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CUSTOM SKULL CAP WITH PRECISION GUIDES FOR DEEP INSERTION OF CELLULAR-SCALE MICROWIRE INTO RAT BRAIN

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ABSTRACT

To understand the brain functioning mechanisms, electrophysiological methods represent the most mature approach for recording brain dynamics at millisecond timescales in either local or large spatial scales. Microwire-based microelectrode arrays (MEAs) are a well-established tool for chronic recording of electrophysiologic signals and furthermore have the advantage of minimal brain damage if constructed from cellular-scale (4-100 μm neuron diameter) microwires. However, such cellular-scale MEAs are not widely used by neuroscientists, especially on deep insertion cases, due to the barrier of implantation. Efforts to reduce the size of microwires bring collateral difficulties due to buckling during penetration through membranes (dura/pia) and consequent inability to implant deeply into the brain or in a manner that leaves intact protective biolayers such as the dura mater. In this paper, we developed a custom skull cap with precision guide holes to stabilize the brain and dura, provide sufficient support to microwire along the insertion path, and minimize the unsupported length of microwire during dura penetration and deeper insertion. A cap matched to individual skull anatomy with offset for brain stabilization was designed based on computed tomography (CT) scan of the rat head and fabricated by stereolithography. Micro-milling and wax molding were conducted to fabricate precision insertion guide inside the cap. Animal surgical studies were conducted to test the performance of skull cap and insertion guide. Rats with skull cap attached had survived for multiple weeks until sacrificed by experimenters. Through a test cube with precision guide, a 25 μm diameter tungsten microwire penetrated through the dura mater and was manually inserted over 10 mm into the brain without buckling. In comparison, without the precision guide, insertion of the same microwire caused over 2 mm dimpling of the dura without penetration and finally led to wire buckling. Results showed that the custom skull cap with precision guide holes enabled the insertion of cellular-scale microwire electrodes deep into the brain through the dura mater without buckling.

Keywords: Custom skull cap, deep insertion, brain recording, cellular-scale, buckling, microwire.

NOMENCLATURE

D	Diameter of the microwire
E	Modulus of elasticity of the electrode material
F	Insertion force
I	Moment of inertia of the cross section
L_U	Unsupported length of the microwire
L_B	Buckling length of the microwire
P	Critical buckling force
ρ	Density of the electrode material

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INTRODUCTION

Understanding how the brain works is one of the greatest unsolved scientific challenges. The core component of mammalian brains is the billions of neurons, which operate at millisecond timescales with action potentials lasting approximately 1 ms, synaptic delays ranging from approximately 1-10 ms [1,2], and neural assemblies functioning at tens of ms [3]. Electrical recording methods represent the most mature approach for recording brain dynamics at those timescales in either local or large spatial scales.

1.1 Electrophysiological Recording of Brain

The link between nervous system functioning and electricity has been known since Galvani's study over two centuries ago [4]. Since then, electrophysiological studies have been conducted to measure and manipulate such electrical activities in the brain and many different technologies have been developed to study and query the brain, which generally falls into three categories: electroencephalography (EEG), electrocorticography (ECoG), and microelectrode implants.

As in Fig. 1, the mammalian brain is protected by the scalp, skull, and the meninges composed of the dura mater, the arachnoid mater, and the pia mater. As a non-invasive recording method, EEG records from the surface of the scalp. It has high time resolution and the capability for large-scale recording from all areas of the brain [5]. A semi-invasive method is ECoG, which places electrode grid on (epidural) or under the dura mater (subdural) to cover a large area of the cortex. ECoG records higher resolution signal then EEG by eliminating the signal losses through skull and skin. However, the spatial resolution is still too low to study circuit level electrical activities or single neural firing patterns [6].
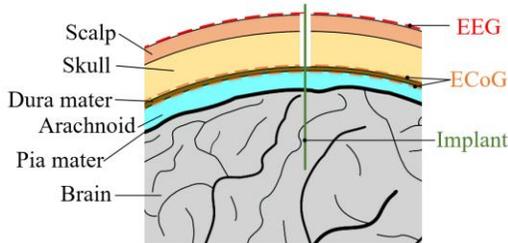
FIGURE 1: Protective layers of mammalian brain and electrophysiological modalities**.**

The most invasive recording method is the microelectrode implants. These microelectrodes are made from silicon-based electrodes or conductive microwire and are designed to interface with a specific brain area to provide the spatial resolution to access and record single neuron activities from deeper brain layers. Neuroscientists study neuronal electrical signals to characterize cognitive processes (e.g., motion, sleep, and memory) at the neuron level [7,8]. A neuron cell is about 4 to 100 μm in size and connects to about 7,000 other neurons via axons [9]. When a neuron fires a signal, the Na^+ and K^+ ion transportation in the axon changes the polarity across the membrane and an electrical signal (about 80-100 mV in magnitude in spike value) is generated. Such in-vivo neuronal electrical signals are distinguishable in a region with a 50-150 μm radius [10]. This area is small and can only be detected by using invasive microelectrode implantation methods.

1.2 Cellular-Scale Microwire Implant

The viability of microelectrodes for neuronal recordings in live mammals was first demonstrated in 1958 by Strumwasser [11] using 80 μm diameter stainless steel wire electrodes. Since then, a wide variety of materials, including the stainless steel, tungsten (W), Ni-Cr, Pt-Ir, and carbon fiber (CF), have been used as microwire electrodes (Fig. 2(a)) for chronic brain recording over days, months and even years [12–24]. More recently, microelectrode technology has emerged by micro-electro-mechanical systems (MEMS) to build silicon-based electrodes. The two most commonly used designs are Michigan probes (Fig. 2(b)) [25], which have enabled high channel count recordings through planar silicon platform design, and Utah array (Fig. 2(c)) [26] using a grid of silicon shanks with recording site at tips. For both microwire and silicon-based microelectrode implants, due to the invasive nature, have the disadvantage of tissue damage (or scarring) during its penetration into the brain. Such damage can worsen over time and finally leads to loss of recording signal.

(a)

(b)   (c)
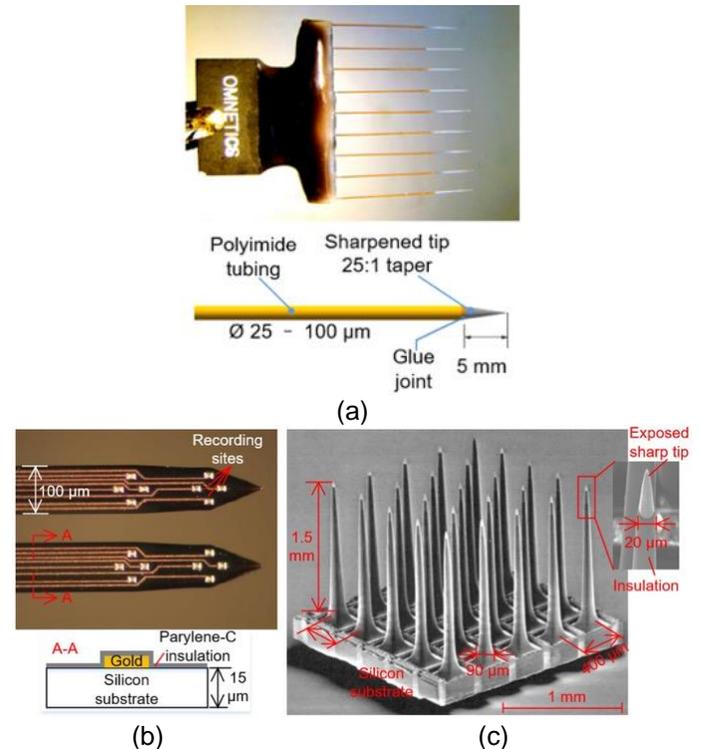
FIGURE 2: Three sample microelectrode implants for neuronal electrophysiology recording: (a) microwire [27], (b) Michigan probe [25], and (c) Utah array [26]**.**

To minimize the brain damage and enable chronic recording of neural signals, cellular-scale microwires with minimal diameter have been developed and implanted, including 7 to 26 µm diameter CF [16,28–30] and 10 to 25 µm metal microwires [12,18]. Such cellular-scale microwires with minimal brain damage are the main focus of this research.

1.3 Buckling of Cellular-Scale Microwire

A major challenge for the wide utilization of cellular-scale microwire is buckling. The dura mater, a tough, dense, and thick membrane layer surrounding the brain (0.4 – 1.2 MPa Young's modulus for rat brain dura), is hard to penetrate and causes excessive dimpling during microwire insertion [31]. Even after dura removal at local areas, the pia mater on the brain surface can still cause buckling of thin cellular-scale microwires [32]. Current studies use bundles of cellular-scale microwires for deep insertion and tetrode-based recording [18,28] or use support structure (e.g. silicon shanks and tapered wire) to insert the electrode into certain depth [12,16]. Such methods mitigate the minimal brain damage advantage of the cellular-scale microwires. Also, insertion depth of cellular-scale microwires are usually less than 2 mm while the maximum rat brain depth is over 10 mm.

Figure 3 shows insertion tests conducted on three types of microwire electrodes into brain-mimicking polyvinyl chloride (PVC) phantom material. The Ø 75 µm sharp Pt-Ir wires successfully penetrated 30 mm inside the brain phantom (Fig. 3(a)). However, the 10 mm long W (Ø 18 µm) and CF (Ø 7 µm) microwires buckled and failed to penetrate the PVC phantom (Figs. 3(b) and (c)).

75 µm Pt-Ir   15 µm Tungsten   7 µm carbon fiber

(a)   (b)   (c)
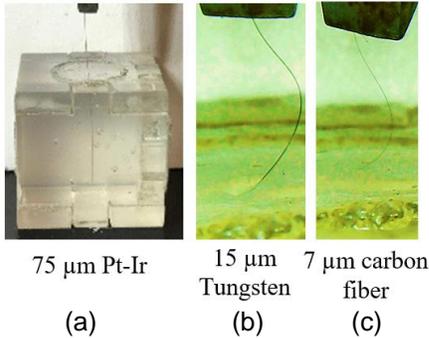
FIGURE 3: Phantom insertion test: (a) successful insertion of 30 mm long Ø 75 µm diameter Pt-Ir microwire and buckling of 10 mm long (b) Ø 18 µm W and (c) Ø 7 µm CF microwires to the PVC phantom.

The microwire critical buckling load P is determined by the Euler's column equation:

$$P = \frac{n\pi^2 EI}{L_U{}^2} \qquad (1)$$

where E is elastic modulus, I is the second moment of inertia of the microwire, L_U is unsupported length during insertion, and n

is the end condition shown in Fig. 4. The I for a cylinder shape microwire of diameter D is:

$$I = \frac{\pi D^2}{32} \qquad (2)$$

During microwire implantation, once the insertion force F exceeds the critical buckling load P, microwire buckling occurs. At the critical buckling condition, when the insertion force is equal to critical buckling load, the unsupported length is equal to the buckling length L_B:

$$F = \frac{n\pi^2 EI}{L_B{}^2} \qquad (3)$$

To avoid buckling and even allow cellular-scale microwire penetration through dura mater, two options are available: decreasing the insertion force F or increasing the critical buckling load P. Decrease of the insertion force F can be obtained by using a sharpened microwire and our tests show that sharpened wire reduced the insertion force by 50% compared to blunt ones of the same diameter [33].
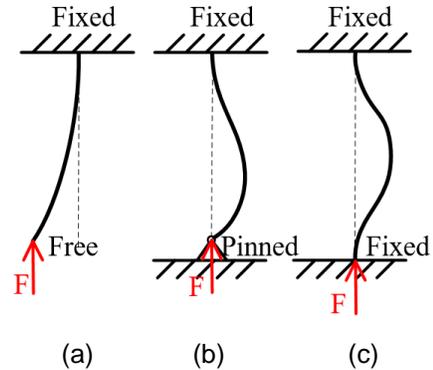
FIGURE 4: End conditions of microwire buckling.

To increase the critical buckling load P for a given microwire material, diameter, and shape, providing sufficient support on the unclamped end of microwire to make the end condition closer to the fixed condition (n=4) and minimizing the unsupported length L_U to ensure it is smaller than the buckling length during insertion L_B are the two major options. Current surgical practice of stereotaxic or manipulator-based insertions cannot be used for these thin cellular-scale microwire arrays since they require a long length of wire above the top of the brain that will itself become a point of flexion and buckling due to the excessive unsupported length.

In this paper, a new insertion method is developed to implement cellular-scale microwire deep into the brain using precision guide holes on a custom skull cap in a manner that leaves intact protective biolayers such as the dura mater – often leading to infection near implantation sites if removed.

MATERIALS AND METHODS

In this study, to increase the critical buckling load, we inserted microwires through precision guide holes on a custom skull cap designed to stabilize both the brain and dura (Fig. 5). The custom pre-designed skull cap rest directly against the brain surface to hold the brain in place. Precision-molded guides in the skull cap at custom insertion locations provided full-length support to the microwire down to the point of insertion and fixed the free end during membrane penetration. During insertion, the microwire grippers were kept close to the top of the cap and guide so that the unsupported length L_U was smaller than the buckling length L_B all the time. In this section, key components of this concept will be presented, including the design, fabrication, and attachment methodologies of the custom skull cap and the precision molded guides.
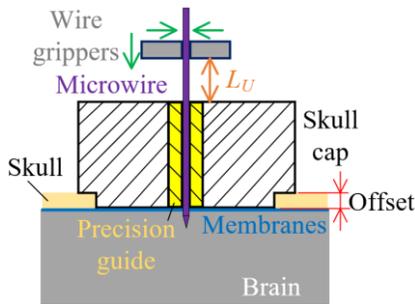
FIGURE 5: Custom skull cap with precision guides for dura penetration and deep insertion.

2.1 Design and Fabrication of the Custom Skull Cap

The design and fabrication methodology of the custom skull cap (Fig. 6) had the following steps:

- *Pre-drilling of skull cap locating holes*: A full scalp incision was conducted down the midline. Scalp skin was pulled away and temporalis muscle were pulled away from temporal ridges to expose the sides of the skull. A 0.7 mm diameter micro drill was used to pre-drill two holes in the left parietal bones and two in the right. These holes remained throughout the animal's subsequent life to serve as both fiducial markers and locating holes to attach a skull cap onto the skull. We could therefore design skull cap and all other coordinates like insertion sites using these reference holes, a high efficiency method which did not rely on unrealistic precision by surgeons.
- *CT-scan of the skull with pre-drilled holes*: The rat with pre-drilled holes was scanned using CT (Skyscan® microCT machine by Bruker with 35 µm resolution).
- *3D skull geometry reconstruction*: CT-scan data were processed to build 3D skull geometry (pre-drilled holes highlighted in red) for cap design.
- *Custom cap design based on skull geometry*: Custom skull cap design was created with the bottom surface geometry identical to the outer surface of the rat skull, as in middle-right picture in Fig. 6. The thickness of the cap depended on headstage fixation needs of the neuroscience application. Based on the

CT-scanned locations of hole positions and orientations, fixation screw holders were adjusted to fit each skull.
- *Cap offset for brain stabilization*: The center area of the skull cap bottom was offset by 1.5 mm (obtained from our preliminary study) to rest against the dural surface upon cap attachment. Note that this did not rest against the brain surface but the dura – thereby reducing tissue irritation on the brain. An outer rim step of 1 mm width was left to rest the cap against the skull bone edge after craniotomy.
- *3D printing of the skull cap design*: The skull cap design was sent to a stereolithography (SLA) additive manufacturing machine (Form 2 by FormLabs) and printed with Class 1 bio-compatible resin for surgical implant use (Dental SG by FormLabs).
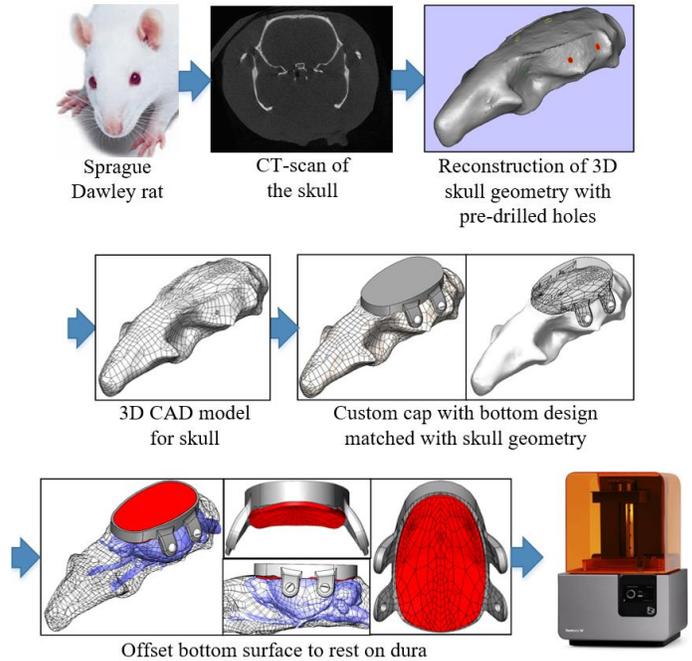
FIGURE 6: Procedure for design and fabrication of the custom skull cap.

2.2 Surgical Procedure for Cap Attachment

To attach the printed custom skull cap onto a rat head, rat hair at the incision site was trimmed and an anterior/posterior incision approximately 25 mm in length was made with a sterile scalpel to expose the skull. A dental drill with burr bit sizes 0.5, 0.7, and 0.9 mm was used to create windows in the non-sutured portions of the parietal, frontal, and occipital bones of the skull. Cranial sutures were then removed by iteratively shaving down the bone above them until dura was reached, taking care to apply saline to keep the dura moist and prevent tearing. Prior to head-cap placement, the exposed dura was covered with triple antibiotic ointment in petroleum jelly. Then the printed skull cap was placed onto the opening and fixed by screws in the anchor holes drilled prior to CT scan.

2.3 Fabrication of Precision Guide for Microwires

To provide sufficient support along the insertion path, an idea to mold a microwire guide hole using the microwire itself and wax was studied. The fabrication for a single microwire guide includes the following steps (Fig. 7):

- Feed the microwire through a hole generated by micro-milling in the cap and apply tension to keep it straight,
- Pour molted wax into the hole with the microwire inside as mold to create a precise guide,
- Cut with a sharp blade along bottom of the cap to remove excess wax for a smooth brain contact surface,
- Pull the microwire out of the mold to form a precision guide at the targeted insertion site.
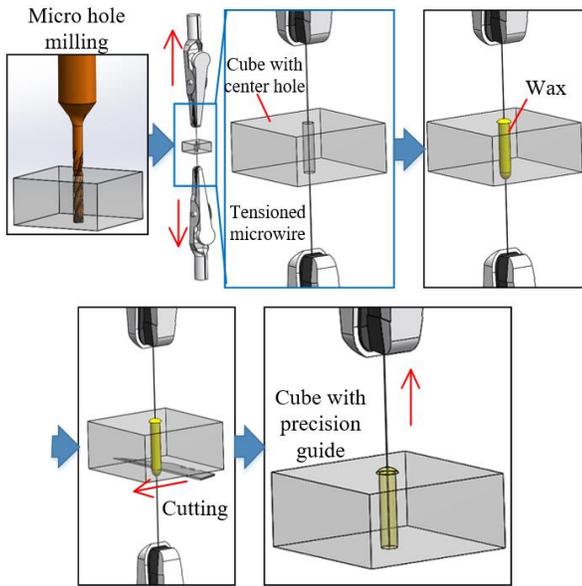
FIGURE 7: Procedure for fabrication of the precision insertion guide.

2.4 Animal Test for Deep Penetration through Guide

A test cube fabricated by SLA with precision guide for a single 25 µm W microwire was used to test the capacity of this approach for dura penetration (Fig. 8(a)).
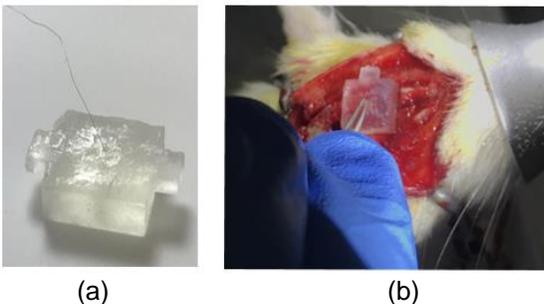
FIGURE 8: Animal trial for deep insertion through guide: (a) fabricated test cube with precision guide and (b) tweezer driven insertion of microwire into the brain.

Rat craniotomy surgery was performed as described in Section 2.2 with the dura mater kept in place. The test cube was placed on the dura mater and the microwire was fed into the brain through dura manually with a pair of tweezers, as shown in Fig. 8(b).

RESULTS

Both a custom skull cap and a precision guide test cube were designed, fabricated, and tested on live rats.

The rat skull after the craniotomy as described in Section 2.2 is shown in Fig. 9(a). Figure 9(b) presents the brain offset of the skull cap that rest on the dura surface. We have attached skull caps to two rats using the methods described and both of them showed good survival for multiple weeks until sacrificed by experimenters (Fig. 9(c)).
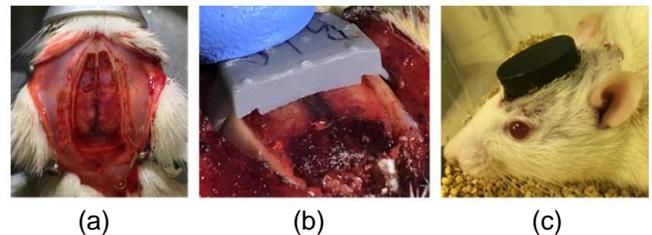
FIGURE 9: Rat surgery for skull cap attachment: (a) skull opening after craniotomy, (b) demonstration of brain contact by skull cap reset and (c) rat with skull cap attached.

Using the tweezer driven insertion through the precision guide as in Fig. 8, the 25 µm W microwire penetrated through the dura mater and inserted over 10 mm into the brain without buckling (Fig. 10). In comparison, without the precision guide, insertion of the same microwire caused over 2 mm dimpling of the dura without penetration and finally led to buckling of the microwire.
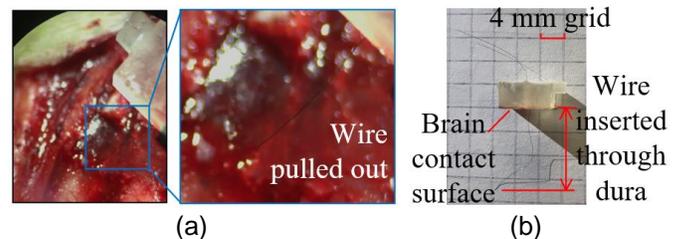
FIGURE 10: Animal trial for deep insertion through guide: (a) fabricated test cube with precision guide and (b) tweezer driven insertion of microwire into the brain.

DISCUSSION

In this study, the skull cap was designed based on CT-scan of specific animal used (Sprague Dawley rats, 250-500 g). For neuroscientists without CT scanner availability, we can explore animals from each common rat strain (Sprague-Dawley, Long-

Evans, Fisher, others) and test the generalizability of skull geometry both within and across strains. A generalized skull geometry can be developed for rats (or each strain if necessary) and neuroscientists can then design custom caps using bregma-lambda lengths in individual rats. For attachment, the fixation screw holes can be drilled when placing the cap after craniotomy rather than prior - this may reduce precision but not beyond current stereotaxic techniques and would obviate the need for CT scanning. In this way, this computer aided design and additive manufacturing enabled methodology can widely benefit the neuroscience community.

Since the skull cap was custom designed and attached precisely, it could be used as an animal-specific coordinate system. CT head scans (bone) and T1 MRI (brain structures) of the head of each animal can be co-registered (Fig. 11), which directly aligns the skull cap geometry with the rat brain coordinates [34]. Based on that a targeted recording region of the brain could be identified for microelectrode placement and the target locations can be projected onto the skull cap top surface to create custom insertion openings. Alternatively, for neuroscientists without MRI scan capability, the targeted insertion sites can be identified based on brain atlas coordinates. After the insertion locations and openings are determined, precision insertion guide could be molded accordingly for deep insertion of arrays of cellular-scale microwires into the brain through the dura mater, enabling whole-brain chronic recording with minimal damage at arbitrary locations according to neuroscientists' needs. Insertion of such microwire arrays will be difficult for manual operation due to complexity, reliability, and repeatability. Instead, a computer-controlled accurate insertion tool will be needed.
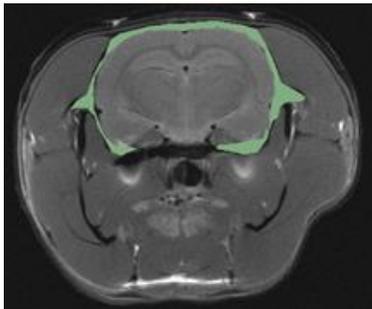
FIGURE 11: CT/MRI co-registered images of a rat brain. The CT image identified the bone for the design of the skull cap. MRI image identified target region for brain-wide placement of microelectrodes.

CONCLUSION AND FUTURE WORK

A new cellular-scale microwire insertion method based on a custom skull cap by additive manufacturing and precision insertion guide through molding was developed and tested on live rats. Results showed that the new method enabled the insertion of cellular-scale microwire electrodes deep into the brain through the dura mater without buckling, which is impossible under current surgical practice of stereotaxic or manipulator-based insertions. This work overcomes a key barrier of cellular-scale microwire buckling to arbitrary and non-infectious implantation of cellular-scale microwires which would otherwise maximize chronic recording quality. Future work includes insertion of microwire microelectrode array through guide holes simultaneously and development of computer-controlled implementation tools to replace the manual tweezer driven process.

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