomically specific somatosensory potentials from the primary somatosensory area (Heppelmann et al., 2001). Furthermore, research utilizing linear arrays of surface microelectrodes to investigate the ferret visual cortex has demonstrated the reliability of cortical surface micro-field recordings for representing activity of the underlying neurons (Weliky et al., 2003). In this study, we demonstrate the ability to collect micro-field potentials from the cortical surface of an animal model utilizing a microelectrode array that is suitable for use with human neurosurgical patients and could be used in further studies to investigate cortical areas not previously described at this level of detail.

2. Methods and materials

Biocompatible polyimide and gold were selected as the desired materials for the surface microelectrode array. A microelectrode array consisting of individual electrode contacts with bidirectional spacing in the range of 300–500 μm was desired to detect microfield potentials at a spatial resolution consistent with the geometrical spacing of cortical columns in mammals (Bugbee and Goldmann-Rakic, 1983; Mountcastle, 2003). A 2×4 microelectrode array, consisting of 8 individual 350-μm square gold electrode contacts with bidirectional spacing of 150 μm and insulated by Kapton polyimide, was assembled from commercially available printed circuitry linear arrays. The commercially available printed circuits were 1×20 linear arrays of gold contacts with dimensions of 350 μm × 1.5 cm and a one-dimensional spacing of 150 μm (Flex circuit cable assembly, Samtec Inc., New Albany, IN). In order to combine multiple linear arrays to produce a multidimensional array, with dimensions similar to the cortical column distribution of mammals, the electrode contact end of two individual linear arrays were measured and cut using a #5 stainless steel blade in a microscopically guided manner in order to achieve linear arrays with the new dimensions of the electrode contacts were 350 μm × 350 μm in contrast to the original 350 μm by 1.5 cm. A commercial grade adhesive (UHU All Purpose solvent free, UHU GmBH & Co., Buhl, Germany) was applied to the back surface of one of the linear array strips. The second linear array strip was then applied and the correct spacing between the arrays was achieved under microscopic guidance to within 5 μm of the desired spacing. The spacing was maintained and microscopically verified after the adhesive had thoroughly sealed. The final product (2×4 microelectrode array, consisting of 8 individual 350-μm square gold electrode contacts with bidirectional spacing of 150 μm and insulated by Kapton polyimide) was then interfaced with the Biologic data acquisition equipment, as described in previous research work, to record electrical activity from the sub-dural cortical surface (Kitzmiller et al., 2006).

A qualitative cytotoxicity evaluation of the Kapton and gold surface microelectrode array utilized optical, fluorescent, and scanning electron microscopy. Mammalian cortical cells (harvested rat pup cortical cells, embryonic day 18) and human cortical cells (obtained from America Tissue Culture Collection, cell line CRL-10442 (HCN-1A)) were prepared according to specifications and cultured onto glass slides (control) and the surfaces of the microelectrode arrays (experimental). After 96 h, cells were stained with FURAII, a calcium dependant fluorescent stain taken-up only by viable cells, and evaluated with fluorescent microscopy. Viable cells were observed on both the control and experimental surfaces. Test specimens and cultured cells were then coated with a monolayer of gold to facilitate imaging using scanning electron microscopy (SEM). Images suggesting the appearance of dendritic and/or axonic growth on the experimental surfaces are shown in Fig. 1. The results of this qualitative analysis, which demonstrated that the microelectrode and control surfaces were not toxic to the human and mammal cells (Black, 1999), along with the widely accepted use of polyimides and gold in biomedical devices (Kanno et al., 2002; Klinge et al., 2001; Liu et al., 2003; Schneider and Steiglitz, 2004), suggest that the Kapton and gold microelectrode array is suitable for use with human patients.

Implementation of the surface microelectrode array consisted of collecting visual evoked potentials (VEPs) from the sub-dural occipital cortex of a pig under anesthesia. All procedures involving animals were approved by The Ohio State University Institutional Animal Care and Use Committee in accordance with the NIH Guide for the Care and Use of Laboratory Animals. Anesthesia was induced in the pig using telazol intra-muscularly at a concentration of 6 mg/kg and the animal was intubated and prepped for surgery. Anesthesia was maintained for the rest of the experiment with isoflurane (2% via inhalation). A craniotomy to remove the bone overlying the occipital lobe was performed to expose the cortex. The dura matter was carefully removed, exposing the sub-dural cortical surface. Utilizing both a stereotaxic porcine brain atlas as well as detailed anatomical diagrams from other publications involving recordings from area 17 of the porcine brain, the microelectrode array was placed on the left side, mediolaterally along the caudal pole of the lateral

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