Patient-specific Contour-fitting Sheet Electrodes for Electrocorticographic Brain Machine Interfaces

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Abstract—**Non-invasive localization of certain brain functions may be mapped on a millimeter level. However, the inter-electrode spacing of common clinical brain surface electrodes still remains around 10 mm, and some electrodes fail to measure cortical activity due to unconformable plain electrode sheets. Here, we present details on development of implantable electrodes for attaining higher quality electrocorticographic signals for use in functional brain mapping and brain-machine interfaces. We produced personalized sheet electrodes after the creation of individualized molds using a 3D-printer. We created arrays to fit the surface curvature of the brain and inside the central sulcus, with inter-electrode distances of 2.5 mm. Rat experiments undertaken indicated no long term toxicity. We were also able to custom design, rapidly manufacture, safely implant and confirm the efficacy of personalized electrodes, including the capability to attain meaningful high gamma-band information in an amyotrophic lateral sclerosis patient. This sheet electrode may contribute to the higher performance of BMI's.**

I. Introduction

Recent developments in the area of brain machine interfaces (BMIs) have led to the possibility of a seamless interface between the human brain and devices [1]. To achieve this, neural signals must decoded to interpret their meaning, where decoding relies on the quality of the measured neural signals, particularly those of the high gamma-band range (60 – 200 Hz).

One practical method for obtaining high quality neural activity is intracranial electrodes. Brain surface electrodes or electrocorticographic (ECoG) electrodes are less invasive because they do not penetrate the brain tissue. We have shown that intra-sulcal ECoG electrodes on the motor side of the central sulcus provided a higher performance than those of the gyral ECoG [2].

However, the inter-electrode spacing of standard clinical ECoG electrodes still remains at about 10mm. In addition, the gyral and sulcal surface of the human brain is curved with bumps, depressions and grooves, called gyri and sulci, thus making a one-fits-all approach to the design of electrodes, which has been the mainstay until now, inefficient. Actually, standard clinical ECoG electrodes often fail to measure cortical activity due to unconformable plain electrode sheets.

With these in mind, we aimed to create a high density array of electrodes designed to match the contour of an individual's brain surface as well as to place electrodes both on the gyral surface, and inside the central sulcus. In this article, we also describe the placement of patient-specific cortical electrodes into an ALS patient.

II. Methods

A. Electrode Sheets

1) *Sulcal Electrode Sheet*: We individualized the shape of the sheet containing the electrodes using a press mold system. Our method sandwiches the electrodes in-between silicone sheets individualized to fit the surface of an individual patient's brain.

Informed consent was obtained from healthy volunteers and patients, after authorization from the medical ethics committee of our institution. First we took a 1 mm thin-slice MRI series of the subject's brain. We then imported the MRI data into BrainVISA 4.0.2 (http://brainvisa.info/), where we ran the sulci extraction routine which allowed us to generate a 3D image of the brain surface, and also exudate the majority of the sulci (Fig. 1A). The 3D data of the central sulcus were then imported into two 3D computer aided designing (CAD) software (Mimics v14.12, 3-matic v5.1, Materialise N.V. Leuven Belgium). The surface data of the motor side was selected for further processing with 3-matic.

Next, sides were extended downward from the surfaces, after which, a base was then added to generate CAD data for a mold of the central sulcus. Then an inverse of this mold was produced, so that we now had both male and female molds. Holes were placed in the four corners of the base of the molds to allow for adjustments of the thickness of the silicon electrode sheets (Fig. 1A).

Using this data, we then used a 3D printer (Polyjet 3D printer, Objet Geometries Ltd., Israel) to create the actual molds (Fig. 1B). We marked the desired positions of the electrodes on the mold surface, with the surface facing the motor bank of the central sulcus having 35 electrodes while

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the surface facing the sensory bank had 15, since the primary motor cortex provides greater information on motor function. We also placed a higher emphasis on the hand-knob area in the form of higher electrode densities.

A silicone sheet (SILASTIC MDX4-4210) was then heated and placed on the mold. The silicone sheet was then carefully removed from the molds after cooling naturally to room temperature. The same process was repeated to produce 3 sheets; motor side, sensory side, and intermediate between these two. Next, holes were punched out for the electrodes at predetermined locations. Platinum electrodes were in-set into these locations. Flexible stainless leads (diameter 0.05 mm polyurethane coated, impedance ≤ 80Ω) were attached individually to each of the electrodes (impedance: electrodes ≤ 10Ω, lead ends (platinum) ≤ 10Ω). The lead wires passed through a silicone tube. To fix the electrodes, wires, and silicone tube, a silicone adhesive was added and the second silicone sheet placed on top and compressed in the mold (Fig. 1B). The process was repeated for the sensory side electrodes, the end result being 2 sets of plate electrodes sandwiched between 3 silicone sheets (Fig. 1C).

2) *Gyral Electrode Sheet*: Using the same process, we also created patient-specific gyral electrodes. These sheets were designed to have electrodes on only the side facing the cortical surface, and the locations and densities of the electrodes were tailored to match the functional areas of this surface. Next, the same 3D printing methods were used to create a model of the subject's brain to confirm that the manufactured electrodes fitted properly into the central sulcus, and onto the surface of the brain.

B. *Strength, Cytotoxicity and Biocompatibility Tests*

In order to test the safety of the electrodes before implantation into patients, we undertook the following tests.

1) *Physical Tests*: Prior to clinical trials, to test the strength of the sheet electrodes, a 3 dimensional sheet electrode (10 mm x 60 mm silicone electrode sheet with 50 mm x 1.3 mm diameter lead) was prepared and underwent dynamic tensile and compression tests (TENSILON RTF1250 (A&D), Gauge length 25 mm, stretching speed 500 mm/min, load cell 1kN, 10kN, 22°C 57% humidity).

2) *Cytotoxicity Tests*: Cytotoxicity tests were undertaken with concern to the effects of 3D-high density electrode extract on Chinese hamster fibroblasts (JCRB0603:V79) in accordance with the ISO 10993-5: 2009(E) Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity, ISO 10993-12: 2007 (E) Biological evaluation of medical devices - Part 12 : Sample preparation and reference materials standards, and other related Japanese protocols. In these tests, the sheet electrodes were broken down into 2 x 15 mm sections containing all the constituents of the electrodes. Ten mL of medium per 1g of morcellation was added to these sections and then, sealed, shielded from light, and cultivated with the Chinese hamster fibroblasts (JCRB0603:V79) for 24 hours. As positive controls, polyurethane films containing 0.1% and 0.25% zinc diethyldithiocarbamate (referred to respectively, as positive control A and B respectively) were used, while a high density polyurethane film was used as a negative control.

3) *Biocompatibility Tests*: 3D-high density electrodes and control materials (diameter 20 mm) were implanted subcutaneously into 12 male rats and then removed after 26 weeks to examine the effects of the subject material on the implanted rats. The electrodes and a control material were symmetrically implanted subcutaneously at the dorsal end of the spinal column while the subject was under intraperitonial anesthesia, with the electrodes implanted on the left side and the control (high density polyethylene sheet (1 mm x 50 mm x 100 mm) implanted on the right side of the scapula.

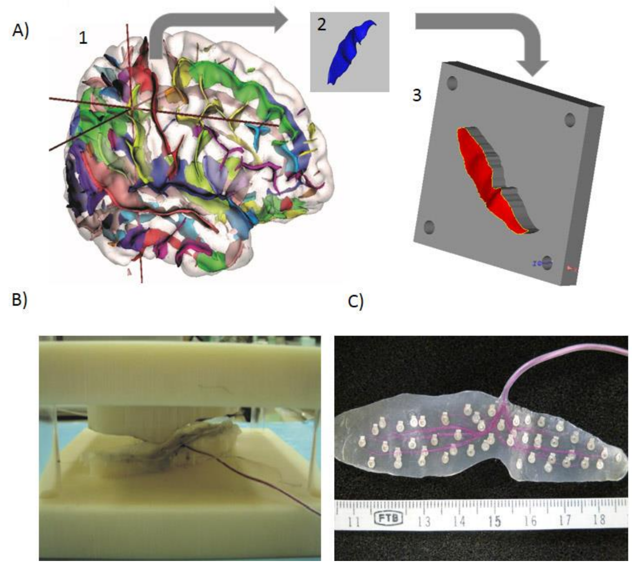

Figure 1. A) Sulci shown on a 3-dimensional image of the brain, generated with BrainVISA® from a subjects MRI data. CAD data of a mold created from the surface of the central sulcus was created with 3-matic®. B) Silicone sheet compression between male and female molds created with a 3D printer. C) A silicone sheet is created on the mold, and holes were made for electrode embedding. Flexible stainless leads were then connected.

C. *Clinical Test*

We designed 3D personalized electrodes for temporary implantation into an Amyotrophic lateral sclerosis (ALS) patient, as part of our clinical brain machine interface trial on severe ALS patients. The patient was a 61 year old male, who was only able to communicate using eye movement and a letter chart, or using an assistive communication device by a switch triggered by minute movements of the patient's lips. He had a total quadra-paralysis and was in a locked-in state. Informed consent was obtained. The trial was thoroughly reviewed and authorized by the medical ethics committee of our institution. Pre-operative magnetoencephalography (MEG) were undertaken to test the suitability of the patient, prior to electrode implantation.

IV. Results

A. *Electrode Sheets*

1) Central Sulcus Electrode Sheet: We were able to manufacture an array of electrodes with an inter-electrode distance between electrodes of 2.5 mm (a density of 16 times that of previous standard types), and we were able to create

sheet electrodes molded to fit inside the central sulcus with a total of 50 plate electrodes (35 facing the motor bank and 15 facing the sensory bank). The length of the central sulcus electrode shown is around 95 mm x 24 mm. Unlike the standard-type electrodes that we have previously placed within the central sulcus at our institution which were strip electrodes (4 x 1 electrodes) in one dimension, our patient-specific sheet electrode was 2 dimensional (11~17 x 2~3 electrodes). Distances from the surface of the sheet electrode to the mold were 2.2 mm and 0.1 mm at maximum length extremities, and 3.8 mm and 1.2 mm at maximum width extremities, with an average distance of 1.8±1.4 mm (mean±SD). The thickness varied between 0.81 ~ 0.96 mm at sampled locations. Using a 3D model of the same subject's brain, also created with the 3D printer, we confirmed that the electrodes fitted into the central sulcus.

2) Gyral Surface Electrode Sheet: The sheet shown here has 70 electrodes, which are located at various densities in accordance with anatomically perceived functionality, such as the hand-knob. As well as matching the contour of the patient's cortical surface, the sheet electrodes are softer than standard electrodes and are thus less invasive. They may also be placed over the top of the sulci electrodes to cover a predetermined surface of the brain.

B. Strength, Cytotoxicity and Biocompatibility Tests

1) Physical Tests: The electrodes passed the set strength level (silicone sheet 5N, leads 50N) tests with values of 9.58N for the silicone sheet, and more than 60N for the leads.

2) Cytotoxicity: Using the 100% negative control extract we confirmed that the number of colonies were almost unchanged. The IC50s for Positive Control A and B were 0.91% and 57.0% respectively. The IC50 for the positive control was 2.31µg/mL, thus indicating no strong cytotoxicity on colony growth.

3) Biocompatibility: One out of 12 rats showed slight swelling at the sites of implantation four days after sub-cutaneous placement. In this subject, swelling on the electrode implanted side continued for 41 days, while swelling on the control implanted side was also observed for 19 days. Superficial abnormalities disappeared after 20 days on the control implanted side and 42 days on the electrode implanted side but reoccurred on the electrode implanted side 175 days after implantation. Examinations after the completion of the test period indicated the presence of an abscess most likely due to infection at the time of implantation. None of the other 11 subjects developed abnormalities over the test period.

C. Clinical Test

In this clinical test, we designed only gyral electrodes. After the creation of gyral molds using our patient-specific method described previously (Fig. 2A), sheet electrodes were manufactured targeting mainly the primary motor cortex; 53 plate electrodes over the primary motor cortex with a higher density over the hand knob, 17 over the premotor cortex, and 24 over the somatosensory cortex (Fig. 2B). We used a neuronavigational system for presurgical planning and intraoperative navigation to determine the optimal site for craniotomy. Intraoperatively, we performed craniotomy at the pre-determined site, and identified the pre-operative anatomical features of the cortical surface (pre-central gyrus, and cortical veins etc.). We also reconfirmed the location of the central sulcus through N20 phase reversal of somatosensory evoked potentials. The sheet electrode was placed subdurally based on these pre-operative and intra-operative findings. The electrodes closely fitted the contour of the brain surface as was designed (Fig. 2C). Postoperatively, EEG monitoring showed that clear ECoG signals were obtained from all electrodes (Fig. 2D). Notably, localized high gamma band activity induced by motor imaginary tasks were clearly detected by the electrodes located over the hand-knob area (Fig. 3). During the clinical test, real time control of a robotic arm was also evaluated (not shown in this paper). The electrodes were removed as scheduled 21 days after implantation without any further deterioration in neurological symptoms.

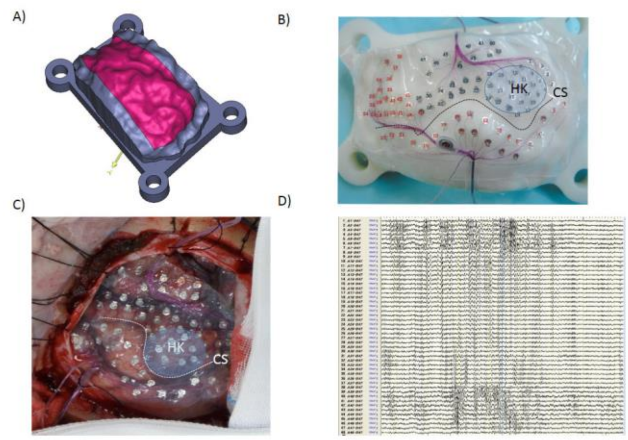

Figure 2. A) CAD model of ALS patient's brain surface covering S1, M1 and the pre-central gyri indicated in pink. B) Completed sheet electrodes placed on a brain surface model. CS indicates the central sulcus, and HK indicates the hand knob. C) Intra-operative image after placement of electrodes, with the white dotted line indicating the central sulcus and the hand knob area indicated in blue. D) EEG monitoring confirming signals attained from all electrodes.

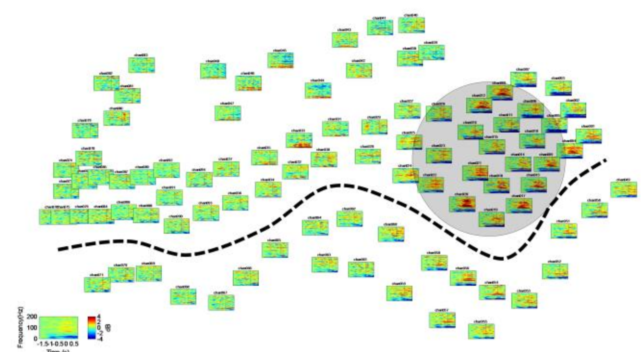

Figure 3. High gamma band activity on the cortical surface surrounding the central sulcus. Imaginary hand movement produces increased high gamma band activity in the areas surrounding the hand knob (shaded area).

V. Discussion

In the present study, by using semi-automated methods to map sulci and by utilizing CAD software and 3D printers, we were able to rapidly design and manufacture patient-specific cortical sheet electrodes with high spatial resolution for not only gyral but also sulcal implantation.

We obtained high quality signals from every electrode, including high frequency information after temporary implantation into an ALS patient.

Using our method, we were able to manufacture a sheet electrode array for placement into the central sulcus. Due to its patient-specific design, the electrode is less invasive than the standard sheet electrodes. Electrode locations can also be altered to provide higher densities within the central sulcus over areas such as the hand knob, and can be placed over the whole length of the central sulcus. Our electrodes also allow for electrodes to be placed in the direction of the motor bank, as well as the somatosensory bank, which may provide the opportunity for the sensory feedback required in close-loop systems [3].

Using the above method, we were also able to manufacture a sheet electrode for placement over the gyral surface. These sheet electrodes are patient specific and designed to match the individual surfaces of a patient's brain, thus meaning they apply less pressure at localized areas of contact than the previous types of flat 2-dimensional sheet electrodes, because all of the electrodes are in contact with the brain surface. This also means that compared to flat electrode sheets, there is a greater chance of attaining useful EEG from all electrodes.

It is also possible to increase the density of electrodes over cortical areas of higher importance, for example the hand knob. In our ALS patient trial, readable signals were obtained from all plate electrodes on the implanted sheet. It is noteworthy that we were successfully able to gain gamma-band information from specific functional areas such as the hand knob. Our high density electrodes successfully detected a variety of gamma band activities that differed from electrode to electrode despite electrodes being in close proximity (approximately 3 mm inter-electrode spacing) to one another.

The power of high gamma-band information is weak and it is difficult measure this range using standard forms of scalp EEG or MEG. On the other hand we have previously shown that gamma-band activity is useful for predicting motor activity using standard sized cortical electrodes [4], [5]. Using the high-density patient-specific cortical electrodes described in this study, we were able to measure gamma-band activity with high spatial resolution even in an ALS patient with complete paralysis.

Regarding safety, we have successfully completed the non-clinical studies necessary to move on to clinical trials, including those related to physical strength, cytotoxicity, and biocompatibility, as well as long term stability. In our ALS patient clinical trial we implanted our sheet electrode for 21 days, with no new neurological symptoms incurred after electrode removal. We will continue clinical evaluations to confirm the safety and efficacy of these sheet electrodes, moving towards the implantation of a fully-implantable wireless system [6].

VI. Conclusion

We developed a high-density patient-specific sheet electrode that fit within the sulci or on gyral surfaces. They are designed and rapidly manufactured with semi-automatic methods involving the use of a 3D-printer and resulted in the effective attainment of ECoG signals. We temporarily placed this patient-specific sheet electrode into an ALS patient and were able to attain readable signals from all plate electrodes and measured localized high gamma band activity in the hand knob area. We believe that this sheet electrode will contribute to higher performance BMI systems.

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