Published in final edited form as:

J Neurosci Methods. 2017 February 01; 277: 21–29. doi:10.1016/j.jneumeth.2016.12.005.

A testbed for optimizing electrodes embedded in the skull or in artificial skull replacement pieces used after injury

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Abstract

Background—Custom-fitted skull replacement pieces are often used after a head injury or surgery to replace damaged bone. Chronic brain recordings are beneficial after injury/surgery for monitoring brain health and seizure development. Embedding electrodes directly in these artificial skull replacement pieces would be a novel, low-risk way to perform chronic brain monitoring in these patients. Similarly, embedding electrodes directly in healthy skull would be a viable minimally-invasive option for many other neuroscience and neurotechnology applications requiring chronic brain recordings.

New Method—We demonstrate a preclinical testbed that can be used for refining electrode designs embedded in artificial skull replacement pieces or for embedding directly into the skull itself. Options are explored to increase the surface area of the contacts without increasing recording contact diameter to maximize recording resolution.

Results—Embedding electrodes in real or artificial skull allows one to lower electrode impedance without increasing the recording contact diameter by making use of conductive channels that extend into the skull. The higher density of small contacts embedded in the artificial skull in this testbed enables one to optimize electrode spacing for use in real bone.

Comparison with Existing Methods—For brain monitoring applications, skull-embedded electrodes fill a gap between electroencephalograms recorded on the scalp surface and the more invasive epidural or subdural electrode sheets.

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Conclusions—Embedding electrodes into the skull or in skull replacement pieces may provide a safe, convenient, minimally-invasive alternative for chronic brain monitoring. The manufacturing methods described here will facilitate further testing of skull-embedded electrodes in animal models.

Keywords

cranioplasty; brain monitoring; skull-embedded electrodes; brain-machine interface (BMI); impedance; electrocorticogram (ECoG); traumatic brain injury (TBI)

1. Introduction

Cranioplasty with artificial bone replacement material is often used after a traumatic brain injury to replace skull sections that are damaged beyond repair or used after therapeutic bone removal in response to infection, tumors, or cranial swelling¹. For large repairs, artificial skull replacement pieces are often custom manufactured for each patient using their own computer tomography (CT) scans to ensure each person's replacement piece closely replicates their natural cranial space and forms a smooth transition to the intact skull¹.

The ability to chronically monitor brain health and watch for epileptic activity development would be quite useful after brain trauma or surgery^{2,3}. However, continuous brain monitoring via scalp surface electroencephalograms (EEGs) can be cumbersome and impractical outside of the clinical setting and may not be possible if the skin is not healthy enough after injury to safely apply the electrodes. Chronically implanting recording electrodes, such as electrocorticographic (ECoG) arrays, within the cranial cavity would allow for more stable long-term brain monitoring but would also increase the risk of further inflammation, contusions and/or infarcts⁴. A low-risk alternative that avoids placing invasive electrodes on damaged brain tissue would be to embed electrodes within the artificial skull replacement piece itself. Custom-fabricated skull replacement pieces have been manufactured from a number of non-conductive materials that are well suited to house conductive recording electrodes (e.g. polymethyl methacrylate (PMMA)^{5,6}, polyetheretherketone (PEEK)^{7,8}, polypropylene polyester^{9,10}, bioceramic porous hydroxyapatite^{11,12}). Electrodes can be embedded within the artificial skull so that the recording contacts are flush with the inner lumen of the skull to avoid any protrusions into the cranial cavity that might cause pressure and further damage.

Electrodes embedded in one's natural skull could also be useful for many applications. Improvements in real-time neural recording and signal processing technology have spawned the development of a number of 'closed-loop' neural recording applications that could all benefit from a stable permanently-implanted but minimally invasive recording option like embedding electrodes within the skull. For example, chronic brain recordings are being investigated as a means to detect upcoming seizures in time to either warn the person or take measures to counteract the seizure^{13–15}. Brain-machine interfacing research has shown that paralyzed individuals can learn to volitionally modulate their sensorimotor field potentials with thoughts of movement, and this modulation can be used to control assistive or therapeutic devices^{16,17}. For people who are fully paralyzed or 'locked-in', maintained

cognitive and sensory responses in their cortical field potentials may be used to drive much needed communication programs^{18,19}. Additionally, researchers are investigating the use of recorded brain activity to continuously update deep brain stimulation settings to more effectively reduce symptoms of Parkinson's disease while minimizing side effects and power consumption^{14,20–22}.

In spite of the many potential advantages of embedded electrodes into artificial skull replacement pieces or directly in intact bone, work on chronic skull-embedded electrodes in primates or humans has been relatively limited²³. The appropriate number and distribution of electrodes still need to be optimized for each specific neurotechnology application. Additionally, unlike subdural or epidural ECoG electrodes that should be thin and flat, skull embedded electrodes can have more elaborate conductive surface structures including conductive channels that extent up into the skull to increase the surface area for charge transfer while maintaining a small contact diameter and high spatial resolution along the inner lumen of the skull. Exploring this electrode design space will require a testbed that allows for comparisons between different individual electrode geometries and comparisons of different spatial distributions of electrodes.

This paper describes how to make and attach a custom-fitted skull replacement piece with embedded electrode arrays in a large animal model. Methods described here can be used as a preclinical testbed to facilitate further development of skull-embedded electrode technology for future use in human. The arrays described are also suitable for use in basic science research in animal models.

We also show how to manufacture a number of different prototype electrode contact designs that make use of the skull's depth dimension to increase each recording contact's surface area while maintaining a constant footprint and spatial resolution along the inner lumen of the skull. Finally, we demonstrate how an artificial skull piece with a high density of electrodes can be used to compare different electrode density options for a desired application simply by comparing different subsets of the available channels. Electrodes embedded in natural bone have to be far enough apart to maintain the health and integrity of the skull. Therefore, the higher density of electrodes that can be installed in this artificial-skull testbed allows one to test out different subsets of contacts to compare different spacing option before deciding on a distribution of electrodes to embed in natural bone.

2. Materials and Methods

2.1 Design Manufacturing

As part of other ongoing studies, two Rhesus macaques were chronically implanted with custom acrylic skull replacement sections containing an integrated 8x8 grid of electrodes designed to record epidural field potentials at the inner lumen of the skull. These skull replacement electrode arrays (SREAs) were custom manufactured to match the curvature of each animal's skull using CT scans to determine precise bone geometry. One animal was sequentially implanted with two different SREAs (designs I and V) and a second animal was sequentially implanted with three different SREAs (designs II, III, and IV). With each new version, the embedded electrodes themselves were modified to alter the surface area and

impedance of the recording contacts while still maintaining a similar spatial resolution over the cortical anatomy. Figure 1A shows the cortical anatomy spanned by the 8x8 electrode grids in all five SREA designs.

To make custom-fitted SREAs for each animal, three dimensional (3D) computer models of the skull and brain were first generated from the computer tomography (CT) and magnetic resonance imaging (MRI) data respectively (figures 1B & C). The software package ‘monkey Cicerone’^{24,25} was used for visualizing the co-registered 3D macaque skull and brain images so that we could customize our SREAs to fit over the premotor and primary motor cortices associated with upper limb function. However, upon inspection of the skull model, we found that the skull model itself contained pronounced ridges and valleys reflecting the underlying anatomical landmarks. Therefore, the MRIs were not essential in this non-human primate model as the CT alone turned out to be sufficient to identify the desired skull section on which to base our SREAs for placement over the desired upper limb cortical locations. Co-registered MRIs may still be useful in other large animal models where the internal skull surface does not reflect the brain surface anatomy as clearly.

The skull replacement portion of the SREA could potentially be manufactured from the computer model directly via rapid prototyping if one is lucky enough to have a local rapid prototyping service that works with biocompatible non-conductive plastics. If that is the case, Solidworks or other 3D software can be used to trim down the computer model of the skull to the desired final SREA shape and to configure holes in the skull replacement piece for insertion of the electrodes once the replacement piece is made (see hypothetical example in figure 1D).

Most researchers, however, typically only have access to rapid prototyping services that use non-biocompatible plastics. Therefore, in this paper, we describe the ‘indirect’ manufacturing method where skull models are first 3D printed with non-biocompatible plastic. Rubber molds are then made from the plastic skulls and the molds are then used to make the final SREAs out of biocompatible acrylic. In this study, external connectors were used in our animal model. Therefore, rubber molds were only made from the intracranial side of the plastic skull because only the inner surface of the SREA needed to match each animal’s inner skull surface geometry. A protective metal chamber mounted over the SREA housed the exposed leads and connectors on the external side of the SREA.

To start, full 3D computer models of the skull were generated for each animal by importing the Digital Imaging and Communications in Medicine (DICOM) standard files into Mimics 3D imaging software (v14.12, 3-matic v5.1 by Materialise N.V. Leuven Belgium). Extraneous or non-contiguous bone segments were manually deleted. Plastic models of the entire cranium were 3D printed (40µm horizontal and 16µm vertical resolution; Objet Eden 260, Stratasys) from the .stl files exported out of Mimics (figure 2A). Having the full 3D skull model was helpful for planning placement of the connector chambers and mounting hardware although only part of the skull model was needed for making the SREA.

Next, silicone rubber (Silicones Inc. # 30094, North Carolina) was poured inside the plastic skull model over the target SREA area to generate a mold of the inner lumen of the skull

(figure 2B). Just enough silicone was included to ensure the target area was covered while still keeping the rubber section small and flexible enough to extract from the hard plastic skull.

Design I—In our initial design, seven-stranded, stainless steel, perfluoroalkoxy (PFA)-coated wires (#793500 A-M Systems; combined Bare Diameter= 0.006 in.; diameter of individual strands =0.002 in) were simply threaded through the rubber mold of the intracranial cavity using a sewing needle (figure 2C). Once the 8x8 grid of wires were inserted, liquid methyl methacrylate acrylic resin (Ortho-Jet powder and liquid mixture, Lang Dental) was then drizzled over the mold surface and allowed to cure thus locking the wires in place. After the acrylic cured, the rubber mold was removed, and the excess acrylic edges were trimmed to the desired final area for the SREA. The wire ends extending out of the intracranial side of the SREA were cut flush with the acrylic using a scalpel. This process left just the cross-sectional area of the multistranded wires as the recording contact surface on the intracranial side of the SREA.

Design II—In the second design, a small section of the same seven-stranded wire was deinsulated near the end of each wire. A ~2mm loop of the deinsulated wire was manually inserted into slits in the rubber mold (figure 2D). As in the first SREA, once the 8x8 grid of wires were arranged in the rubber mold, dental acrylic was poured over the mold and allowed to cure. The excess acrylic around the grid was then trimmed away. The small loops of deinsulated seven-stranded wire protruding from the intracranial side of the SREA were then manually pushed flush against the acrylic (figure 2D inset). With this version, the potential area for charge transfer during recording consisted of nearly the entire outer surface of the seven wires over the entire distance the wire loops protruded from the intracranial side of the SREA. However, in this method, the inner luminal surface was not smooth since the wires still protruded somewhat from the acrylic in spite of being pushed flush against the acrylic.

Design III—In this version, a thin ~2–3mm sheet of the same acrylic was poured directly over the mold without first embedding any wires in place. Holes approximately 1mm in diameter were then drilled through the hardened acrylic in the 8x8 grid pattern. The same seven-stranded stainless steel wire was deinsulated at the ends to about 5mm and inserted fully into 1mm diameter stainless steel tubes cut from the ends of 19 gauge blunt hypodermic needles (Kahnetics® KDS1912P) as illustrated in the left tube of figure 2E. The tubes were then crimped onto the bare wire on one end to form a secure connection between the tubes and wires. The open ends of the tubes were then inserted into the pre-drilled holes in the acrylic, so that the open end was flush with the intracranial side of the SREA. This tube and wire structure provided a large amount of surface area for charge transfer while still maintaining a small footprint for each electrode on the intracranial side of the SREA (i.e. all the surface area of the seven deinsulated wires as well as the tube's inner lumen and cross-sectional end). Additional acrylic was poured over the outer extracranial surface of the SREA to fully cover and lock in place the metal tubes as well as insulate the bare metal surface of the extracranial tube ends.

Design IV—Designs III and IV were very similar with only two differences. First, instead of crimping a single length of deinsulated seven-stranded wire into the steel tube, the tube was crimped onto a loop of deinsulated wire thus providing twice as much wire surface area for charge transfer (illustrated on the right in figure 2E). Second, instead of drilling holes in the dental acrylic after curing, holes were formed in the SREA base during the initial curing process. Specifically, the tips of sharp 19 gauge hypodermic needles were first cut off from their connectors and inserted into the rubber mold (figure 2F). Once the 8x8 grid of needles were in place, the acrylic was poured over the mold. After curing, the mold and all hypodermic needles were removed leaving a thin ~2–3 mm sheet of acrylic with an 8x8 grid of 1mm diameter holes. Figure 2G shows a close-up of the resulting acrylic piece with four of the holes already filled with the loop-n-tube electrodes. As in design III, once the tubes were in place, additional acrylic was used on the extracranial side to lock everything in place and insulate any exposed metal surfaces.

Design V—Similar to design IV, in this final version, an acrylic base with an 8x8 grid of 1mm holes was made using the silicon mold with inserted hypodermic needles. However, instead of inserting steel tube electrodes into the pre-made holes in the acrylic base, this final electrode design used ~1mm diameter solid stainless steel rods for electrodes (316LVM stainless steel 0.04" diameter wire cut to ~5mm lengths, Amazon/Small Parts). Laser etching was used to microtexture the recording ends of 32 of the rods to increase the surface area for charge transfer. Specifically, prior to assembly, one end was laser etched using a LPKF ProtoLaser S (LPKF Laser & Electronics, Tualatin, OR) by cutting 15-micron-wide bands approximately 40 microns apart. This band pattern was etched twice in perpendicular directions resulting in a grid pattern (figure 2H, inset). Only 32 of the 64 electrodes were laser etched in this manner so the plain versions could be used for comparison. The etched and smooth electrodes were arranged in an alternating pattern in the usual 8x8 grid within the acrylic bone replacement piece. In order to attach connecting wires to the extracranial side of the rods, short pieces of 17 gauge 316 stainless steel tubing (Amazon/Small Parts) were used to crimp the seven-stranded stainless steel wires onto the extracranial ends of each rod. The crimped connections were covered with additional acrylic, and the excess acrylic trimmed away to form a compact SREA that fit within the craniotomy (completed SREA shown in figure 2H).

For all versions, the 64 multistranded stainless steel connecting wires were soldered to two 32-channel ZIF-clip adapters as can be seen in figure 2H (Tucker Davis Technologies, Gainesville, FL). Connectors were arranged to fit within a protective steel chamber (Crist Instruments Co. Inc, Hagerstown MD). In design versions I–III, deinsulated ground and reference wires for each connector were simply placed along the edges of the craniotomy during SREA implantation. However, in versions IV and V, an extra pair of recording electrodes was embedded in the SREA just on either side of the 8x8 grid for use as reference channels when recording. During impedance testing, low-impedance deinsulated ground wires were used for the return path.

2.2 Implantation

All activities in this study were approved by the Cleveland Clinic Institutional Animal Care and Use committee and adhered to all federal regulations. For implantation, a craniotomy just large enough to fit the SREA was made over the upper-limb motor/premotor cortex. A layer of GelFoam absorbable dental sponge (Pfizer pharmaceuticals) was placed over the dura, and the SREA was inserted into the craniotomy with the inner surface of the SREA lying approximately flush with the inner lumen of the skull. The deinsulated ground and reference wires (or just grounds in designs IV and V) were tucked into the craniotomy along the outside edges of the SREA being careful not to let the different ground/reference wires touch and short together. Additional strips of GelFoam were placed into the craniotomy around the edges of the SREA to fill any remaining gaps. Methyl methacrylate acrylic resin (Ortho-Jet powder and liquid mixture, Lang Dental) was then poured over the extracranial surface of the SREA and surrounding skull to seal off the craniotomy and affix the SREA in place.

A mix of titanium bone screws and bone connector strips consisting of a series of connected metal rings (Stryker, Kalamazoo, MI) were used to further secure the SREAs in place (designs I and II only used bone screws with the screw heads extending up into the acrylic). For designs III–V, one end of each connector strip was secured to the skull underneath the skin, which formed a tight stable bond over time. Multiple connector strips were used per implant based on space available. We did not have any issues with the skin receding away from these metal strips as has been suggested by others²⁶. A metal protective chamber was fitted over the SREA, and additional acrylic was used to hold the connectors in place within the chamber and to secure the chamber to the screws and connector strips. Figure 3 illustrates how the hardware and dental acrylic were used to form a secure, stable, percutaneous connection to the SREAs.

When replacing SREAs with newer versions, the old acrylic was first carefully removed using a hand-held Dremel. When possible, well-integrated bone connector strips and screws were left in place and reused. New screws and bone connector strips were installed only as needed. With all SREA replacement procedures, a fresh layer of dissolvable GelFoam was placed over the dura and packed in the craniotomy around the edges of the SREA before new acrylic was applied.

Macaque 1's reimplantation with a second SREA (design V) took place almost two years after the first (design I) although the first had stopped recording usable signals about a year earlier. Upon removal of the first SREA, it became apparent the skull had partially regrown under the original SREA thus pushing the SREA partially out of the original craniotomy (recall only bone screws were used to affix this first headcap to the skull). Granulation tissue had filled in the additional space under the raised acrylic cap. This granulation tissue was removed and the animal's craniotomy resized before the replacement SREA was installed.

2.3 Impedance measures

For each SREA design, impedance spectroscopy was periodically performed where the impedance was measured across different channels over a range of frequencies using

Autolab potentiostat (PG-STAT12, Eco Chemie, Utrecht, Netherlands; standard two-cell configuration with a working electrode and ground). The range of frequencies at which impedance was tested varied during different sessions as part of a separate much larger impedance spectroscopy study that spanned both intra and extracortical electrodes. Reporting the full impedance spectroscopy results is beyond the scope of this electrode manufacturing methods paper. Therefore, we focus our analysis in this paper on the one frequency at which impedance was consistently collected across all SREA designs—1.3KHz.

The animals were implanted with these SREAs as part of other brain-machine interface and cortical signal analysis studies. Electrode designs were updated based on the needs of these other ongoing studies. Impedance was collected intermittently depending on time available and the requirements of the other ongoing studies. In any given session, impedance was often only tested on a subset of channels due to time constraints, and the subset measured was alternated on different sessions. Impedance and the number of failed electrode channels was assessed over two post-implant time ranges: less than three months post implantation versus greater than eight months post implantation. These two epochs capture initial impedance characteristics likely to be seen in short-term monitoring applications as well as the impedance values and the likely electrode failure rates one should expect in more chronic recording applications.

Some electrode channels had abnormally high impedance values suggesting a bad connection somewhere between the recording contacts and the ground. We conservatively defined a ‘failed channel’ as any channel with a 1.3KHz impedance value greater than ten times the median value of all contacts for that particular electrode design collected during the first epoch where impedance data was recorded.

2.4 Using high-density SREA’s to compare electrode spacing options

Artificial skull replacement pieces can be made with a very high density of electrode contacts. However, electrodes embedded in natural skull need to be far enough apart to maintain good vascularization of the bone. By using a high-density of contacts in an SREA during the initial phase of electrode development, one can evaluate different subsets of the available electrodes to optimize the location and/or spacing of a smaller numbers of electrodes for a given application prior to trying electrodes in the natural skull. Here we give a simple example of how one could compare electrode density options by evaluating subsets of electrodes taken from the high density of contacts available with the artificial SREAs.

This demonstration makes use of data collected as part of another ongoing study where animals performed target-directed reaching movements when SREA’s I–III were installed. We have previously reported results from optimizing arm movement decoding from these data when all available channels were included in the optimization process²⁷. Here we extend the analysis to assess how well one could decoded arm movements when the density of electrodes over the arm area was reduced by half or reduced to 1/8th. Figure 4 shows the three density options compared. Note in the half-density option, both possible subsets of 32 electrodes with the indicated spacing were analyzed separately and the results averaged. In

the 1/8th density option, all possible subsets of eight electrodes with the illustrated spacing were analyzed separately and the results averaged for each recording session.

A total of 63 recording sessions of brain and arm movement data were evaluated using the same decoding optimization steps previously reported in Marathe et al. for the full-density SREA²⁷. In this analysis, we compared using all 64 channels vs. using only 32 or 8 raw signals in the optimization process. As we have previously reported, the optimization process used recursive signal selection and cross-validation to ensure performance results were not artificially inflated due to overfitting the many possible features from the high-density data. Our previously reported results already showed optimal decoding was achieved when more features were used than would be available in the 1/8th density option. However, to more fairly compare decoding differences that can be attributed directly to electrode *spacing* and not just due to the differences in the total number of electrodes and features used for decoding, in this analysis, we capped our decoders to all use the same number of features (i.e. the best eight processed signals produced by common spatial pattern analysis – *times*– the same seven fixed power bands per signal – *equals*– 56 total features regardless of electrode density).

3. Results

3.1 impedance results

The box and whisker plots in figure 5 show the median and upper/lower quartiles of the 1.3 KHz impedance values from all intact measured contacts combined across all data collection sessions during the early versus late post-implantation epochs.

As anticipated, simply cutting multistranded wire flush with the SREA's intracranial surface (design I) resulted in the highest impedance with a starting median value over 10KOhms. This impedance also doubled by the time this particular SREA was retested before explantation almost two years later. This substantial impedance increase was likely due to the ingrowth of bone under the SREA before we implemented the more stable implantation method shown in figure 3. Electrodes affixed to the skull as in figure 3 did not experience the same bone ingrowth.

Using a small loop of the same deinsulated multistranded wire in design II was somewhat successful at lowering the impedance below that of design I, but not by the large amount expected based on the larger exposed surface area. During explantation of design II, we observed that the wires had left tough thickened impressions in the dura suggesting a tight layer of scar tissue had formed focally around each wire loop that protruded into the intracranial cavity. This tight tissue encapsulation of the wires may have offset some of the impedance reductions expected from the larger exposed wire surface in design II.

The wire-in-tube design options were more successful at lowering the impedance, although the benefits of looping the wire in design IV were minimal (3.7 versus 3.4 KOhms for designs III and IV respectively in the early epoch).

Laser etching the intracranial surface was also an effective way to increase surface area and reduce impedance compared to the equivalent un-laser-etched contacts (i.e. 3.4KOhms for laser-etched vs. 4.9KOhms for flat; distribution of the daily medians was significantly different at $p < 0.004$, ascertained via a two-sample Kolmogorov-Smirnov test). However, this relative difference between the flat and laser-etched electrodes disappeared in the later epoch ($p = 0.4$), which may have been due to tissue growth filling in the tiny spaces on the laser-etched surface.

3.2 Electrode failure assessment

To assess how well different electrode designs held up over time, figure 6 shows the percentage of the measured channels that were considered bad connections in each epoch during each data collection session (i.e. had impedances > 10 times each design's starting median value). The individual black dots indicate the daily percentages and horizontal bars indicate the means of these percentages across days. Note the variability in this metric can come from true changes in the number of bad channels over time as well as changes in which channels were measured during each session. Recall, on some days, impedance was only collected on a subset of the electrodes if time was limited. This practice could make this percent-bad-channel metric go up or down depending on if the bad channels were in the recorded or skipped subset for that day. Generally, the channels skipped due to time limitations would be varied on different days so that the mean value of this metric would be a reasonable estimate of the overall metric for each SREA.

Note the first two designs that only used the multistranded wire had lower failure rates compared to designs that required crimping tubes or rods to the wire (designs III–V). All crimped designs had a higher percentage of bad channels initially and that percentage increased over time. Design V was the most unstable with almost half of the electrodes failing by the later epoch.

3.3 Electrode density comparisons

The electrode density analysis showed that electrode density did have a significant impact on the accuracy with which arm position could be decoded from electrodes located at the inner lumen of the skull. As with our previous analysis in Marathe et al²⁷, both Kalman filtering and optimal linear estimation were assessed. For Kalman filter analysis, when all electrodes were included in the decoder optimization process, decoding accuracy (as measured by R^2) was 10% better (higher) than with the half density electrode distributions and 38% higher than with the one-eighth density configurations in spite of using the *same* number of features for decoding in all case. Even more benefits of high-density spacing were seen when decoding with optimal linear estimation. The high-density spacing performed 16% better than half-density, and 71% better than one-eighth density. Paired t-tests showed all differences were significant with $p < 0.0001$.

4. Discussion

In this paper, we describe manufacturing methods for a preclinical testbed to further the development of skull-embedded electrode technology. The testbed described here can be

used as a starting point to efficiently refine electrode designs for incorporating electrodes into pre-formed artificial skull replacement pieces, such as those used after traumatic brain injury, or for implantation into natural bone. Embedding electrodes in real or artificial skull should enable the detection of brain signals with a spatial resolution somewhere between that of electroencephalograms (EEGs) and electrocorticograms (ECoGs)²⁸. For brain monitoring applications that don't require the resolution only attainable with more invasive recording options, skull embedded electrodes have a lot of advantages—especially for chronic or continuous monitoring applications. Unlike EEGs, which can be unsightly, uncomfortable, and difficult to put on and maintain outside of a clinical setting, skull embedded electrodes provide a more permanent option that can provide continuous stable recordings potentially for days, months, or even years. If coupled with a fully-implanted wireless transmitter, skull embedded electrodes could be a safe, comfortable, discreet alternative to EEGs. Additionally, with proper electrical insulation, skull-embedded electrodes could potentially bypass the problems with artifacts from scalp muscles that often overpower EEG recordings.

For people who need a section of skull replaced due to injury or disease, building electrodes directly into the artificial skull replacement piece could provide continuous brain monitor with little additional risk. Being able to monitor brain health and the development of seizure activity is particularly useful after a traumatic brain injury^{2,3}. After injury, putting electrodes, such as ECoG arrays, within the cranial cavity could potentially compound the injury by causing additional irritation and damage⁴. Embedding electrodes in one's artificial skull replacement piece so that the recording contacts are flush with the inner skull surface would help to avoid excess pressure and irritation to the dura and brain.

In this study, only design II had any part of the electrode extending into the cranial cavity. Even though the wires that extended into the cranial cavity were small (~0.006 inches in diameter) and were pushed flat against the inner skull surface, we still saw focal thickening and scarring of the dura just around each wire loop location upon explantaion. This focal scarring at each contact was not seen in any of the other explanted designs. This observation suggests that extending the contacts into the cranial cavity even a little bit can cause irritation and dural scarring over time.

One important but underexplored advantage of skull-embedded electrode technology is that the skull depth dimension perpendicular to the cortical surface can be used to increase the recording contact surface without increasing the contact area parallel to the cortical surface. Making use of this depth dimension has the potential to improve recording resolution in two ways. Adding surface area in the depth dimension enables one to lower impedance, which will reduce thermal noise interference. Maintaining a small contact sizes parallel to the cortical surface is also key to maximizing spatial resolution because smaller contacts enable one to use a finer grid of electrodes over an area of interest.

This ability to increase surface area without sacrificing spatial resolution also has advantages for cortical stimulation applications such as stroke rehabilitation²⁹, seizure disruption³⁰, chronic pain³¹, and psychiatric disorders^{32,33}. When stimulating, the amount of current that can safely be delivered is limited by electrode surface area because the current density has to

be maintained within the electrode's safe limits to prevent degradation of the metal and tissue damage. Using the skull depth dimension to increase electrode surface area may enable one to chronically deliver higher levels of more focal current than with equivalent flat electrodes with the same small cross-sectional footprint.

In this study, designs III, IV and Vb, made use of this depth dimension to increase surface area and all three of these designs had the lowest starting impedance values. However, the impedance benefits of the laser etched design (Vb) over its flat counterpart (Va) disappeared in the later epoch which may be due to tissue ingrowth and encapsulation throughout the tiny microscale crevices etched onto the contact surface. Although design III had a slight increase in impedance in the later epoch, the much deeper channels in the wire-in-tube design may be more resistant to encapsulation as they did not appear to be filled with tissue upon explantation.

Most of the individual prototype electrode designs evaluated in this study could be further developed for use in either natural bone or artificial bone replacement pieces. However, even if one's goal is to develop electrodes only for use in natural skull, the artificial-skull testbed described here has several advantages for use in the early stages of electrode development. In order to maintain the health and integrity of natural bone, electrodes have to be far enough apart to maintain good vascularization of the surrounding bone. The acrylic testbed described here allows for a higher density of electrodes than would be feasible for use in natural bone. Using this high-density acrylic testbed can speed up the initial electrode refinement process by generating more side-by-side comparisons of different electrode designs within the same animal, same cortical locations, and even sharing the same connectors and ground/reference channels. By testing multiple electrode designs within the same high-density SREA, many of the confounding factors that would normally add variability to the collected data can be accounted for thus reducing the number of data samples and animals needed for testing.

For example, in design V, we compared two different electrode surface treatments with a large sample size of 32 electrodes for each treatment using just one animal. The high-density of contacts possible in this acrylic testbed enabled us to collect data on a much larger number of electrodes than would be possible to safely implant in the same postage-stamp-sized region of natural skull. The two electrode types being compared were evenly interspersed over the same small brain region using shared connectors and shared references/grounds. This configuration ensured that any variability in the day-to-day differences in how well the cables/grounds were connected would impact the impedance of both types of electrodes equally thus allowing us to use more robust paired statistics on the daily median values to assess the *relative* impedance differences between electrode types.

The fact that both etched and flat contacts in design V used the same grounds/references and shared the same connectors turned out to be particularly important in this design, which was prone to failure over time. This failure was likely due to mechanical weakening of the crimping tubes used to connect the electrode rods to the wire connector leads. Figure 6 shows that both the flat (Va) and etched (Vb) designs had similar distributions of bad channels across days in the later epoch, which would be consistent with degradation of the

common grounds/references and/or poor attachment to a shared connector. Future electrode designs could be improved by the use of biocompatible conductive epoxy instead of or in addition to any type of crimp joints.

Figure 5 reveals two things about design V. First, the initial impedance benefits of laser etching seen in the early epoch disappeared by the late epoch, and second the median impedance of both types of electrodes appeared to decrease over time. This unexpected impedance drop can be explained by the fact that, in both groups, the electrodes that failed started out with higher impedances (i.e. weaker connections) to begin with. Therefore, when these weak, higher-impedance electrodes finally failed, they were dropped from the median calculation thus causing this median impedance metric for each group to decrease.

Additionally, the lab and all its equipment were moved and impedance cabling was updated between the early and late epochs of design V. Therefore, we can't rule out that these system changes may have also contributed some bias in the impedance measures. Again, these technical factors should have affected the flat and laser-etched electrodes equally, so the *relative* differences between electrode types should still be valid even if the absolute values may reflect some offset in the measurements.

An additional advantage of performing initial electrode development in this high-density acrylic testbed is the ability to compare the usefulness of different subsets of the higher-density electrodes when planning to use a lower-density electrode distribution in natural bone in subsequent subjects. Again, by initially collecting high density data in an artificial skull, one can remove the confounds of variability in animal behavior, attention, and brain state by comparing different subsets of data collected from the same animal over the same time period.

In the arm-movement decoding example tested here, we were able to estimate the trade-off between electrode density and the accuracy with which one can decode arm position. In this case, we showed the accuracy of arm movement prediction significantly declined even when electrode density was just cut in half and really suffered with the one-eighth density option. While the results from this analysis suggest the higher-density of electrodes available with an artificial skull piece would provide better movement control for brain-computer interfacing applications, the quantifiable comparison data can be used to weigh the risks and benefits of proceeding with an artificial-skull or natural-skull approach for the companies developing the technology and the end users deciding between options.

Although the testbed described here was intended for initial preclinical development of skull-embedded electrode technology, the methods described could be used 'as is' for animal research in basic science studies as well. As shown in this study, the high density of contacts was useful for maximizing the information extracted about arm movements from motor cortex. For long-term research studies, an epidural electrode location may be just as useful as a subdural electrode placement given the tendency for tissue growth under electrode arrays placed subdurally over time³⁴.

In this initial phase of animal testing, we used percutaneous connectors, which enabled us to focus on refining and evaluating the electrode array itself as well as testing how useful the

signals would be for closed-loop cursor control applications²⁷. Having direct access to connectors gives one the ability to easily switch between recording, stimulation, and impedance spectroscopy as needed, although wireless interfaces with similar capabilities are now under development³⁵. For chronic human use, a fully implanted wireless transmitter and power source will be needed for most applications, and many research groups are developing wireless transmission and power systems with the capacity to handle the numbers of channels and sampling rates appropriate for skull embedded electrode systems^{35–37}. These advances in wireless technology make further development and evaluation of skull-embedded electrodes for human use a worthwhile endeavor, and this preclinical testbed can help facilitate that development process.

Acknowledgments

We would like to thank Ryan Klatte, Dave Dudzinski, and Barry Kuban of the Cleveland Clinic engineering and electronics cores for their assistance in generating the plastic skull models and laser etching the electrodes. We would also like to thank Drs. Andre Machado and Jorge Gonzalez-Martinez for their neurosurgical perspective on practical applications as well as Tina Emancipator, Erin Bynum, Jacob Cox and Loren Schmidt for their surgical assistance and assistance in data collection. Finally, we would like to thank our funding sources: National Institutes of Health NINDS R01 NS058871, the China Scholarship Council fellowship No.2010625038, and the Cleveland Clinic. The views and conclusions contained in this document are those of the authors and should not be interpreted as representing the official policies, either expressed or implied, of the Army Research Laboratory, U.S. Department of Veterans Affairs, or U.S. Government. The U.S. Government is authorized to reproduce and distribute reprints for Government purposes notwithstanding any copyright notation herein.

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Highlights

- A preclinical testbed is demonstrated for embedding electrodes in artificial skull
- Options are explored for increasing electrode surface area using the skull depth
- Novel electrode designs could also be embedded in the bone directly via burr holes
- The testbed's high contact density allows one to optimize electrode spacing
- High density of contacts possible in artificial skull improves movement decoding

Figure 1.

A) The 8×8 grid of dots indicate the approximate placement of the 64 recording channels of all SREAs used in this study. The implant location was chosen to target upper-limb areas of the motor and premotor cortices for other ongoing studies (ArS = arcuate sulcus; CS = central sulcus). B) Example 3D macaque skull computer model generated from a CT scan. C) Example 3D macaque brain model generated from its co-registered MRI scan, D) Example computer model of a larger SREA with pre-formed electrode holes for direct manufacturing out of biocompatible material (not part of this study).

Figure 2.

A) 3D-printed plastic skull. B) Silicon rubber is poured into the plastic skull covering the target area for the SREA. C) In design I, a sewing needle was used to thread electrode wire through the rubber in a grid pattern (figure shows insertion in progress with a grid overlay). Note the shadows on the rubber mold itself show there are ridges on the inner lumen of the skull that reflect the sulci/gyri of the underlying cortex. These ridges can be used to target electrodes over the desired anatomical landmarks. D) In design II, small ~2mm loops of deinsulated wire were inserted into slits in the rubber mold. Pouring acrylic over this configuration results in an SREA with small loops of deinsulated wires sticking into the cranial cavity (inset). These wires were then pushed flat against the acrylic before final implantation. E) Diagrams of the steel tubes with multistranded deinsulated wire inside used as electrodes in designs III (left) and IV (right). F) In designs IV and V, 'place holder' tubes made from hypodermic needles were inserted in a grid pattern into the rubber mold. Once completed, the full grid of tubes resulted in a skull-shaped piece of acrylic with an 8x8 grid of holes in which electrodes were later inserted. G) The left panel shows a close-up of the cured acrylic with holes made using the hypodermic needles in design four. Four of the holes have already been filled with the tube electrodes each containing a loop of deinsulated multistranded wire. The right panel shows the untrimmed molded acrylic after all the tubes were inserted. H) The final design V SREA with two expanded views of the laser-etched contact of one example electrode.

Figure 3.

Cut-away illustration showing how the SREAs were implanted and secured. Once an SREA was placed within the craniotomy, titanium bone connector strips comprised of a string of connected metal rings were screwed to the skull to make 'legs' that extended under the scalp. The remainder of each bone strip was bent up and incorporated into the acrylic headcap that sealed the craniotomy as well as secured the connectors in place within a protective metal chamber.

Figure 4.

Array densities compared by reanalyzing the same data using different subsets of the original 64 recording electrodes. Black dots visually indicate the three different uniform electrode spacing options compared. Note, in the half-density option, the assessment was repeated with both possible half-density subsets (i.e. black dots and grey dots). For the 1/8th density option, all possible subsets were assessed that have the same relative spatial density pattern shown by the eight black dots in the plot on the right.

Figure 5.

Box and whisker plots showing the median (black center line) and upper/lower quartiles (grey box top/bottom) of the 1.3KHz impedance values collected from all intact measured contacts combined over all data collection sessions for each SREA design in (A) the early (<3 mos.) and (B) late (>8 mos.) post-implantation epochs. Lower column labels indicates the SREA design number; columns 'Va' and 'Vb' indicate the flat and laser-etched electrodes in design V respectively. Whiskers indicate 1.5 times the interquartile range. Individual tick marks denote any data that fell outside 1.5 times the interquartile range. The numbers above each column indicate the number of testing days included in that data. Note, to estimate the number of channels outside the 1.5 interquartile range on a given day, one would divide the number of tick marks by the number of days above each column.

Figure 6.

Percentage of tested channels that were assumed to have a bad connection due to 1.3KHz impedance values being > 10 times the median value for each design in the first recorded epoch. Dots are for individual testing sessions. Note, many values were the same between days resulting in some dots plotted on top of each other. Bars indicate the means of these percentage values across all recorded sessions. For design V, Va=flat and Vb=laser etched.