Microelectrode Array Insertion System Using Ultrasonic Vibration to Improve Insertion Mechanics and Reduce Tissue Dimpling and Trauma in the Cortex

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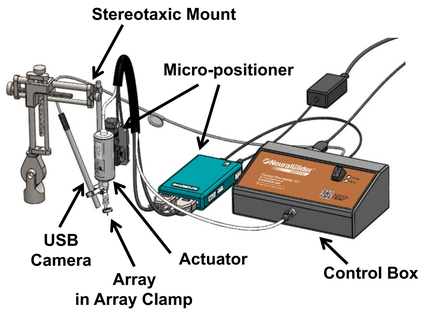
Introduction

Intracortical Electrode Arrays (IEAs) provide direct access to extracellular neural signals in the brain with high temporal and spatial resolution. Unfortunately, chronically implanted IEAs have limited functional lifespans that impede significant clinical translation. The forces applied to cortical tissue during insertion can cause insertion trauma leading to the formation of glial scars and loss of neurons at electrode sites. Superior tissue response and device longevity has been demonstrated with ultra-fine microwire (<15 µm diameter) and flexible (*e.g.*, polyimide) arrays, but these require extra mechanical support to prevent buckling/breaking during insertion. These also add complexity and time to the insertion process, limiting adoption.

We have shown that ultrasonic-vibration reduces insertion trauma and enables reliable insertion without support structures or stiffeners and, in some cases, enables insertion through intact dura. Benchtop insertion studies in agar and *ex vivo* tissue models, as well as *in vivo* insertion studies support the potential of vibrated insertion for improved insertion mechanics of a range of IEAs.

The NeuralGlider® Inserter

+ Ultrasonic actuator produces axially-directed micro-vibrations in IEA shanks during insertion; actuator power specifies displacement magnitude.
+ Micro-positioner linear stage (0.5 µm resolution) mounts to stereotaxis.
+ RoHS compliant control box.
+ Low profile USB microscope camera, with stereotaxis mount included.
+ LabVIEW-based GUI controls the micro-positioner and actuator and records position data.
+ Couplers are available for a wide range of IEA styles, offering clamping and polyethylene glycol (PEG) mechanical bonding, among others (not shown).

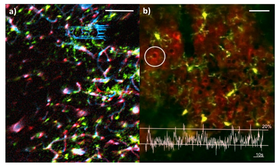


Ongoing Research Collaborations

Revealing microglia and neuron response at the neural interface of IEAs inserted with vibration

TK Kozai, University of Pittsburgh[3]

+ Microwire & silicon IEAs will be inserted at an angle to enable two-photon imaging of microglia behavior and neuron excitability around a vibrated IEA.
+ Data will reveal how the reduction of insertion force and tissue dimpling improves the neural interface at the cellular level.



Long-term electrophysiology performance with vibrated insertion of ultrafine IEAs in vivo

Actuated Medical, Inc. with the Pennsylvania State University

+ Evaluation of electrophysiology outcomes (SNR, unit detection) and IEA 'lifetime' in vivo in a rodent study following vibrated insertion of carbon fiber arrays.

Improving inserting of shape-memory polymer probes (Qualia) in mouse cortex

Jonathan Fadok, Tulane University

+ Qualia softening probes are initially rigid but soften when inserted in vivo; flexibility can cause insertion challenges.
+ Chronic studies will be conducted in mouse cortex to compare outcomes with and without vibration.

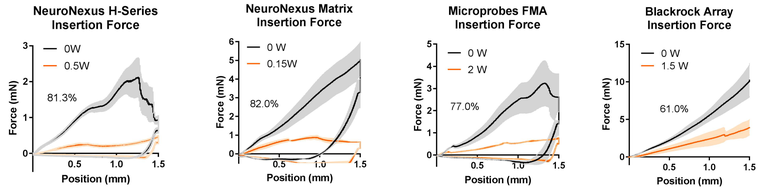
Improved surgical outcomes during implantation of floating IEAs in gyrencephalic cortex

Actuated Medical, Inc. with Pennsylvania State University; Matthew Smith, Carnegie Mellon University

+ NeuroNexus Matrix silicon shank arrays have reduced insertion force when inserted with vibration.
+ Acute insertion testing (porcine) and chronic implant testing (non-human primate) will evaluate the benefit and safety of vibrated insertion in the large-animal brain.

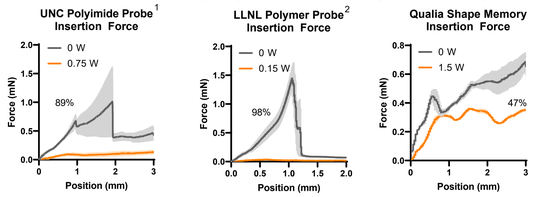
Vibration Reduces Insertion Force

Rigid IEA Shanks (silicon, microwire)



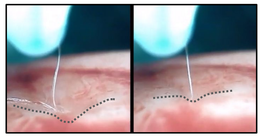
Insertions (and retractions) into agar model (0.5% base with 1.5% top layer), to 1.5 mm depth. NeuralGlider Inserter coupler type and optimized Actuator power settings vary by array. Curves show mean ± s.e.m. for n≥3 insertions for each condition.

Flexible IEA Shanks (polymer, softening materials)



Insertions (and retractions) into agar model (0.5% base with 1.5% top layer), to 2-3 mm depth. NeuralGlider Inserter coupler type and optimized Actuator power settings vary by array. Curves show mean ± s.e.m. for n≥3 insertions for each condition. Insertions with LLNL probe included stiffener.

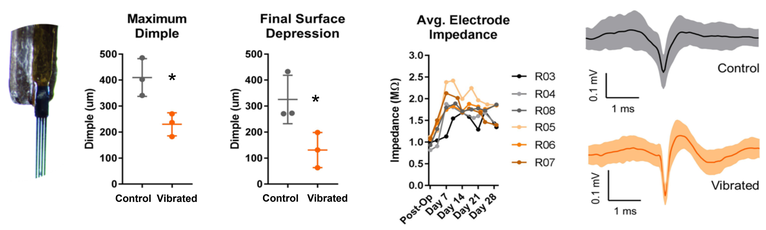
Qualia Labs Softening Probes



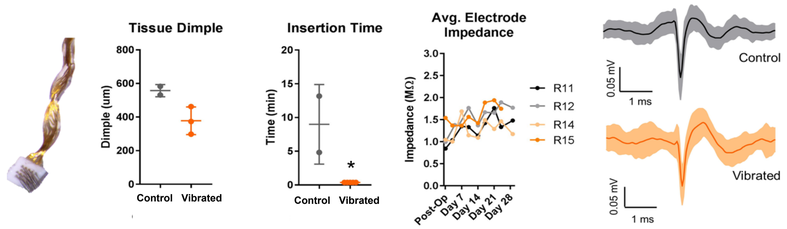
Ex vivo tissue testing (porcine). Without vibration, flexible probes buckle and **~83%** of insertion attempts fail; With vibration, insertion failures reduce to **~23%.**

Vibrated Insertion - Chronic *In Vivo* Studies

+ **NeuroNexus Arrays** – 4 shank silicon arrays with H-series connectors, 16 electrode sites, inserted 1-1.25 mm into in vivo rat barrel cortex using PEG Coupling; reduced dimpling and cortical surface compression (p<0.01)* with vibration, without impairing electrode function. Average unit waveforms recorded post-operatively.



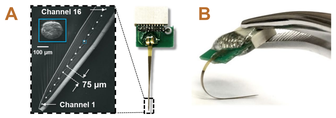
+ **Microprobes FMAs** – 16-shank floating microwire arrays, inserted 1 mm in vivo into rat barrel cortex. Reduced insertion time (p<0.01)*, bleeding incidence (qualitative analysis not shown), and some dimple reduction with vibration. Average unit waveforms recorded post-operatively. Study completed with male Sprague-Dawley rats.



*A selection of chronic preclinical studies shown; NeuralGlider Inserter has also been tested with fixed microwire IEAs in vivo. Preliminary studies show that recording performance was comparable for vibrated (actuated) and non-vibrated (control) array insertions, supporting overall safety of approach. No significant histological differences were noted (immunohistochemistry data not shown). * indicates significant difference between group at p < 0.05. Study completed with male Sprague-Dawley rats.*

Improved Outcomes *in vivo* – Flexible Polyimide IEAs

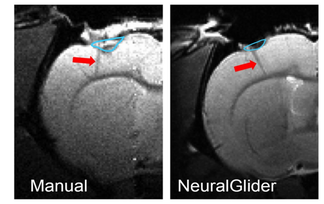
University of North Carolina researchers, Ian Shih and SungHo Lee, evaluated the NeuralGlider Inserter for insertion of flexible, MRI-compatible polyimide single-shank probes.[1]



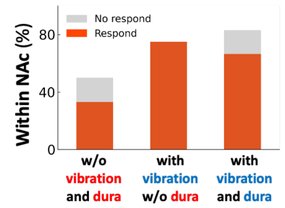
The thin-film layered design is intended to facilitate implantation without the use of a temporary stiffener, but flexibility impairs targeting precision at sub-cortical depths. Standard (non-vibrated) insertion also requires durotomy during surgery.

(A) Electron microscopy showing the electrode tip. Probes have vertically aligned 16-channel electrodes.
(B) The flexibility of the polymer-based DBS probe.

Improved Target Accuracy & Insertion through Dura

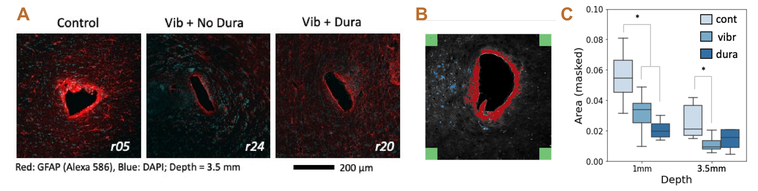


T2 anatomical images of implanted electrodes at the primary somatosensory area of forelimb without (left) and with (right) NeuralGlider. Images acquired with an in-plain resolution of 100 x 100 µm² and slice-thickness of 500 µm. Red arrow = implanted electrode shank, light blue marker = damaged area during implantation due to insertion. Images scanned 2 wk. post-surgery.



Vibrated insertion, through pia alone or through intact dura, improved accuracy of targeting a sub-cortical structure (nucleus accumbens, NAc) in the rat. Targeting success evaluated anatomically (MRI) and functionally (fMRI) via observation of the expected neural response evoked via IEA stimulation of NAc. Total bar height: % success targeting NAc.

Reduced Gliosis at IEA Interface with Vibrated Insertion



(A) Post-implant histology representative images from each insertion condition (red: glial fibrillary acidic protein (GFAP); cyan: 4'6-Diamidino-2-Phenylindole (DAPI)).
(B) Quantification of GFAP staining for assessing glial scar formation by insertion condition. Image represents regions used for analysis (green: area used for intensity normalization; red: GFAP signal above threshold, for quantification; blue: GFAP above-threshold signal excluded from quantification.
(C) Box plot of glial scar area (* p < 0.05; n=6 Control through dura, n=10 vibrated through pia, n=5 vibrated through dural Sprague-Dawley Rats, female, 300-350 g)

References & Acknowledgements

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3. Kozai TDY, Jaquins-Gerstl AS, Vazquez AL, Michael AC, Cui XT. Dexamethasone retrodialysis attenuates microglial response to implanted probes in vivo. *Biomaterials*. 2016;87:157-169.

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