Non-invasive Cell-type-specific Magnetic Neural Modulation

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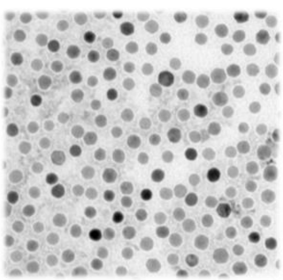
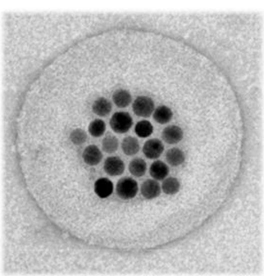
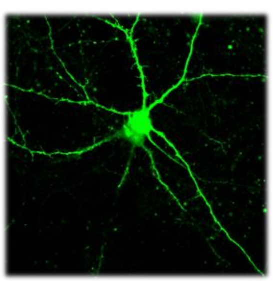
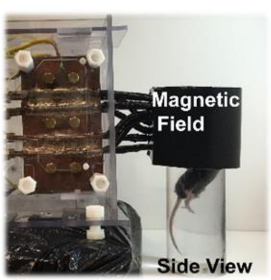
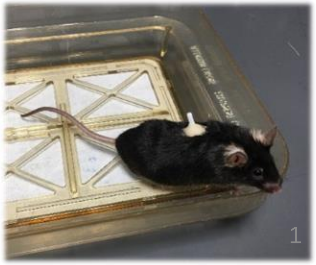
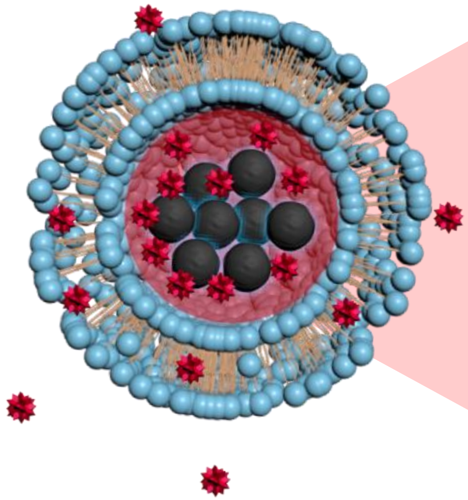





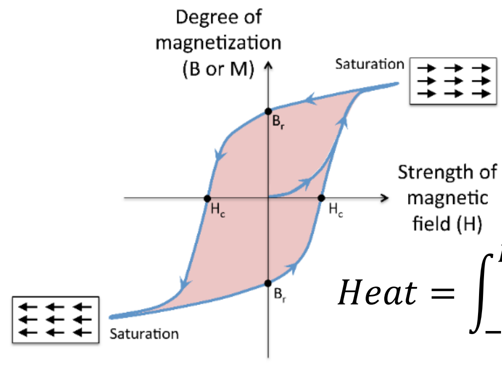




Chemomagnetic Neural Modulation

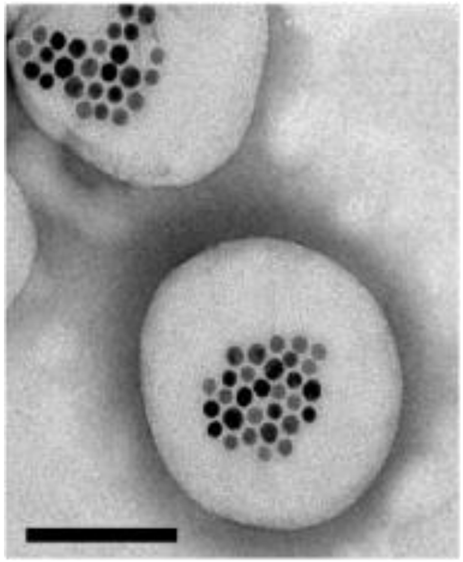


Magnetothermal Effect



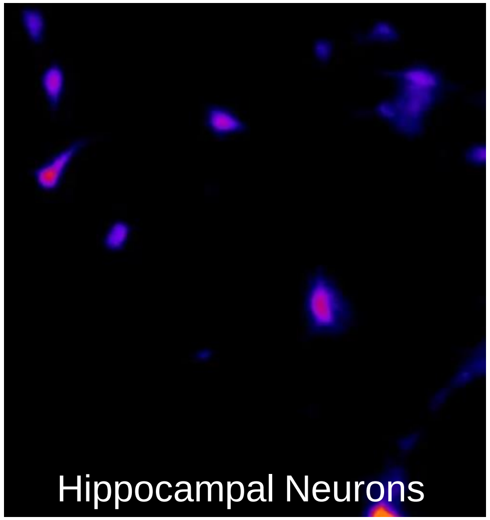
$$Heat = \int_{-H_o}^{H_o} \mu_o M(H) dH$$

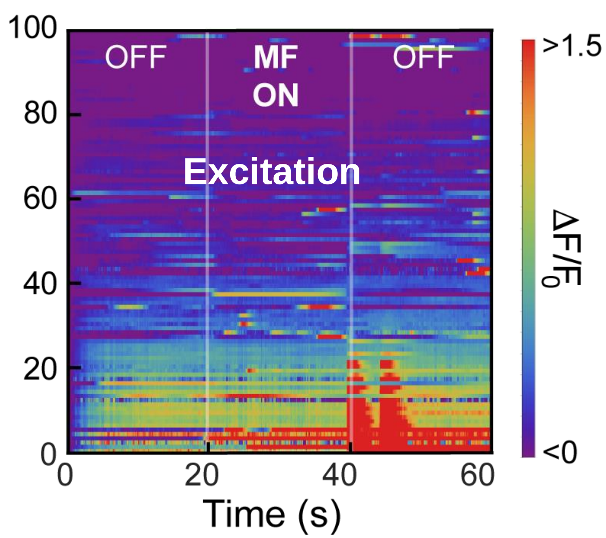
Carrey, et al. J. App. Phys., 2011

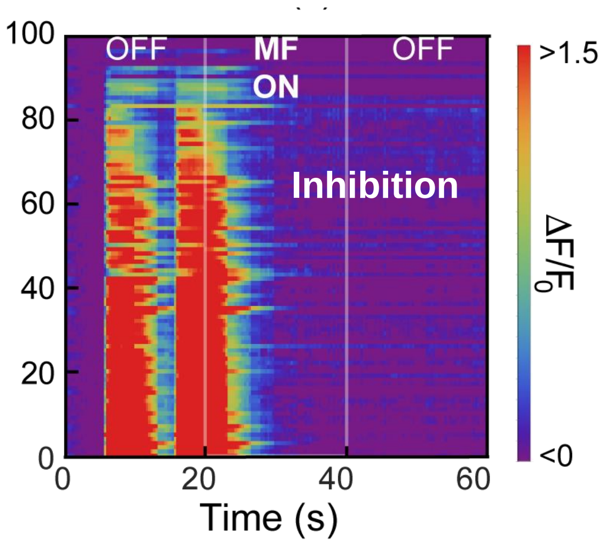


scale bar: 200 nm

Magnetic: **remotely control, non-invasive, whole-brain coverage**



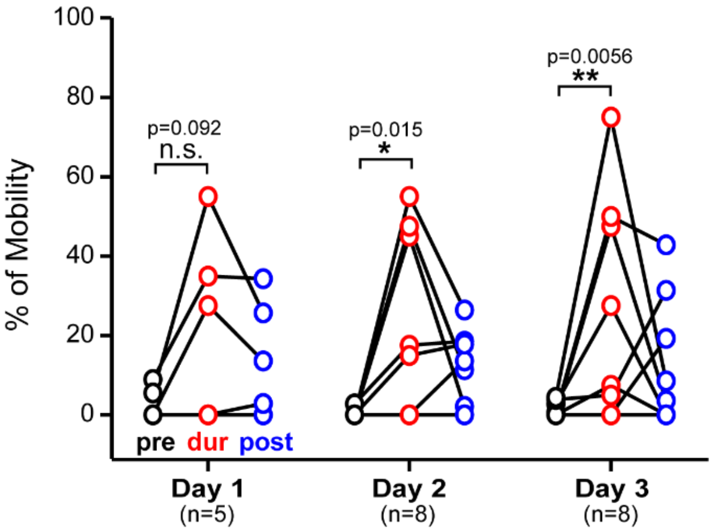




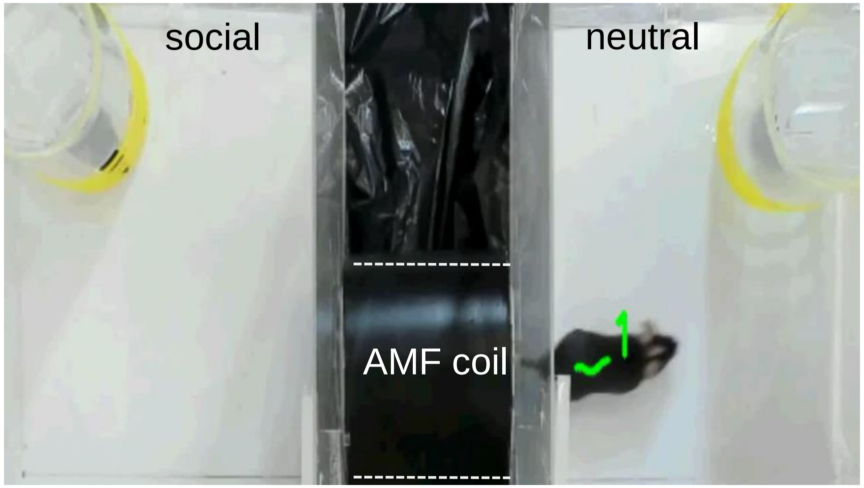
***Rao**, et.al, Nat. Nanotech. 2019*

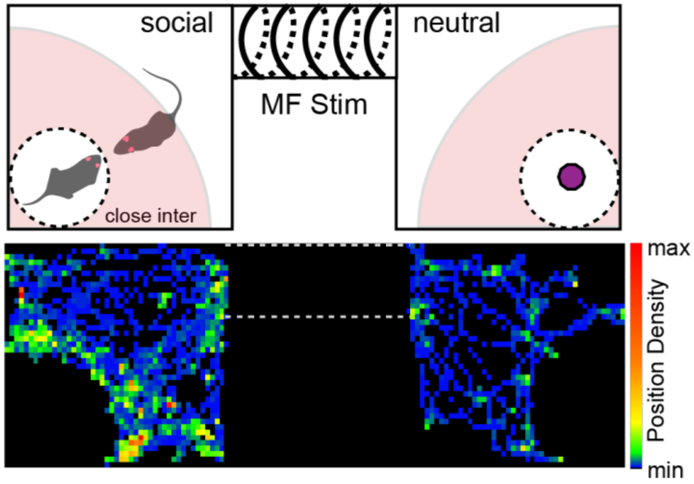
Magnetic Neural Modulation in Behaving Mice

Depression-like behaviors: forced swimming tests



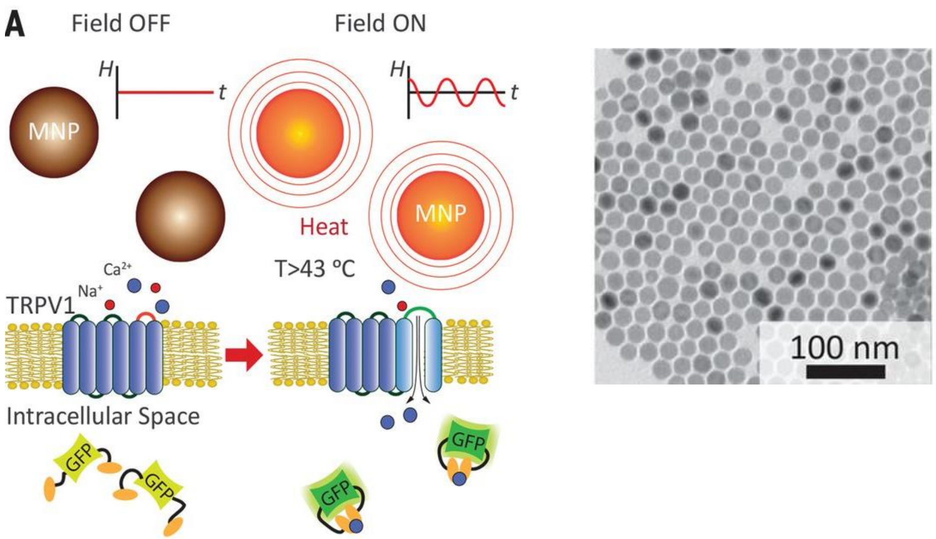
Autistic-like behaviors: social interactions



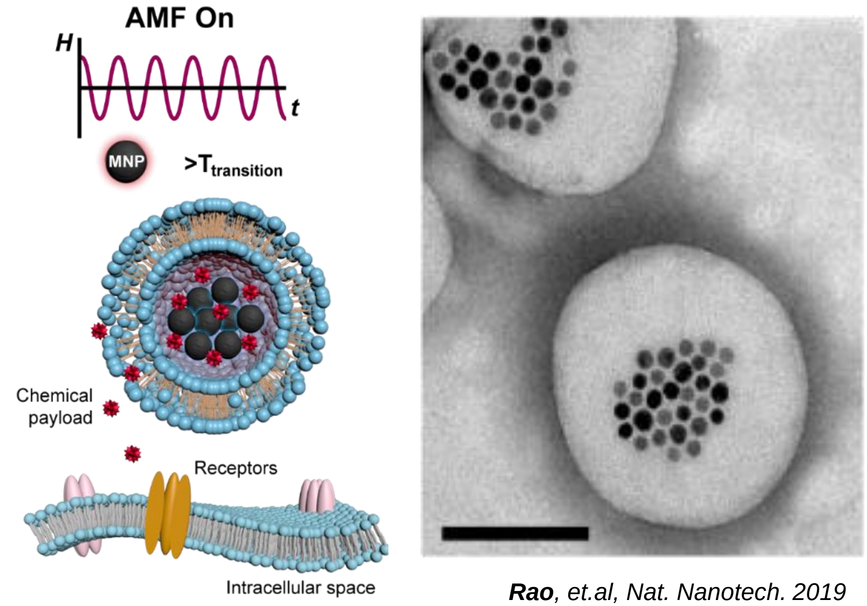


***Rao**, et.al, Nat. Nanotech. 2019*

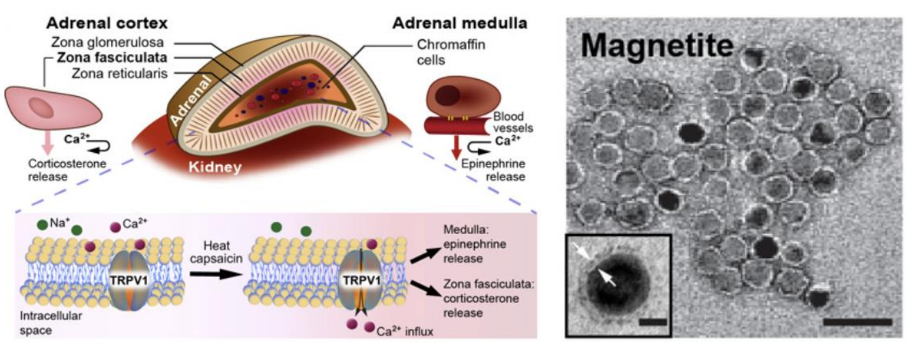
Challenges of Magnetic Neural Modulation



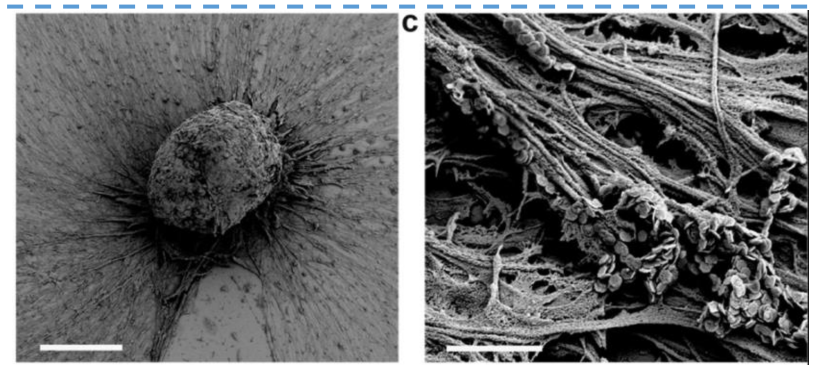
Chen, et.al, Science, 2015



***Rao**, et.al, Nat. Nanotech. 2019*



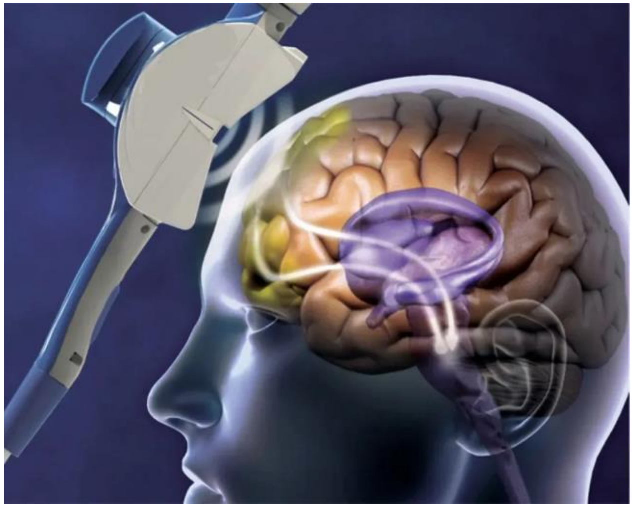
Rosenfeld et. al, Sci. Adv., 2020



Gregurec, et.al, ACS Nano, 2020

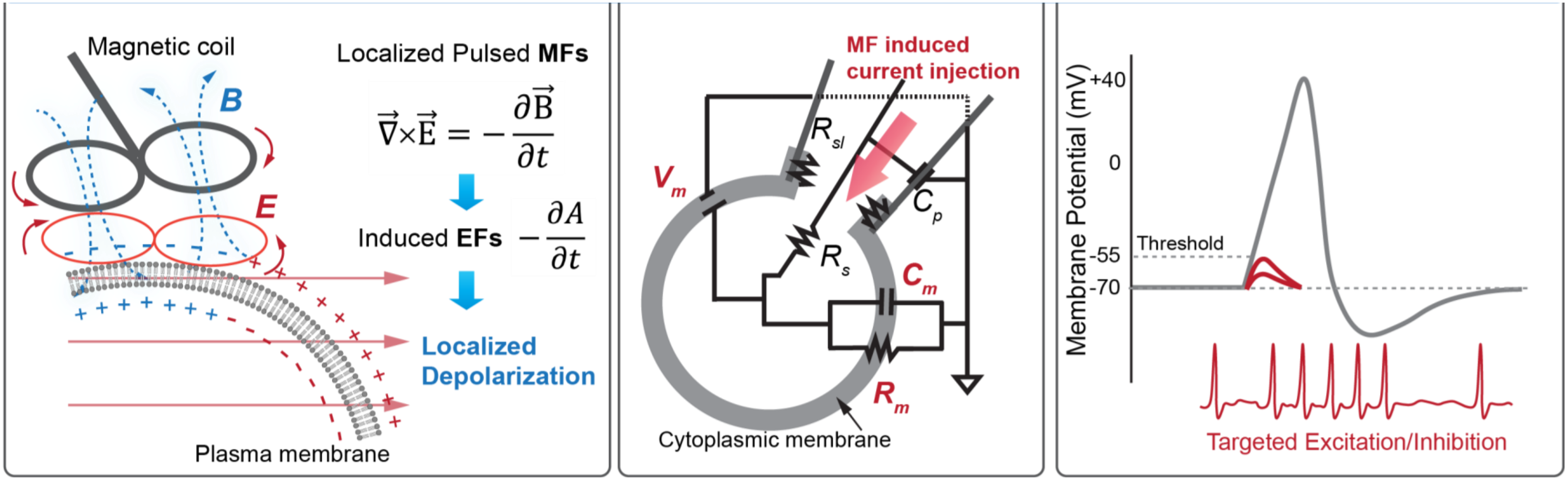
- **Specificity** depends on thermo/mechanical/chemical responsive receptors
- **Magnetic nanomaterials delivery**

Non-invasive Magnetic Stimulation

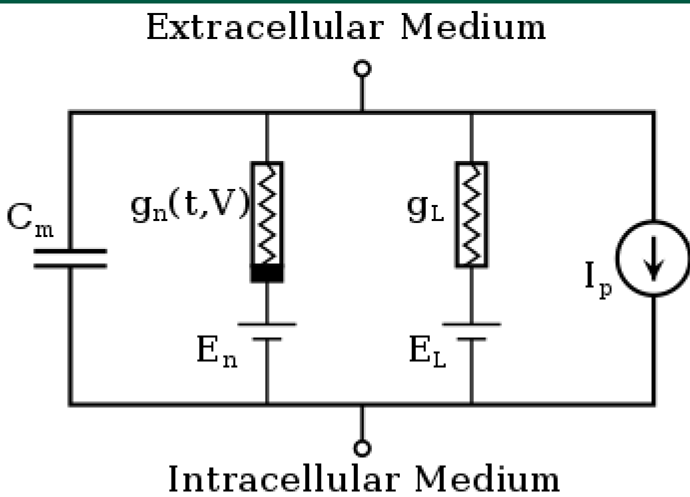


https://www.spineandneurosurgery.com/service/transcranial-magnetic-stimulation

- **Promising clinical evidence:** treatment on major depressive disorder (depression), pain management
- **Lack** of spatial precision and cell-type specificity
- Unclear mechanisms

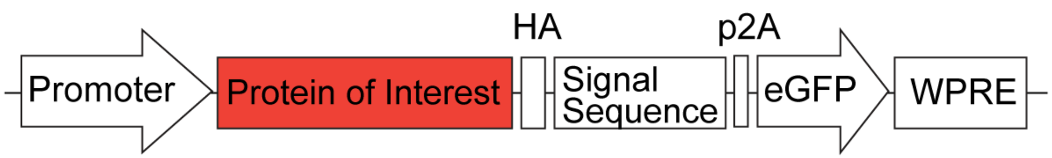


Cell-type-specific Magnetic Neural Modulation



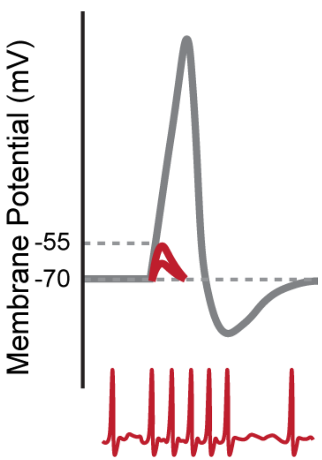
$$I = \boxed{C_m \frac{dV_m}{dt}} + g_K(V_m - V_K) + g_{Na}(V_m - V_{Na}) + g_l(V_m - V_l)$$

Hodgkin–Huxley model



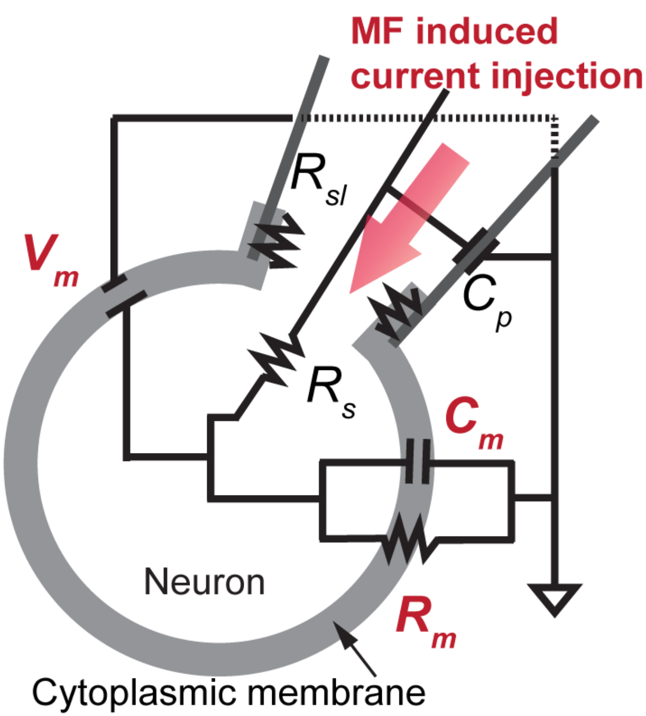
Non-channel protein regulating membrane passive properties:

- C_m
- R_m
- V_m



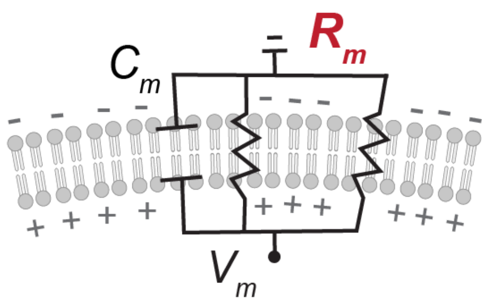
Membrane passive properties

C_m R_m V_m



Membrane Passive Properties and Neural Activity

Membrane resistance



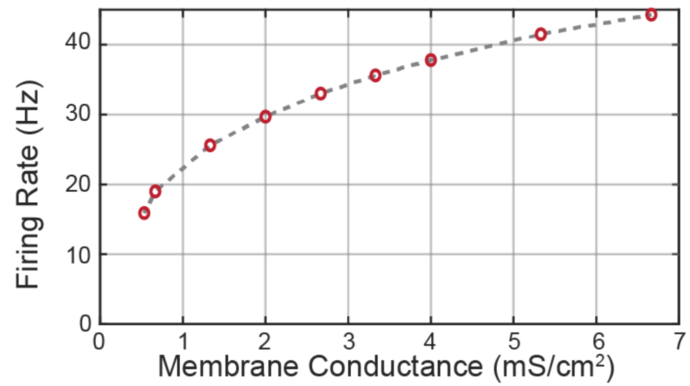
Inhibition

Slower firing rate

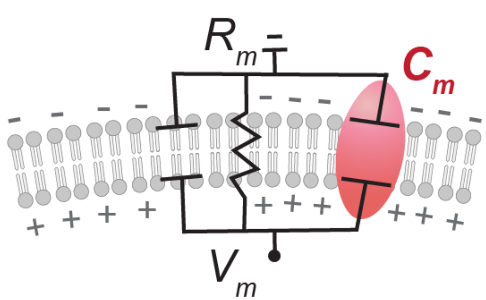
$R_m \rightarrow \tau_m$

Higher firing rate

Excitation



Membrane capacitance



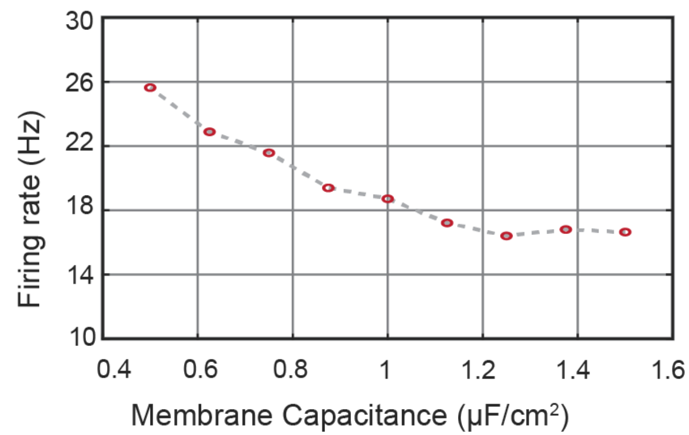
Inhibition

Slower charging

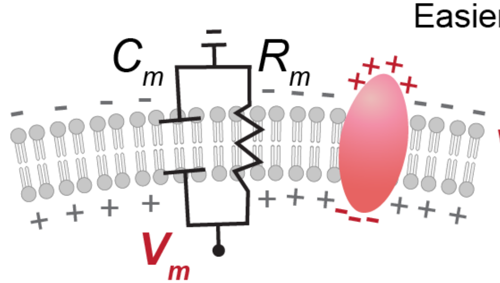
d, k $\rightarrow$ C_m 1 μF/cm²

Faster charging

Excitation



Membrane potential



Excitation

Easier for depolarization

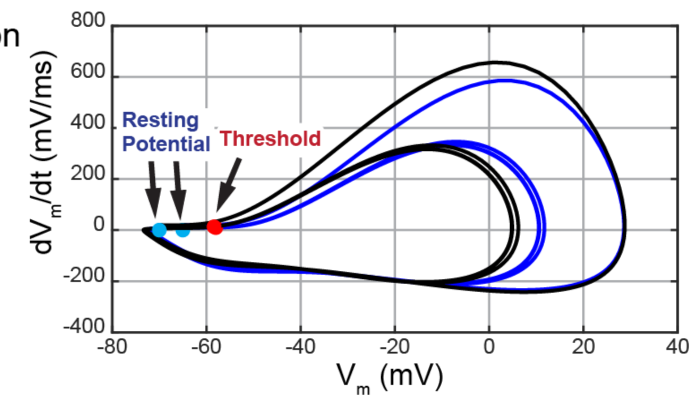
-55 mV

V_m

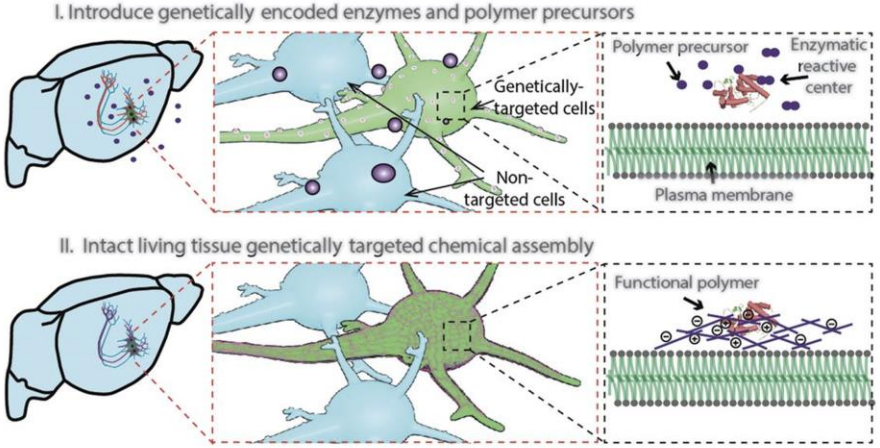
-70 mV

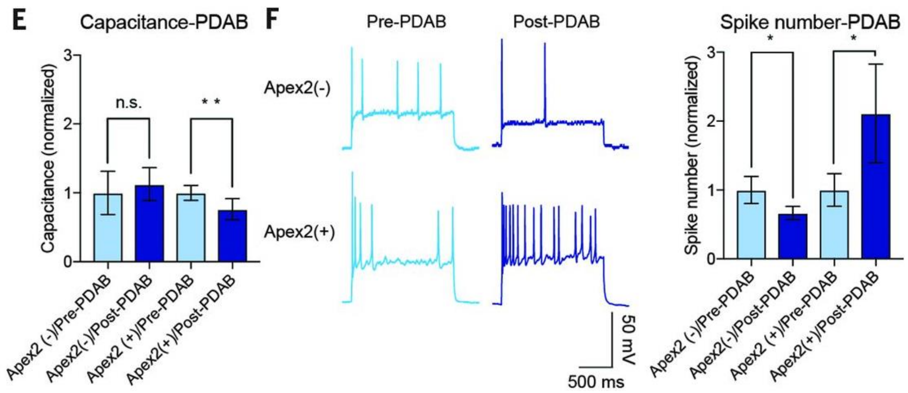
Hyperpolarization

Inhibition

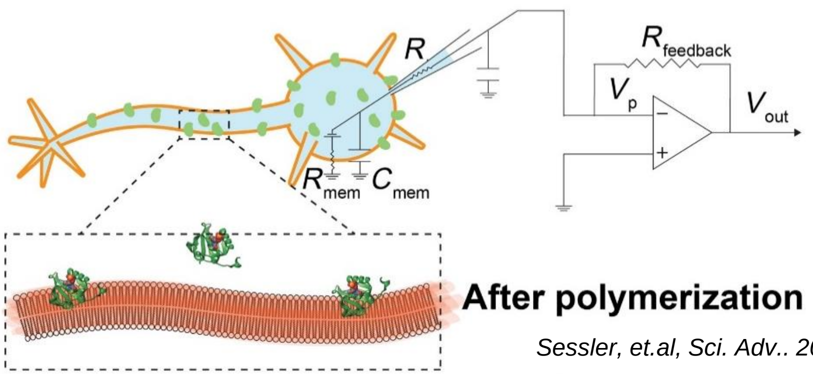


Membrane Modification





Liu, et.al, Science. 2020

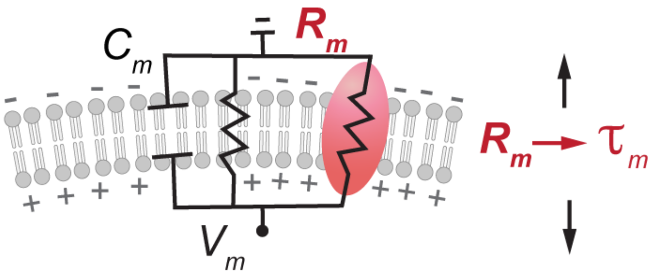


Sessler, et.al, Sci. Adv.. 2022

- Genetically encoded enzyme enabled polymerization
- Optogenetic polymerization and assembly of electrically functional polymers

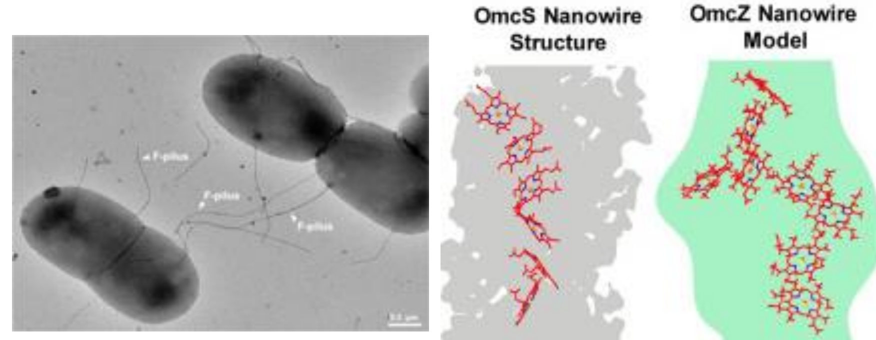
Question: engineering neuron membrane properties through genetic approaches

Aim 1: Toolkit to Regulate Membrane Properties



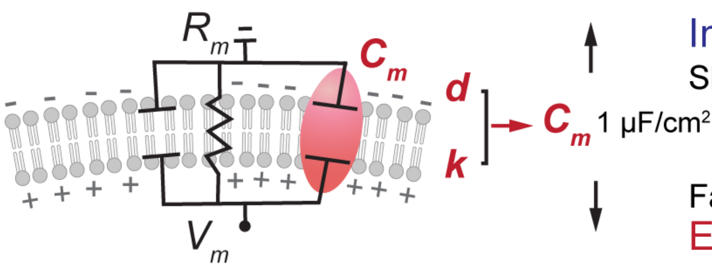
Inhibition
Slower firing rate

Higher firing rate
Excitation



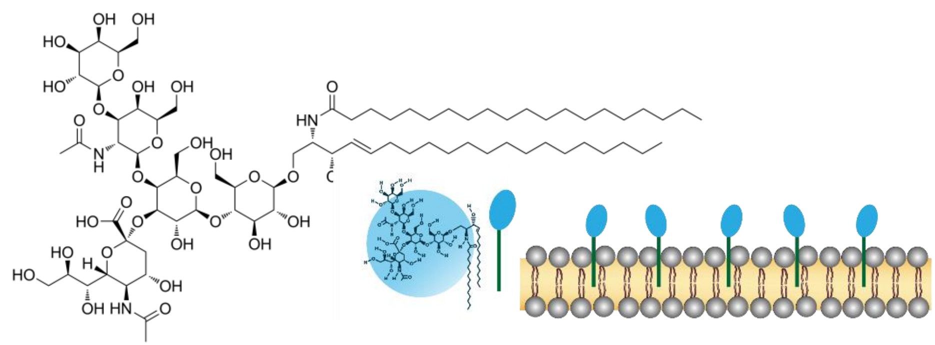
pilA, OmcZ, OmcS (*Geobacteria nanowires*)

Current opinion in chemical biology 59 (2020): 193-201

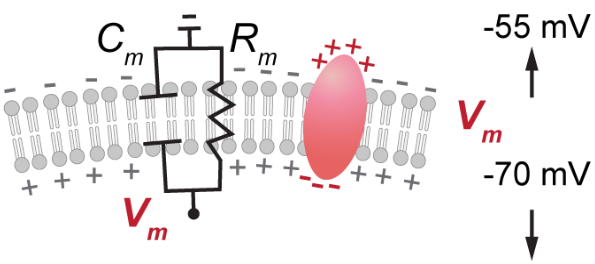


Inhibition
Slower charging

Faster charging
Excitation

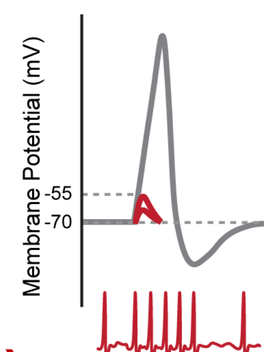


Gangliosides (sialic acid-containing glycosphingolipids: GM1)



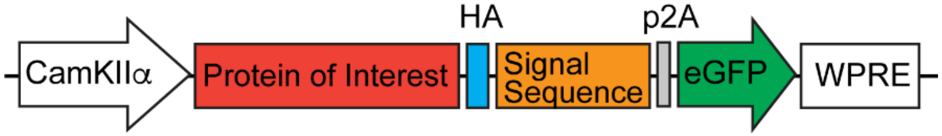
Excitation
Easier for local depolarization

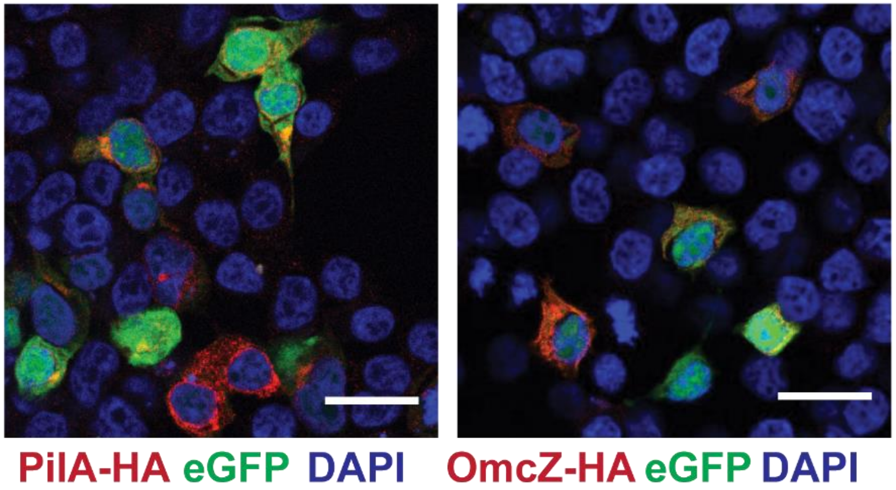
Hyperpolarization
Inhibition

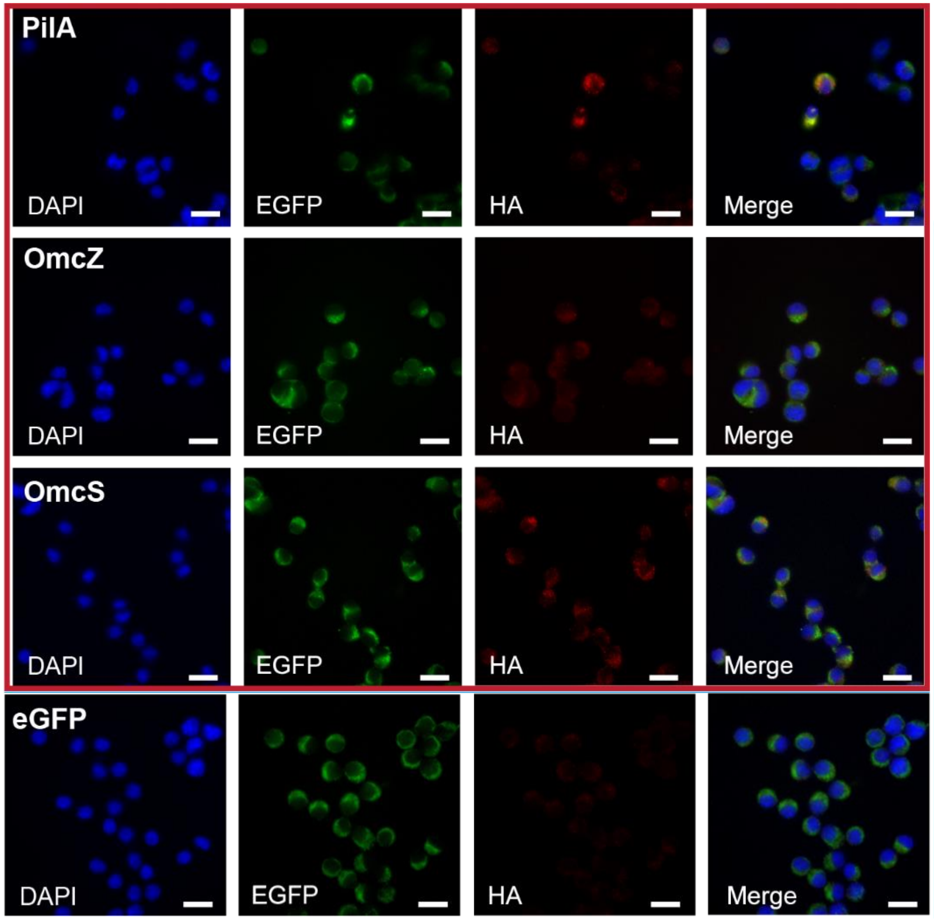


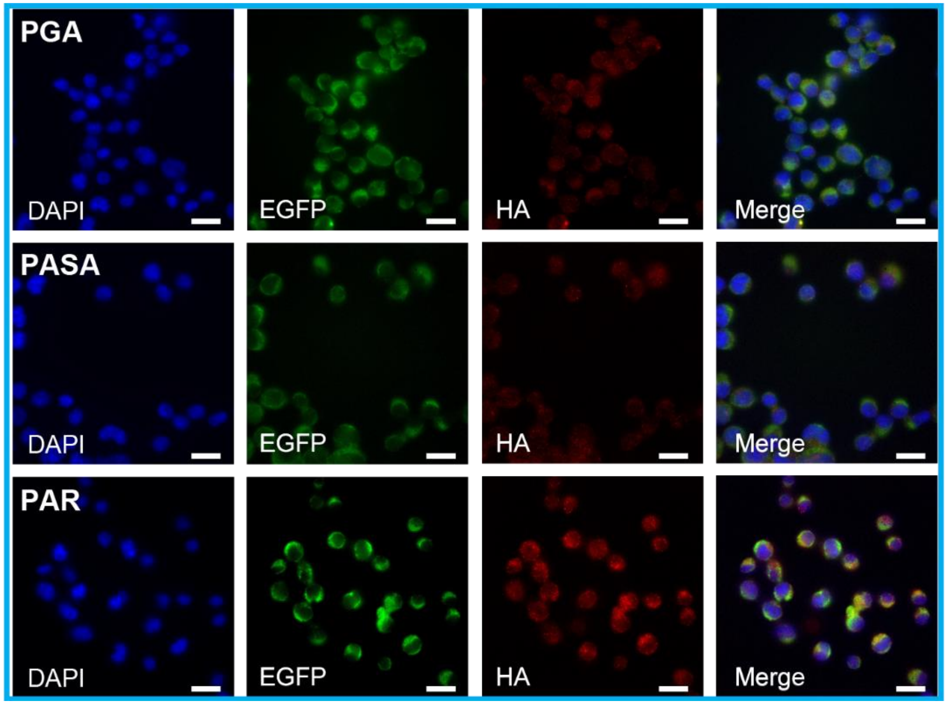
Polyglutamic acid (PGA), Polyaspartic acid (PASA), Polyarginine (PAR)

Aim 1: Membrane-targeted Expression

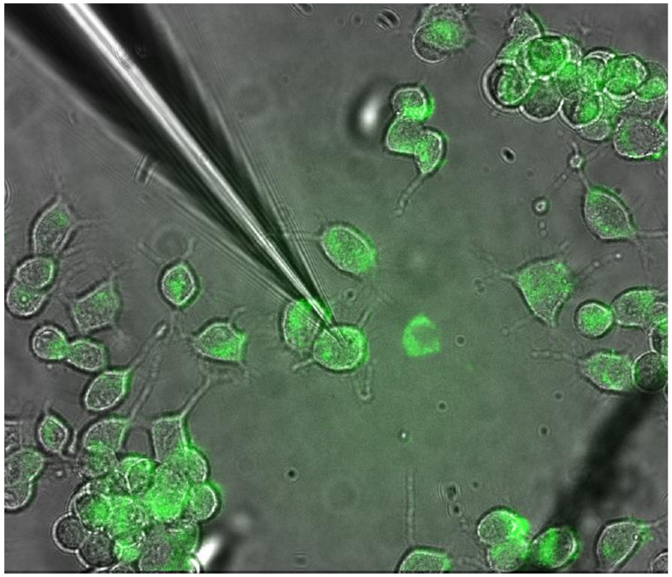




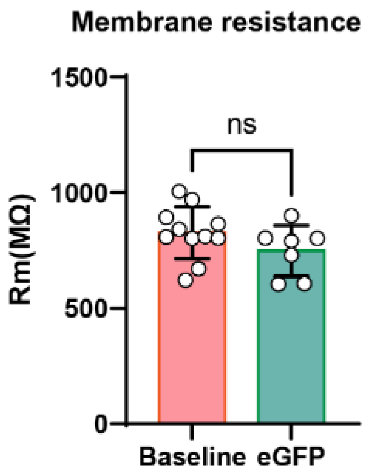


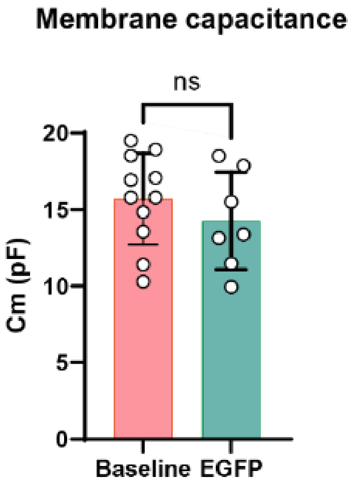


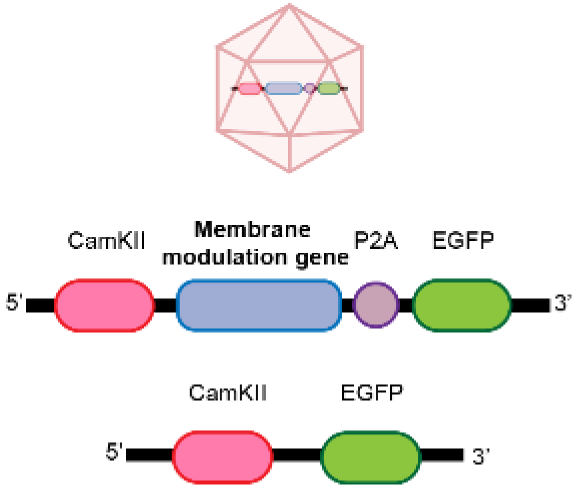
Aim 2: Characterize Membrane Properties

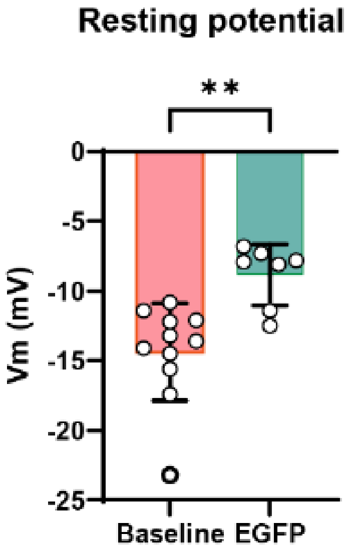


Neuo2A (ATCC® CCL-131)
w/ pilA expression



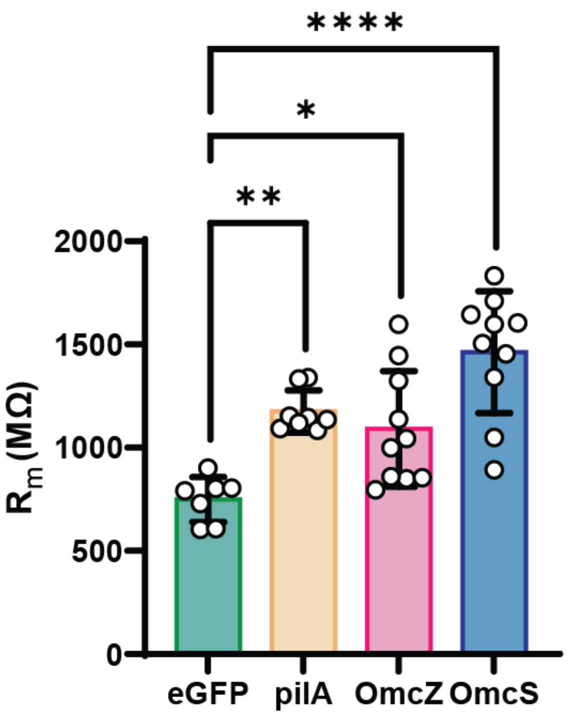


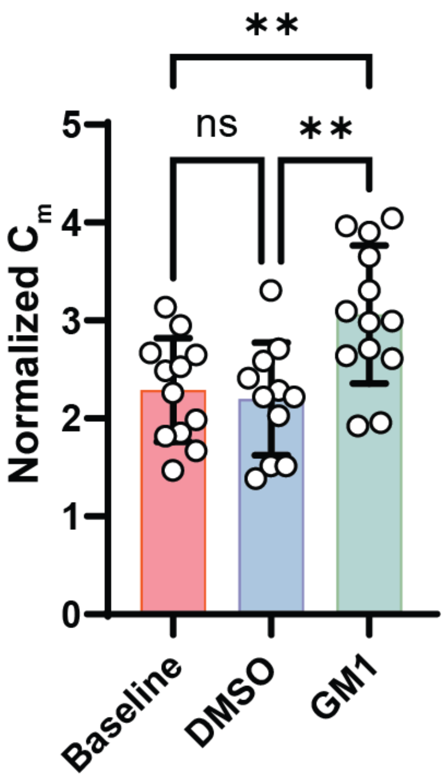




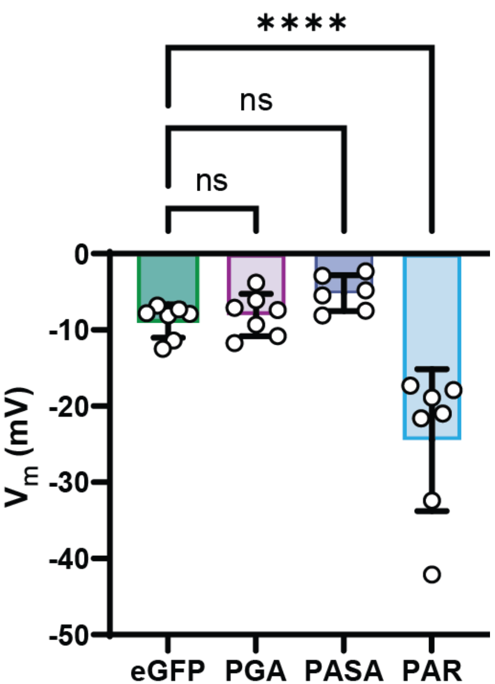
- AAV infection efficiently introduce membrane protein expression
- R_m and C_m remain unchanged
- V_m increased

Aim 2: Characterize Membrane Properties

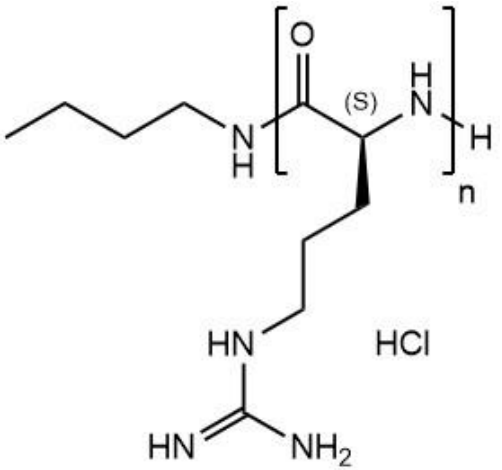




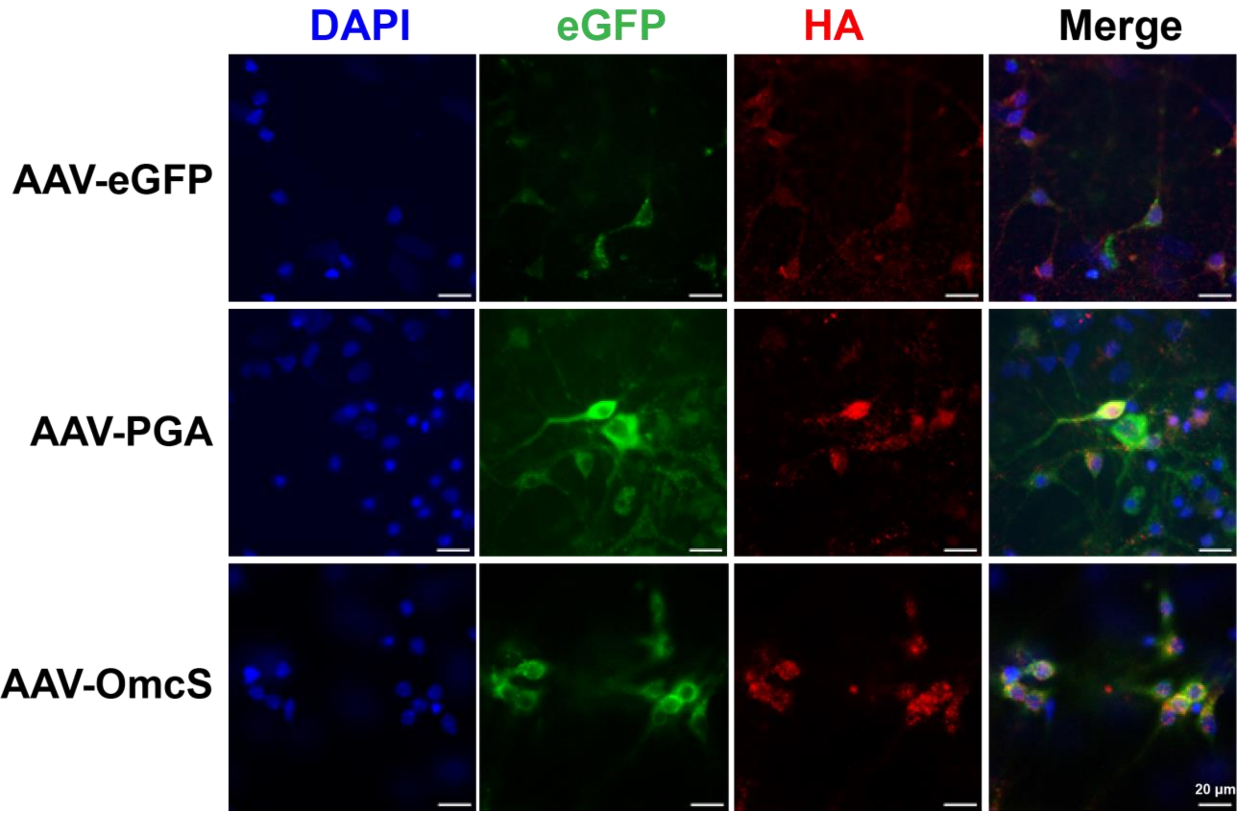
100μg/mL, 37°C, 2h

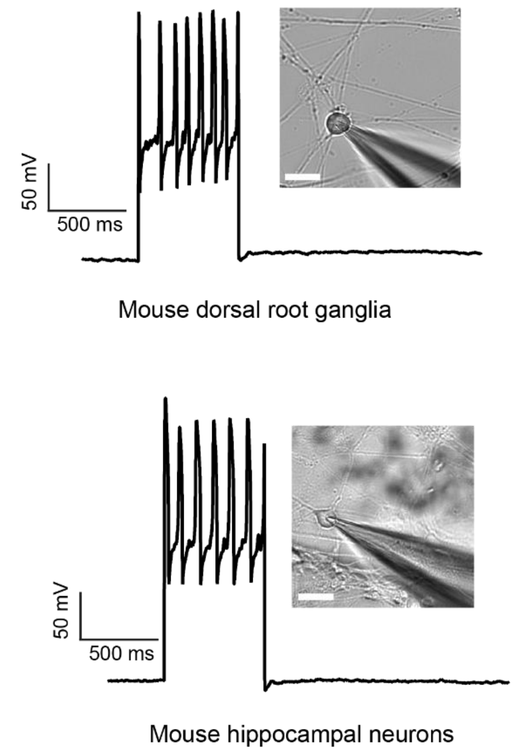


- GM1 incubation increased C_m
- Polyarginine (PAR) is highly positively charged
- Expressed on the extracellular side

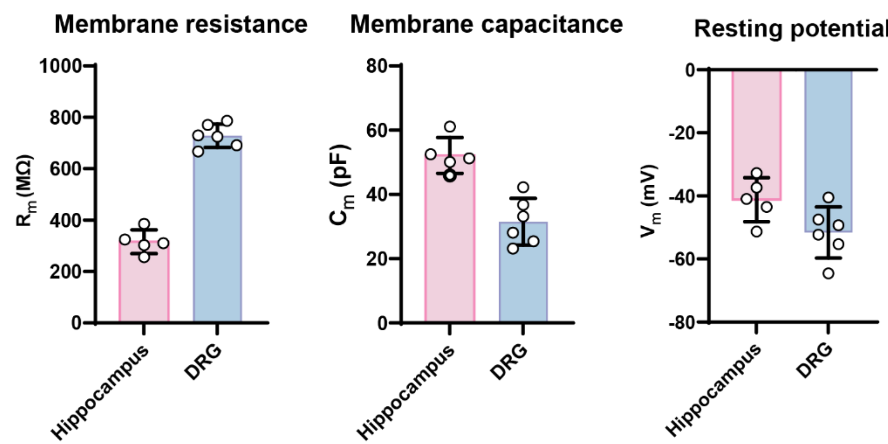


Aim 2: Characterize Membrane Properties

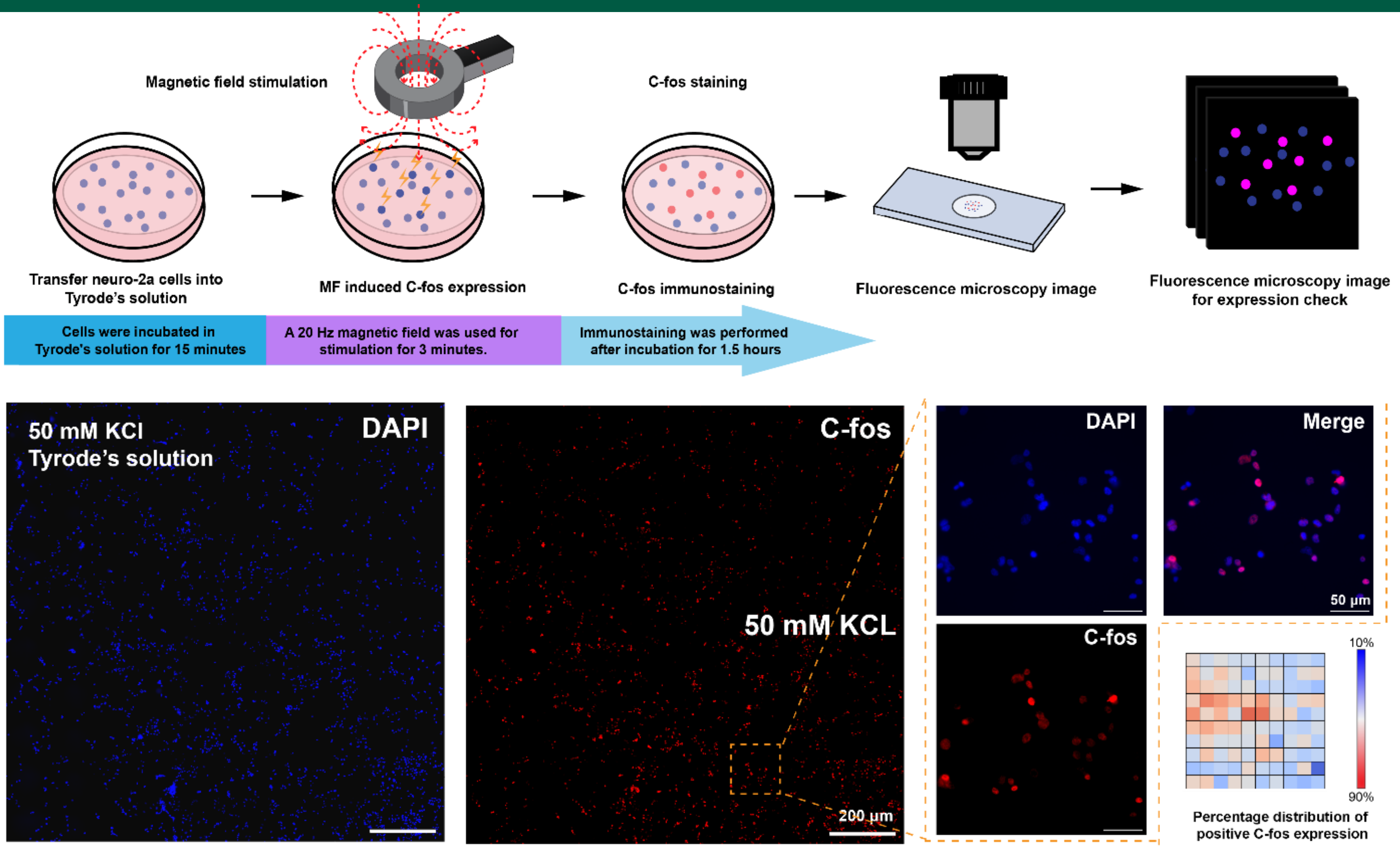




- AAV infected mouse hippocampus neuron cultures
- Membrane-targeted expression

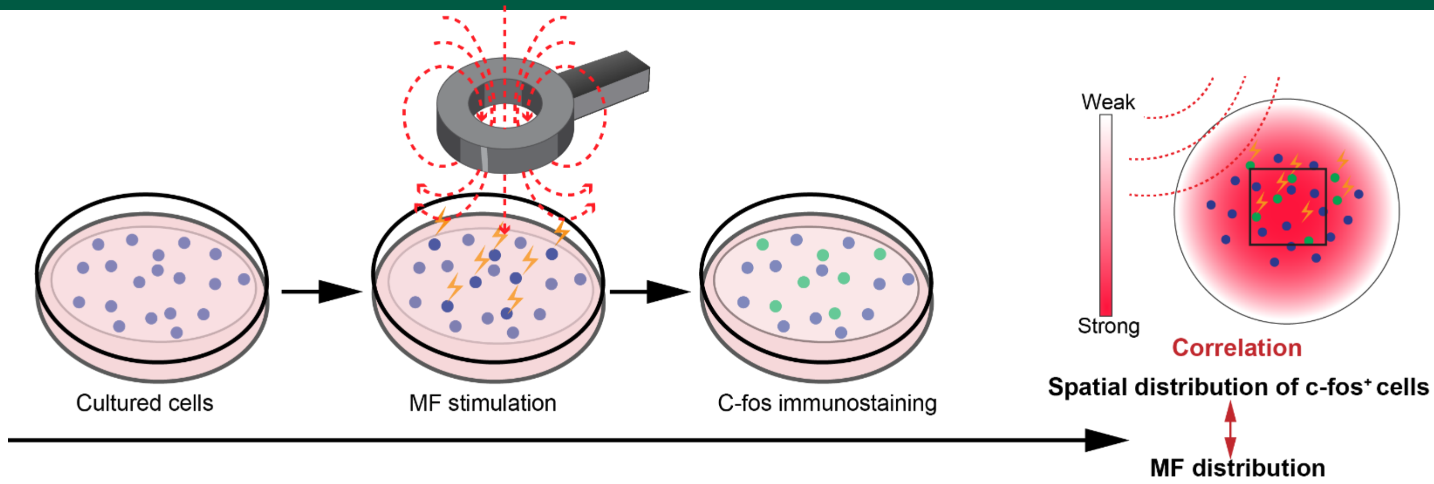


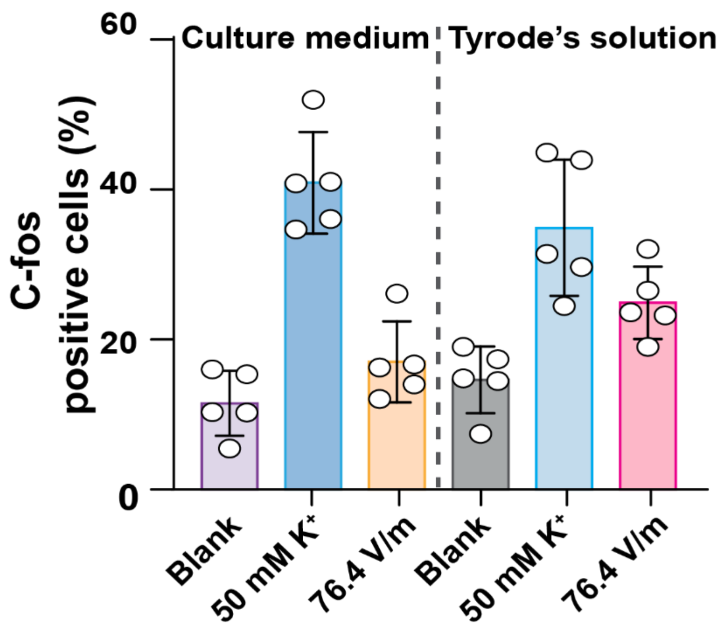
Aim 3: MF-evoked Neural Activity

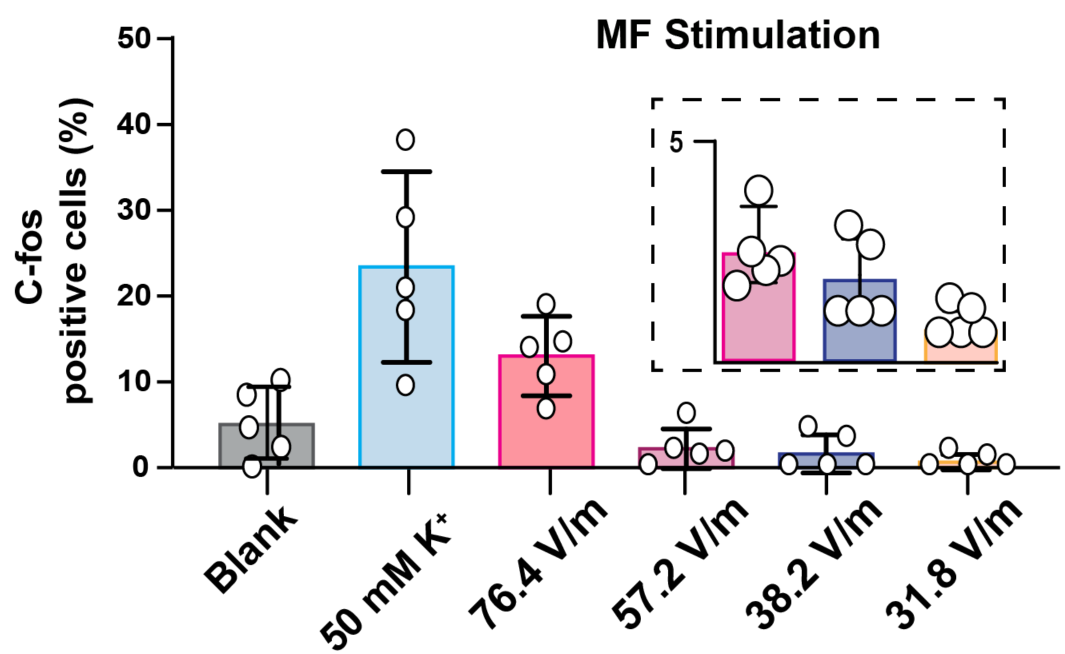


- C-fos: an immediate early gene (IEG) to reflect neuron activity
- Immunohistology and fluorescent microscopy

Aim 3: MF-evoked Neural Activity

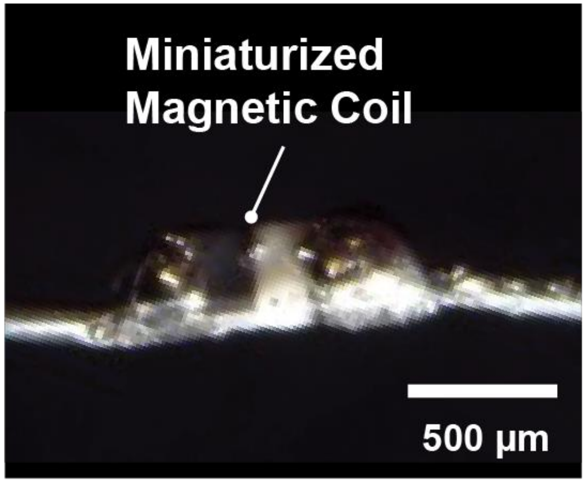


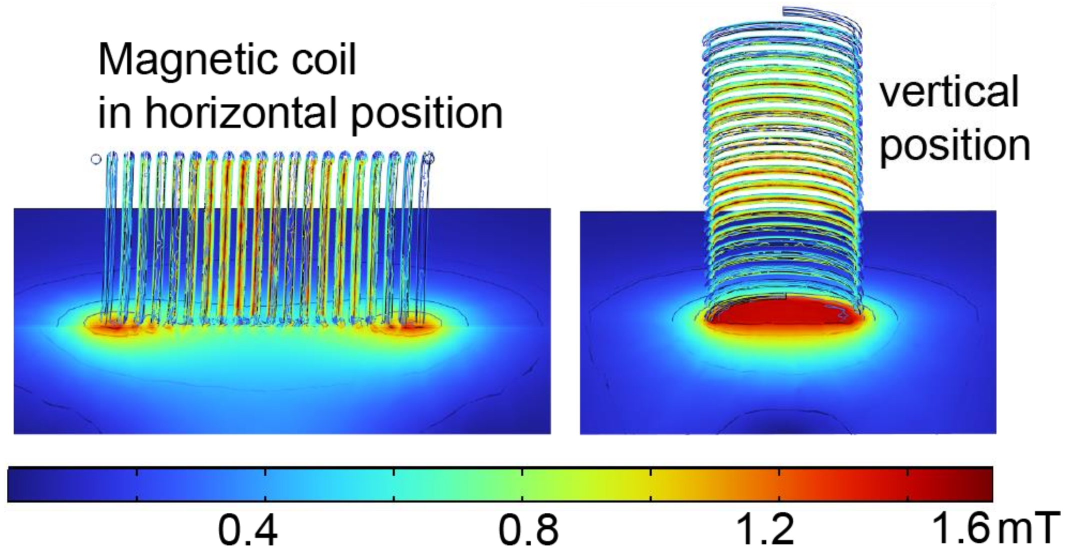


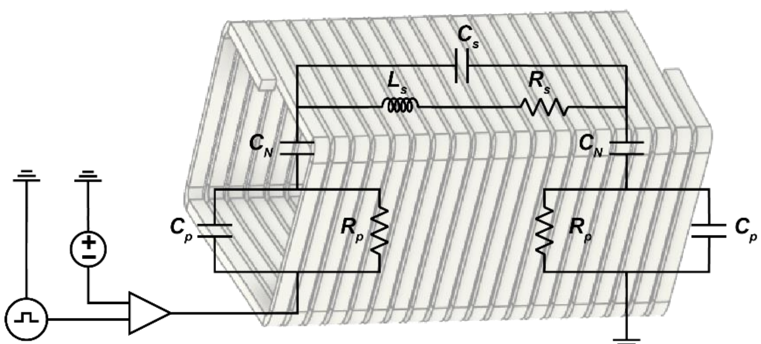


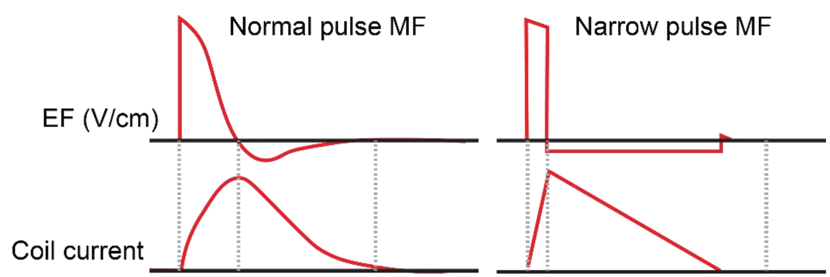
- Large MF coverage to stimulation neural population
- C-fos expression correlation with MF strength and distribution

Aim 3: MF-evoked Neural Activity



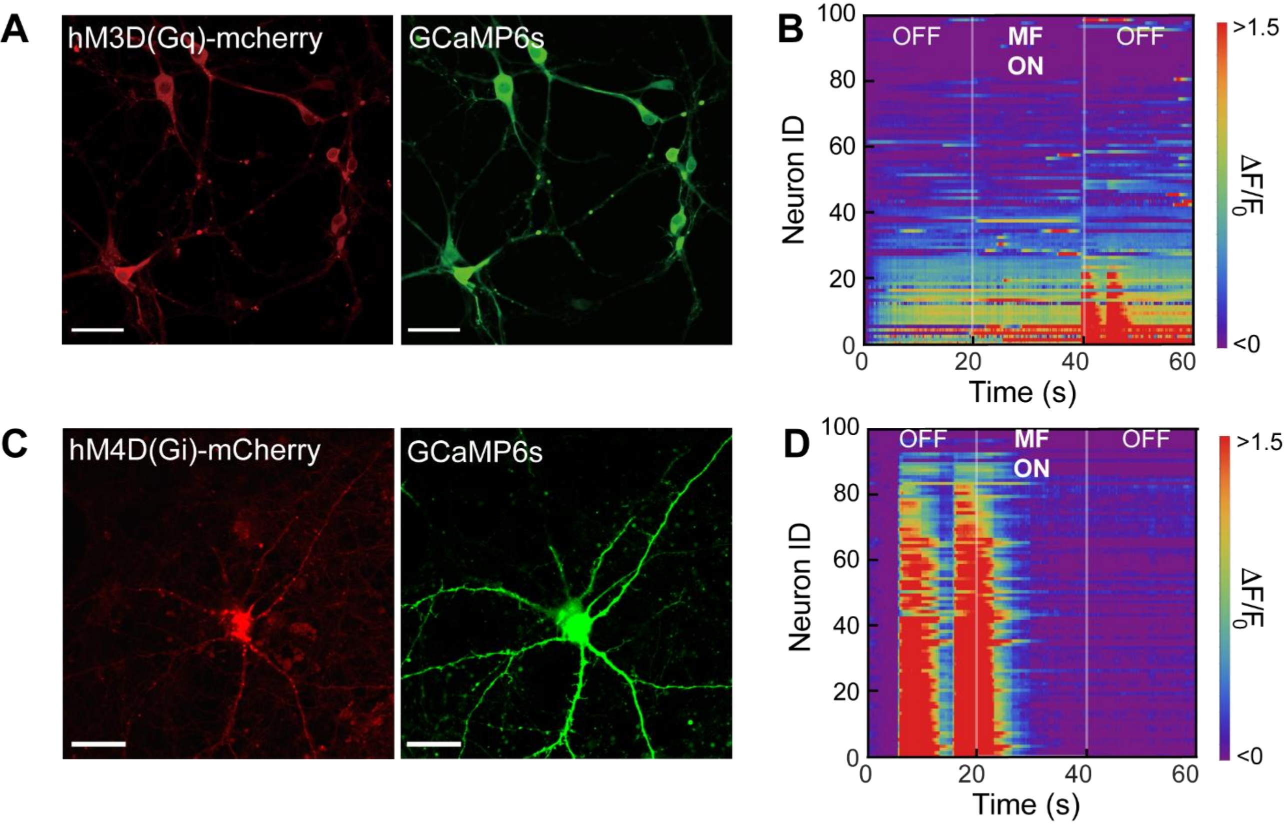




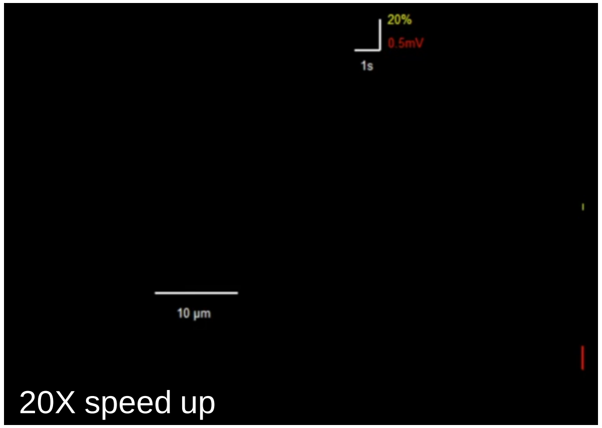


- Single-cell-size magnetic coil design
- Specific stimulation locations: soma, axon hillock, axon terminals

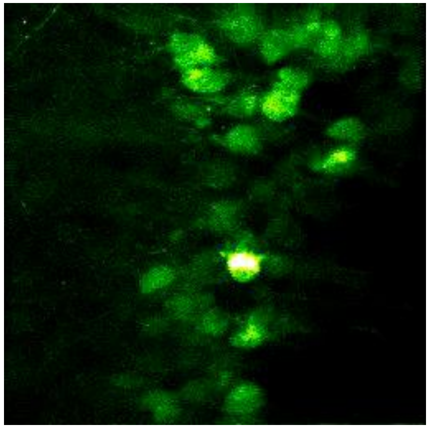
Aim 3: MF-compatible Imaging



***Rao**, et.al, Nat. Nanotech. 2019*



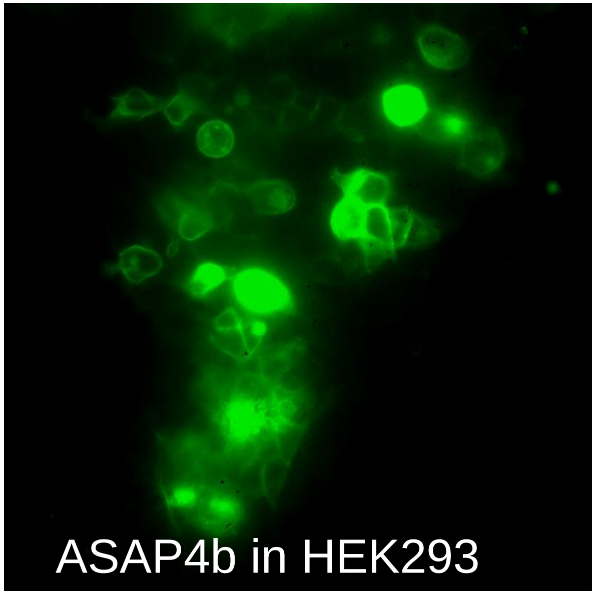
Chen, et. al., Nature, 2013

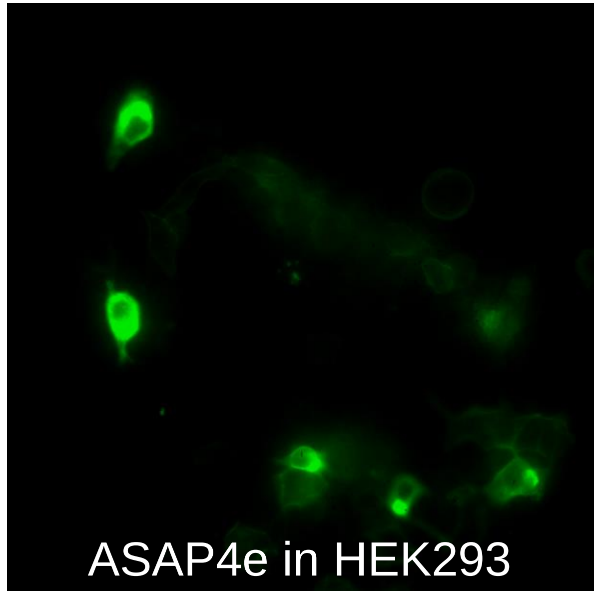


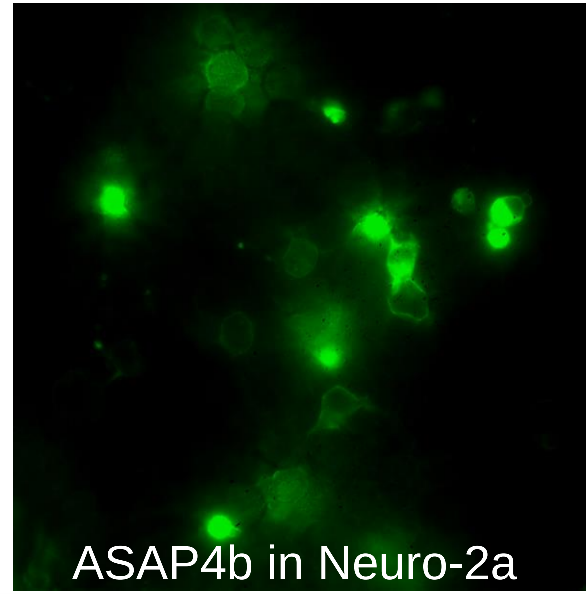
Video courtesy of Dr. Lei Jin at MIT

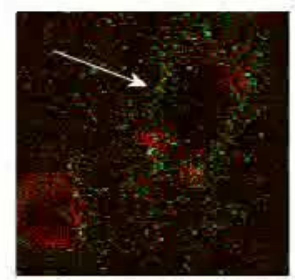
- GCaMP imaging along with AMF (~kHz, 50 mT) stimulation
- Calcium influx as a proxy of neuron activity

Aim 3: MF-compatible Imaging









- A positively tuned voltage indicator
- Challenges in voltage imaging

Evans, et..al, Nat. Methods. 2023

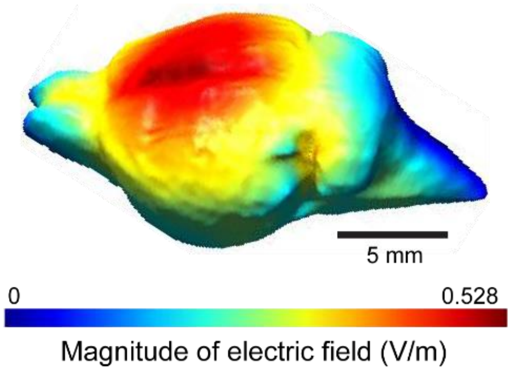
Experimental Plans

In vitro mechanistic study:

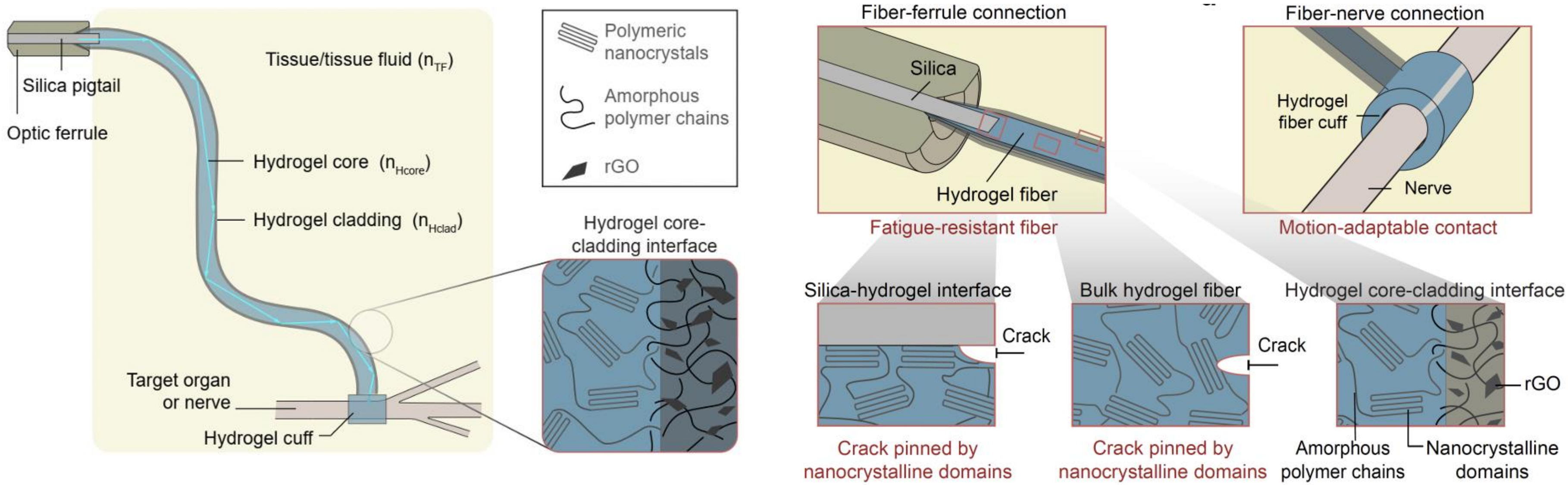
1. Systematically characterize membrane properties changes on hippocampal and DRG neurons
2. Quantify neural excitability
3. Validate patch clamp associated with magnetic stimulation
4. Characterize the specificity of neural excitability with targeted cells

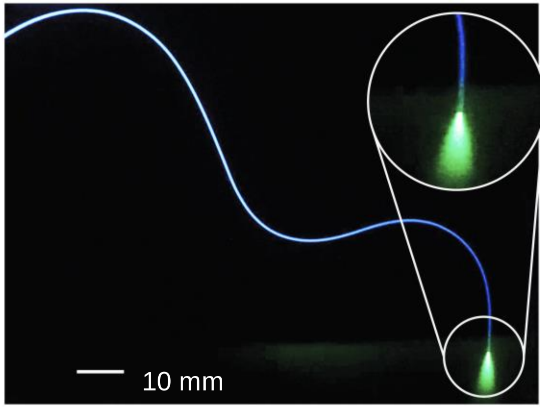
In vivo transcranial magnetic stimulation in mice:

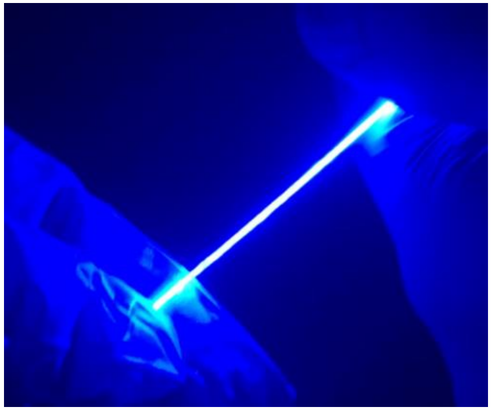
1. AAV-assisted expression
2. Quantify specificity of neural excitation under pulsed magnetic fields

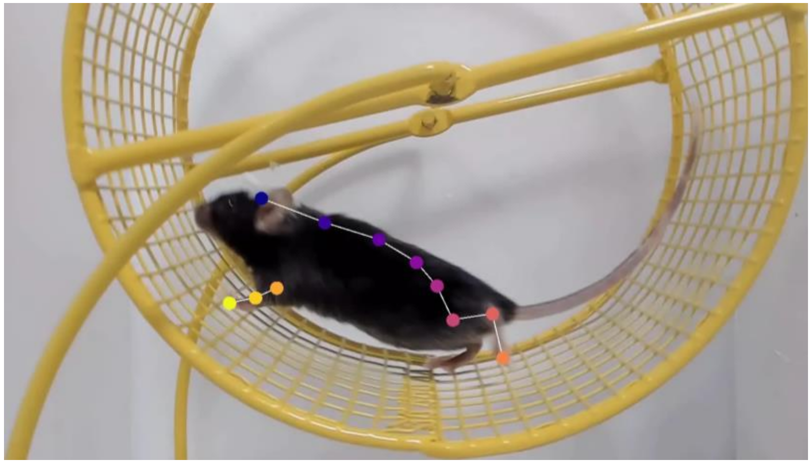


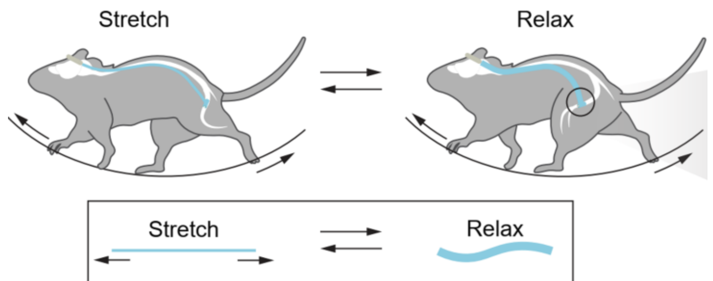
Motion-adaptive Hydrogel Fiber Optics





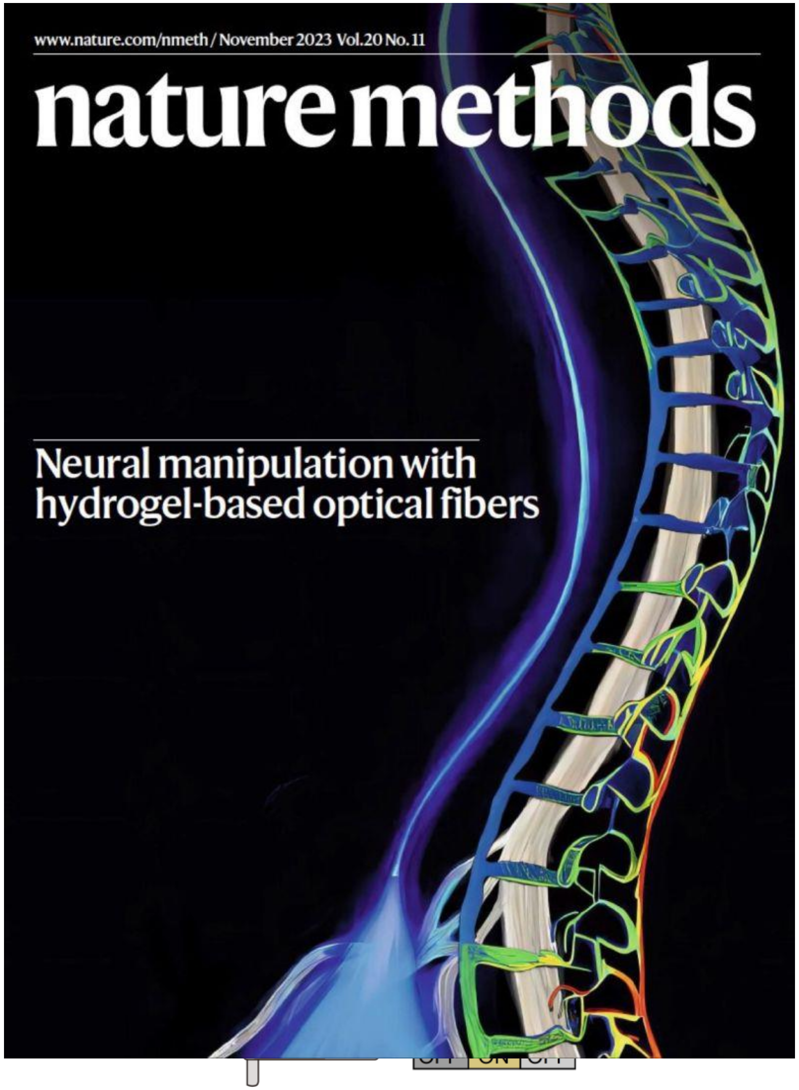


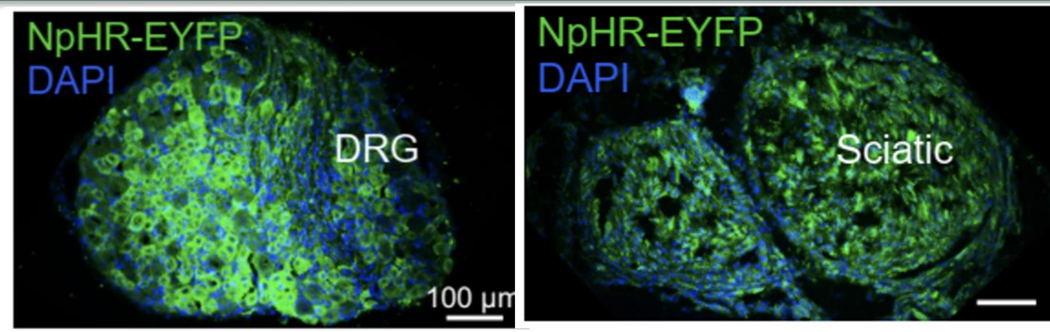


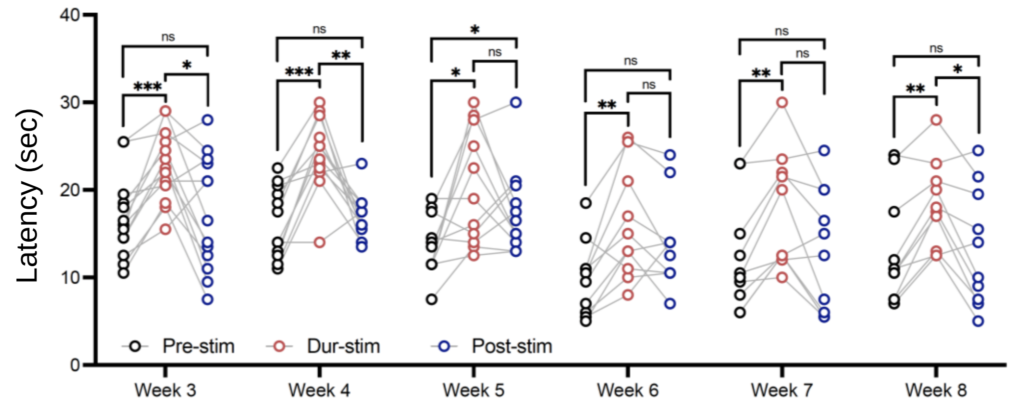


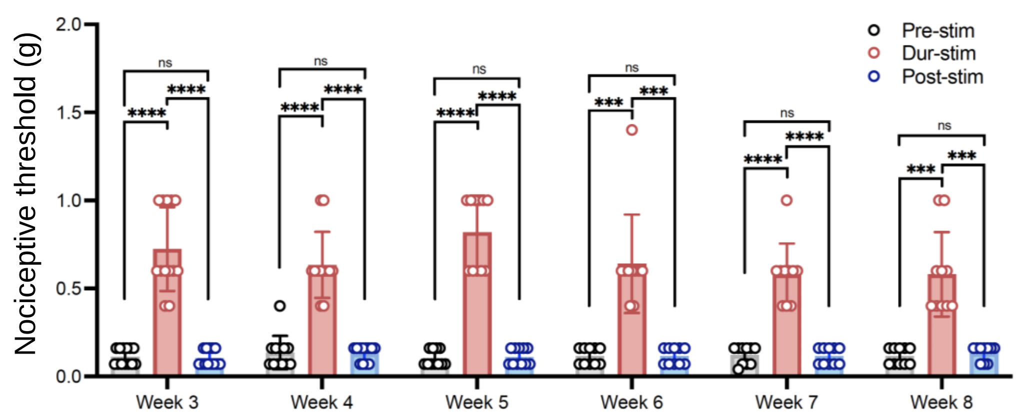
Liu#, **Rao#,***, et. al., Nat. Methods, 2023, DOI 10.1038/s41592-023-02020-9

Optogenetics-enabled Pain Inhibition



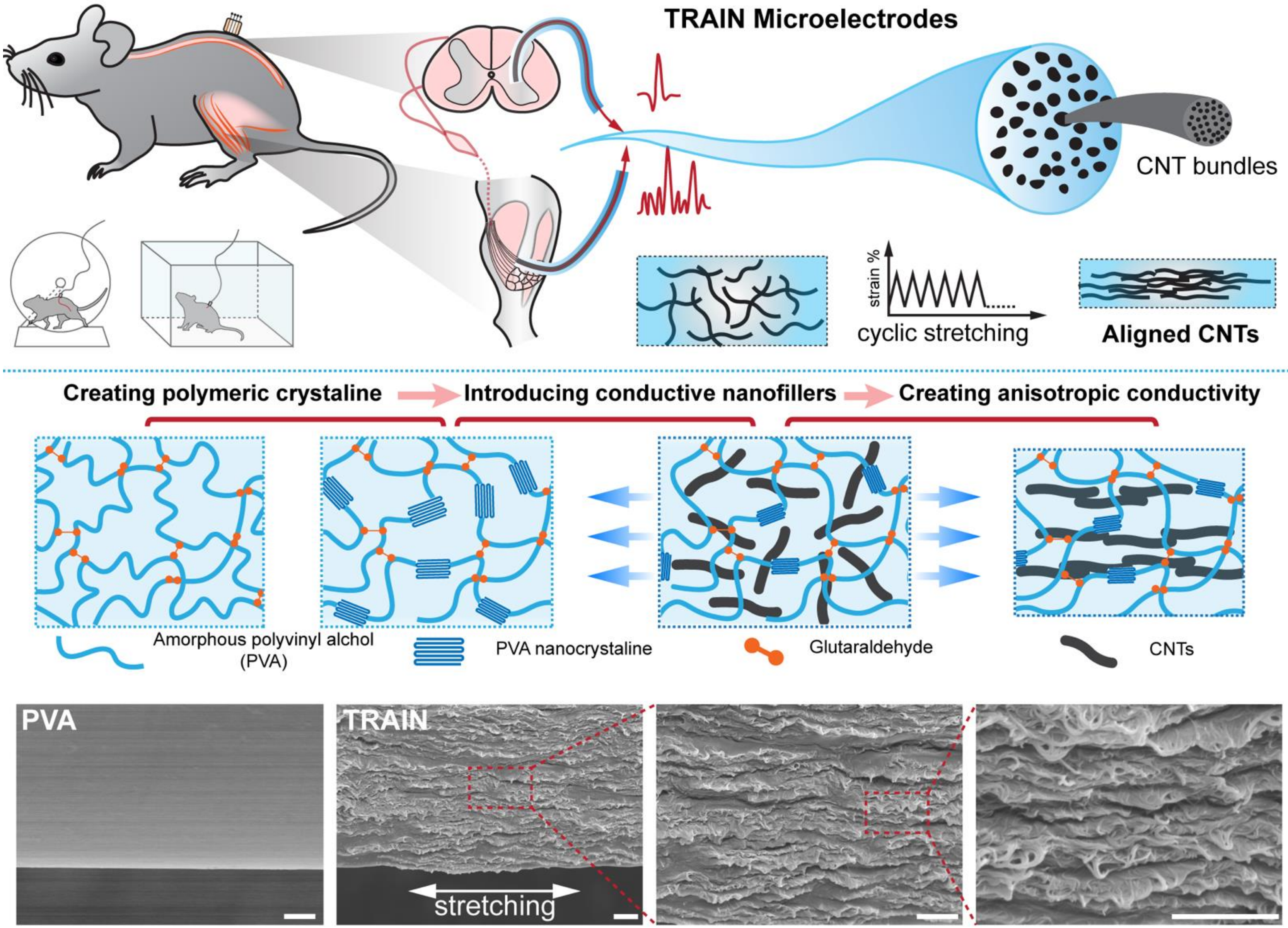






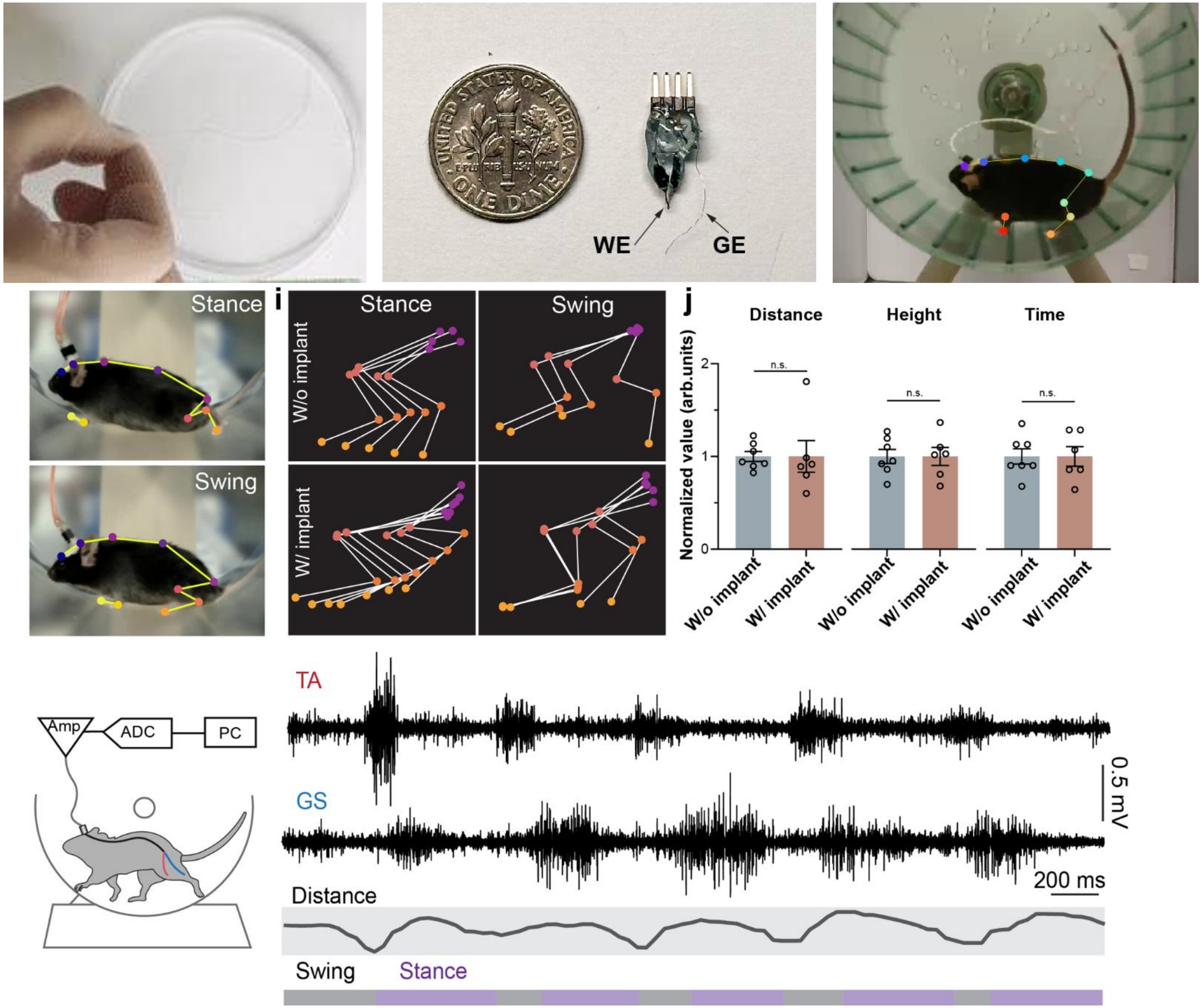
Liu#, **Rao#,***, et. al., Nat. Methods, 2023, DOI 10.1038/s41592-023-02020-9

Anisotropic Hydrogel Microelectrodes



Huang, Xiao, et.al., ***Rao*,*** *in revision*

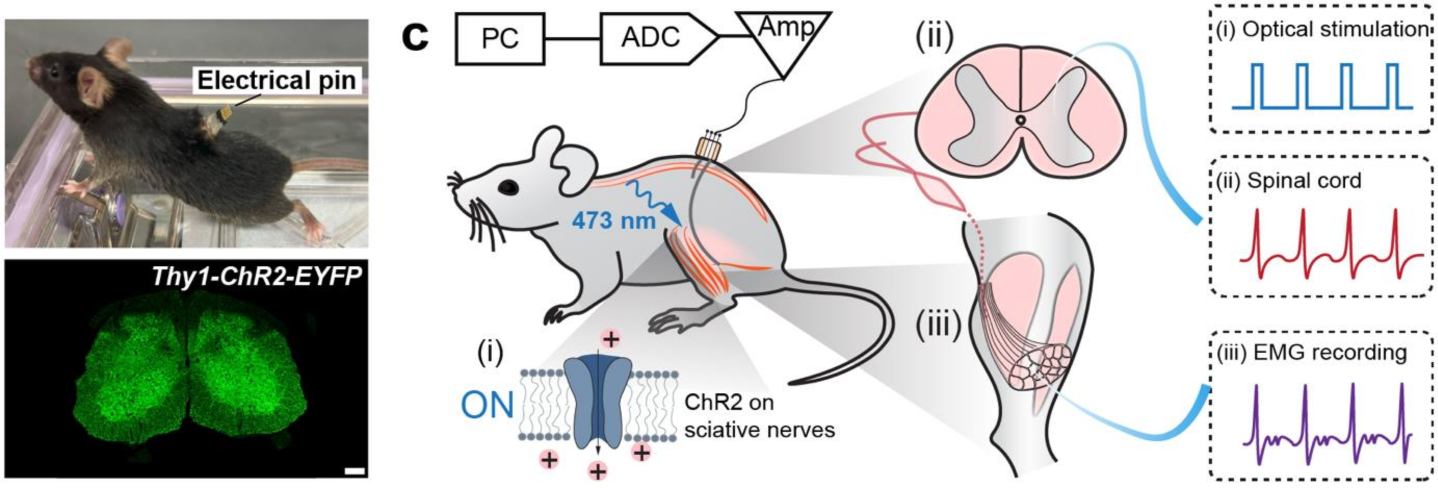
Anisotropic Hydrogel Microelectrodes

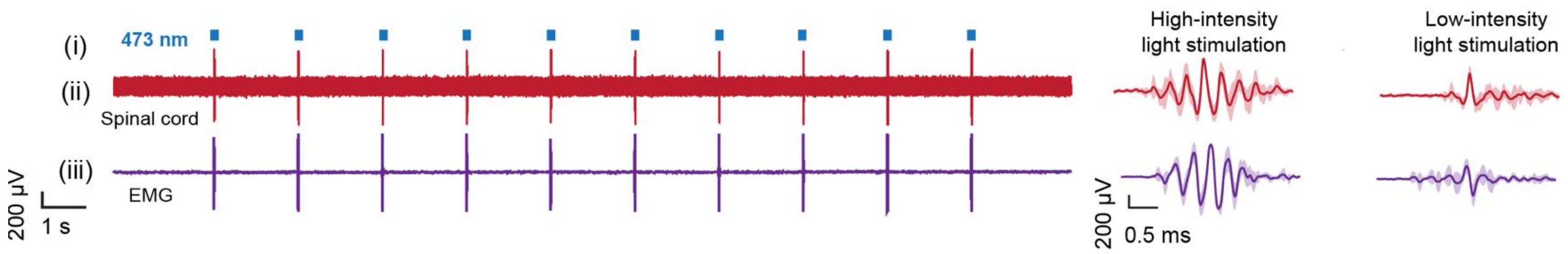


- EMG recording with naturally behaving mice

Huang, Xiao, et.al., ***Rao*,*** *in revision*

Simultaneous EMG/Intraspinal Recordings

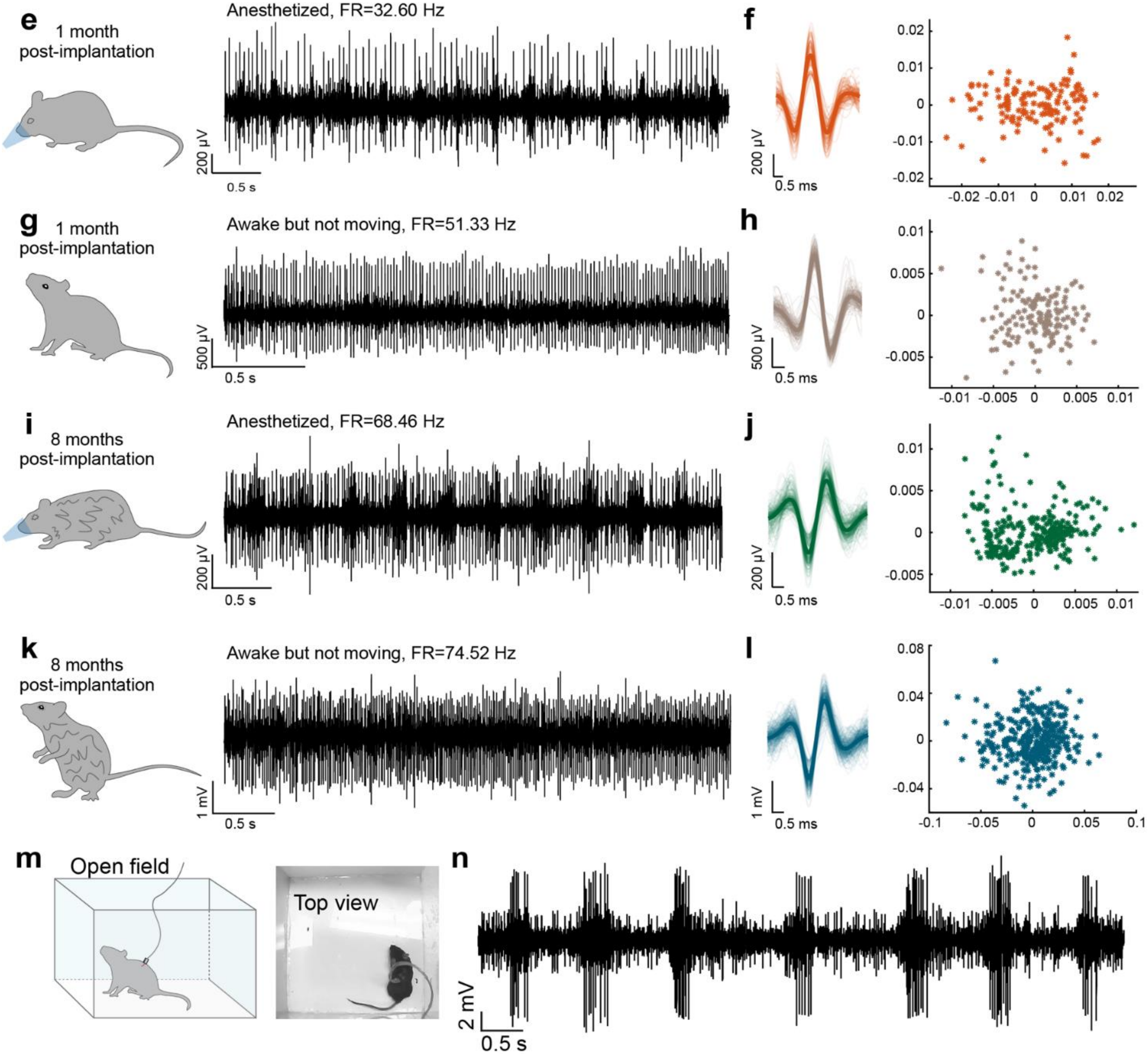




- Simultaneous EMG and intraspinal recordings in vivo

Huang, Xiao, et.al., ***Rao*,*** *in revision*

Intraspinal Recordings during Locomotion



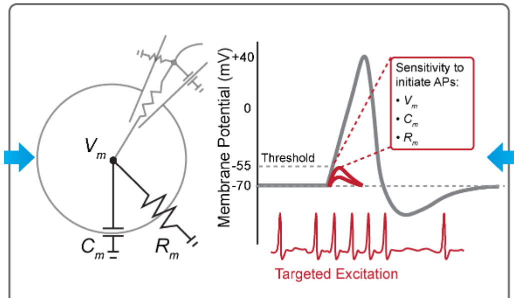
- Intraspinal recordings in naturally behaving mice

Huang, Xiao, et.al., ***Rao*,*** *in revision*

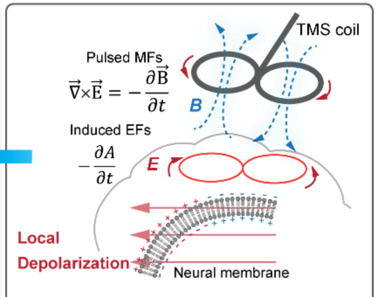
Non-invasive Cell-type-specific Magnetic Neural Modulation

Objectives:

1. *Create a molecular biology toolkit to regulate membrane passive properties*
2. *Characterize their regulation function on membrane*
3. *Test specific neural excitability to MF stimulation*



Neuronal Electrophysiology



Transcranial Magnetic Stimulation

Technical Approaches:

1. *Computation to predict membrane passive properties' regulation on neural excitability*
2. *Membrane-targeted protein expression design*
3. *AAV-facilitated protein expression*
4. *Intracellular electrophysiology recording to characterize membrane passive properties and neuron excitability*
5. *Fluorescent imaging assisted examination on neuron excitability*
6. *MF stimulation on neuron population*
7. *Single-cell MF stimulation*

Accomplishments:

1. *Recruited 1 PhD student (passed qualify exam), 1 rotation PhD student*
2. *Recruited over three undergraduate students working in this project*
3. *Manuscript under preparation*
4. *One invention disclosure submitted*
5. *PI delivered three invited seminar talks, co-chaired and presented in SfN mini-symposium*
6. *Two graduate students presented in Binghamton University BME Expo conference*
7. *One PhD student graduating this Winter, two undergraduate students working in this project went to graduate school*

DoD Benefit:

1. *Mechanistic investigation on pulsed MF stimulation on neuron activity on cellular level*
2. *Spatiotemporally control of neuron activity through non-invasive stimuli, which might modulate motion-, memory-related neural circuit and improve human performance*
3. *Improve TMS treatment with cell-type specificity and personalized medicine*

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Xinxin Xu
Ruobai Xiao (co-mentored)
Dorcas Matuwana (co-mentored)
Katya Dressler

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Chen Lin

Research scholar:
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AIR FORCE OFFICE OF SCIENTIFIC RESEARCH

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Dr. Pat Bradshaw

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