

# Acute microelectrode array implantation into human neocortex: preliminary technique and histological considerations

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**Object.** Researchers at The Center for Neural Interfaces at the University of Utah have designed and produced a silicon-based high-density microelectrode array that has been used successfully in mammalian models. The authors investigate the ability to transfer array insertion techniques to humans and examine the acute response of human cortical tissue to array implantation.

**Methods.** Six patients who were scheduled to undergo temporal lobectomy surgery were enrolled in an Institutional Review Board–approved protocol. Before the patients underwent lateral temporal cortical resection, one or two high-density microelectrode arrays were implanted in each individual by using a pneumatic insertion device. Cortical tissue was then excised and preserved in formalin. The specimens were sectioned and stained for histological examination.

Pneumatic insertion of a microelectrode array into human cortex in the operating room was feasible. There were no clinical complications associated with implantation and no evidence of significant insertion-related hemorrhage. Tissue responses ranged from mild cortical deformity to small focal hemorrhages several millimeters below the electrode tines. Based on initial results, the insertion device was modified. A footplate that mechanically isolates a small area of cortex and a calibrated micromanipulator were added to improve the reproducibility of insertion.

**Conclusions.** A high-density microelectrode array designed to function as a direct cortical interface device can be implanted into human cortical tissue without acute clinical complications. Further modifications to the insertion device and array design are ongoing and future work will assess the functional significance of the tissue reactions observed.

**KEY WORDS** • microelectrode array implantation • cortex • surgical technique

**A**LTHOUGH many techniques and devices have been devised to provide electrical communication with neurons in the intact brain, the microelectrode array is currently the most sophisticated technology available to provide high-density temporal and spatial resolution of neuronal signals.<sup>1</sup> Silicon-based high-density microelectrode arrays have been used in a variety of animal studies to record and stimulate small populations of neurons.<sup>3,5–7,9–11</sup> One type of microelectrode array, which was developed at the University of Utah, consists of 100 microelectrodes with 400-micron spacing. The microelectrodes are each 1.5 mm long and are fabricated on a silicon wafer that measures 4 mm on a side (Fig. 1).<sup>4</sup> A version of this array is currently undergoing testing as part of a brain–computer interface device (J Mukand, et al., unpublished data).

As with the adoption of any new procedure or device, nuances of surgical technique can greatly alter the overall success. As part of the development of a brain–machine interface device, the technical limitations encountered when transferring laboratory techniques to the operating room are being investigated. Previous work has shown that implantation of microelectrodes into cerebral cortex requires

different techniques as the number of electrodes and brain size change.<sup>2</sup> To address the need to insert a high-density microelectrode array reliably to a consistent depth, a high-speed pneumatic insertion device had been created previously.<sup>8</sup> We investigated the transfer of array insertion techniques to humans and examined the acute response of human cortical tissue to microelectrode array implantation.

## Clinical Material and Methods

Adapting delicate small-animal research equipment to the demands of an operating room environment required several preliminary insertion attempts. The results of microelectrode array insertions in the first several patients are not discussed here because histological analysis of the tissue was not possible.

### Patient Population

Six patients who were scheduled to undergo temporal lobectomy for medically refractory epilepsy were enrolled in this Institutional Review Board–approved study. Before each patient underwent lateral temporal cortical resection, one or two high-density microelectrode arrays were implanted in the middle temporal gyrus by using a pneumatic insertion device. Cortical tissue encompassing the array was then sharply excised and preserved in formalin. (Sharp

*Abbreviations used in this paper:* PBS = phosphate-buffered saline; SAH = subarachnoid hemorrhage.

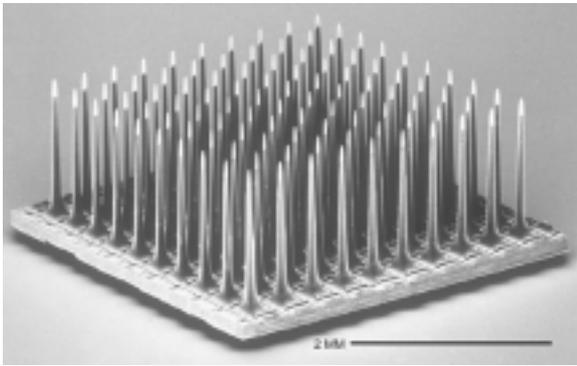


FIG. 1. Electron micrograph showing the silicon-based microelectrode array, which consists of 100 1.5-mm electrodes spaced at 400-micron intervals.

resection was used to avoid inducing histological changes from electrocautery.) Resection does involve mechanical tissue disruption, and it is possible that some histological features later identified were affected by the trauma of cortical resection.

#### Preparation of Specimens

Specimens were equilibrated for 48 hours in 0.1 M PBS containing 30% sucrose. Serial 40-micron sections cut horizontally to the long axis of the electrodes were obtained with a cryostat. Some sections were mounted on slides and stained with H & E, whereas other sections were processed for immunocytochemical studies as described in the text that follows.

Antiserum against neuronal antigen (NeuN; Chemicon International, Inc., Temecula, CA) was diluted in a blocking solution consisting of 4% (vol/vol) normal goat serum, 0.3% (vol/vol) Triton X-100, and 0.1% (wt/vol) sodium azide. Sections were treated for 1 hour with blocking solution at room temperature and then incubated in primary antiserum overnight at 4°C. After three rinses in PBS (15 minutes/rinse), a fluorescence-labeled secondary antibody (Molecular Probes [division of Invitrogen], Carlsbad, CA) diluted in blocking solution to a concentration of 10 µg/ml was applied for 1 hour at room temperature. Sections were counterstained with 10 µM 4,6'-diamino-2-phenylindole-dihydrochloride (Molecular Probes). After washing with PBS, sections were mounted on microscope slides by using Fluoromount-G (SouthernBiotech, Birmingham, AL) and were covered with coverslips. Color digital images were collected with the Coolsnap camera attached to a Nikon E600 microscope.

## Results

Eight microelectrode arrays were implanted into six patients. With most array insertions, a small amount of SAH could be grossly observed. This hemorrhage was limited to within a few millimeters of the array edges and stopped spontaneously. During several insertion procedures, gross extraarachnoid hemorrhage was observed. In all cases this bleeding was stopped quickly with only gentle irrigation with normal saline. Insertion of the microelectrode array did not result in clinically relevant hemorrhage (that

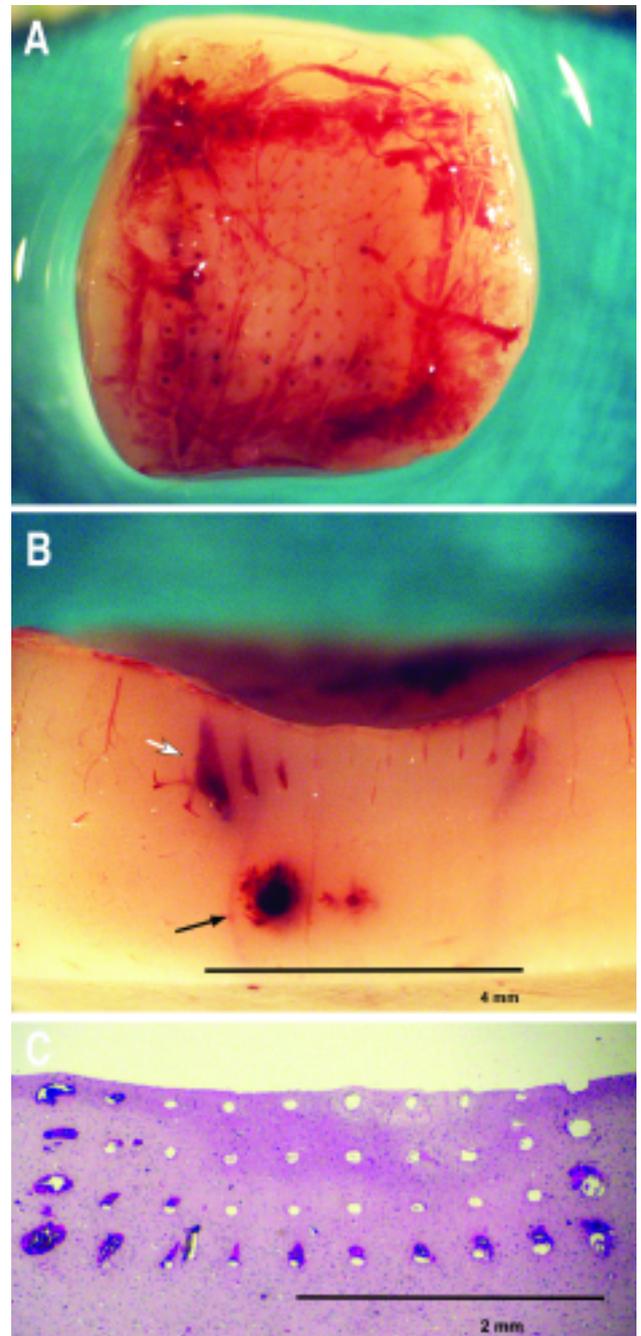


FIG. 2. Photographs showing gross specimens of human temporal neocortical surface after the microelectrode array has been removed. A: Subarachnoid blood can be seen concentrated around the edges of the tissue where the array was implanted. The spacing between each electrode penetration is 400 microns, with the entire specimen measuring approximately 5 × 5 mm. B: Horizontal section showing blood in the outermost electrode tracks (*white arrow*). The surface of the specimen, at the top of the panel, shows a bowing pattern in the tissue that was located centrally under the array. Also visible are two petechial hemorrhages (*black arrow*) located approximately 1 mm below the tip of the electrode tines. C: Photomicrograph of a specimen prepared with H & E staining showing hemorrhage in the outer electrode tracks. These tracks appear elongated toward the center of the array, suggesting cortical deformation followed by stretching and shearing of the tissue at the outer array margins.

## Acute microelectrode array implantation

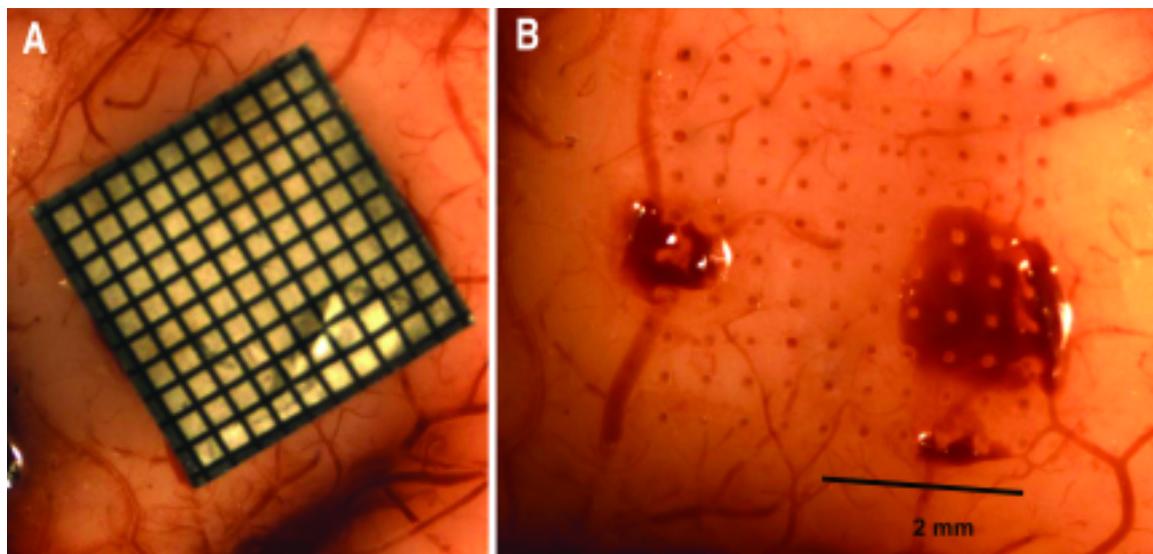


FIG. 3. Photographs of gross specimens showing results of an array implantation after the footplate adaptation had been made to the insertion device. *Left:* No SAH is grossly visible around the edges of the array. *Right:* Once the array has been removed, it is evident that some SAH is present where individual electrodes have directly penetrated cortical vessels.

is, bleeding that would require a surgical maneuver such as electrocautery or tissue manipulation for hemostasis).

Analysis of tissue samples obtained in the first implantations revealed focal areas of tissue shearing at the periphery of the arrays. The electrode tracks at the outer margins of the array contained hemorrhage and the cortex was slightly torn, as evidenced by oblong electrode tracks. Each outer track was torn in the direction of the center of the array. A bowing effect was also noted on the cortical surface. In at least one instance, hemorrhage could be seen 1 to 2 mm below the electrode tines (Fig. 2).

Because the cortical bowing and hemorrhage below the electrode tines had not been routinely observed in array insertions in small mammals, a modification was made to the pneumatic insertion device. A footplate just a bit larger than the array was added to provide slight cortical compression and stabilization during the insertion process.

The addition of the footplate adaptation led to insertions that were generally more consistent with those obtained in smaller animals. In these later cases, the arrays could be inserted more consistently. Subarachnoid bleeding was only evident where individual electrodes penetrated small cortical vessels and not at the edges of the array (Fig. 3). In addition, less gross shearing was visible in the outer electrode tracks.

Histological sections were prepared using tissue samples from procedures in which the arrays were inserted with the footplate adapter. Sectioning was performed parallel to the cortical surface at a depth close to the tips of the electrodes. Most electrode tracks had smooth edges, indicating circumferential tissue displacement. Even close to the electrode tips, however, many tracks contained hemorrhage and had irregular borders (Fig. 4). Because the microelectrode array was not removed until after tissue excision, this finding is most consistent with hemorrhage occurring during insertion.

Two electrode arrays fractured during insertion. Not-

ably, these devices did not have the potting material normally present on the array backing because they were test structures that are typically used to evaluate electrode tip and spacing issues. None of the arrays manufactured using the standard methods suffered from fracture. It was also noted that in several arrays individual electrodes were broken before insertion, emphasizing the need to develop robust and reliable handling techniques to allow these devices to be used in the mechanically demanding operating room environment.

### Discussion

The primary goal of these preliminary investigations was to establish a way to implant the microelectrode array in a safe manner in humans. Pneumatic insertion of microelectrode arrays into human cortex in the operating room was shown to be feasible. In regard to patient safety, insertion of the arrays resulted in no clinical complications, and no significant hemorrhage was visualized intraoperatively.

Important lessons have been learned regarding the transfer of array insertion methods from small animals to humans. With each stage of the transfer of the technique to larger animals, different dynamics of scale come into play. For example, when similar recording electrodes are implanted in rodents for long-term use, one group of researchers has demonstrated improved insertion efficiency by physically immobilizing the cortical surface, affixing it to the surrounding bone with cyanoacrylate adhesive materials.<sup>2</sup>

At the scale of the human brain, cardiac and respiratory pulsations become more profound and may partially explain the shearing seen at the edges of the outer electrode tracks. Additionally, the human pia mater and arachnoid layers pose more of a physical barrier to electrode insertion than they do in nonhuman brain tissue, and these differ-

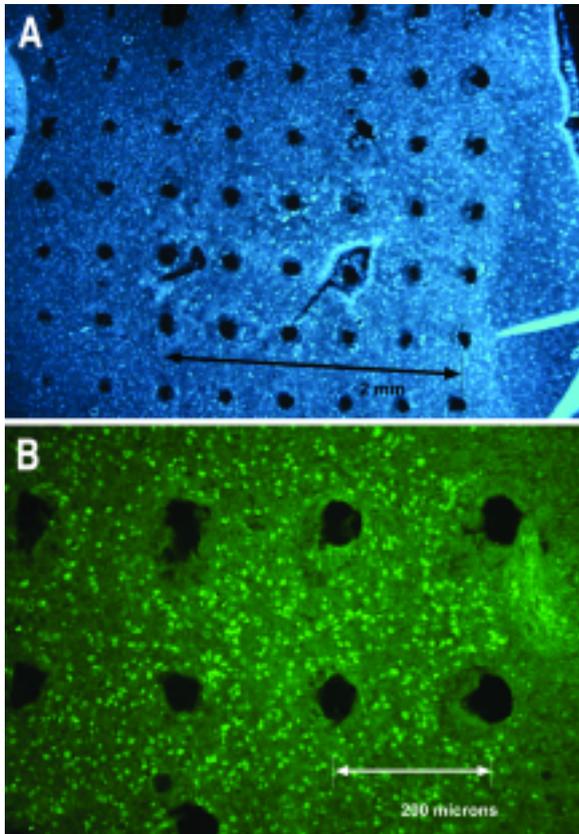


FIG. 4. Photomicrographs showing histological sections cut parallel to the cortical surface at a depth close to the tips of the electrodes. *Left:* Most of the tracks smoothly outline each electrode, but a substantial minority of tracks are irregular, implicating hemorrhage or tissue tearing. This section was stained with 4, 6'-diamidino-2-phenylindole-dihydrochloride, showing the nuclei. *Right:* In this higher-magnification view, the variability in the configuration of the electrode tracks is more evident. It is not precisely known how the acute tissue reactions seen on histological sections correlate with the functional status of individual electrodes. NeuN stain labeling neuron-specific nuclei.

ences may contribute to increased shearing. It may be necessary to weaken these barriers slightly to achieve consistent array insertion. The speed of the pneumatic insertion device has also not yet been fully optimized for human tissue. Higher insertion speeds may be needed to overcome more consistently the physical barriers associated with human cortex.

Support equipment was modified to allow for a more robust system that could withstand the rigors of an operating room environment. Only by attempting to transfer research methodology to humans can such equipment limitations be discovered and addressed. Based on our initial results, the insertion device was modified. A footplate that mechanically isolates a small area of cortex and a calibrated micro-manipulator were added to improve the reproducibility of insertion. Preliminary results lead us to suggest that these modifications will play important roles in consistent array insertions.

It is desirable to create as little tissue disruption as possible during array insertion. One difficulty commonly encountered during long-term use of microelectrodes in ce-

rebral tissue in animal models is the loss of function of individual electrodes over time. Factors that determine which electrodes are lost are myriad, and not all have been identified.<sup>2</sup> It is possible that electrode tracks that have a critical amount of hemorrhage associated with them will later prove to be those of nonfunctional electrodes. The correlation of the short-term functional status of individual electrodes with results of histological analysis will need to be addressed in upcoming studies.

## Conclusions

A high-density microelectrode array designed to function as a direct cortical interface device can be implanted in human cortical tissue without acute clinical complications. The lessons learned from these initial implantations have led to modifications in the technique, which are ongoing. Further studies are necessary to address the functional significance of the tissue reactions observed.

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