BRAIN Initiative Investigators Pre-meeting: Large Scale Recording and Modulation

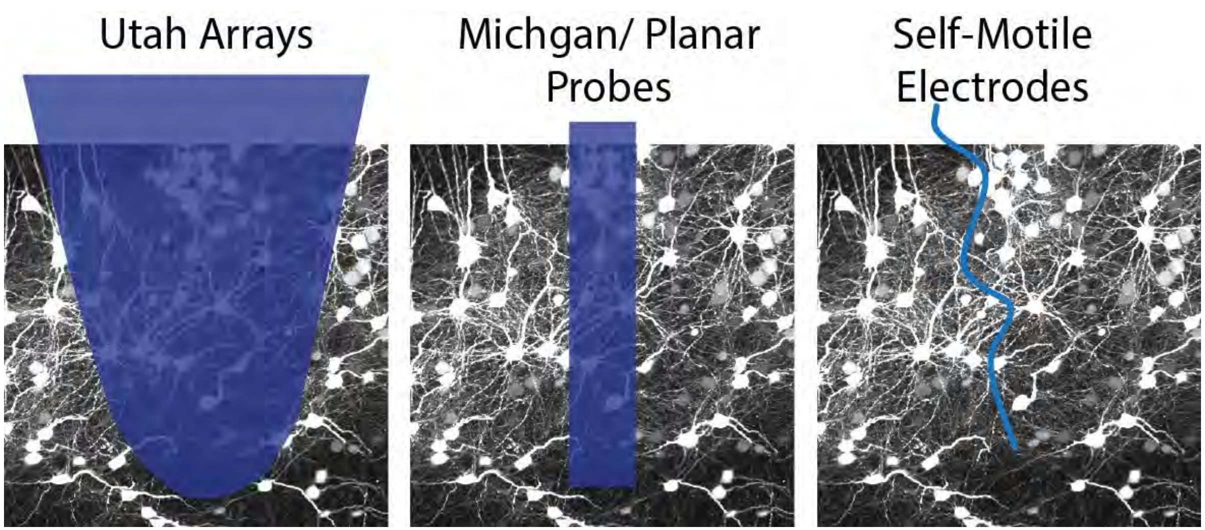
December 9, 2015, 1PM-6PM
Terrace Level Conference Room T500
5635 Fishers Lane, Rockville, MD

Electrodes

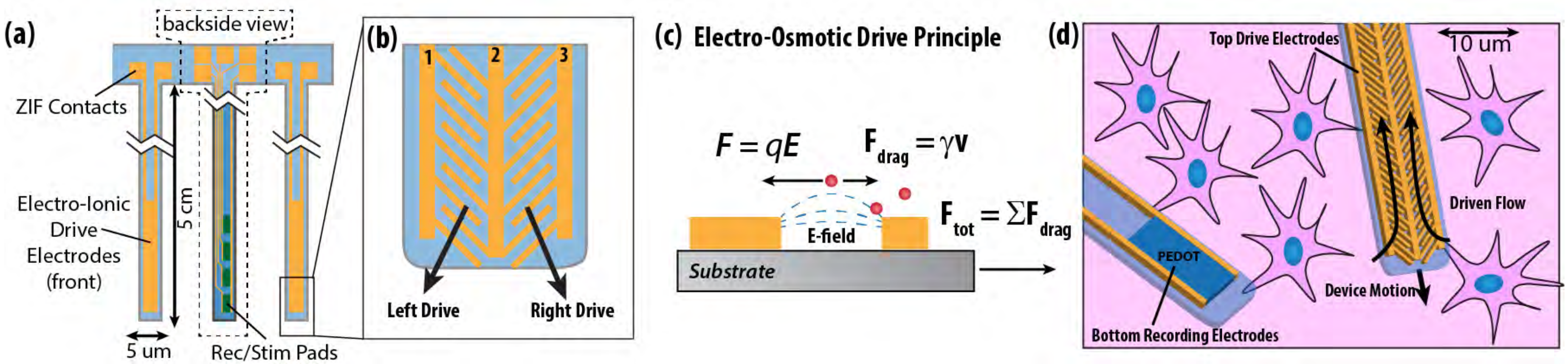
Presentation Order	PI Name(s) All	Title	Project Number
1	MELOSH, NICHOLAS A	Self-Motile Electrodes for Three Dimensional, Non-perturbative Recording and Stimulation	1 R21 EY026365-01
2	PAYNE, CHRISTINE K	Conducting polymer nanowires for neural modulation	1 R21 EY026392-01
3	SCHIFF, STEVEN J. (contact); TADIGADAPA, SRINIVAS	Implantable Brain Microelectromechanical Magnetic Sensing and Stimulation (MEMS-MAGSS)	1 R21 EY026438-01
4	CHESTEK, CYNTHIA ANNE (contact); BERKE, JOSHUA D	Carbon Thread Arrays for High Resolution Multi-Modal Analysis of Microcircuits	1 U01 NS094375-01
5	CULLEN, DANIEL KACY	Biological Living Electrodes Using Tissue Engineered Axonal Tracts to Probe and Modulate the Nervous System	1 U01 NS094340-01
6	FRANK, LOREN M (contact); HARRISON, REID ; TOLOSA, VANESSA	Modular systems for measuring and manipulating brain activity	5 U01 NS090537-02
7	GOODELL, ALBERT BALDWIN	Large-Scale Electrophysiological Recording and Optogenetic Control System	5 U01 NS090557-02
8	LEE, KENDALL H (contact); MANCIU, FELICIA S.; TOMSHINE, JOHNATHAN R	Neurotransmitter Absolute Concentration Determination with Diamond Electrode	5 U01 NS090455-02
9	SABATINI, BERNARDO L (contact); ASSAD, JOHN ; BERDONDINI, LUCA ; DEVITTORIO, MASSIMO	Novel optrodes for large-scale electrophysiology and site-specific stimulation	1 U01 NS094190-01
10	YOON, EUISIK (contact); BUZSAKI, GYORGY ; WISE, KENSALL DAVID	Modular High-Density Optoelectrodes for Local Circuit Analysis	5 U01 NS090526-02
11	HOCHBERG, LEIGH R (contact); NURMIKKO, ARTO	High-Bandwidth Wireless Interfaces for Continuous Human Intracortical Recording	1 UH2 NS095548-01
12	SCHIFF, NICHOLAS D (contact); BUTSON, CHRISTOPHER R; GIACINO, JOSEPH THOMAS; HENDERSON, JAIMIE M; MACHADO, ANDRE GUELMAN	Central thalamic stimulation for traumatic brain injury	1 UH3 NS095554-01
13	WORRELL, GREGORY A	Neurophysiologically Based Brain State Tracking & Modulation in Focal Epilepsy	1 UH2 NS095495-01
10 min presentation	*KORDING, KONRAD P. (contact); SCHAEFER, ANDREAS*	*Massive scale electrical neural recordings in vivo using commercial ROIC chips*	*1 U01 NS094248-01*
10 min presentation	*GARDNER, TIMOTHY JAMES*	*Tunneling microfiber electrode arrays for stable neural recording*	*5 U01 NS090454-02*

“Self-Motile” Electrodes

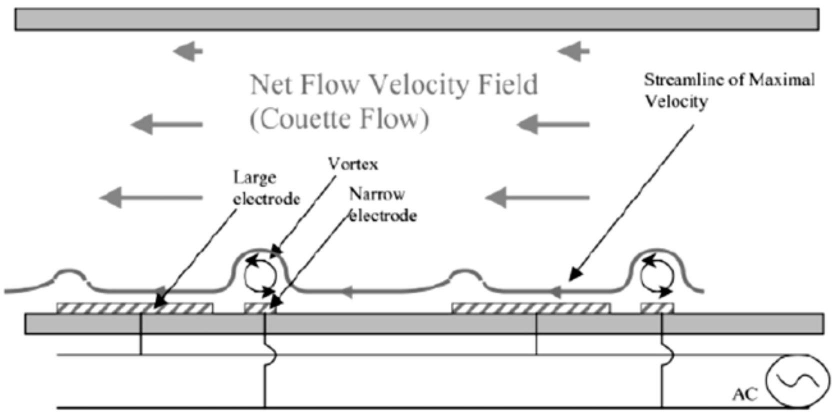
Prof. Nick Melosh, Dept of Materials Science and Engineering, Stanford University
nmelosh@Stanford.edu

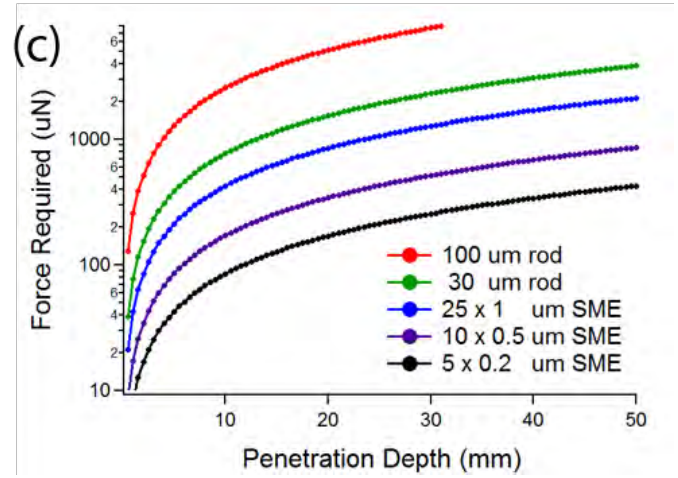


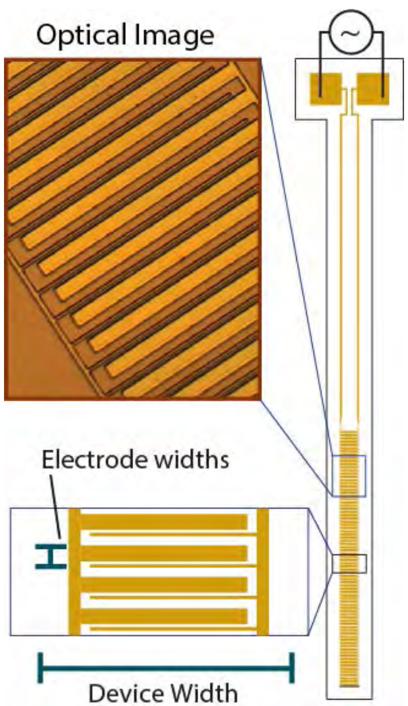
- Traditional electrodes require significant size so they can be pushed in from the back
- Causes tissue damage, limited density
- Instead, we will develop ‘front-wheel drive’ electrodes which pull themselves in

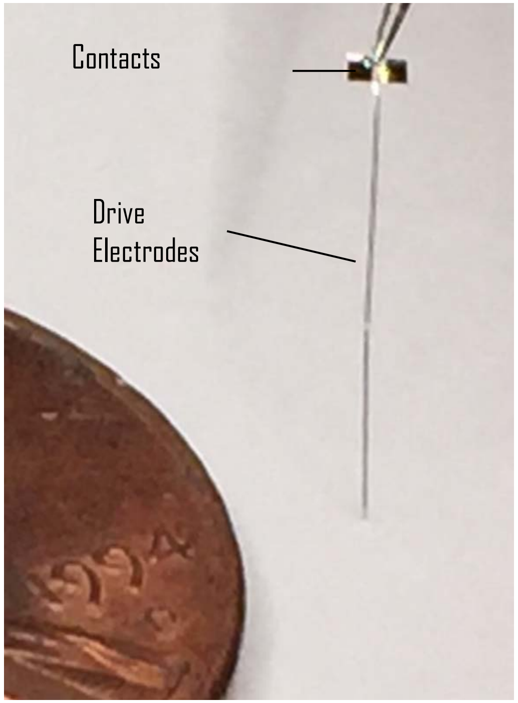


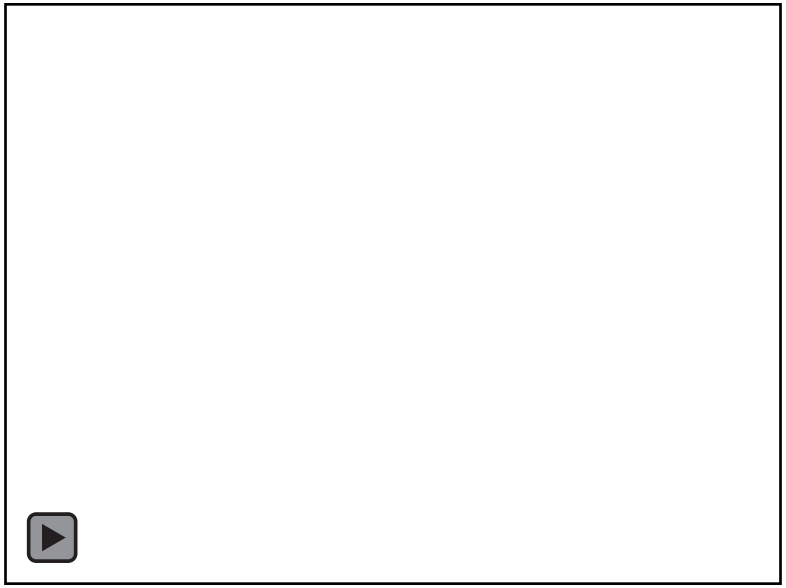
Electro-osmotic Pumping





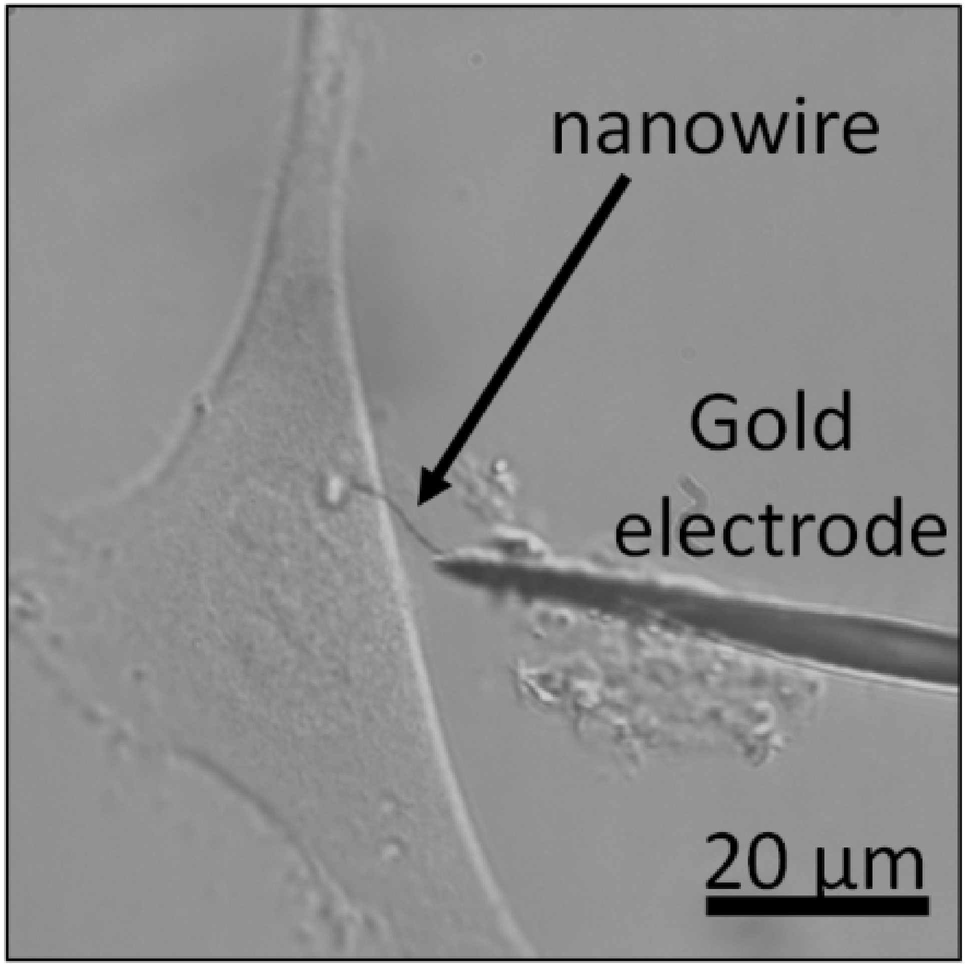






Conducting Polymer Nanowires for Neural Modulation

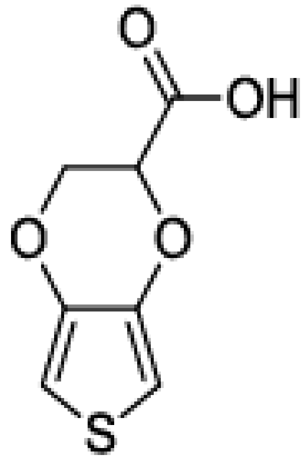
1 R21 EY026392-01



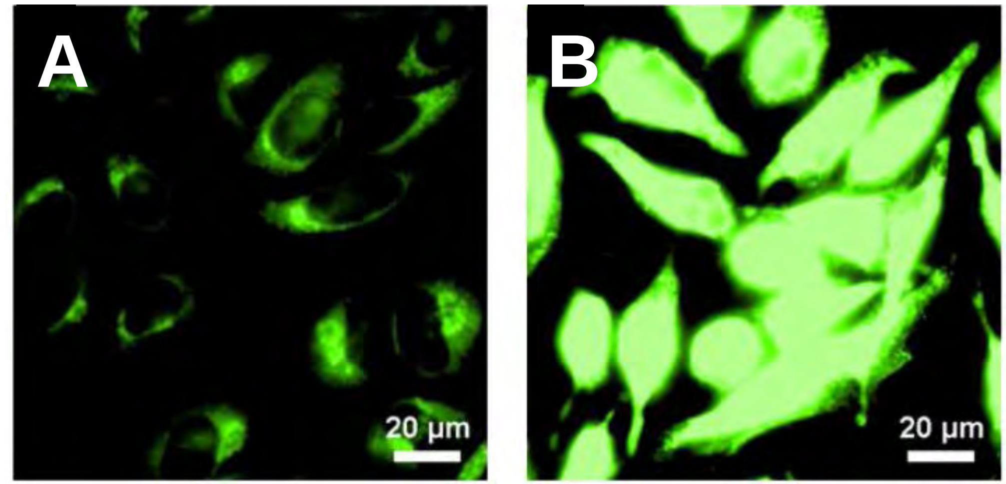
PI: Christine K. Payne, School of Chemistry and Biochemistry, Georgia Tech

co-PI: Bret N. Flanders, Department of Physics, Kansas State University

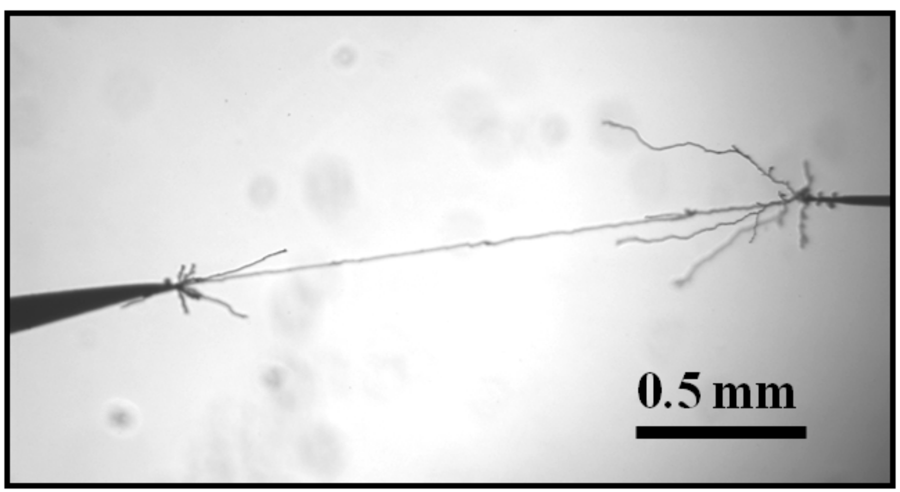
Goals and Challenges



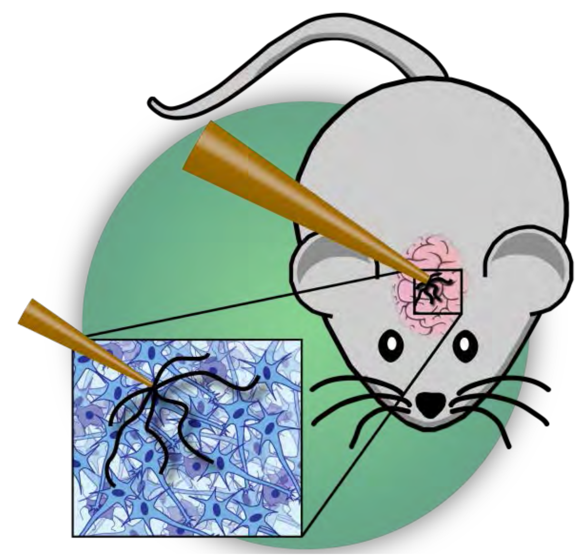
Functionalization
for cellular targeting



Depolarization of single cells



Multiplexing

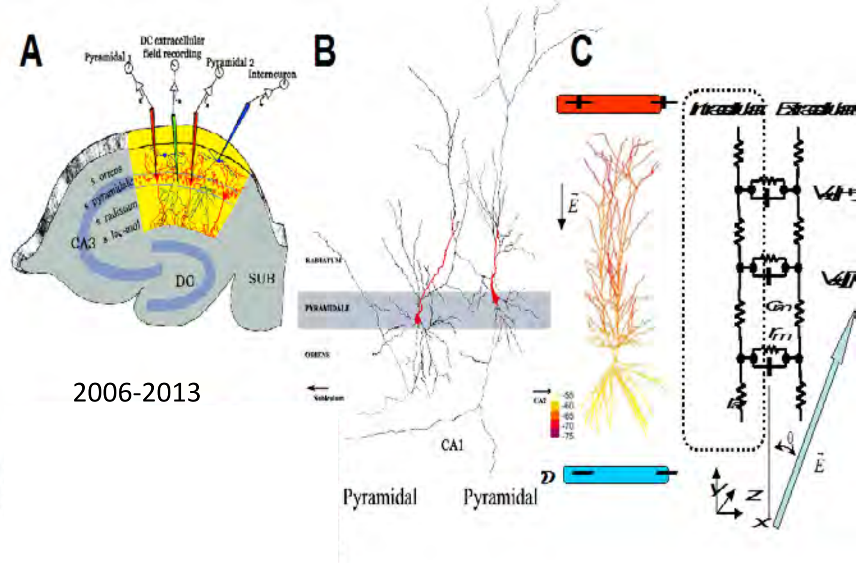


Extension to animal studies

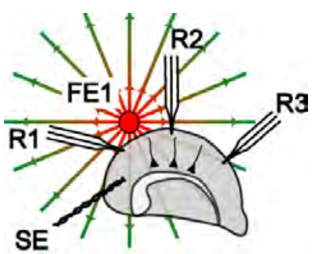
Implantable Brain Microelectromechanical Magnetic Sensing and Stimulation (MEMS-MAGSS)

Investigators: Steven Schiff and Srinivas Tadigadapa

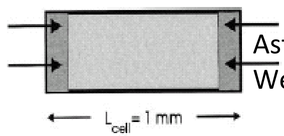
Electrical



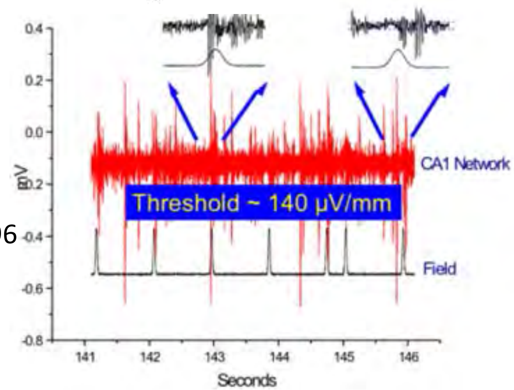
2006-2013



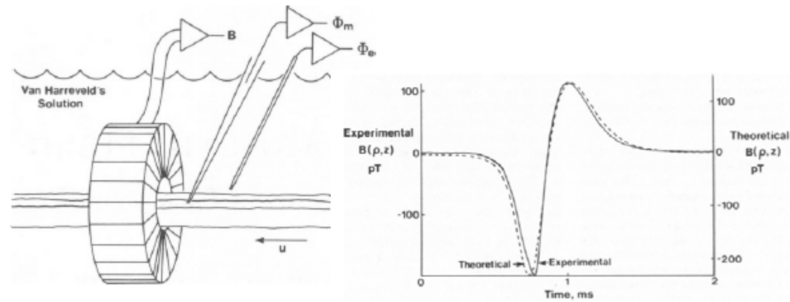
SR	PRL 1996
SZ	J Neurophys 1996
PID	J Neurosci 2001
140 uV/mm	J Neurosci 2003
Propagation	PRL 2005



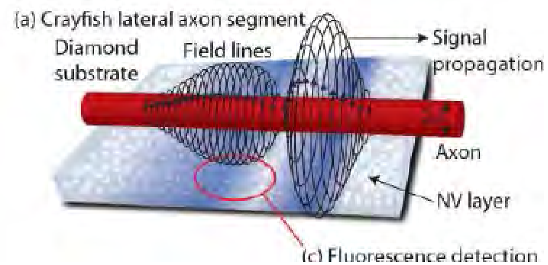
Astumian 1995
Weaver 1998

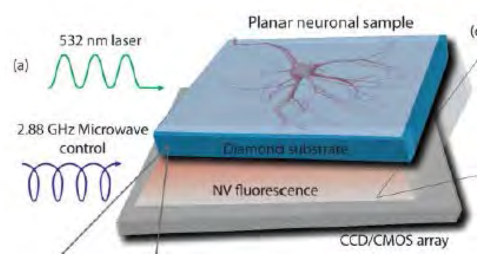


Magnetic



Roth & Wikswo 1985

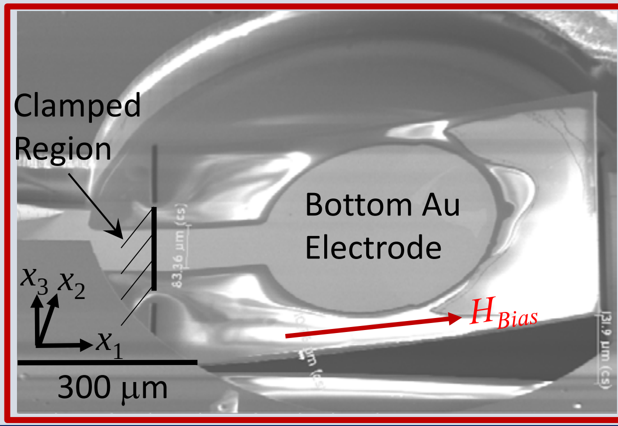


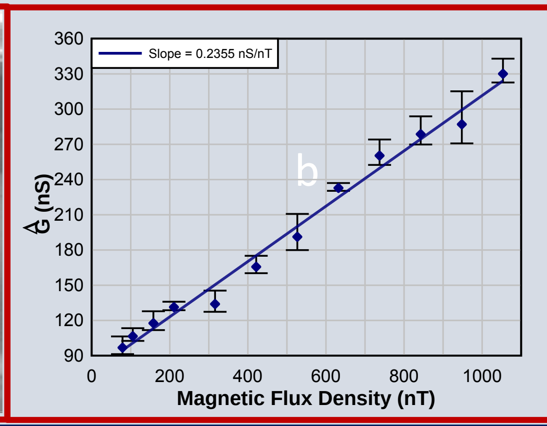


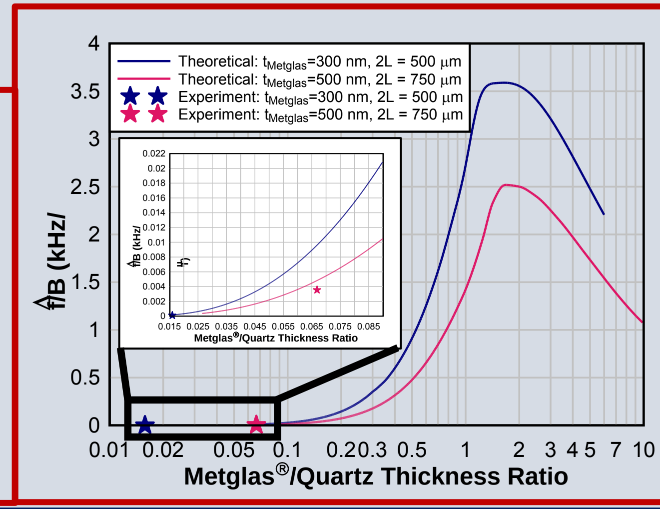
Hall et al 2012

Room Temperature MEMS-Based Sensing and Stimulation

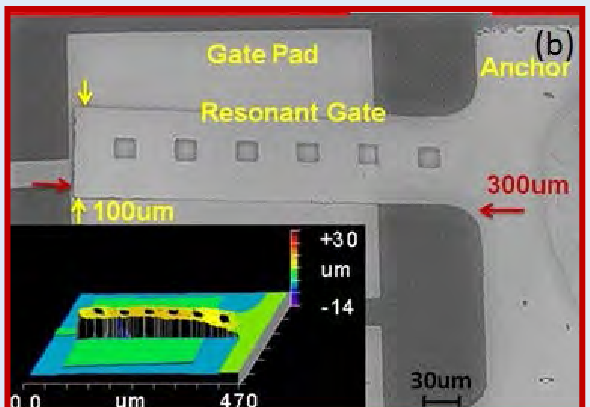
Magnetoflexoelastic Resonator

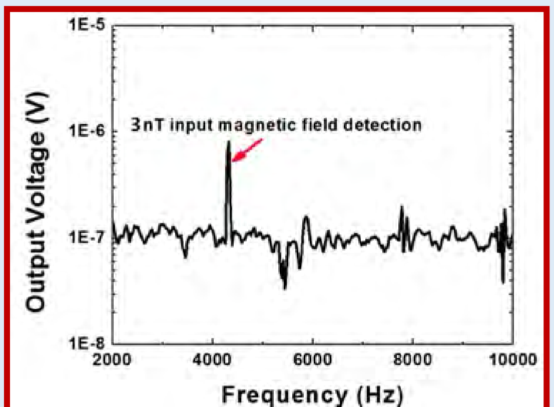






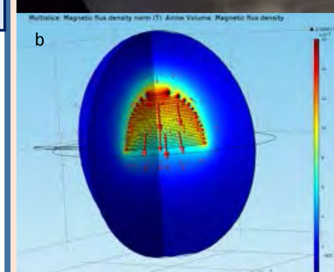
Flexure Gate Transistor

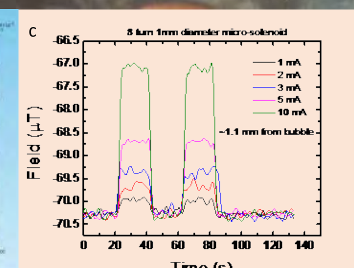




The Challenge is to create microscale magnetometers operating at room temperature and capable of pico – femto Tesla magnetic fields.

Micro-Stimulation

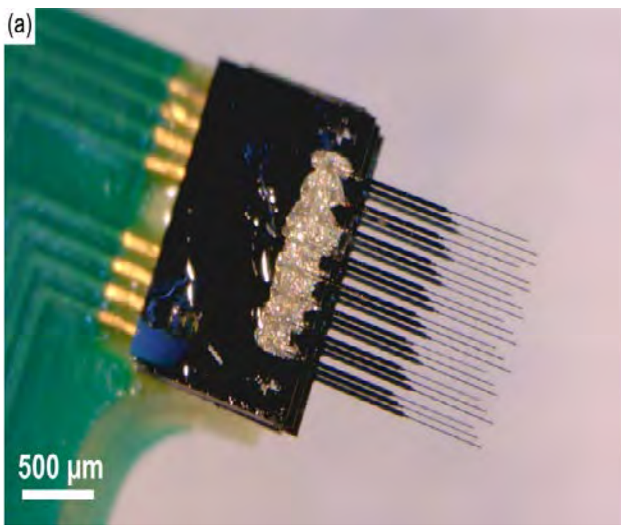




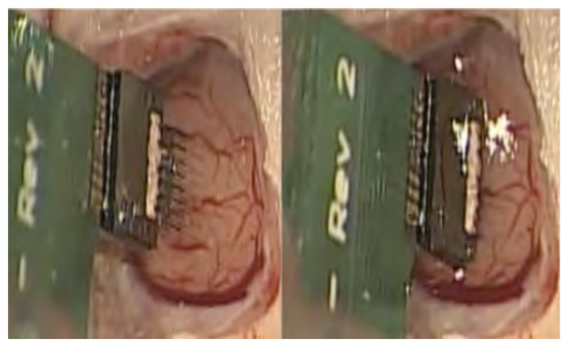
PennState
College of Engineering

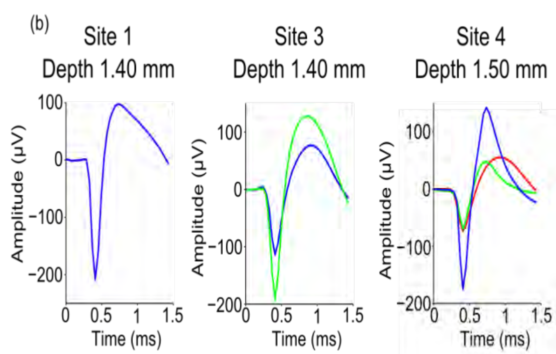
Carbon Thread Arrays for High-Resolution Multi-Modal Analysis of Microcircuits

CoPIs: Cynthia Chestek, Josh Berke, Co-I: Brandon Aragon, Key P: Paras Patel

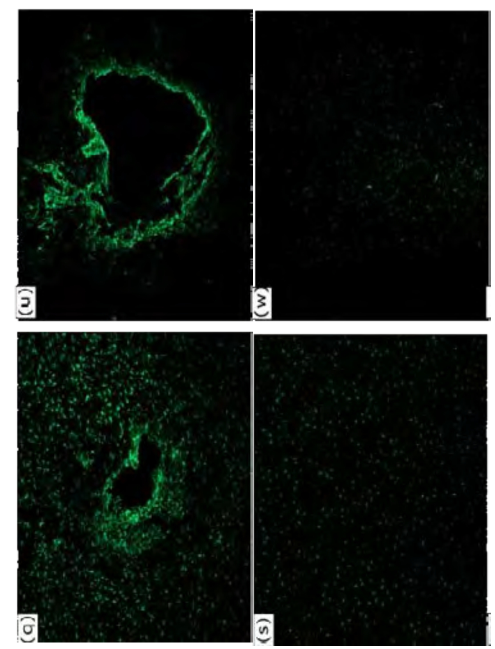


150 µm pitch carbon thread array
(Patel…Chestek, 2015)

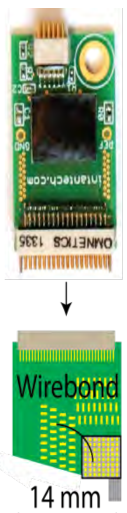


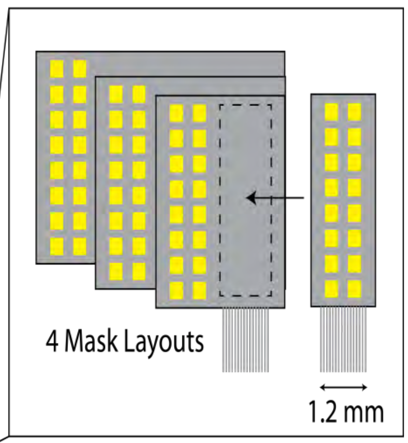


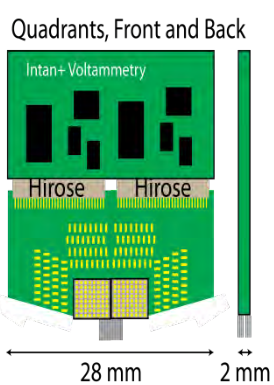
Silicon Probe Carbon Thread



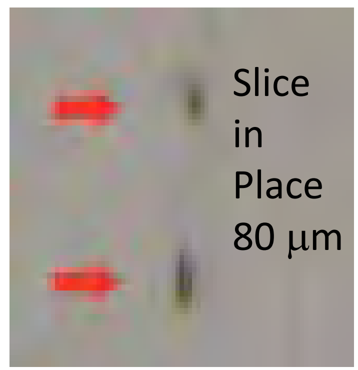
U01 Aims: High Density Array for Mapping Microcircuits and Chemical Sensing

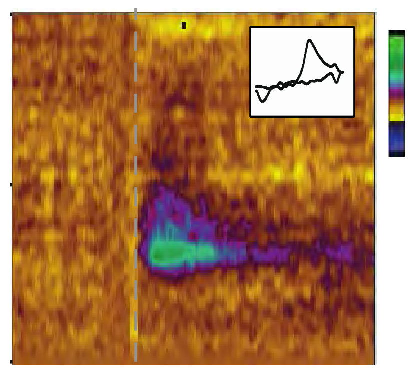




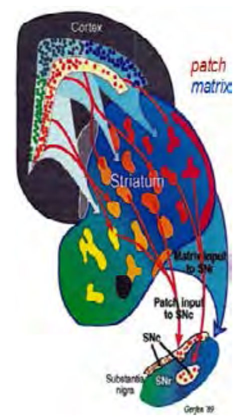


Up to 1024 ch in a rat

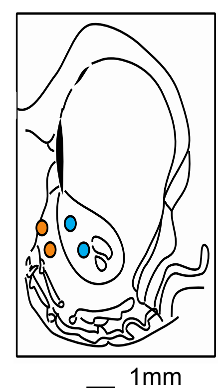




Voltammetry



Microcircuitry in basal ganglia patch matrix



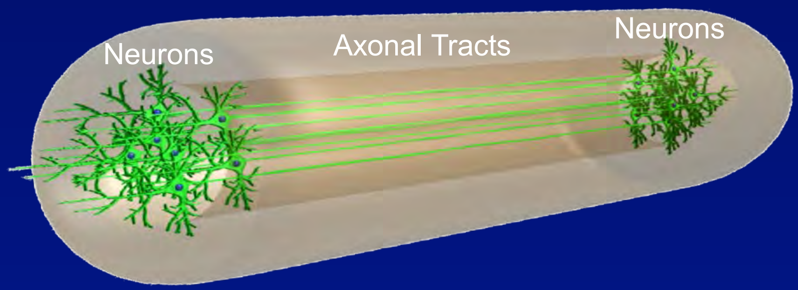
Regional specificity of dopamine in nucleus accumbens

Biological "Living Electrodes" Using Tissue Engineered Axonal Tracts to Probe and Modulate the Nervous System (U01-NS094340)

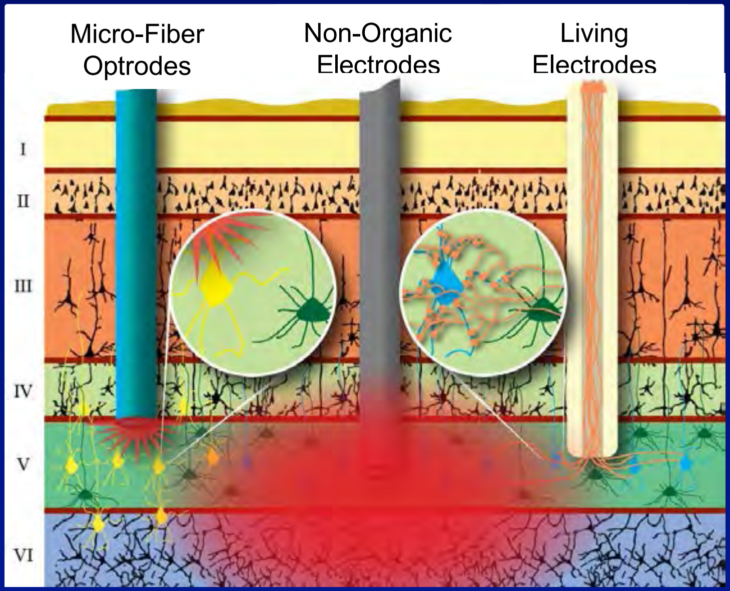
John A. Wolf, Mijail Serruya, Reuben Kraft, Brian Litt, Isaac Chen, Diego Contreras, D. Kacy Cullen (PI)

Primary Site: University of Pennsylvania; Secondary Site: Penn State University

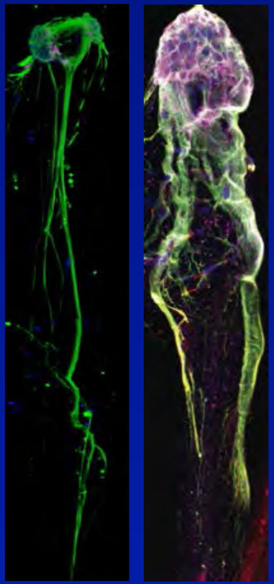
Micro-Tissue Engineered Neural Networks, "Micro-TENNs": preformed miniature constructs with discrete neuronal population(s) spanned by long axonal tracts



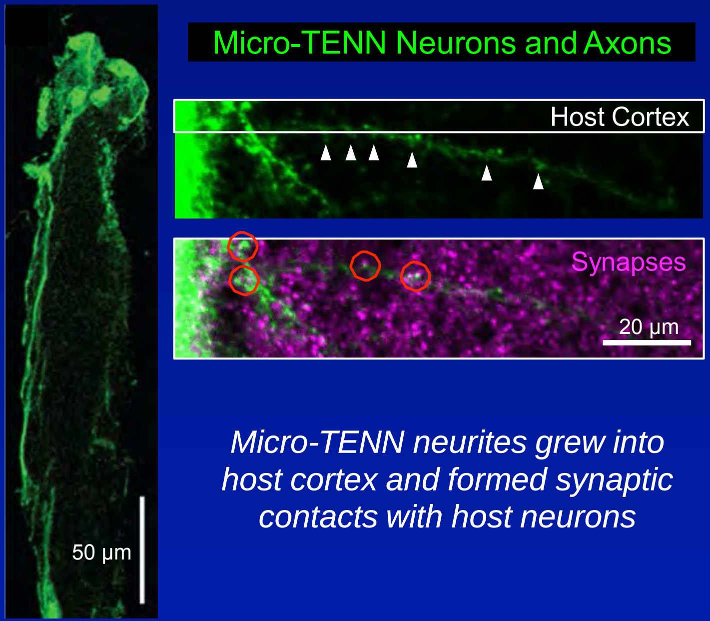
Advantages of "Living Electrodes"



Engineered Axonal Tracts *In Vitro*



Micro-TENN Survival & Integration With Brain



Micro-TENN neurites grew into host cortex and formed synaptic contacts with host neurons

Mechanisms of Action

Target Specificity: integration with specific neuronal subtype(s) while mitigating chronic foreign body response

Synaptic Integration: offers permanence not possible with standard approaches

Biological Multiplexing: robust effect may be elicited by relatively few axons

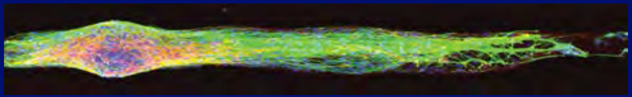
Struzyna LA et al., *Tissue Engineering,* "Restoring Brain Circuitry with Living Micro-Tissue Engineering Neural Networks" (2015)
Harris JP et al.. *J Neural Engineering*, "Advanced Biomaterial Strategies to Transplant Preformed Micro-Tissue Engineered Neural Networks into the Brain" (2015)

Biological "Living Electrodes" Using Tissue Engineered Axonal Tracts to Probe and Modulate the Nervous System (U01-NS094340)

"Living Electrodes" Experimental Paradigm

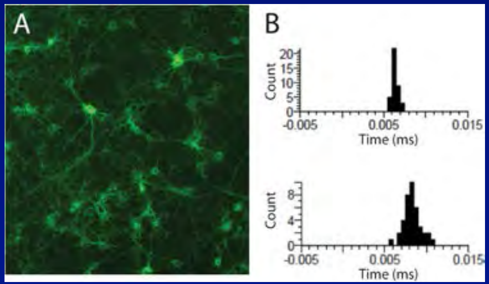
We are constructing tailored "living electrodes" to provide synaptic-mediated integration with specific layers of cerebral cortex in rats.

Phenotype-Specific Micro-TENNs

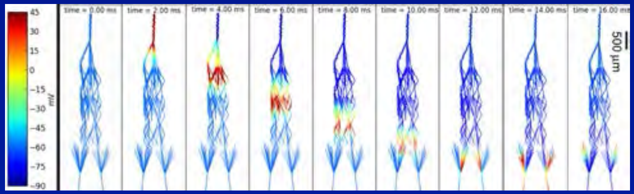


Dopaminergic Neurons/Axons (Tyrosine Hydroxylase); All Axons (β-Tubulin III); Nuclei(Hoechst)

Optogenetic Control

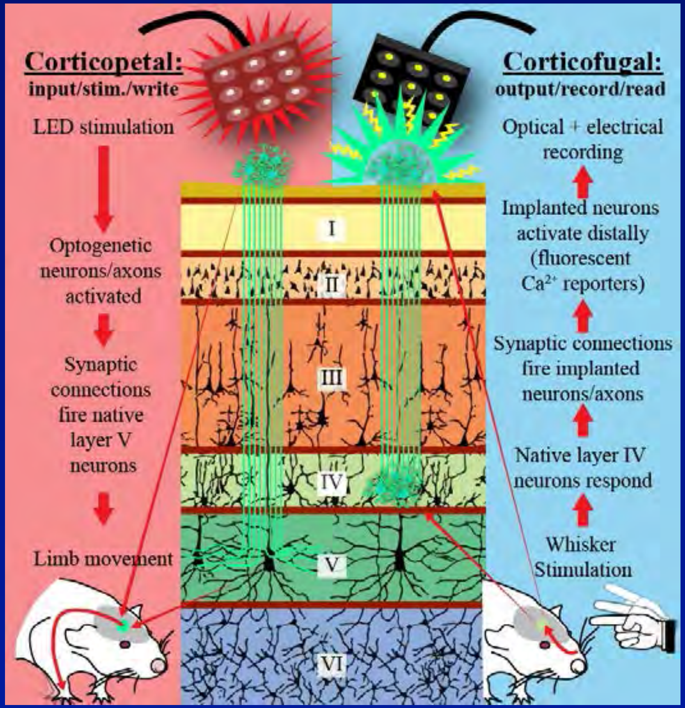


Simulations of Micro-TENN Integration and Function

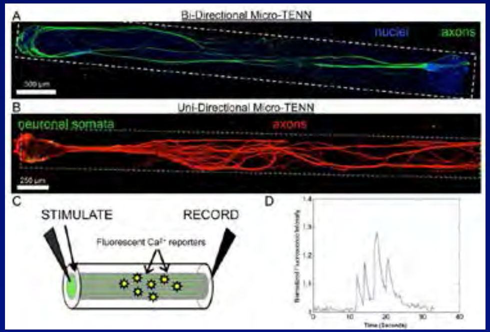


INPUT PLATFORM: Permitting controlled excitation or inhibition of neural circuitry.

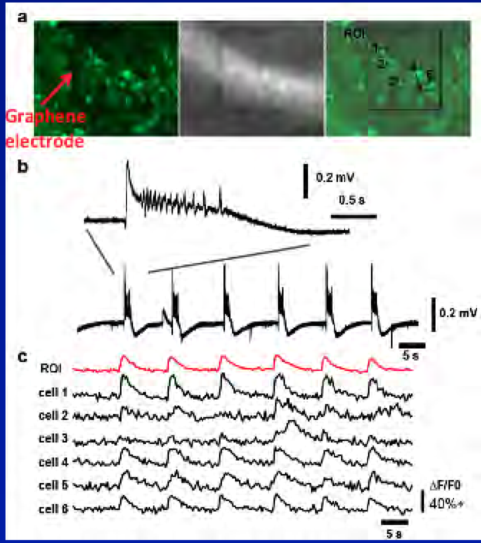
OUTPUT PLATFORM: A facsimile of deep activity may be projected to the surface.



Structure and Function *In Vitro*



Transparent Graphene Micro-ECoG Arrays for Chronic Interface



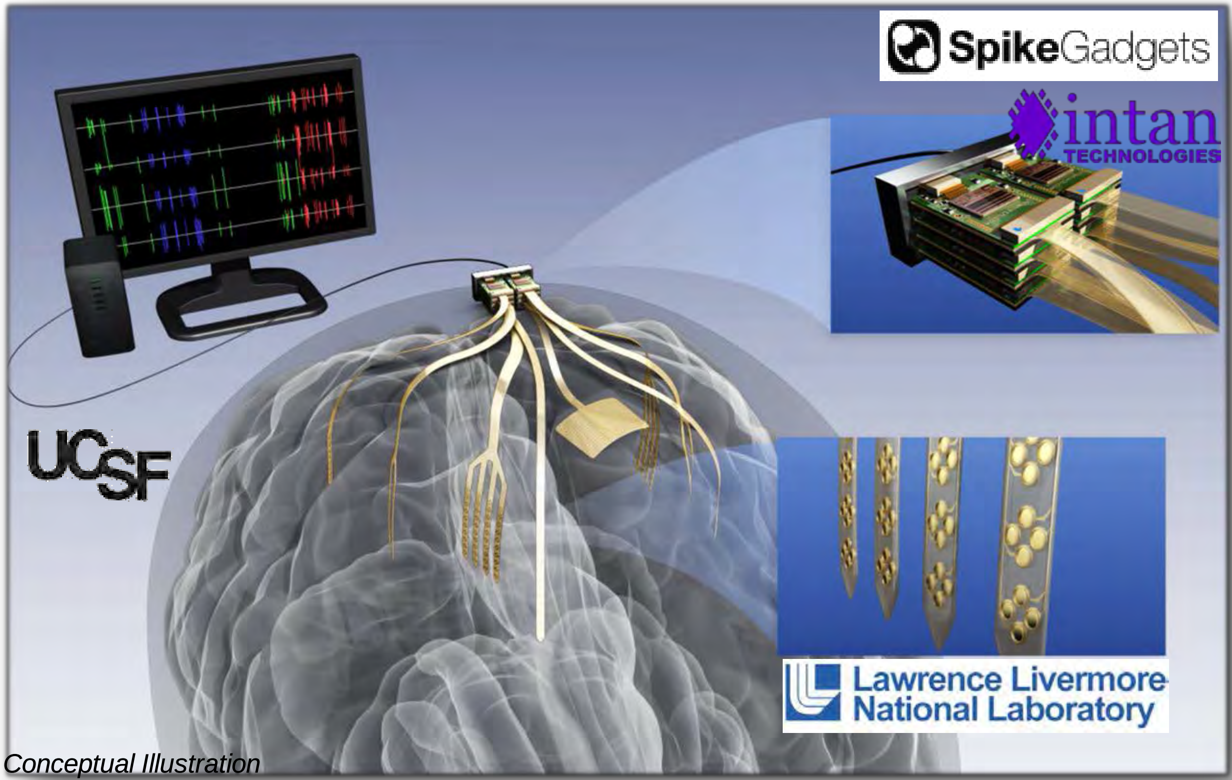
We have demonstrated control of structure, phenotype, maturation/plasticity, and functionality of "living electrode" constructs.

Biological interface with neurons/axons may act as "intermediary" between host and electronics, ultimately enabling prosthetic control, sensory/proprioceptive feedback, and/or neuromodulation.

Cullen DK et al., *Tissue Engineering*, "Microtissue Engineered Constructs with Living Axons for Targeted Nervous System Reconstruction" (2012)
Struzyna LA et al., *Neural Regeneration Research*, "Restoring Nervous System Structure and Function with Tissue Engineered Living Scaffolds" (2015)

Modular systems for measuring and manipulating brain activity

PIs: Loren M. Frank[1,2], Vanessa M. Tolosa[3], Reid Harrison[4]
[1]Dept. of Physiology, UCSF; [2]Howard Hughes Medical Institute; [3]Materials Engineering Division, Lawrence Livermore National Lab; [4]Intan Technologies

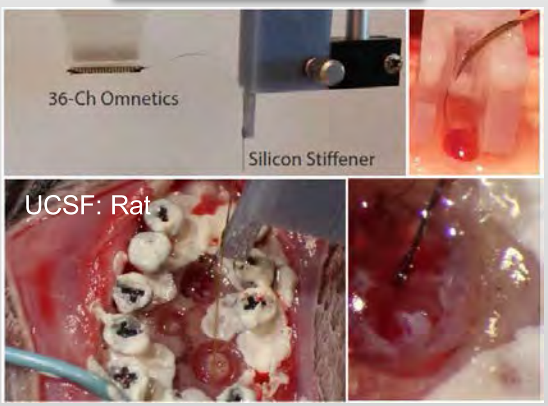


Conceptual Illustration

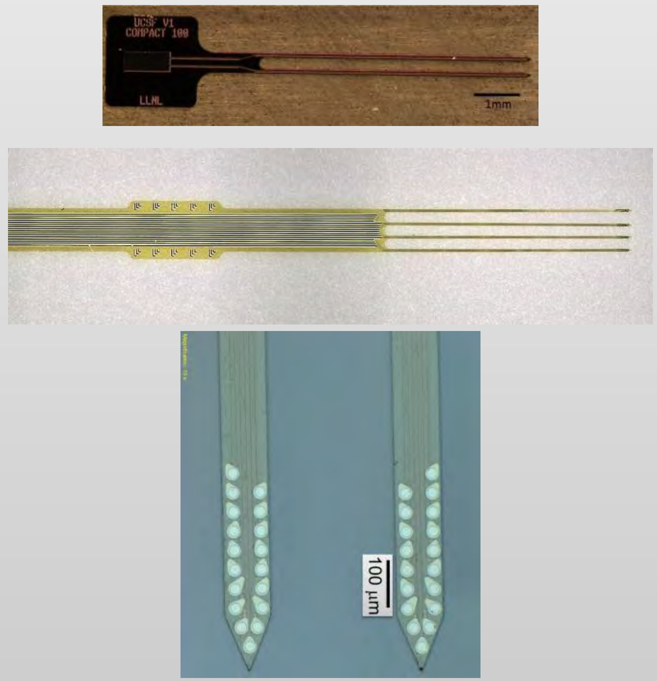
No technology currently exists that allow for large scale, distributed measurements of neural activity across many sites in awake, behaving animals

Toward technology for understanding distributed brain circuits

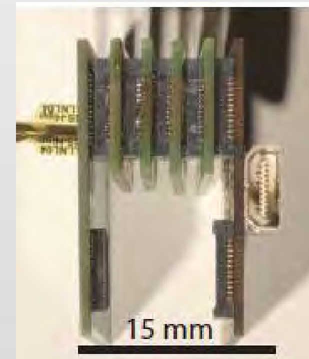
Surgical Method



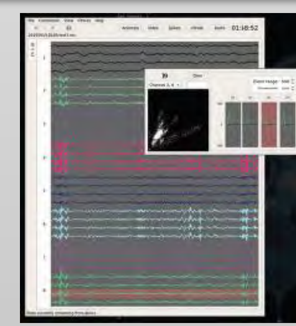
Flexible Probes



Mini Headstage



Open Source Software



Polymer probes allow long-lasting, high-density recordings in awake, freely behaving animals

Large-Scale Electrophysiological Recording and Optogenetic Control.

Baldwin Goodell[1], Charles M. Gray[1], Bijan Pesaran[2] and David Sheinberg[3]
1.Gray Matter Research, LLC, Bozeman, Montana 2.New York University, New York, NY 3.Brown University, Providence, RI

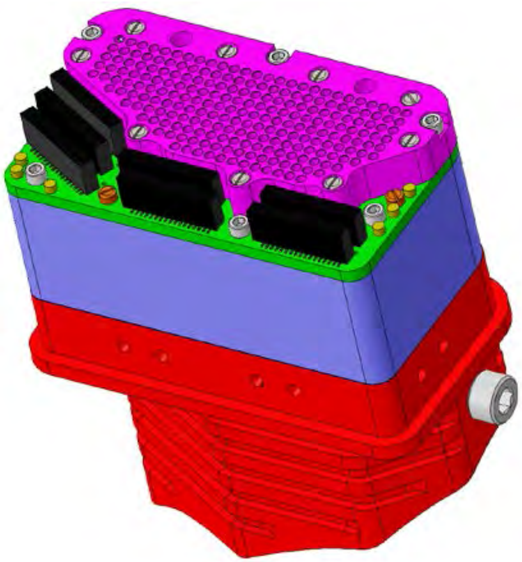


Figure 1. 220 channel electrode microdrive with 32mm travel targeting OFC, dACC, vACC, area-25, dlPFC, FEF, Caudate, Putamen, ventral Striatum, PMd, M1, Amygdala, Thalamus, Hippocampus (Bijan Pesaran, NYU)

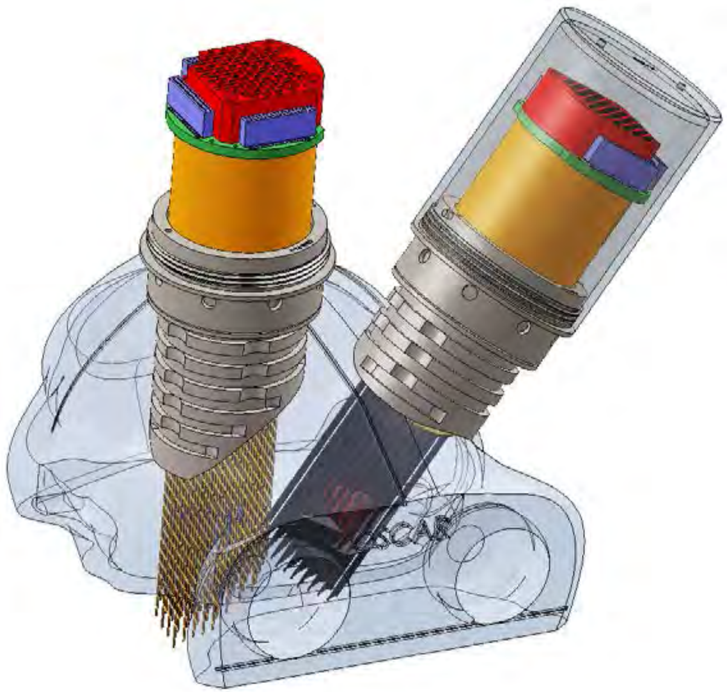


Figure 2. Dual 96 channel electrode microdrives with 32mm of travel targeting vmPFC (left hemisphere), Anterior Insula (right hemisphere) (Jon Wallis, U.C. Berkeley)

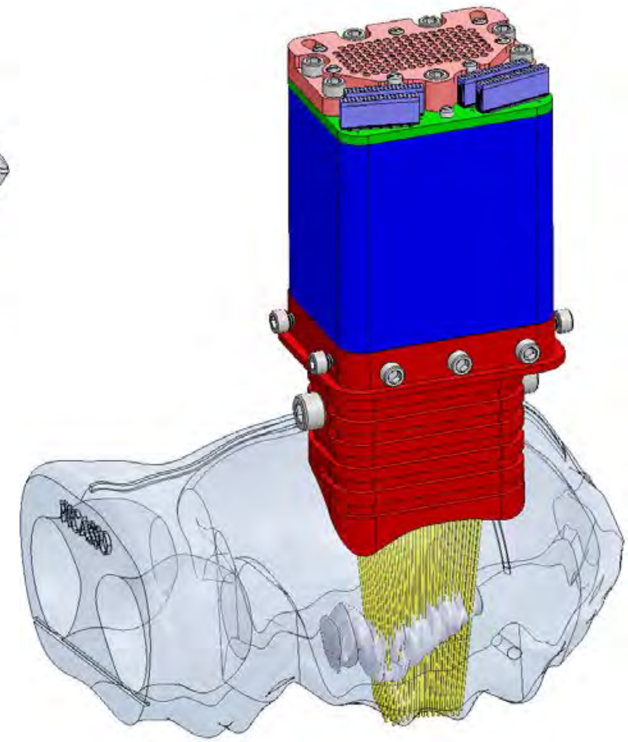


Figure 3. Convergent 128 channel electrode microdrive with 40mm of travel targeting Full AP extent of left Hippocampus (Shih Cheng Yen, National Univ. Singapore)

BRAIN Initiative Symposium

NIH (NINDS) U01 NS090455, Year 2 of 3

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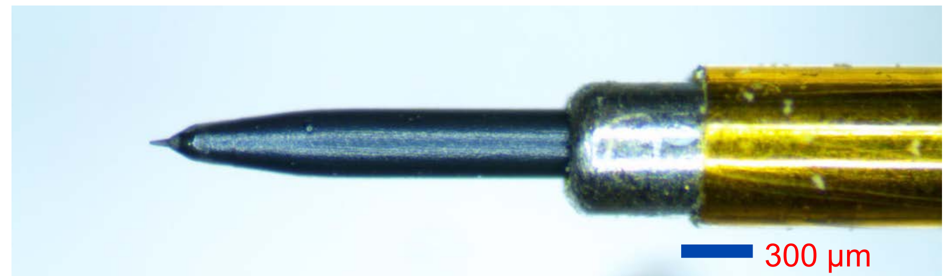
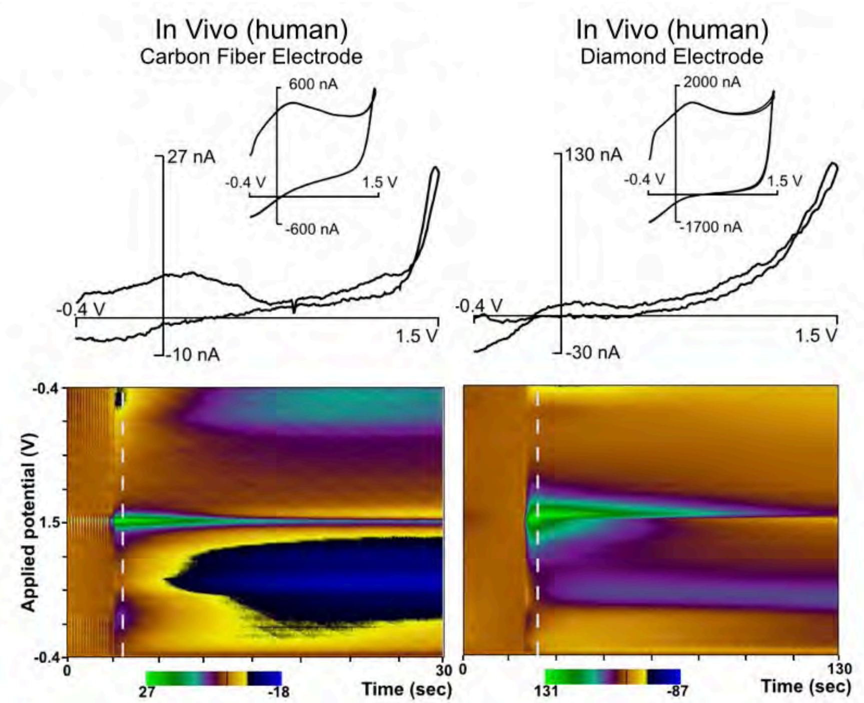
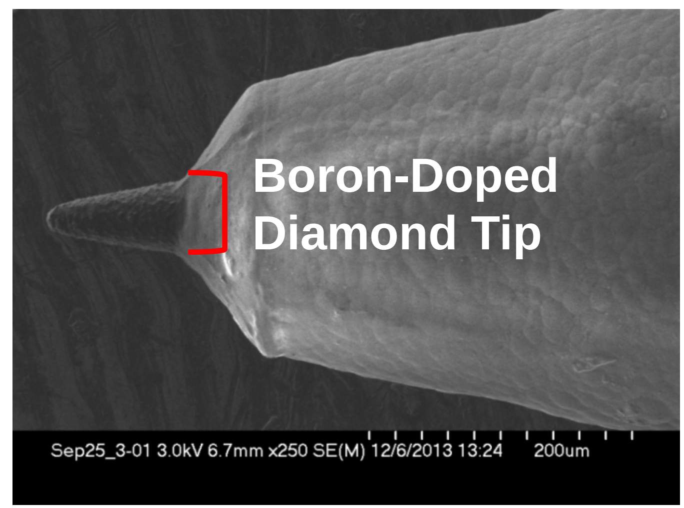
Diamond Electrode Fabrication (Aim 1)

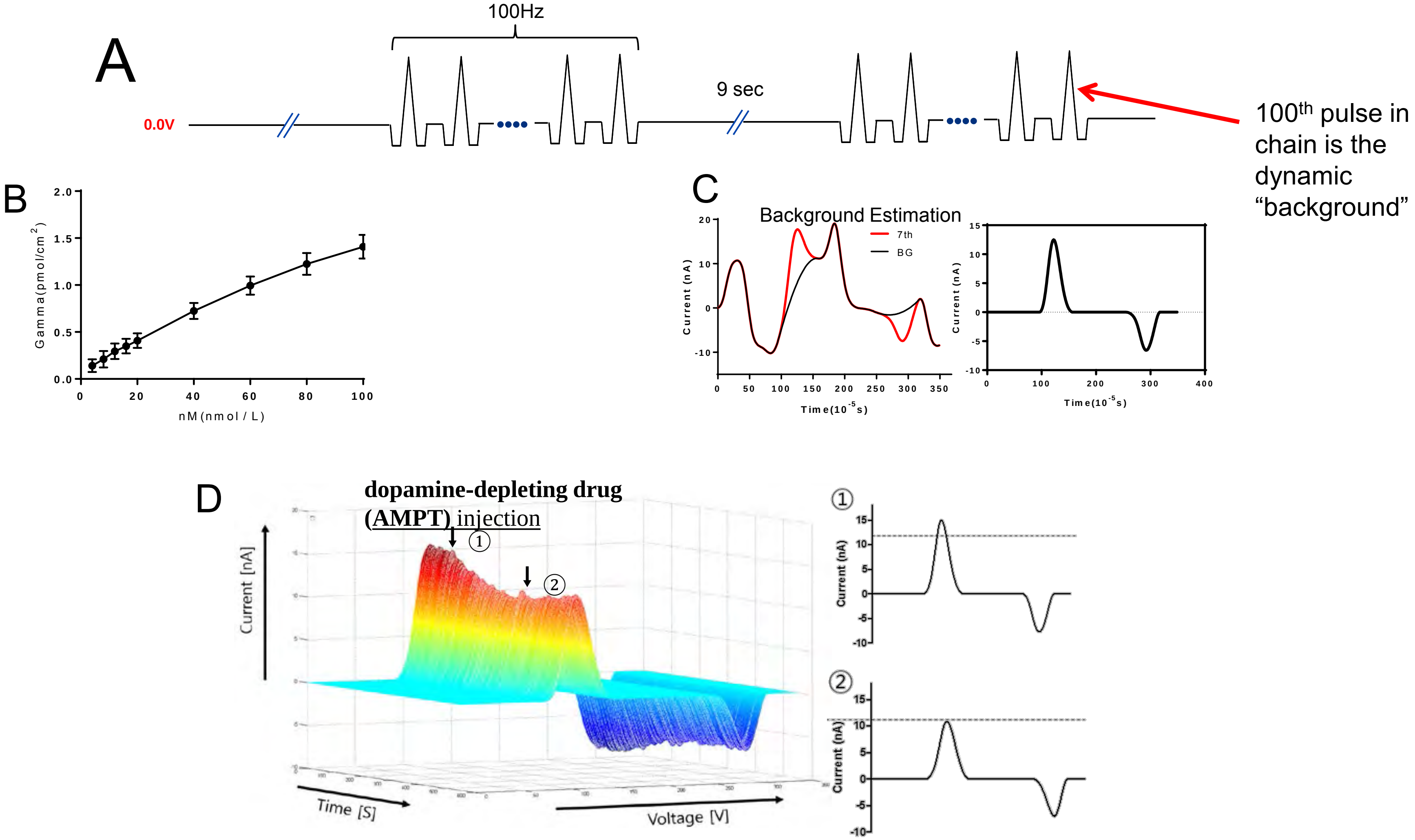
- Acute electrode for human (and large animal) use constructed using FHC microtargeting electrode design as a point of departure
- Chronically-implantable (flexible) diamond-tipped electrode nearing completion







Dopamine concentration calibration and Pharmacological Test *in vivo* (Aim 2)



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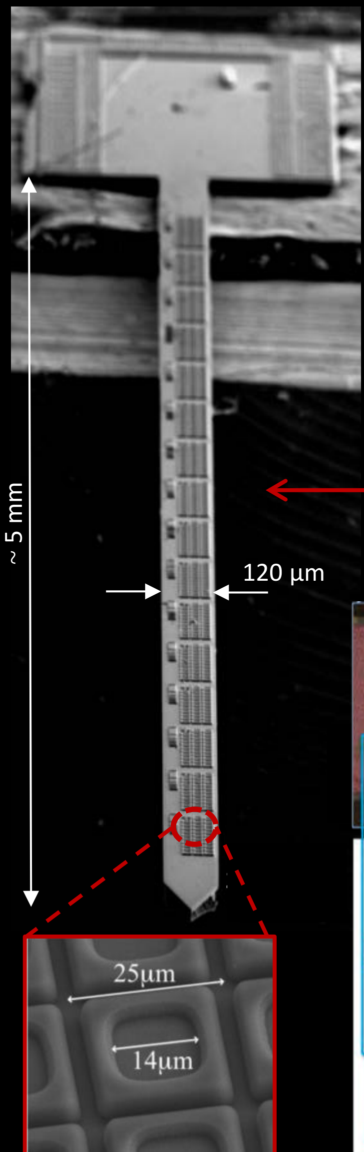
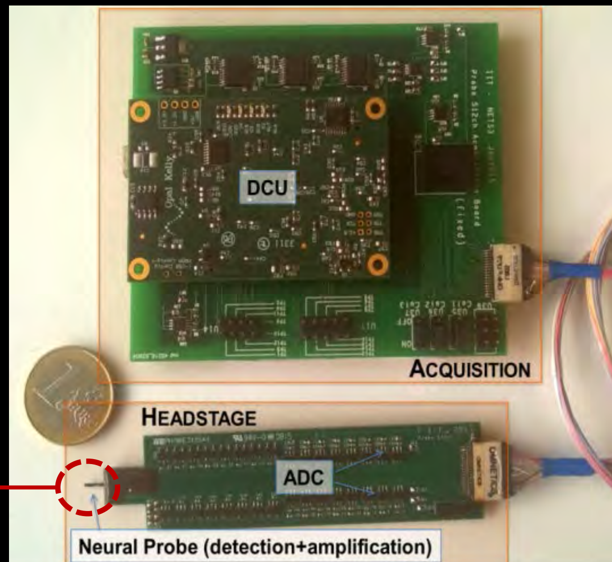
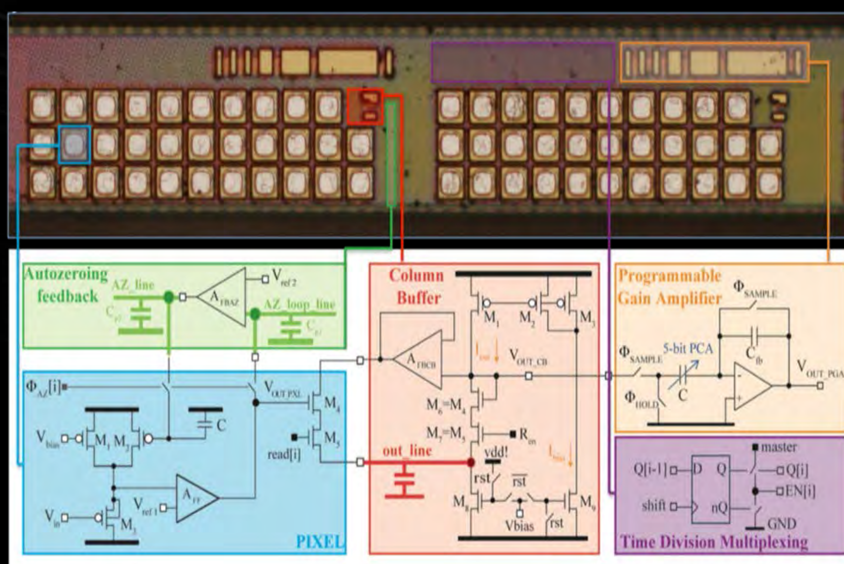
AIM I - IMPLANTABLE CMOS-MEA PROBE PLATFORM FOR ACUTE RECORDING FROM THOUSANDS OF NEURONS SIMULTANEOUSLY





	target	achieved *generation I*
# electrodes-pixels on signle shaft	1024	512
pitch [µm]	< 30	25
electrode size [µm x µm]	< 20 x 20	14
pow er consumption [mW]	< 40 [(a)]	3,6 [(b)] 2,5 [(c)]
full-array sample frequency/el. [kHz]	> 20	30
programmable gain range [dB]	~[40 ; 70]	[42; 72]
shaft size (thickness x w idth) [µm x µm]	~50 x 100	30[(d)] x 100
ADCs	off-chip	off-chip
# probe pads	< 10	36
number of simultanously recording probes	>4	8 of 512 el.
noise level [μV_{RMS}]	< 20	12,7 [(e)] 8,4 [(f)]
recording bandw idth [kHz]	~ [0.1; 8]	[1;8]

(a) to ensure local ΔT< 2°C (*see . H. Marblestone et al., 2013*)
(b) worst case
(c) with on-chip power scheduling
(d) minimal thickness for the wedge-like shape
(e) on 1Hz - 10 kHz
(f) on 100Hz - 10 kHz



DONE

- probes designed and realized in 0.18 µm CMOS technology
- robust autozeroing circuit for compensation of DC-offsets and light stimuli implemented
- electrode post-processing for shaft shaping and electrodeposition (e.g. Pt) implemented
- HW & SW interface ready

NEXT

- ADCs to be integrated on-probe to reduce probe pads
- in-vivo experimental validation
- Integration with multipoint emitting optical fibers (MPFs)

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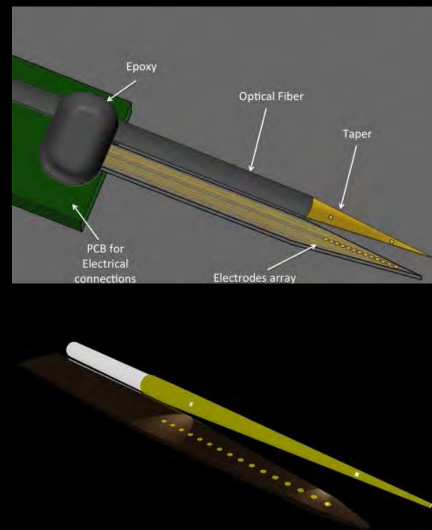
AIM II – TAPERED MULTIPOINT EMITTING OPTICAL FIBERS (MPFs) FOR SPATIALLY ADDRESSABLE *IN VIVO* OPTOGENETICS

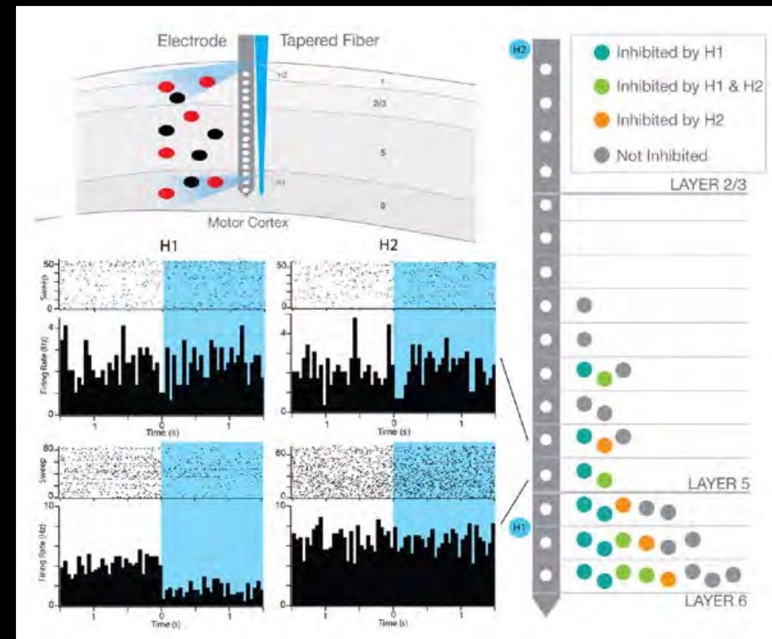
❑ 2W-MPF (two windows)

Working principle

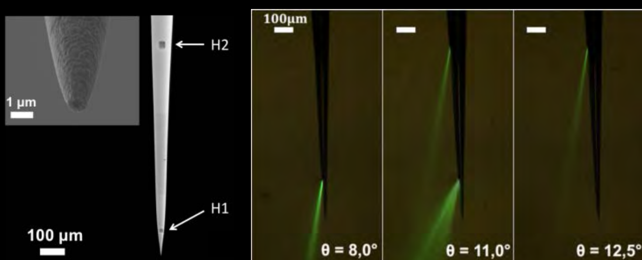
Coupling with commercial MEA



Validation in vivo

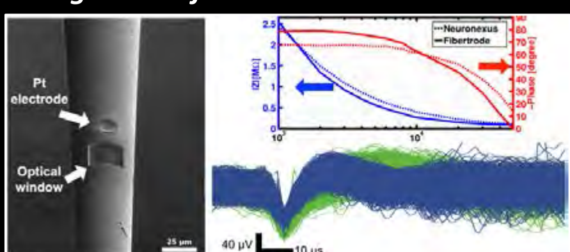


Fabrication and validation in vitro

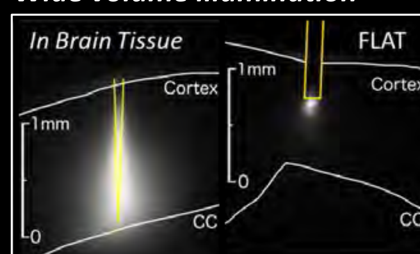


❑ Additional Innovation (preliminary tests)

Integration of microelectrodes



Wide volume illumination



DONE

- Fabrication of a two-windows optical fiber
- Validation and characterization in vitro of the site selection properties
- Coupling with a commercial MEA in vivo electrode
- Validation in vivo by selective stimulation of two different cortical layers

NEXT

- Increasing the number of optical windows
- Optimization of positioning relative to electrodes
- Integration with implantable CMOS-MEA probes

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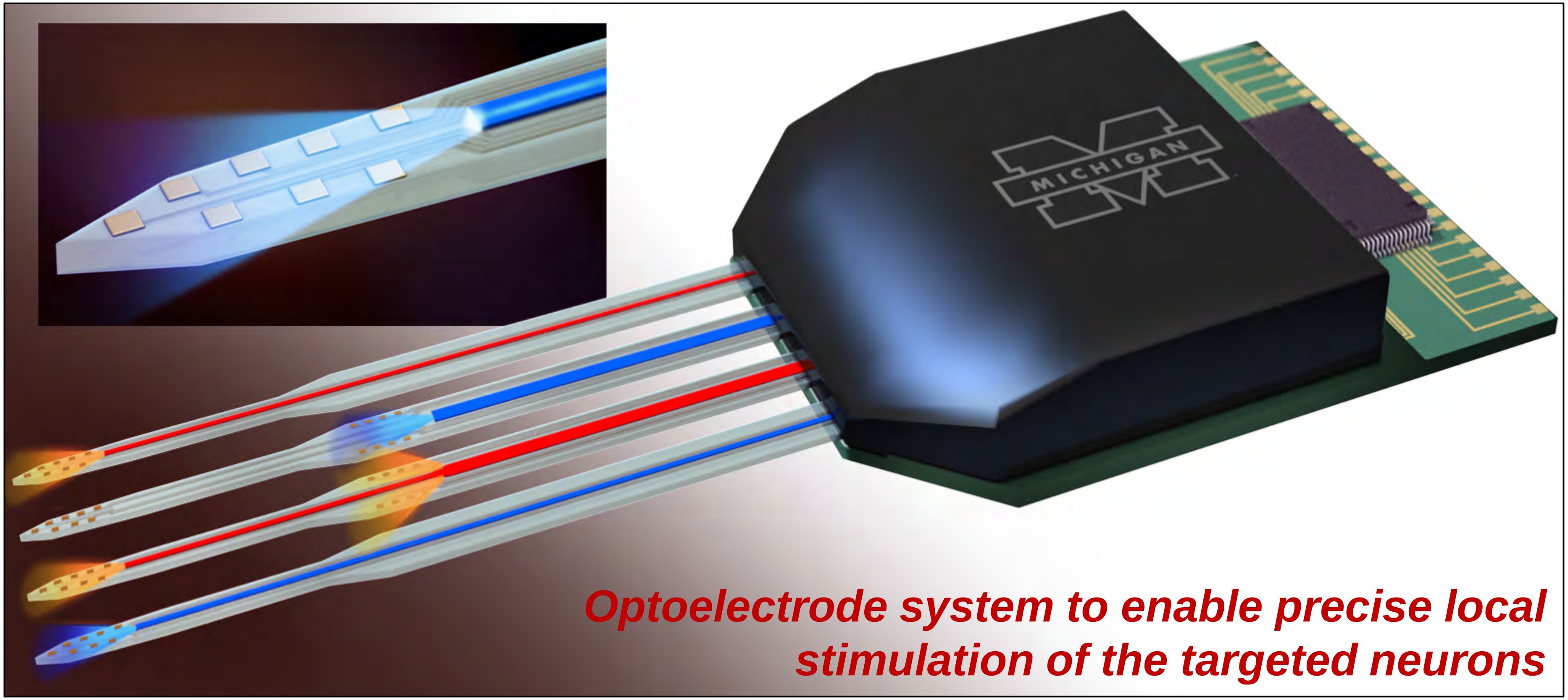
Modular High-Density Optoelectrodes for Local Circuit Analysis

Euisik Yoon[1], Ken Wise[1], John Seymour[1], György Buzsáki[2]

[1]*Department of Electrical Engineering and Computer Science,* University of Michigan

[2]*The Neuroscience Institute,* New York University School of Medicine



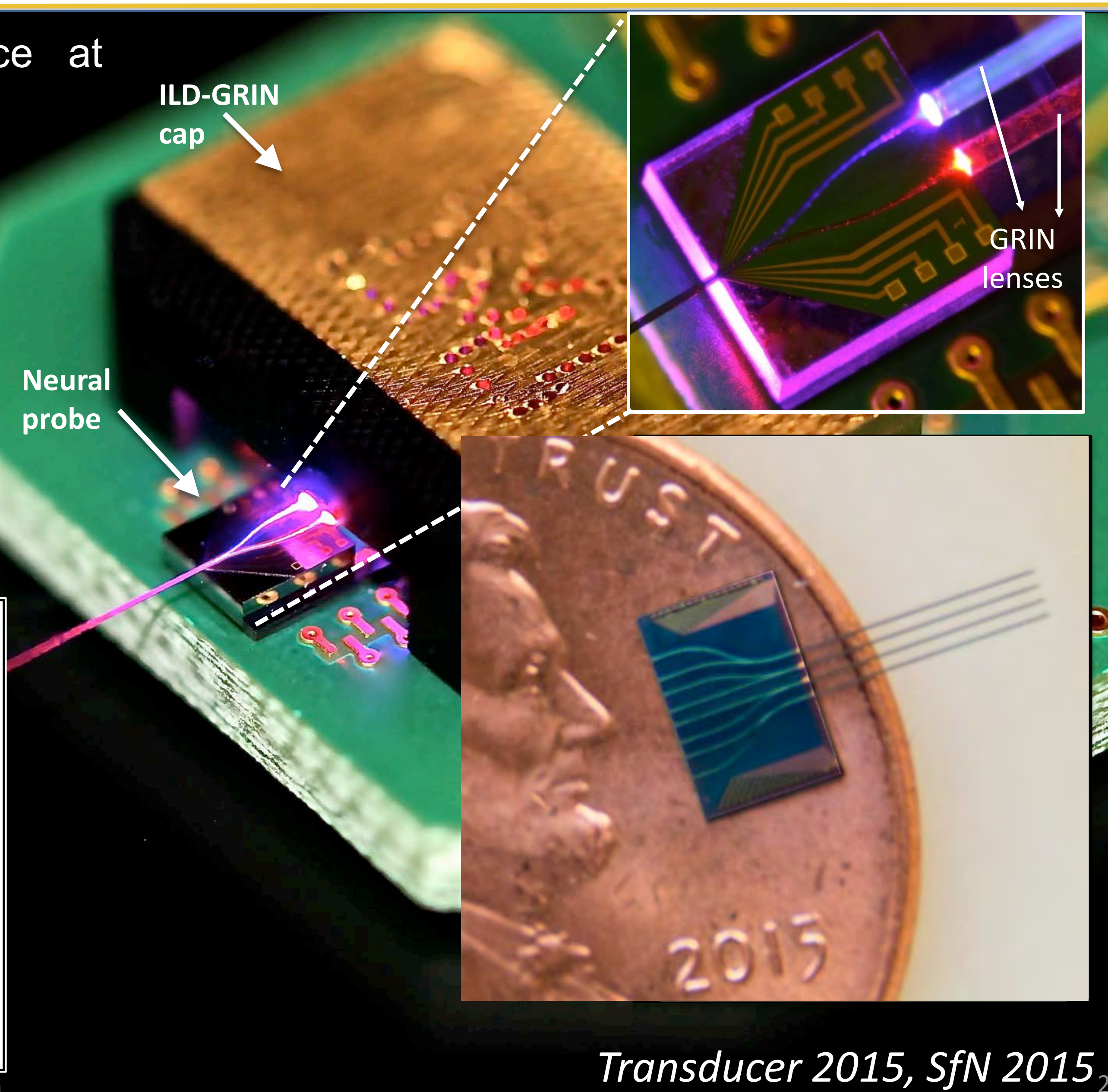
Fiberless multiple color generation, Compact and scalable

Monolithic integration, Thermal and EMI noise isolation

Fabricated Fiberless Dual-Color Optical Probes

Achieved optical irradiance at waveguide tip:

2905 mW/mm^2 for 635nm
1928 mW/mm^2 for 405nm

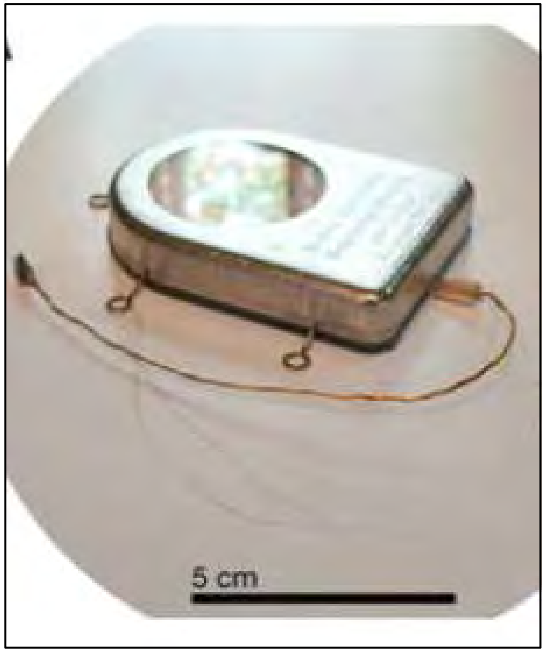


Current controlled light emission at tip

Transducer 2015, SfN 2015

High-Bandwidth Wireless Interfaces for Continuous Human Intracortical Recording

Co-PIs: Leigh R. Hochberg, MD, PhD and Arto Nurmikko, PhD



- Hermetically sealed, ultralow-power, **100-channel, full bandwidth wireless implant** for intracranial/intracortical BCI; state of art custom microelectronics, ASICs, etc.
- **Implanted in three primates for up to ≈2 years** – freely moving (home cages)
- Wireless RF link based on novel ASIC (>50 Mbit/sec, **distances 1-2 meters**)
- Inductive coupling for **battery charging** (presently 7.5 hrs continuous use; < 30 minute re-charging period)
- **UH3:** Early Feasibility Study in BrainGate multi-site collaboration; 6 participants with SCI, brainstem stroke, or ALS, over 3 years.

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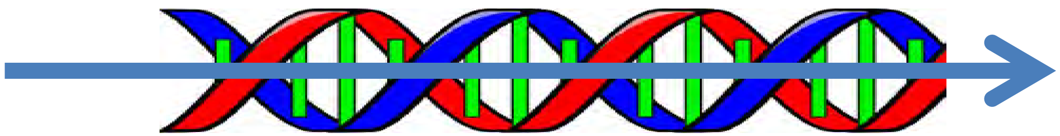
High-Bandwidth Wireless Interfaces for Continuous Human Intracortical Recording

Co-PIs: Leigh R. Hochberg, MD, PhD and Arto Nurmikko, PhD

Engineering/
Manufacturing
Track

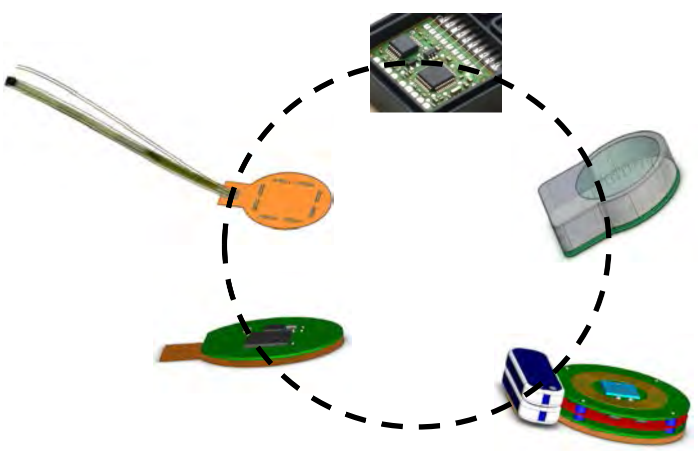
Human compatible
Medical device system

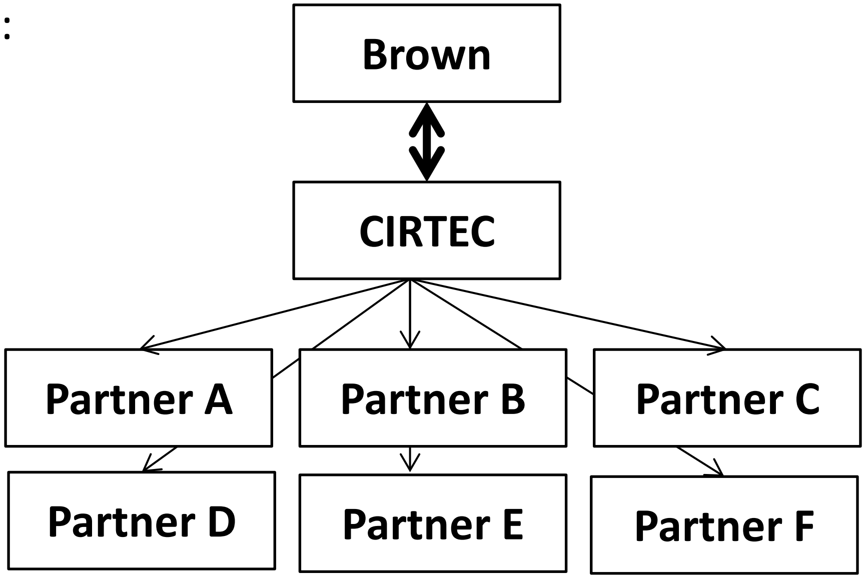


Clinical/Regulatory
Track

Early Feasibility Study IDE
(Academic Sponsor-Investigator)

Implantable Device Manufacturing Flow:





UH3 NS09554 'Central thalamic brain stimulation for traumatic brain injury'

<u>Weill-Cornell Medical College:</u>
Nicholas Schiff, MD (PI)
Joseph J. Fins, MD
Jonathan Baker, PhD
Sudhin Shah, PhD
Laurel DeGeorge, MA

<u>Harvard/Spaulding Rehabilitation</u>
Joseph T. Giacino, PhD (PI)
Sabrina Taylor, PhD

<u>Cleveland Clinic :</u>
Andre Machado, MD, PhD (PI)

<u>Stanford University:</u>
Jaimie Henderson, MD (PI)
Brian Rutt, PhD
Stephanie Kolakowsky-Hayner, PhD
Jason Su, (PhD)

<u>University of Utah</u>:
Christopher Butson, PhD (PI)
Andrew Janson, (PhD)

Specific Aims

- **<u>Aim 1</u>: To establish the safety of CT-DBS in patients with severe-to-moderate brain injuries and outcomes of GOSE 6-7.** We will assess the safety of implantation of DBS electrodes within the central thalamus in this new patient population and characterize any stimulation related adverse effects.
- **<u>Aim 2</u>: To establish measures of efficacy of CT-DBS stimulation in patients with severe-to moderate brain injuries and outcomes of GOSE 6-7.** We will collect a broad range of outcome measures across six domains of function (cognitive, social participation, psychological health, quality of life, vocational, and global function) to identify sensitive measures of efficacy of CT-DBS. As behavioral function in patients in this range of recovery is multi-dimensional and CT-DBS effects in this population are undemonstrated, these measurements will be crucial to advance the further development of clinical trials.
- **<u>Aim 3:</u> To obtain and analyze critical human subject data to guide device design enabling effective and robust modulation of the DTTm in the human central thalamus.** We will combine high-resolution anatomical and diffusion tensor imaging studies with computational biophysical models and *in situ* imaging of electrode positions implanted in the 12 thalami of 6 patients to establish probabilistic models of behavioral and electrophysiological (far field, local field, and microelectrode recording) effects and their variation with respect to coverage of the DTTm in the human thalamus. These studies will guide the development of next-generation multi-electrode systems.
- **<u>Exploratory Aim 1:</u> To obtain and analyze physiological data obtained from the Activa PC+S device during wake and sleep periods to assess CT-DBS effects on brain function.** We will use the sensing capabilities of the Activa PC+S system to record stimulation-linked activation of local thalamic populations during acute stimulation and longitudinally across spontaneous wake and sleep periods to develop a database to study underlying mechanisms of long-term changes in brain function associated with CT-DBS as measured in our prior studies in two human subjects shown below.

Neurophysiologically Based Brain State Tracking & Modulation in Epilepsy

Gregory Worrell, Mayo Clinic, Medtronic, UMinn, UPenn

- **1/3 are drug resistant (1M people in US)**
- **Brain stimulation devices (VNS, RNS, PC): Gaps**
  - Modest efficacy (rarely seizure free)
  - Data poor (EEG, Sz. catalogs, manage & share)
  - Device analytics limited (No off-body-analytics)
  - Device life (~5 yr. not rechargeable)

Next Generation Therapeutics

Acquisition

iEEG Telemetry

Wide bandwidth

Analytics (local/distributed)

Sz. detection & diary

Evoked responses

Behavioral state

Sz. forecasting

Therapy

Intelligent stim.

Continuous control