

Monitoring and Modulating Circuit Activity in Pain: Promise of the BRAIN Initiative

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Disclosures



NeuroLux

Co-founder and part owner.

NeuroLux manufactures ultraminiaturized micro-LED devices for wireless optogenetics.



@NeuroLuxInc

BRAIN INITIATIVE

BRAIN RESEARCH
THROUGH ADVANCING
INNOVATIVE
NEUROTECHNOLOGIES



The BRAIN initiative is aimed at revolutionizing our understanding of the human brain. By accelerating the development and application of innovative technologies, researchers will be able to produce a revolutionary new dynamic picture of the brain that, for the first time, shows how individual cells and complex neural circuits interact in both time and space.

BRAIN INITIATIVE TIMELINE

2013:
 - Obama announces BRAIN Initiative.
 - NIH, NSF, and DARPA commit \$100M for 2014.

2014:
 - FDA and IARPA join.
 - Initiative establishes long-term vision and research priorities.

2016 – 2020:
 - \$400M per year funding period dedicated to the development of new tools and technologies

2021 – 2025:
 - \$500M per year funding period for application of new tools to study of the brain

FEDERAL PARTNERS

NIH Development of new tools and techniques

DARPA Rehabilitation of warfighters and civilians

i7 Cognition and computation in the brain

NSF Fundamental biology and technology development

FDA Regulation of neurological medical devices

RESEARCH PRIORITY AREAS

1) Brain Cell Types
 - Identify the many different cells that comprise the brain and determine their functions

2) Tools for Circuit Diagrams
 - Map connections between nerve cells to define neural circuits within the brain

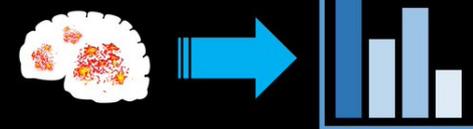
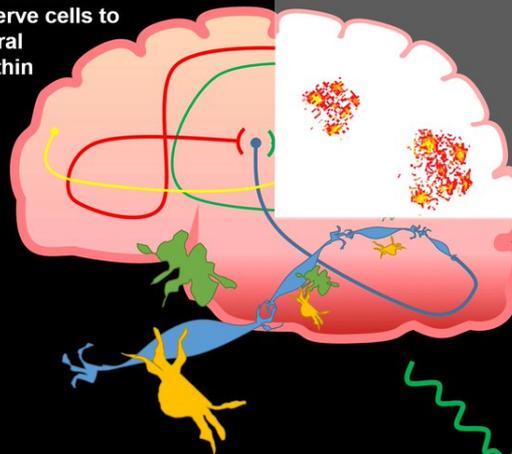
3) Technology to Monitor Neural Activity
 - Monitor activity of individual nerve cells and neural circuits over the breadth of the entire brain simultaneously

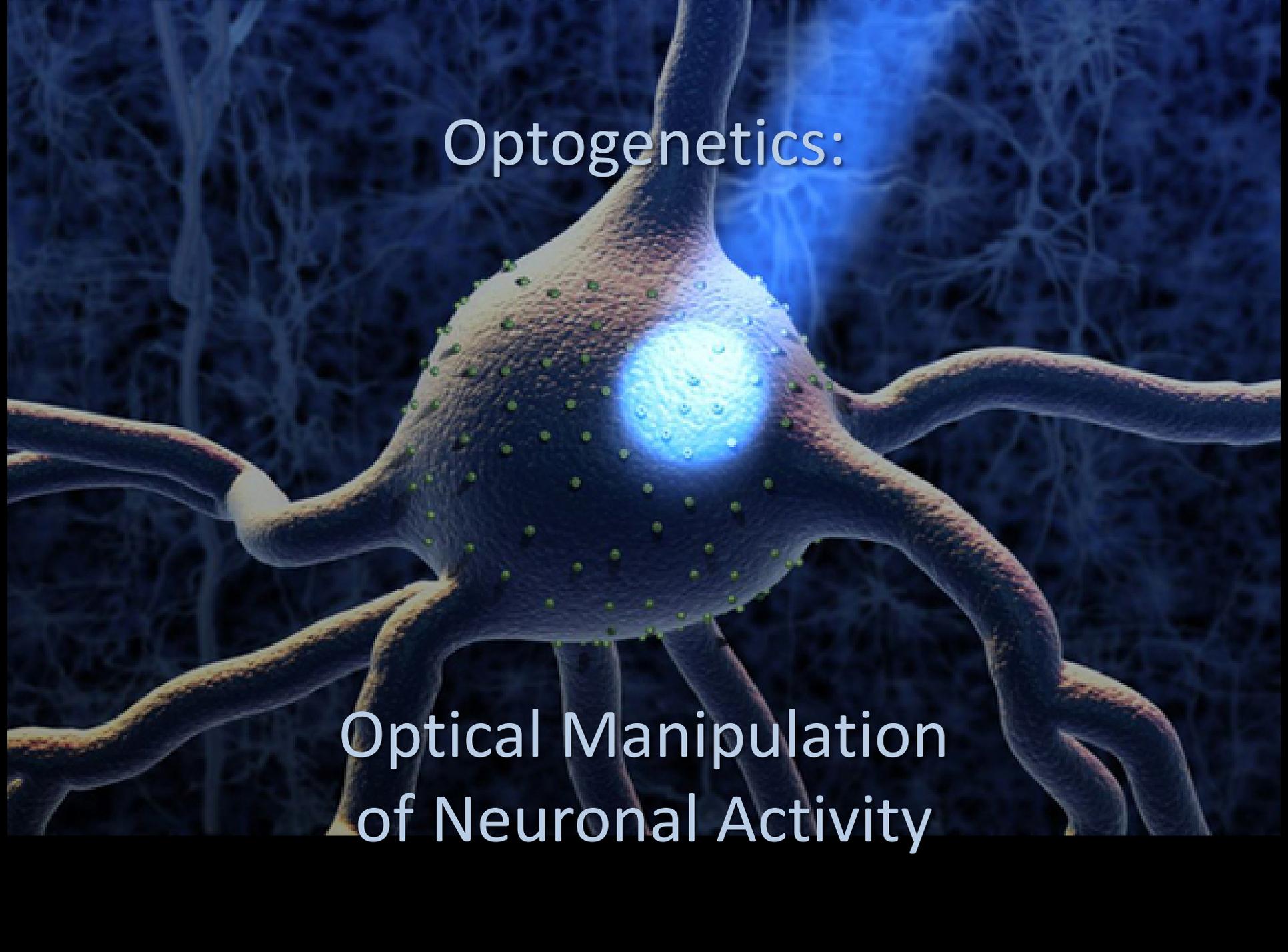
4) Precise Interventional Tools
 - Determine the role of different neural circuits in behavior by targeted manipulation

7) Integrated Approaches
 - Combine the tools and findings of other priority areas for a comprehensive understanding of brain function

6) Human Neuroscience
 - Study the human brain and work toward treatments for disorders

5) Theory and Data Analysis Tools
 - Develop new methods to work with data acquired during study of the brain



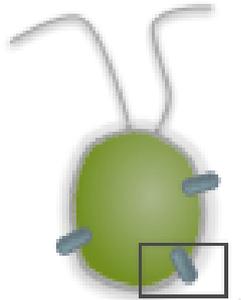
A 3D rendering of a neuron with a glowing blue nucleus and green dots on its surface, set against a background of a neural network.

Optogenetics:

Optical Manipulation
of Neuronal Activity

How optogenetics works

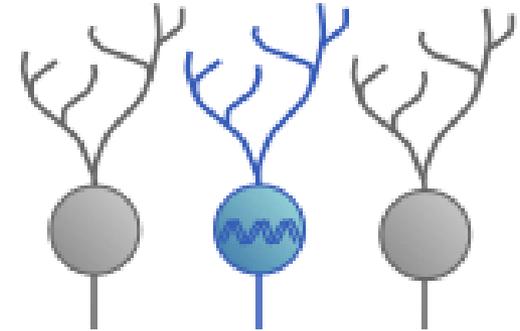
A light-sensitive protein from algae



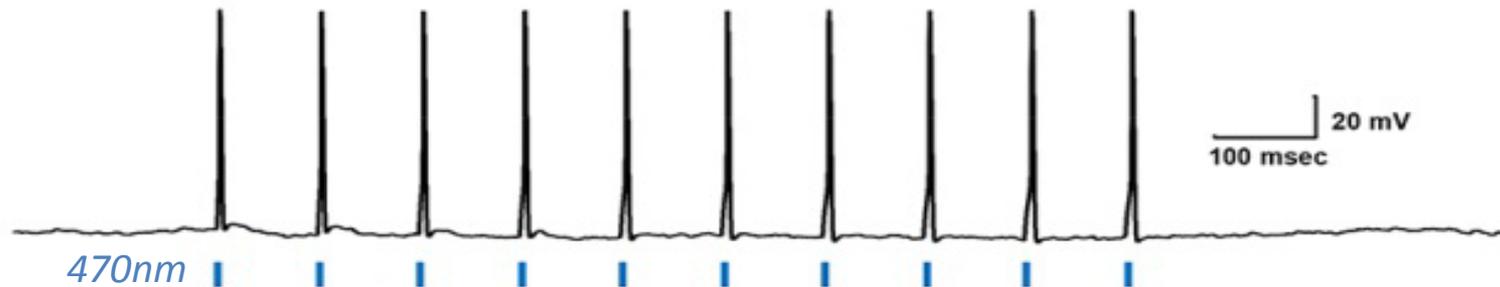
Take the gene for this protein...



... and insert the DNA into specific neurons in the brain

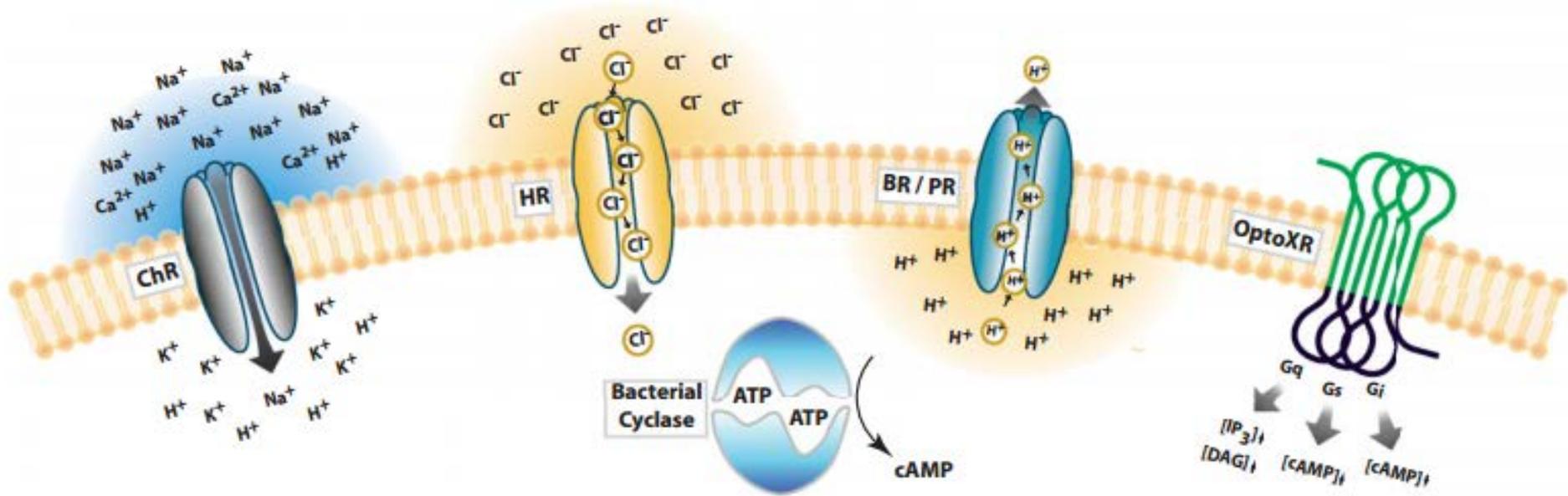


<http://neurobyn.blogspot.com/>



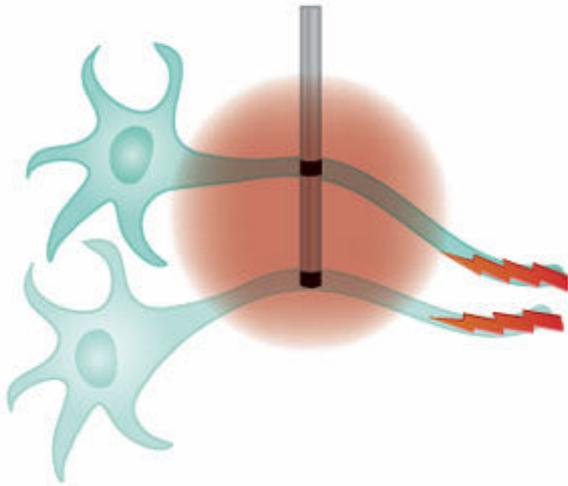
Bryan Copits

Optogenetics – Multiple “Opsins”

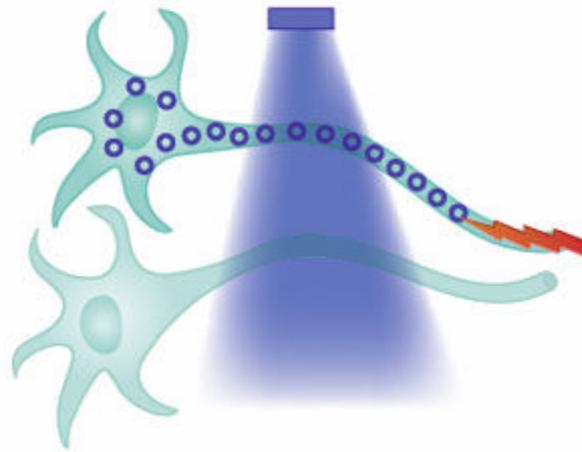


Optogenetics >> Electrical Stimulation for cell type-specific control

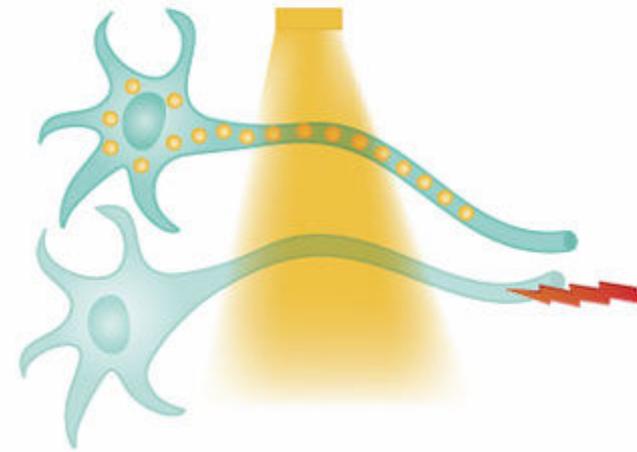
Electrical stimulation



Optogenetic excitation



Optogenetic inhibition

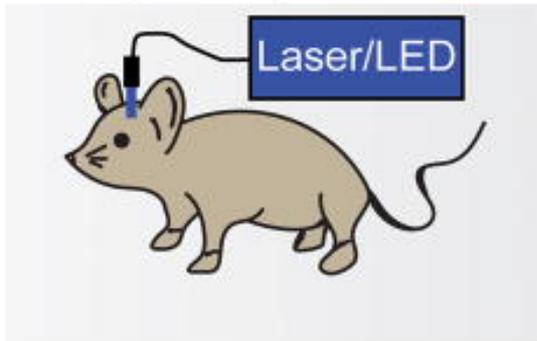


Optogenetics:

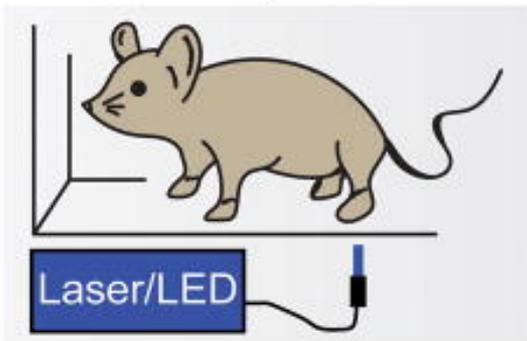
Approaches to Light Delivery

Traditional Light Delivery Methods

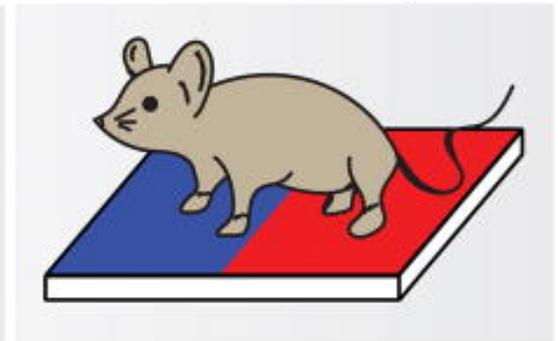
Implanted optical cable



External optical cable



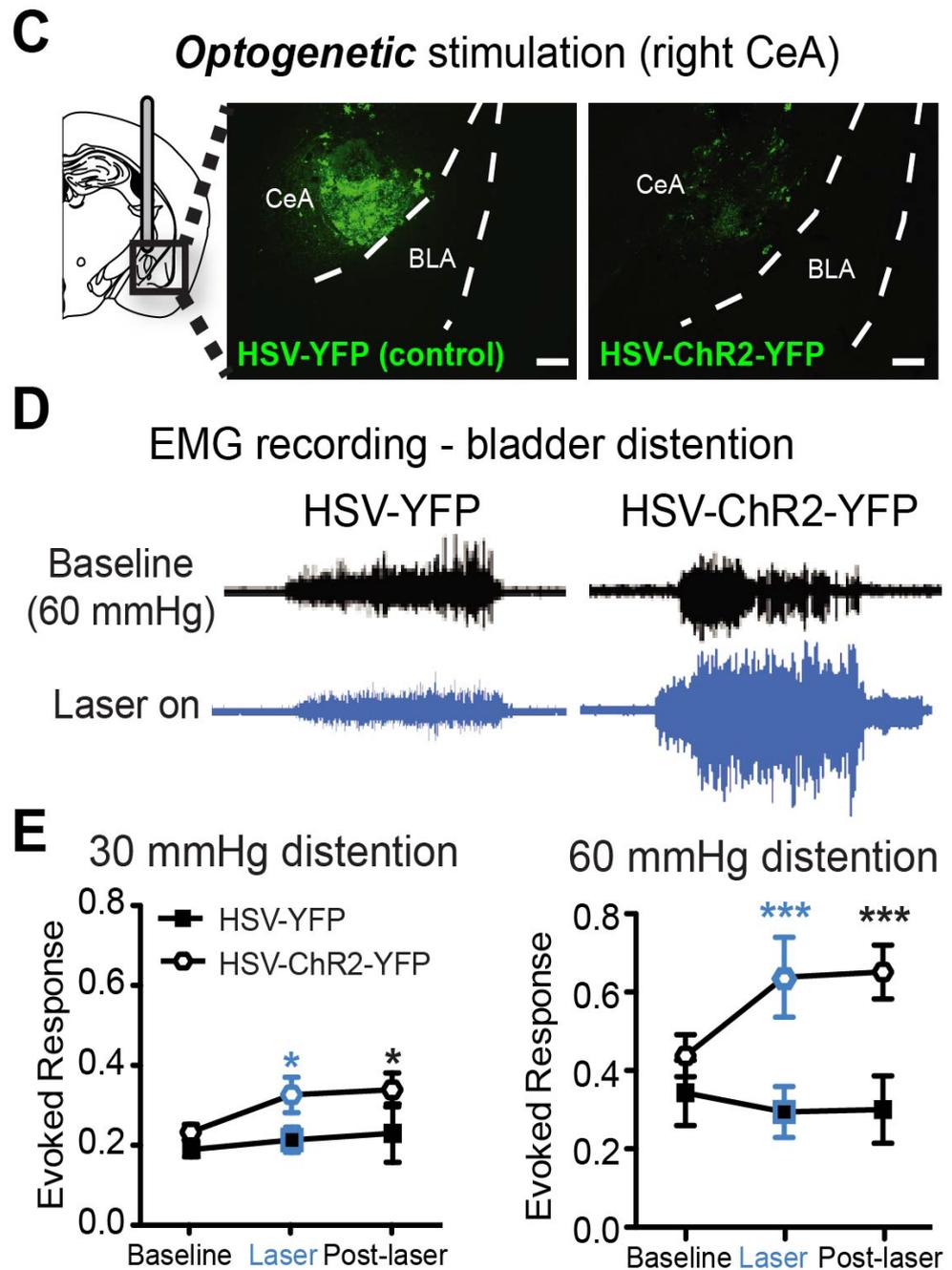
Floor LED array



Can we use optogenetics to study pain circuits?

Optogenetic Stimulation of CeA Enhances Bladder pain

Crock/Kolber et al
J. Neuroscience, 2012



Fiber coupling leads to constraints on experimental design and significantly impacts animal behavior

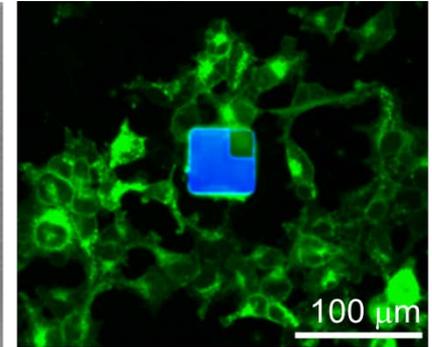
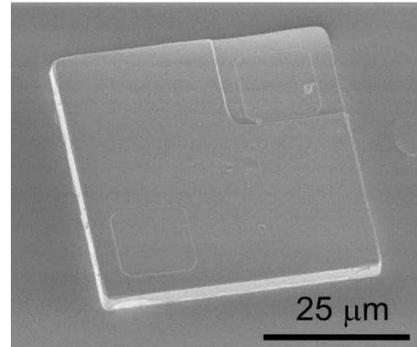


micro-LED Development

-collaboration with
John Rogers, Northwestern Univ.

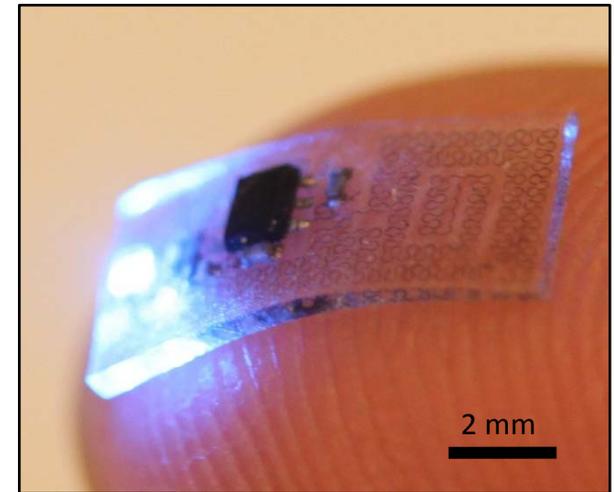
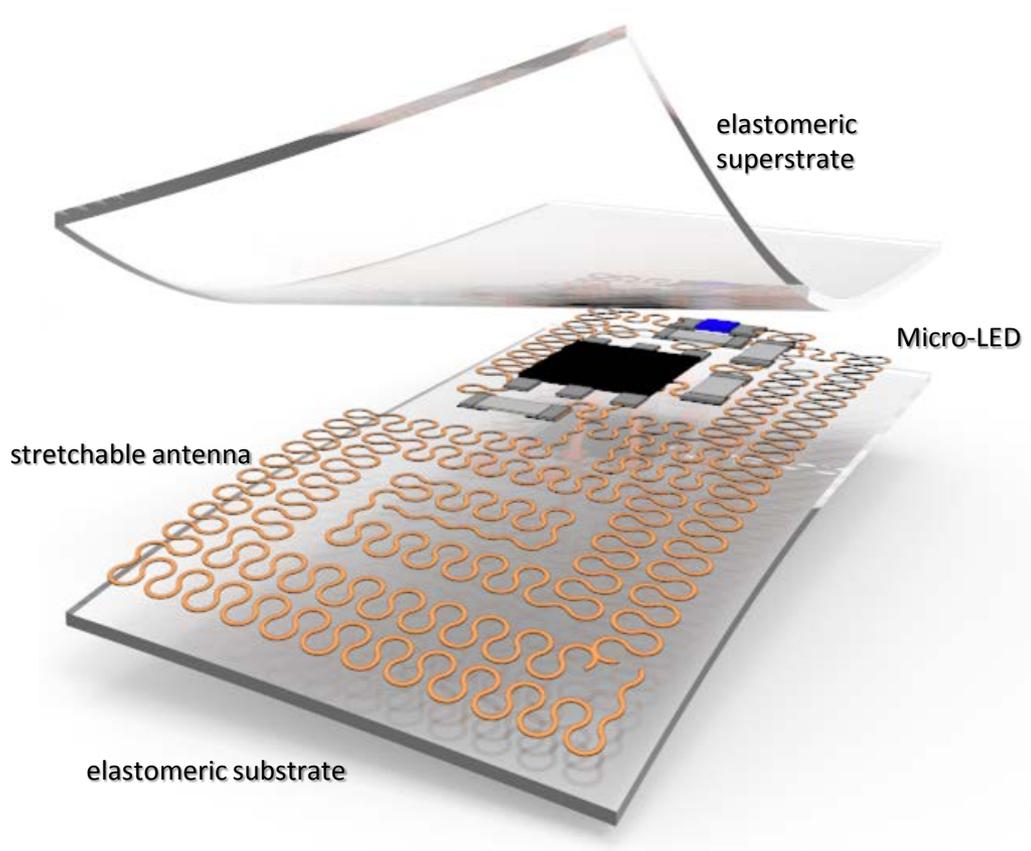


**Michael Bruchas,
Washington Univ.**

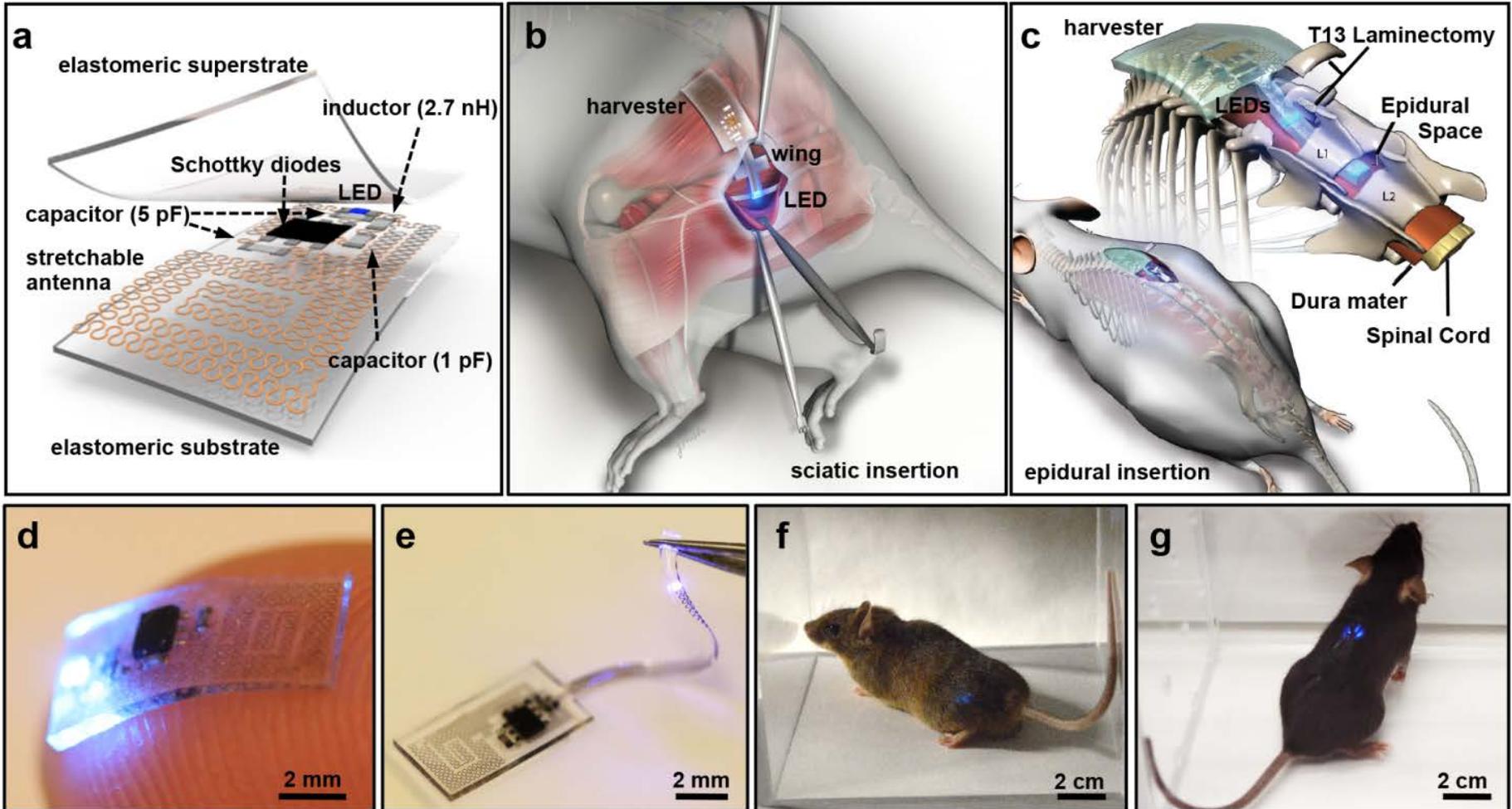


Kim et al, *Science*, 2013

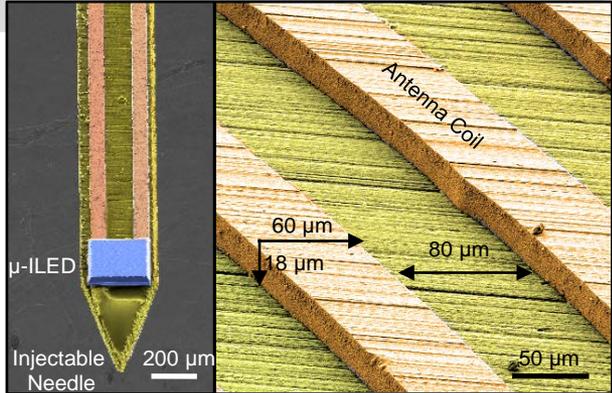
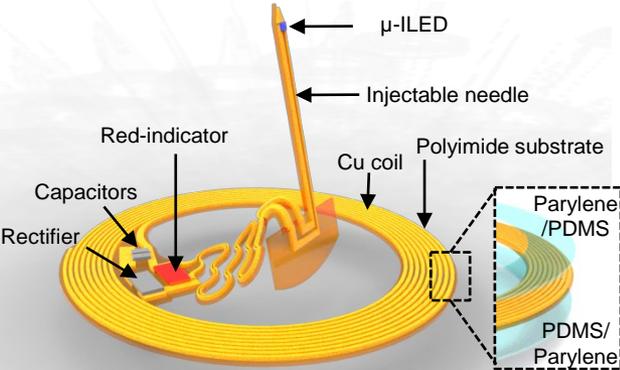
Design of RF-Powered Fully Implantable Devices



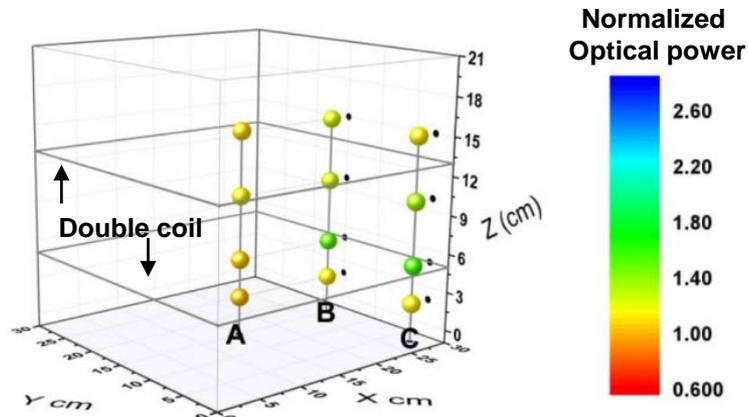
Soft Optoelectronics Systems for Diverse Wireless Applications



Near Field Communication (NFC) Powered Devices

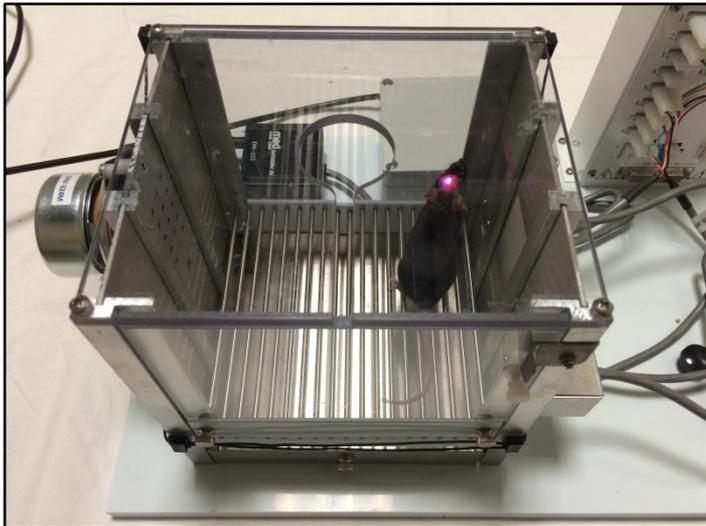


NFC Devices: versatile application



Coil position: 5 , 13 cm in z axis

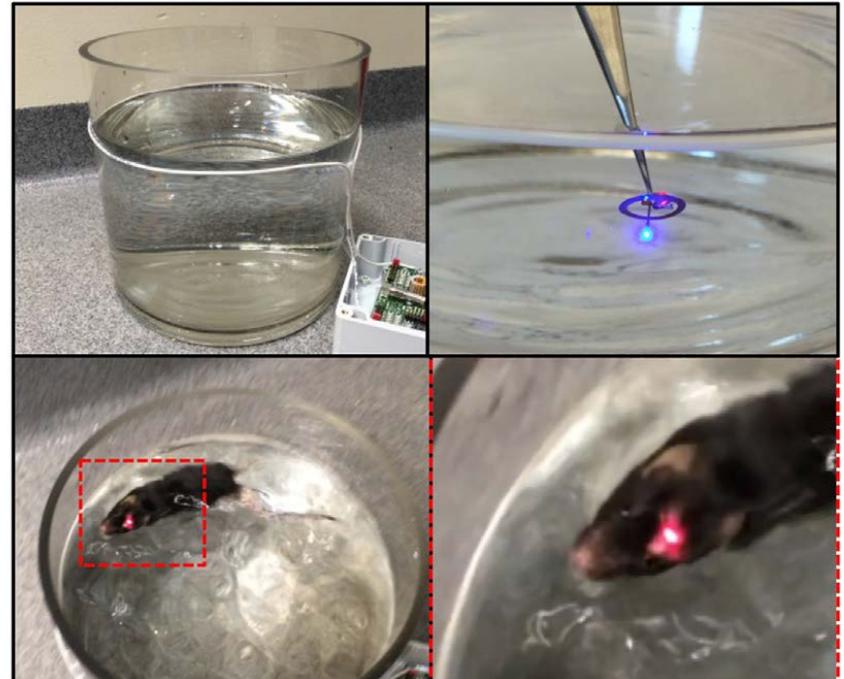
Operant Chamber



Conditioned Place Preference Box

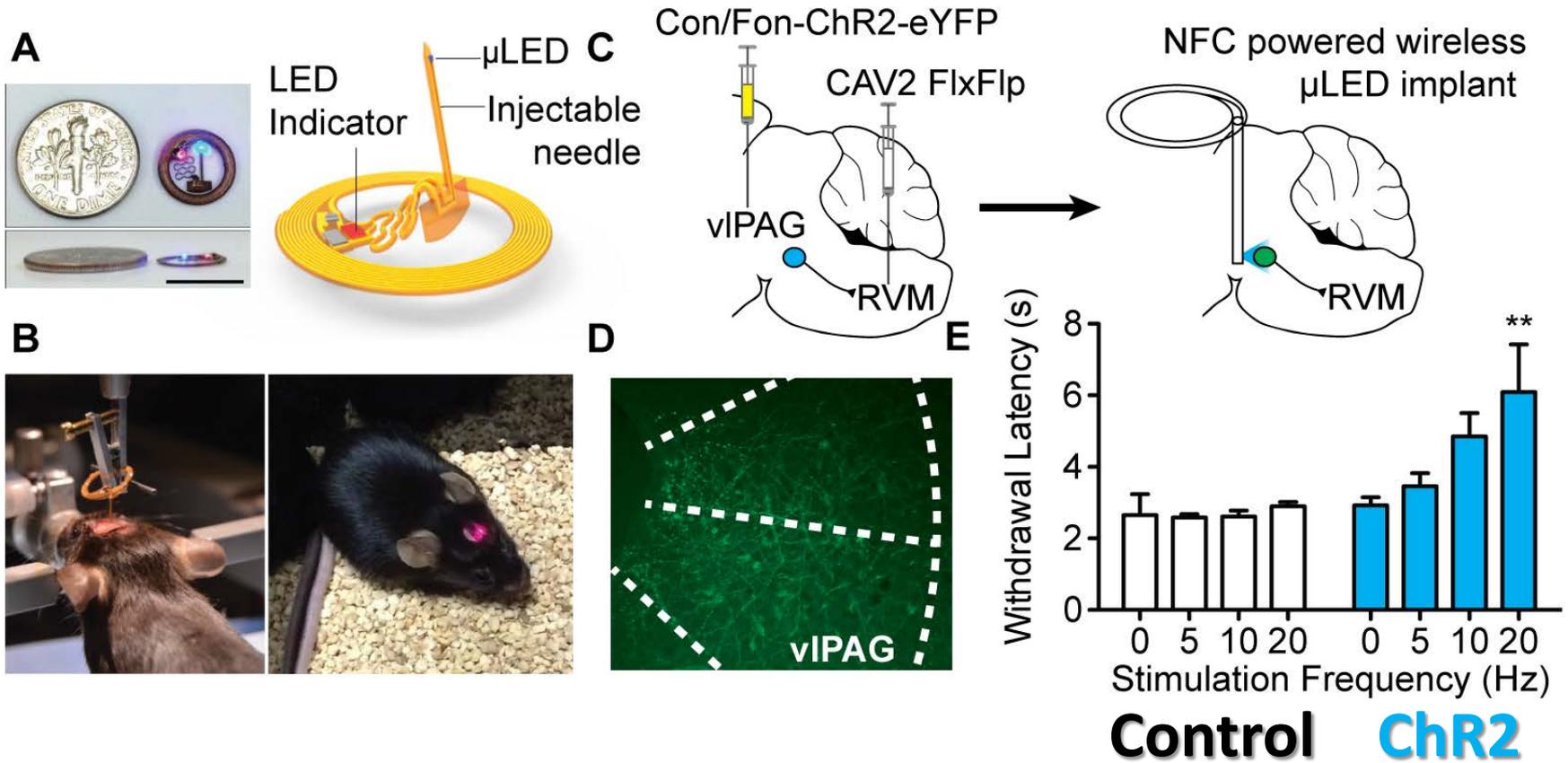


Forced Swim Test



NFC Powered Devices

PAG Stimulation-induced analgesia in freely moving mice

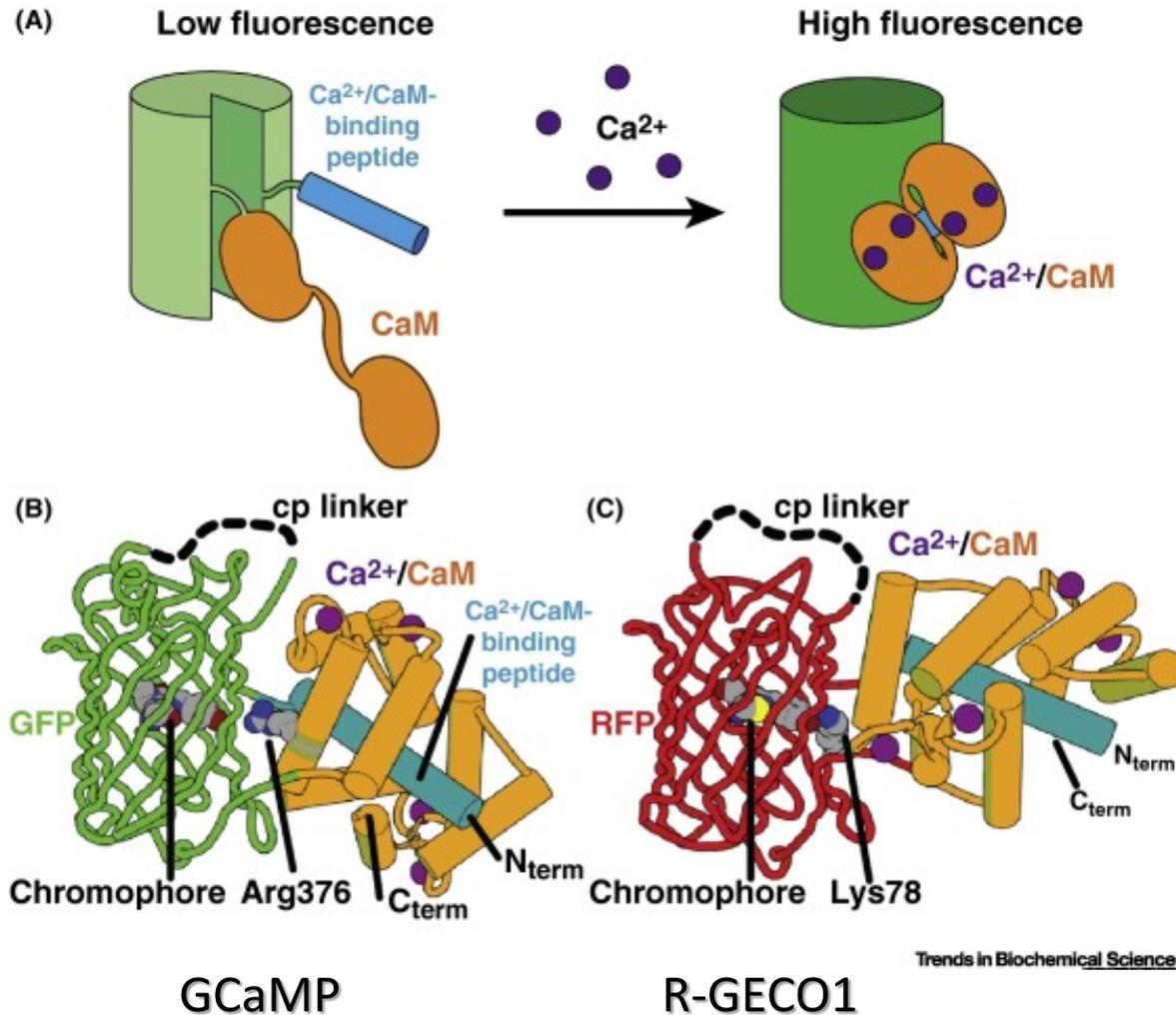


Optogenetics: The Future

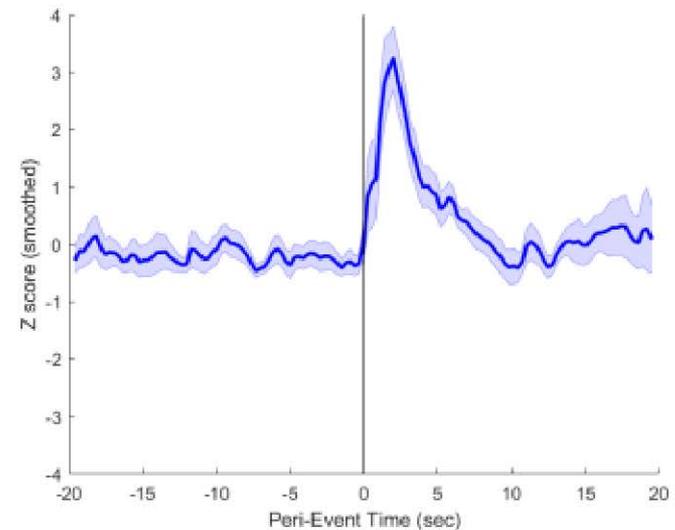
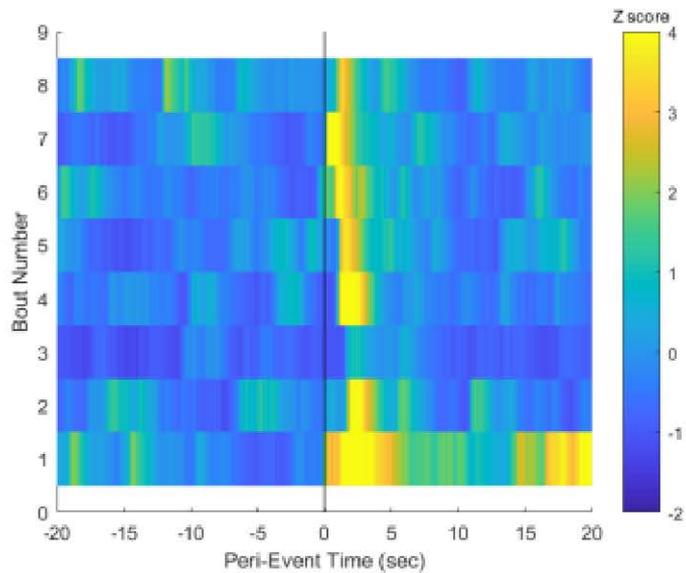
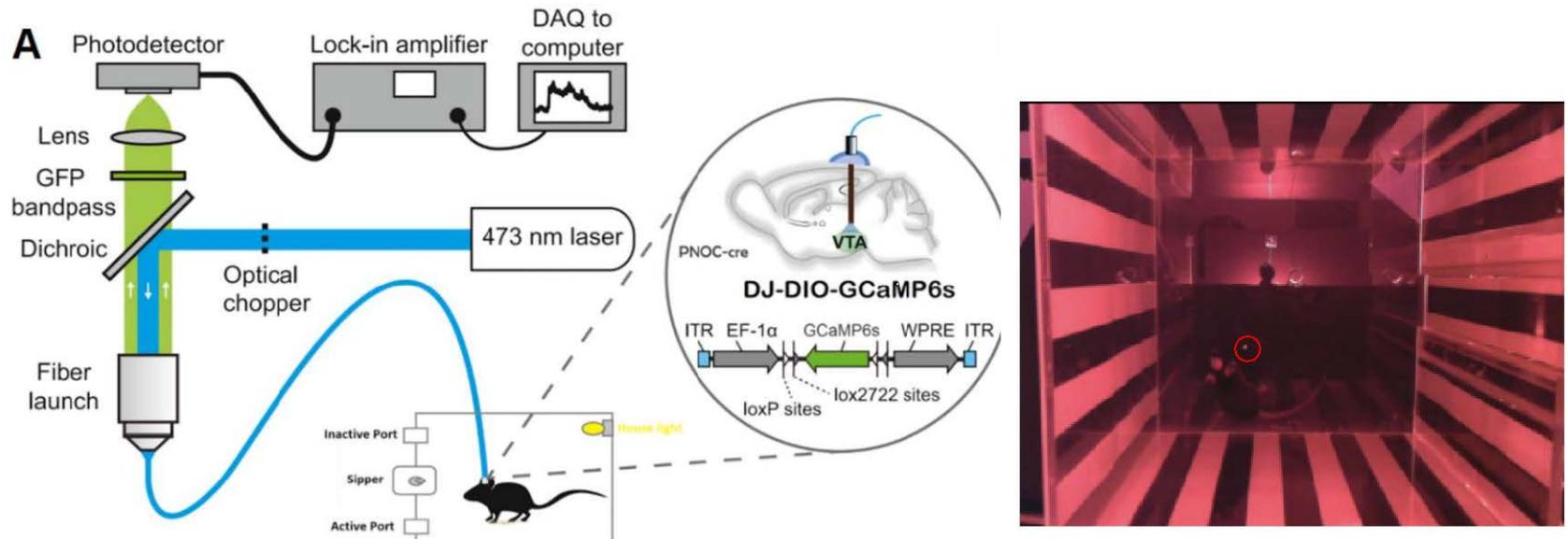
- Integration with wireless monitoring of neuronal function/firing
- Closed-loop control of brain function
- Multi-site control
- Optical regulation of
 - Cell signaling (oMOR, etc)
 - Gene expression
 - Pharmacology

Optical Monitoring of Neuronal Activity

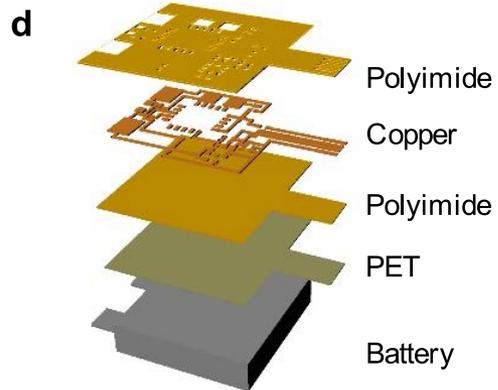
Genetically Encoded Ca^{2+} Sensors for monitoring neuronal activity



Fiber Photometry: Calcium Transient Detection



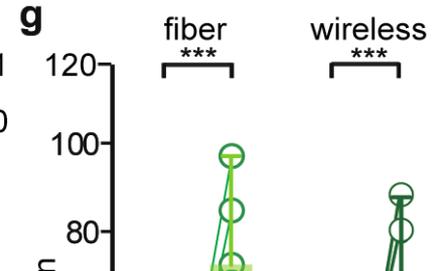
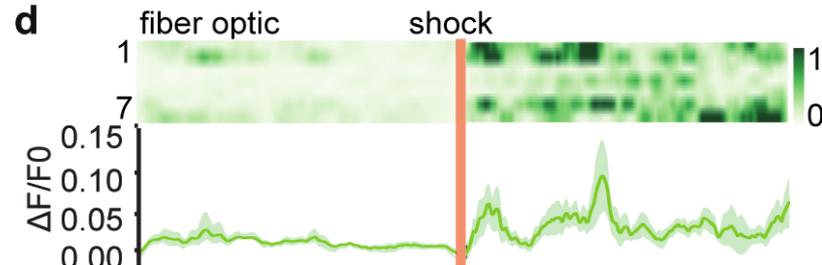
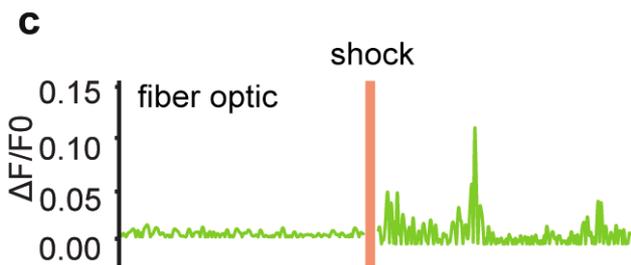
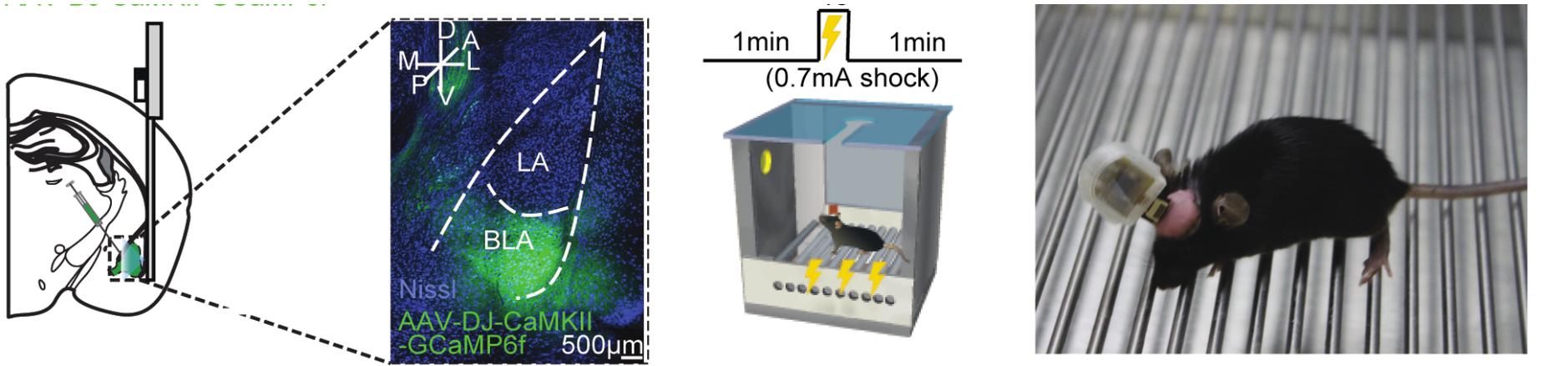
Wireless Photometry



e

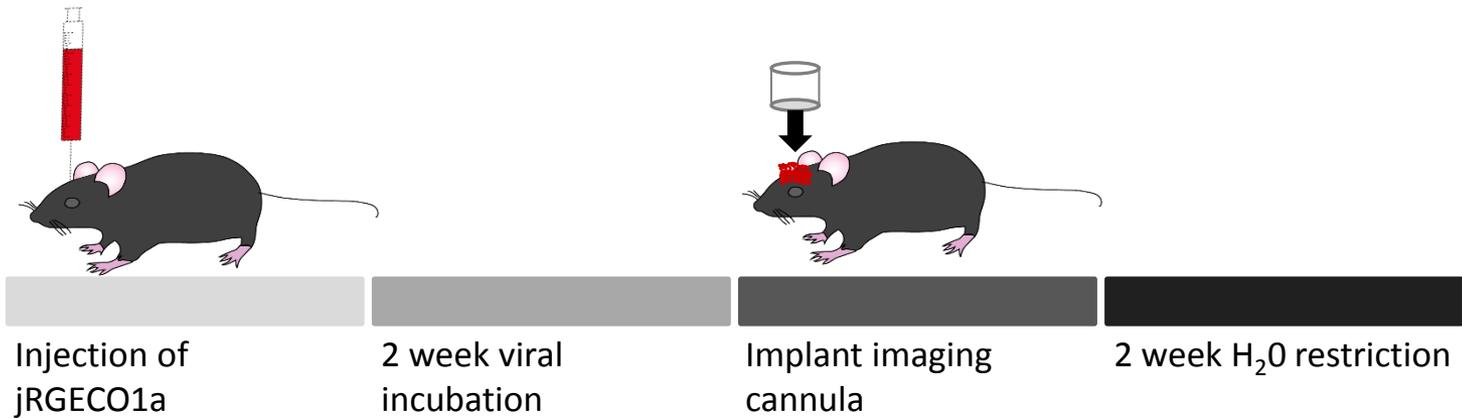
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Wireless Photometry

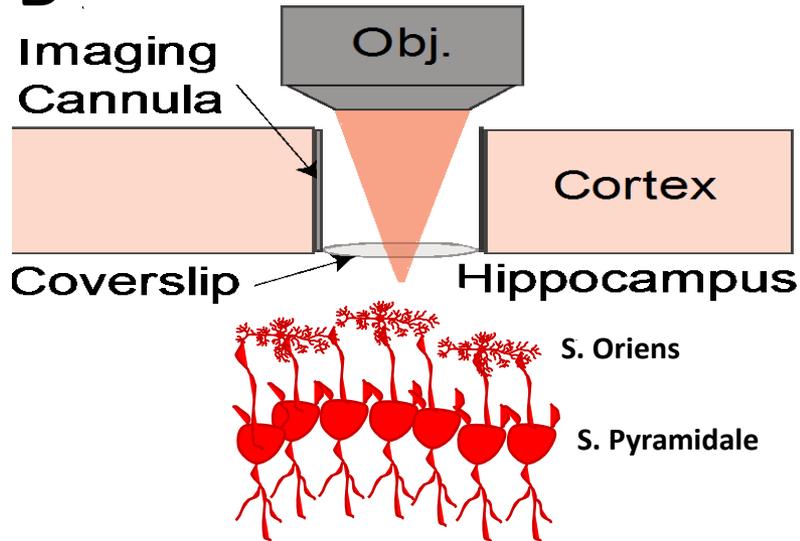


Cellular Resolution *in vivo* imaging in rodent models

A

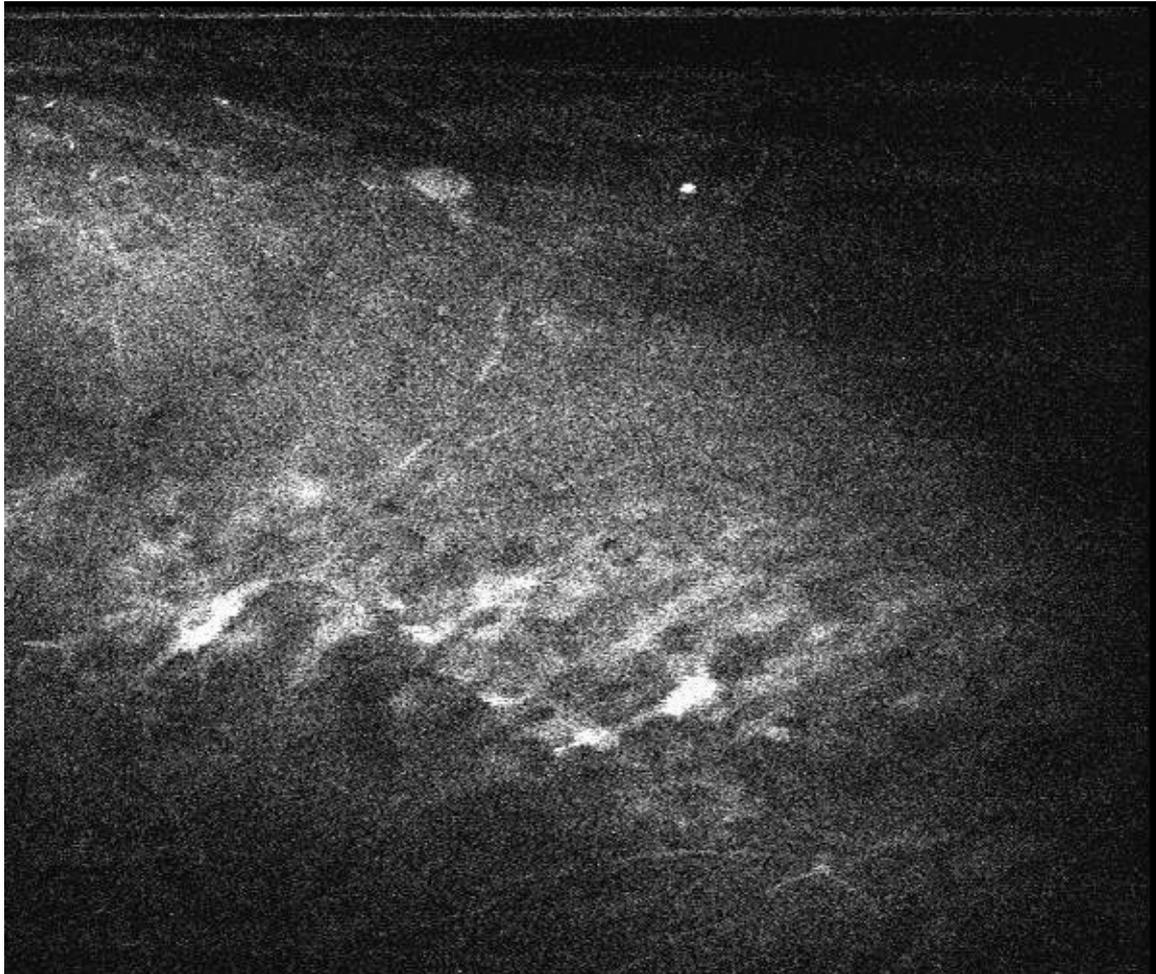


B



Cellular Resolution *in vivo* imaging in rodent models

AAV1.Syn.NES-jRGECO1a.WPRE.SV40



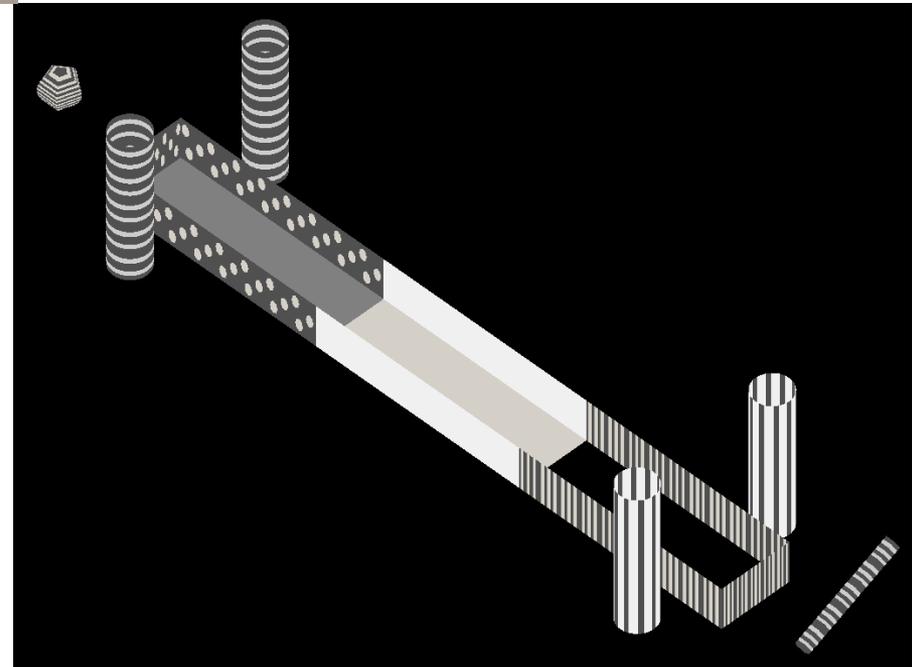
Jose Moron-Concepcion Laboratory, WashU

1. Bring the behavior arena to the microscope: Development of a virtual reality CPP paradigm

Classical 3-chamber CPP apparatus



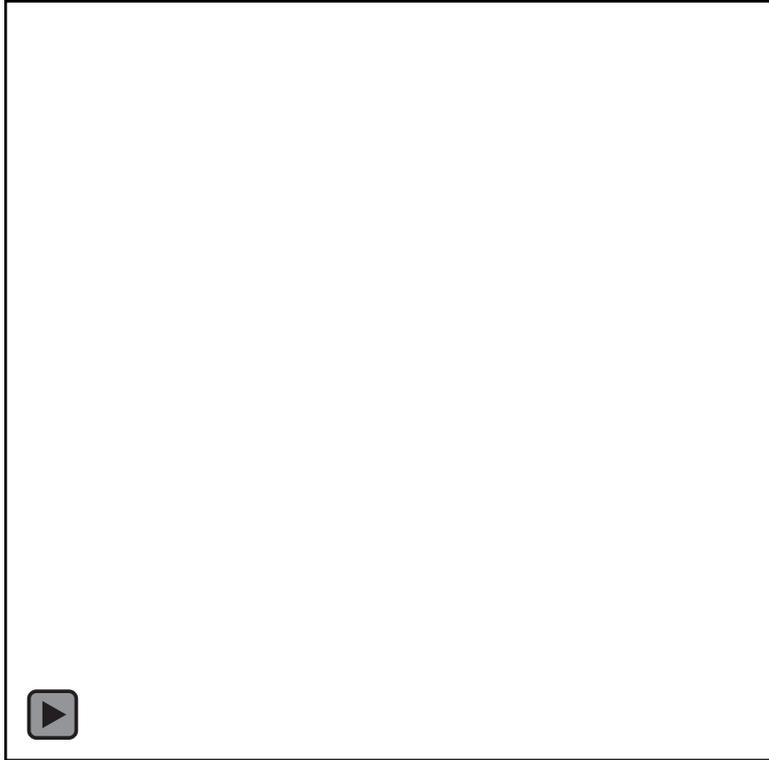
Virtual reality CPP environment



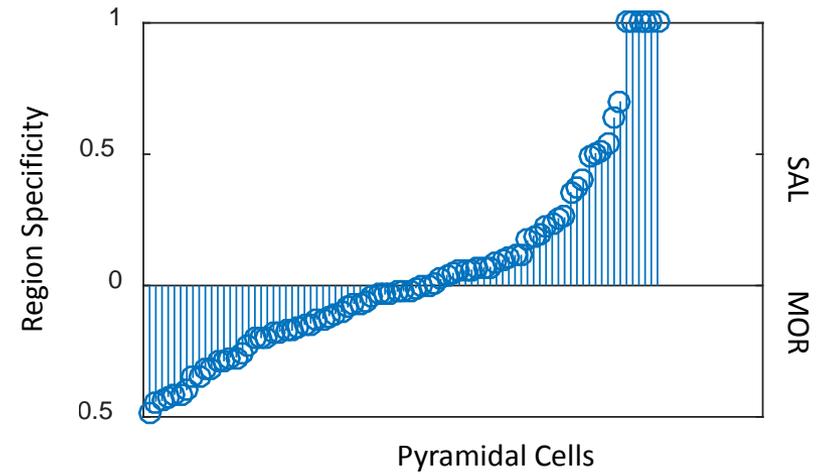
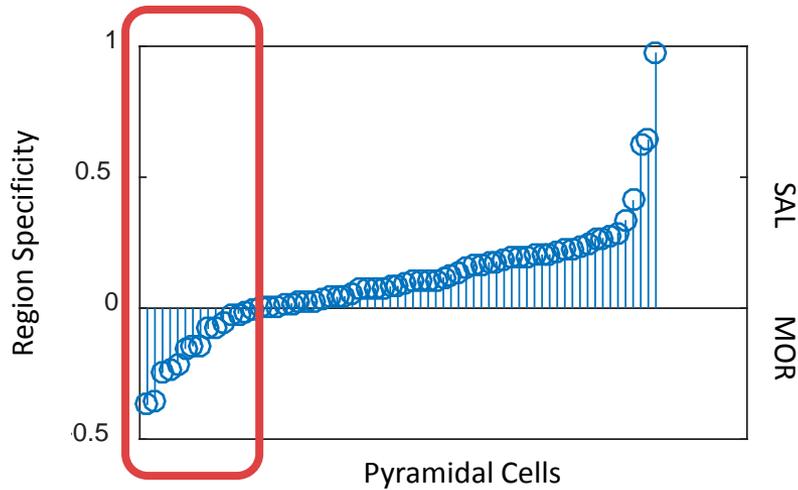
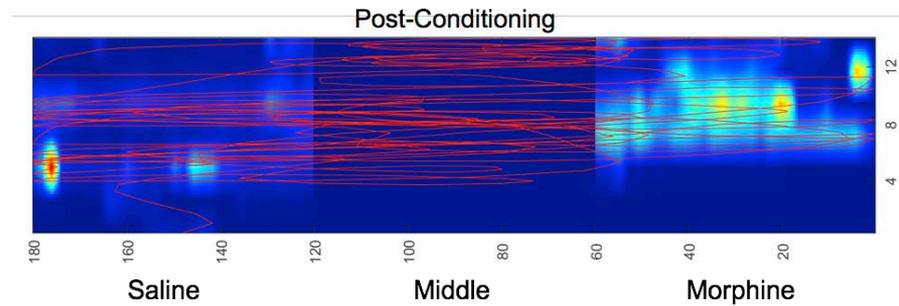
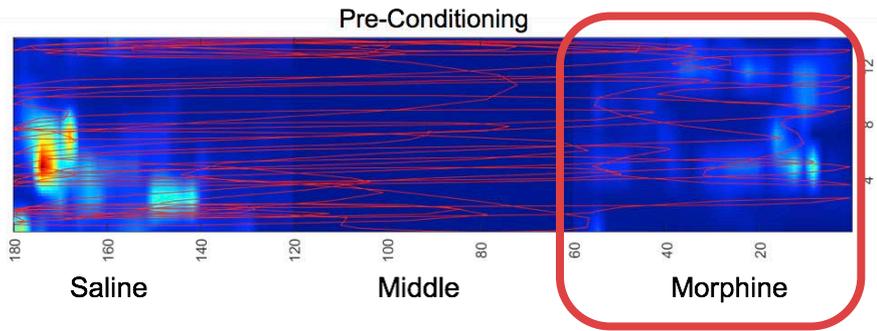
VR-CPP



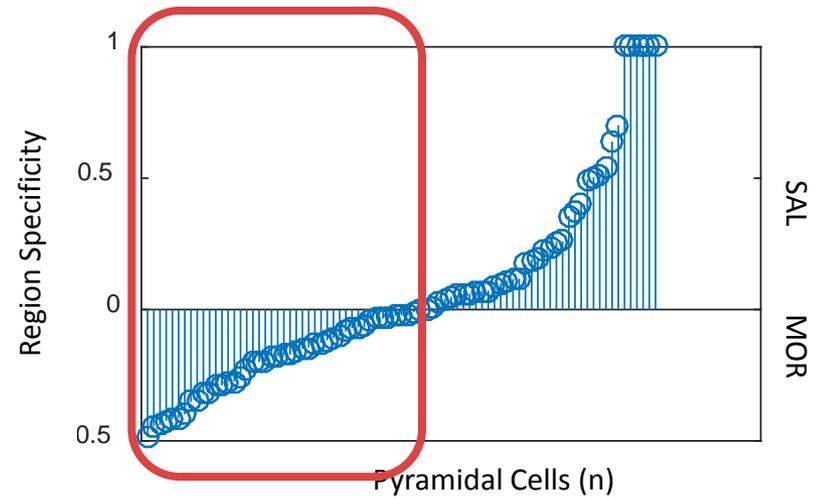
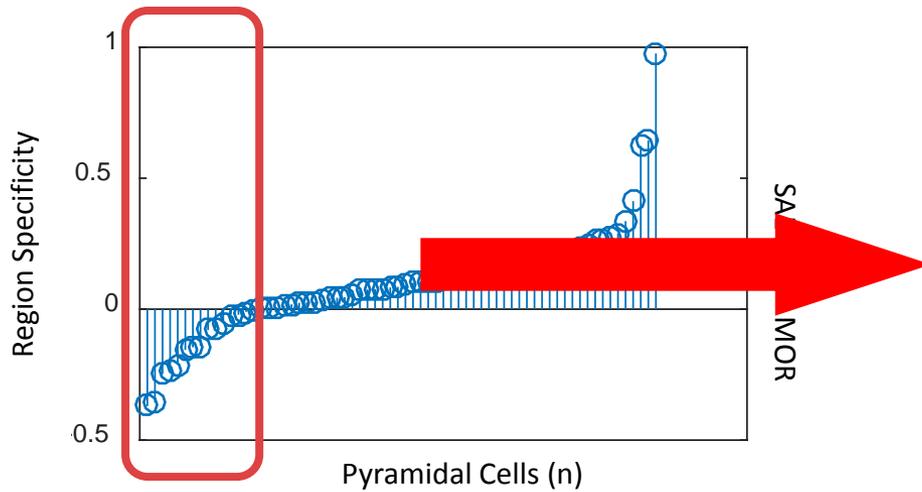
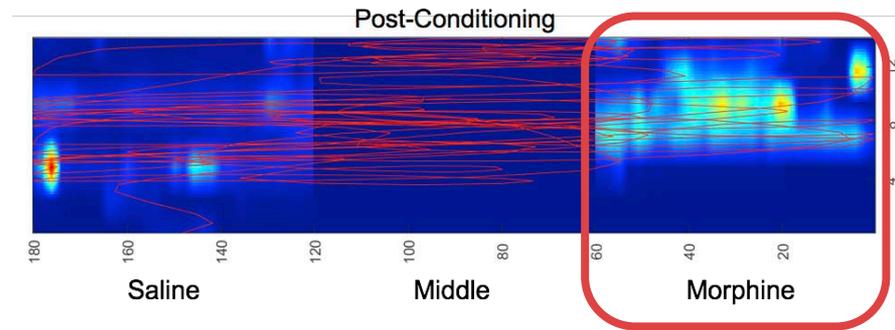
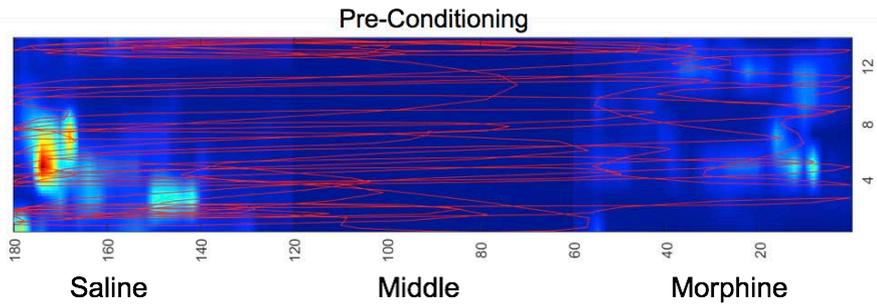
In vivo imaging using 2-photon microscopy during VR- CPP navigation



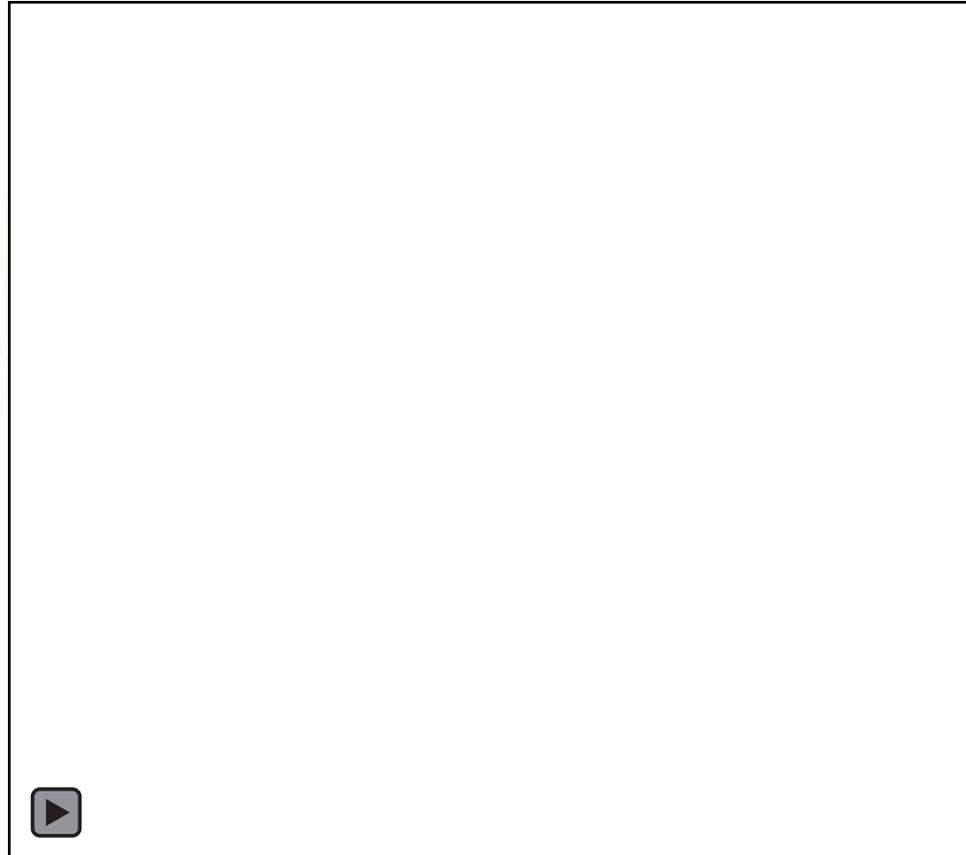
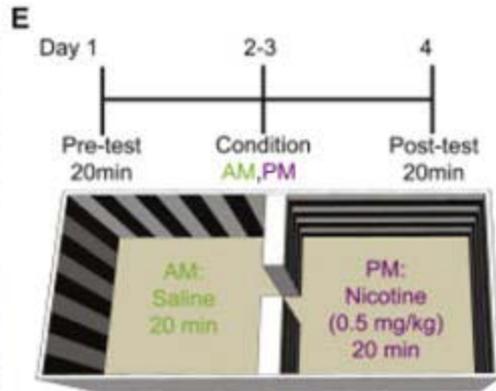
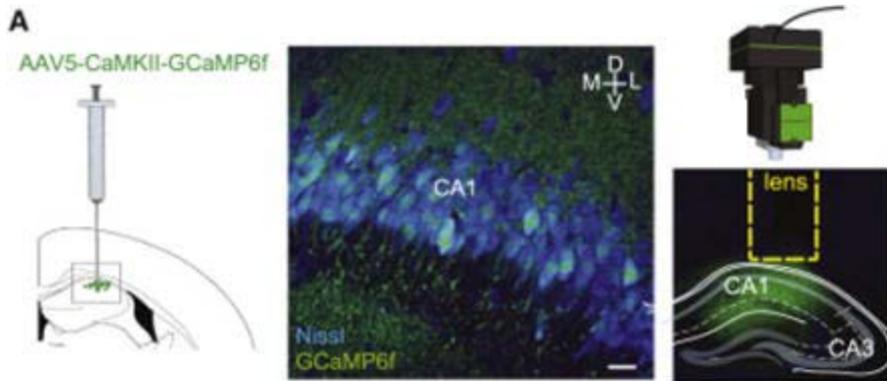
In vivo imaging using 2-photon microscopy during VR-CPP navigation



In vivo imaging using 2-photon microscopy during VR-CPP navigation



2. Bring the microscope to the behavior arena: Mini-scopes for *In Vivo* Imaging of Neuronal Activity in Freely Moving Animals



Optical Monitoring of Neuronal Activity: The Future

- Wireless imaging
- Faster/higher fidelity Ca^{++} sensors or Genetically-encoded voltage indicators (multiple in development)
- Imaging combined with optical and electrical stimulation/inhibition

The Promise of the BRAIN Initiative: What has the BRAIN Initiative done for pain research?

- New technologies that allow future studies to identify
 - Cells and circuits that change associated with chronic pain – new targets
 - How the brain responds to effective treatments

BRAIN Initiative: Notice of Support for Research on the Fundamental Neurobiology of Pain Processing

The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is aimed at revolutionizing neuroscience through development and application of innovative technologies to map neural circuits, monitor and modulate their activity, and understand how they contribute to thoughts, sensations, emotions and behavior.

The purpose of this announcement is to notify the research community that NIH welcomes BRAIN Initiative applications targeting central nervous system nociceptive and pain circuits, as appropriate to the goals and requirements of specific BRAIN Initiative FOAs. Pain conditions represent an important public health problem and NIH continues to support research into pain pathologies through normal Institute and Center appropriations. However, pain and nociception are also components of normal nervous system function, and the BRAIN Initiative is committed to understanding pain circuits along with brain circuits underlying other sensory, motor, cognitive and emotional functions. It is expected that the unique opportunities of the BRAIN Initiative will enable production of detailed maps of pain circuits, and the adoption of powerful new tools for monitoring and modulating pain circuit activity, leading to significant advances in the understanding of pain and nociception.

<https://grants.nih.gov/grants/guide/notice-files/NOT-NS-18-008.html>

- A model for innovation and success
 - Focused goals with dedicated new funds lead to innovation and rapid progress

Collaborators:



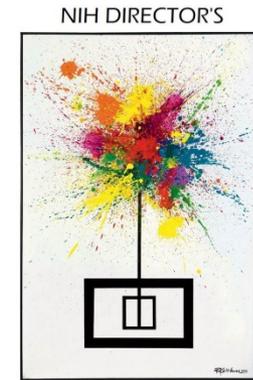
**Michael Bruchas,
Washington University
Pain Center**



**Jose Moron-Concepcion
Washington University
Pain Center**



**John Rogers,
Northwestern Universtiy**



NIH DIRECTOR'S
TRANSFORMATIVE
RESEARCH
AWARD



NFC Powered Devices: Adaptation for Optogenetic Manipulation of Spinal Cord

