

Tools for Mapping and Fixing the Brain

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Understanding and fixing the brain is a problem of scale

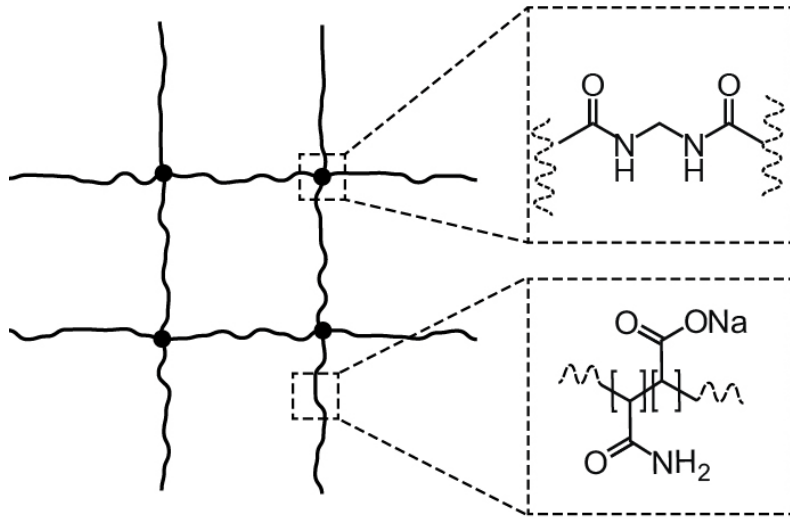
Organized at nanoscale, *but* spanning centimeters (10^7 range)

Computing with millisecond events, *but* spanning years (10^{12} range)

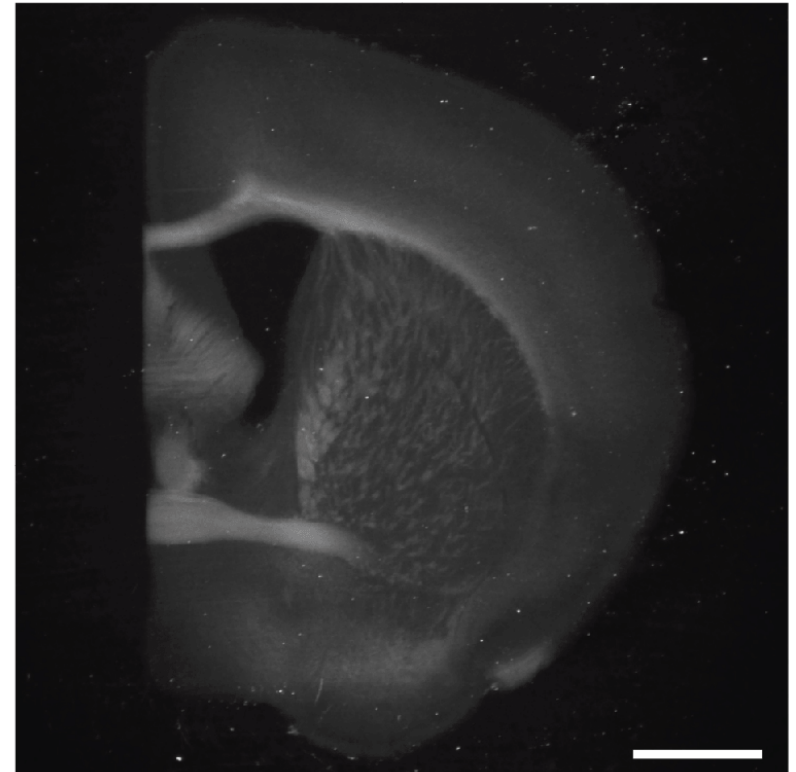
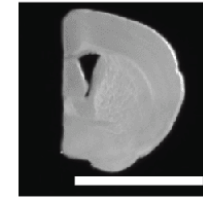


Embed a tissue in a dense polymer that can be swelled by water

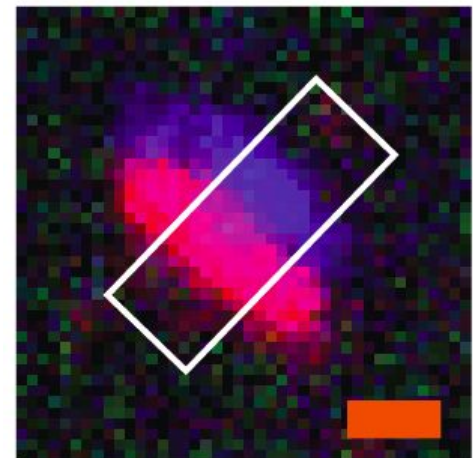
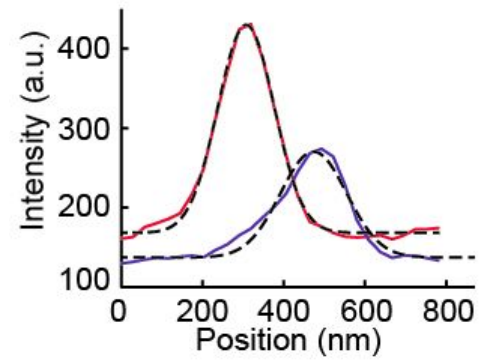
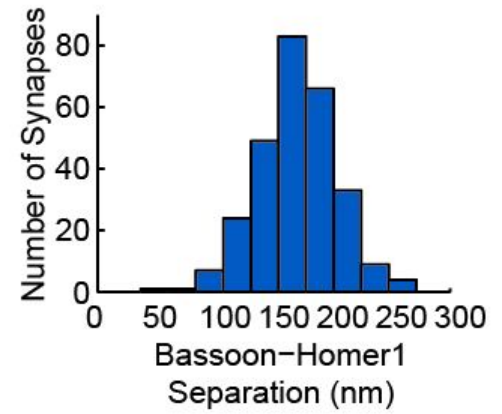
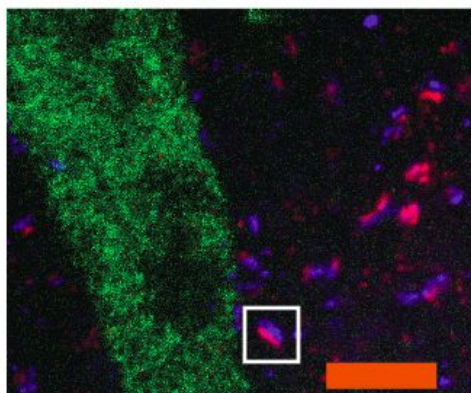
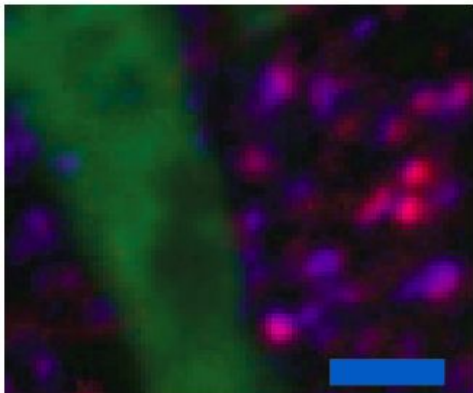
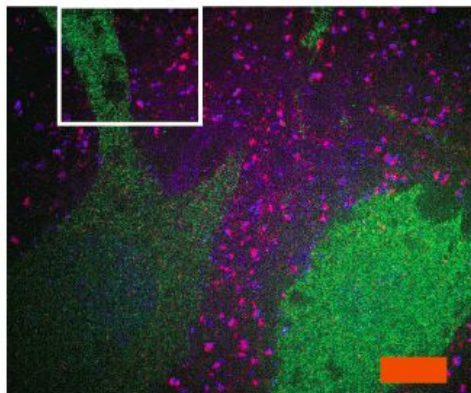
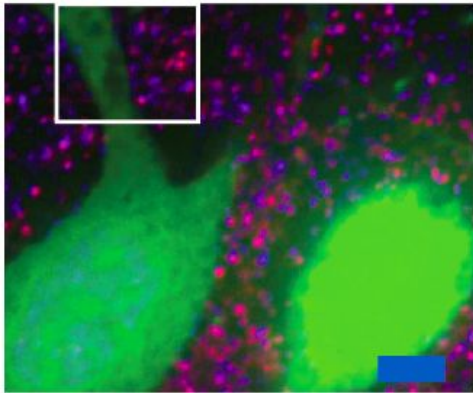
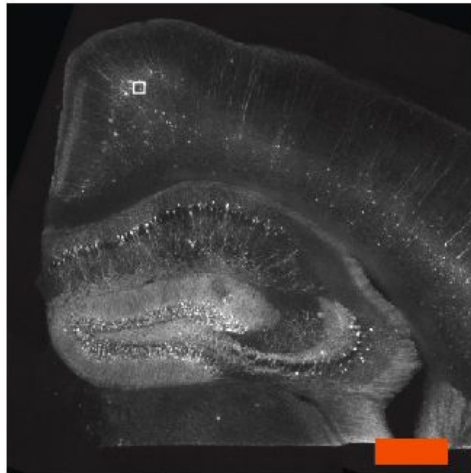
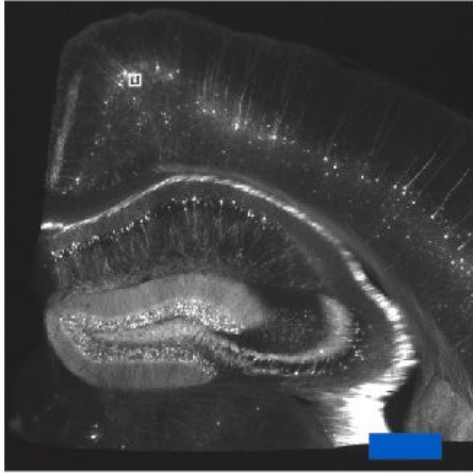
Polyacrylate:
polymer that swells in water
(found in baby diapers)

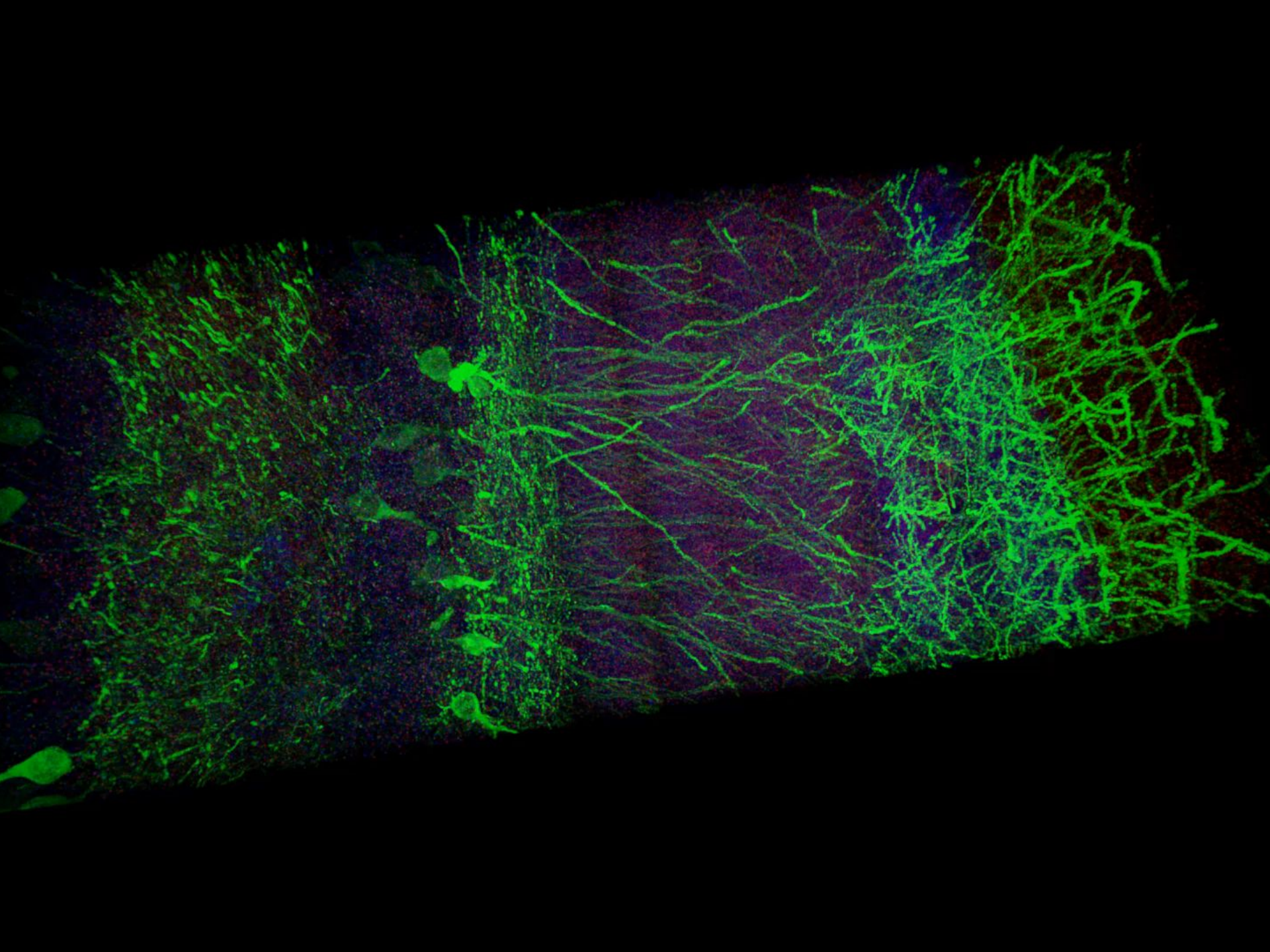


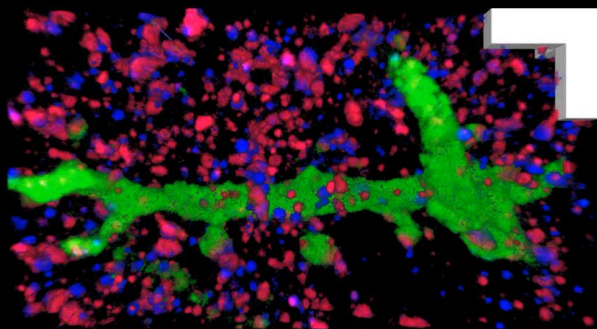
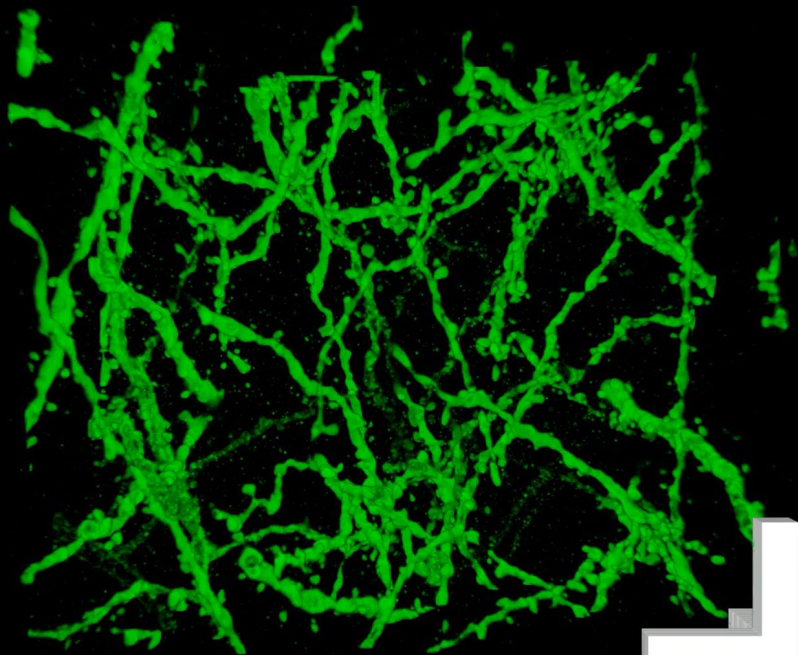
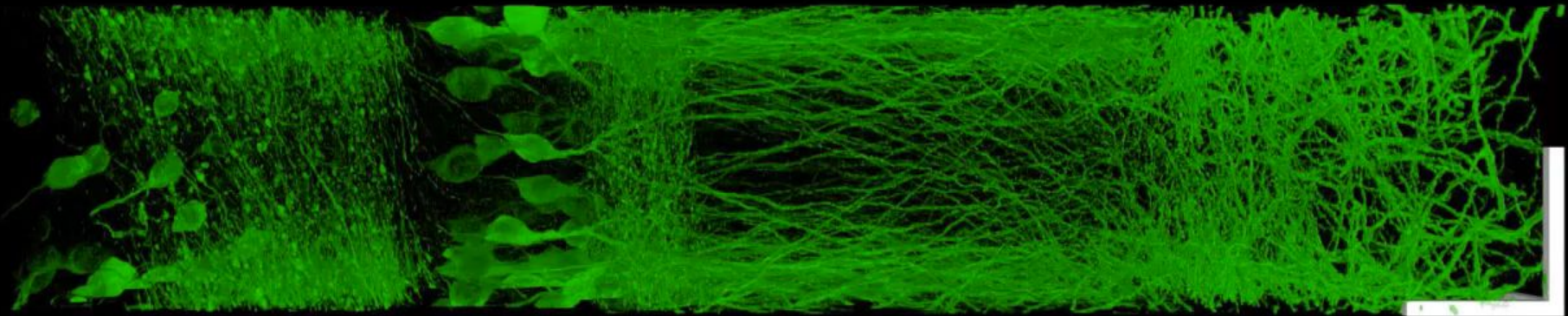
Embed a brain in permeating
polyacrylate polymer network,
then add water



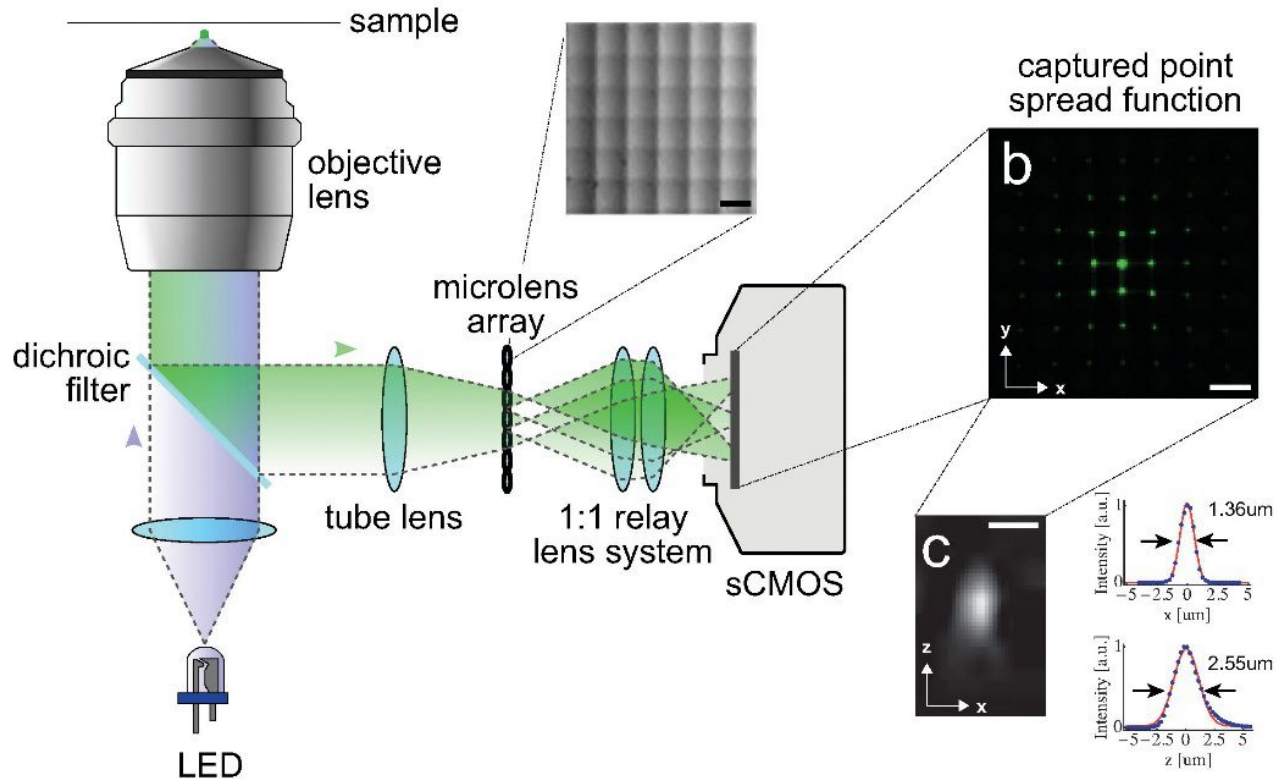
Before expansion: After expansion (~4.5x):
confocal microscopy confocal microscopy





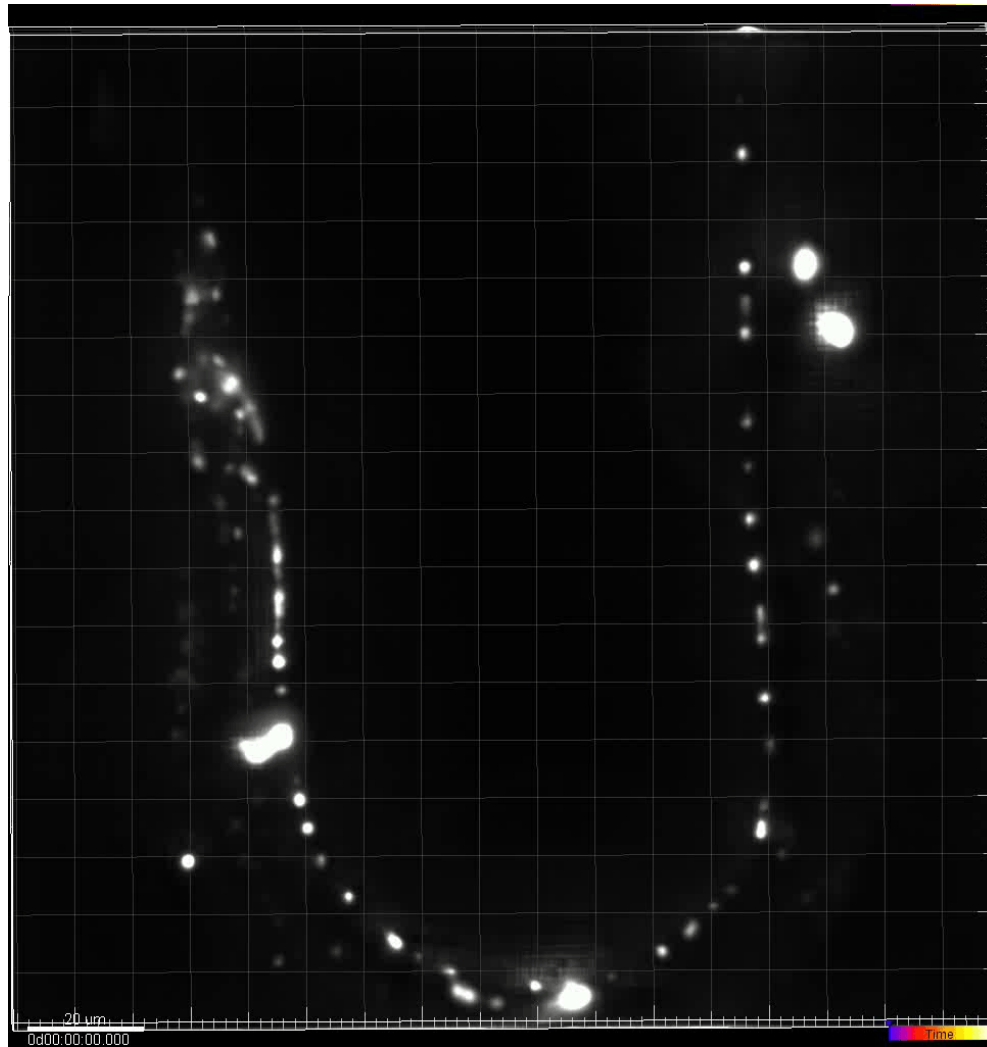


Simultaneous, whole-animal, 3-D microscopy: light-field imaging

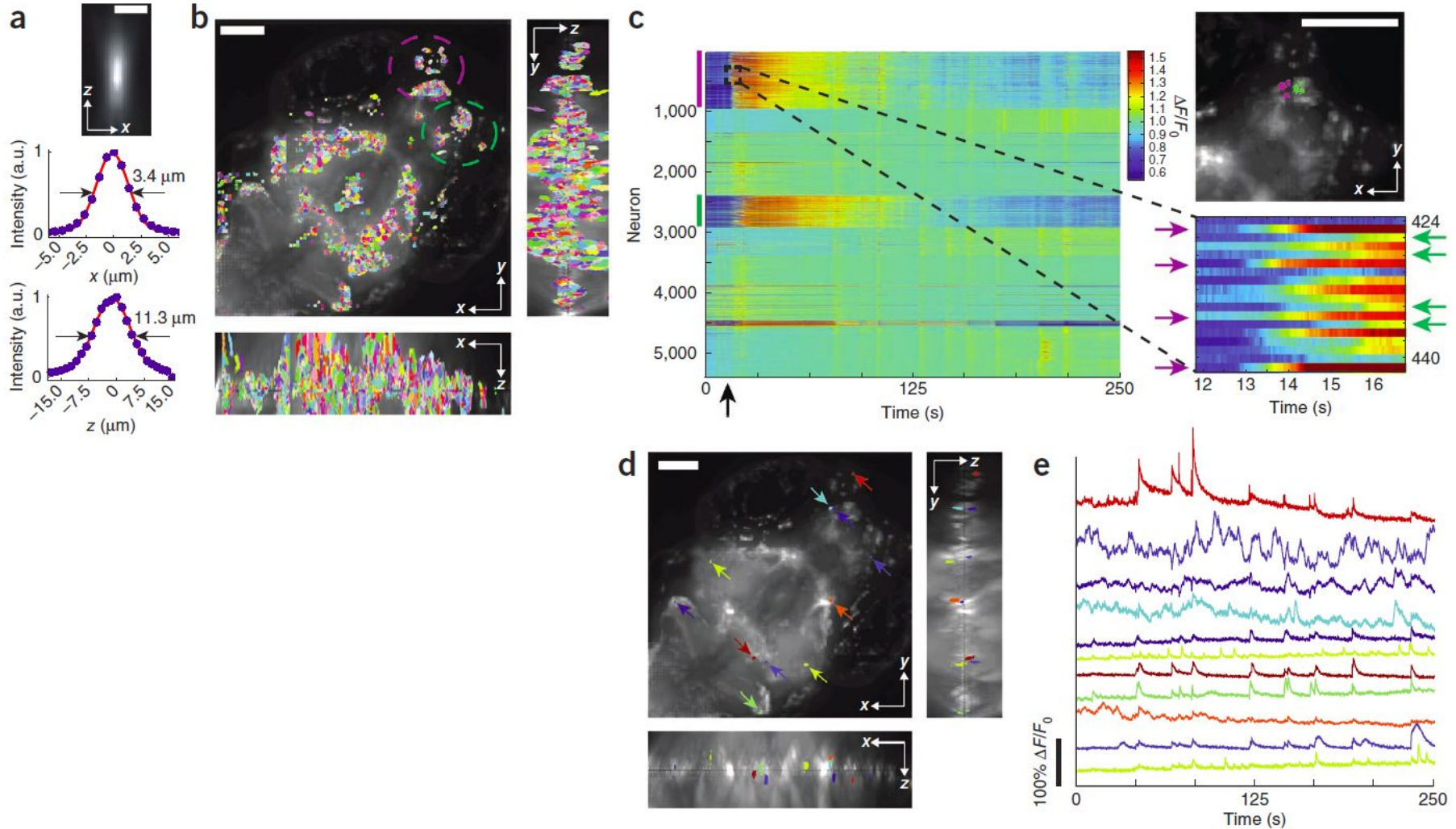


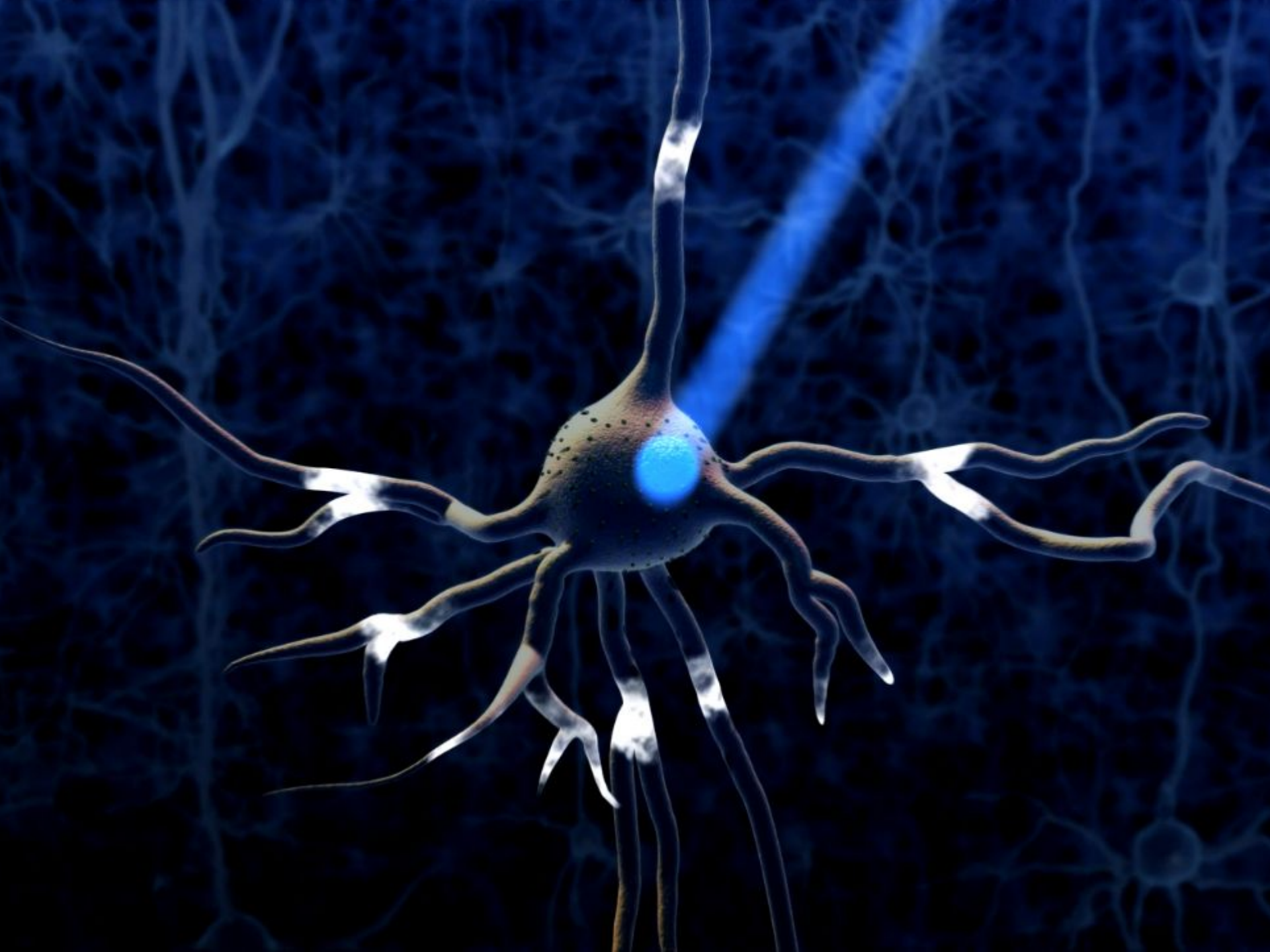
Prevedel*, Yoon*, et al. (2014) *Nature Methods* 11:727-730.

Imaging neural activity throughout organism with known connectome



Imaging zebrafish neural activity in 3-D (at 20 Hz, below)



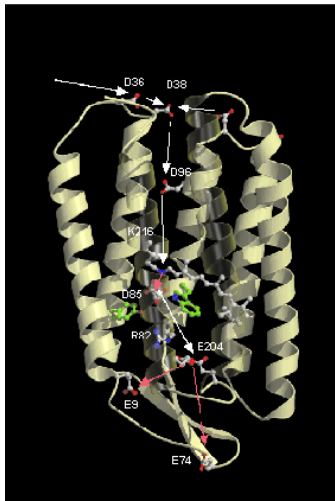


Bacteriorhodopsins:

Light-driven proton pumps



<http://www.genome.duke.edu/genomelife/2011/03/systems-under-stress/>

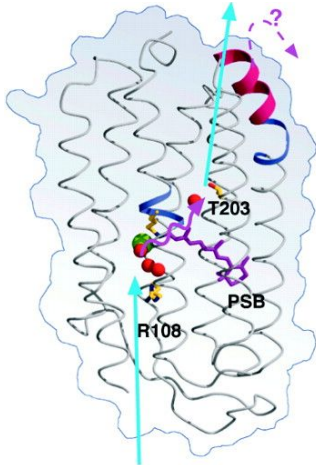


http://www.biochem.mpg.de/523002/Protein_BR

D. Oesterhelt and W. Stoeckenius (1971) Rhodopsin-like Protein from the Purple Membrane of Halobacterium halobium. Nature New Biology 233:149-152.

Halorhodopsins:

Light-driven chloride pumps



<http://www.sciencemag.org/content/288/5470/1390.full>

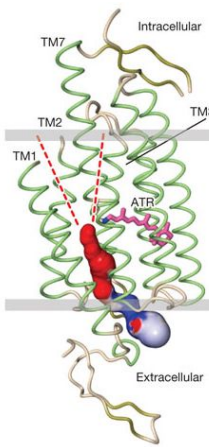
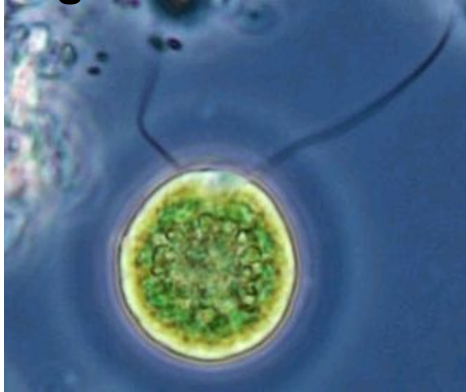
Matsuno-Yagi A, Mukohata Y (1977) Two possible roles of bacteriorhodopsin; a comparative study of strains of Halobacterium halobium differing in pigmentation. Biochem Biophys Res Commun 78:237-43.

Matsuno-Yagi A, Mukohata Y (1980) ATP synthesis linked to lightdependent proton uptake in a rad mutant strain of Halobacterium lacking bacteriorhodopsin. Arch Biochem Biophys, 199:297-303.

Schobert B, Lanyi JK (1982) Halorhodopsin is a light-driven chloride pump. J Biol Chem, 257:10206-12

Channelrhodopsins:

Light-driven cation channels



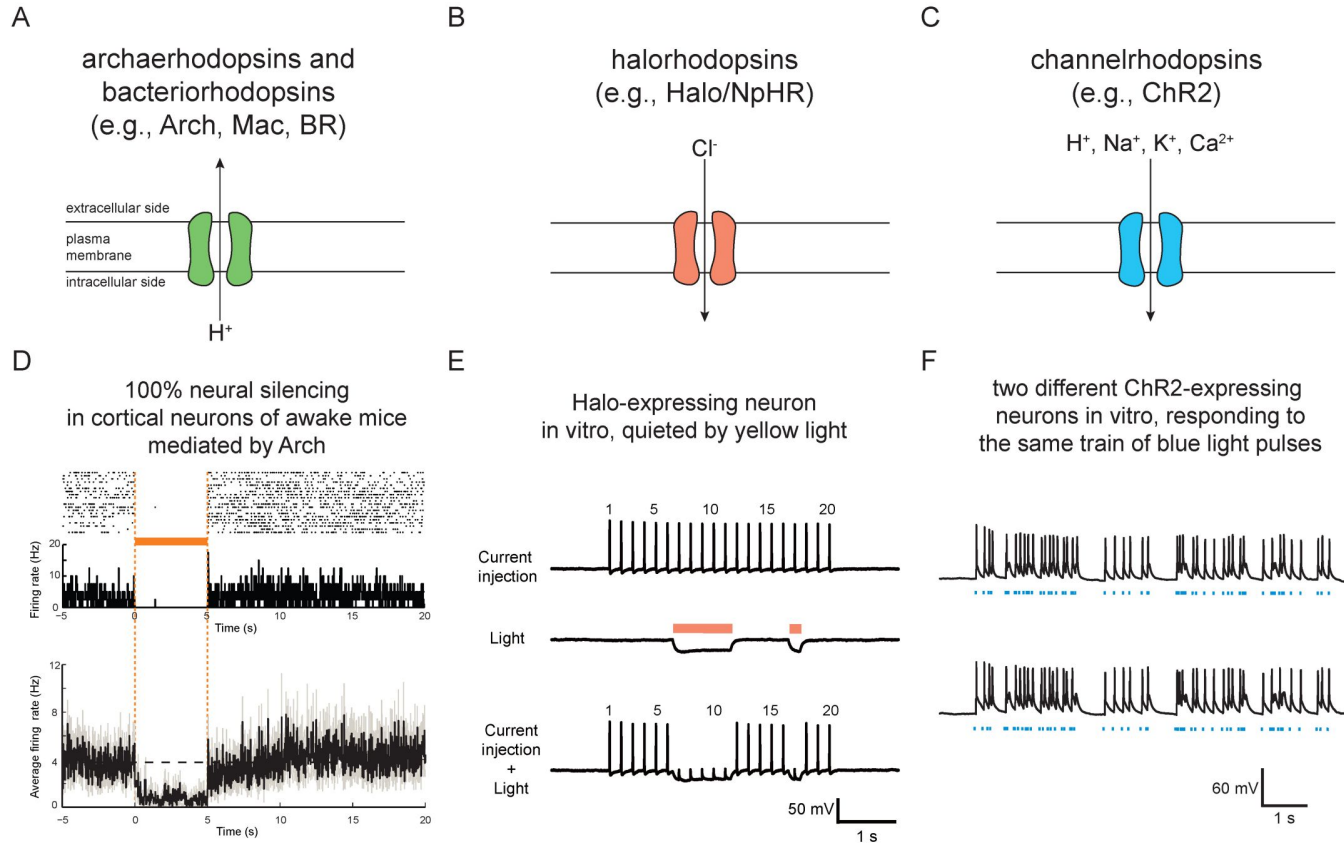
<http://starcentral.mbl.edu/microscope/portal.php?pagetitle=assetfactsheet&imageid=224>

<http://www.nature.com/nature/journal/v482/n7385/full/nature10870.html>

Nagel G, Ollig D, Fuhrmann M, Kateriya S, Musti AM, Bamberg E, Hegemann P (2002) Channelrhodopsin-1: a light-gated proton channel in green algae. Science, 296:2395-8.

Nagel G, Szellas T, Huhn W, Kateriya S, Adeishvili N, Berthold P, Ollig D, Hegemann P, Bamberg E (2003) Channelrhodopsin-2, a directly light-gated cation-selective membrane channel. Proc Natl Acad Sci U S A, 100:13940-5.

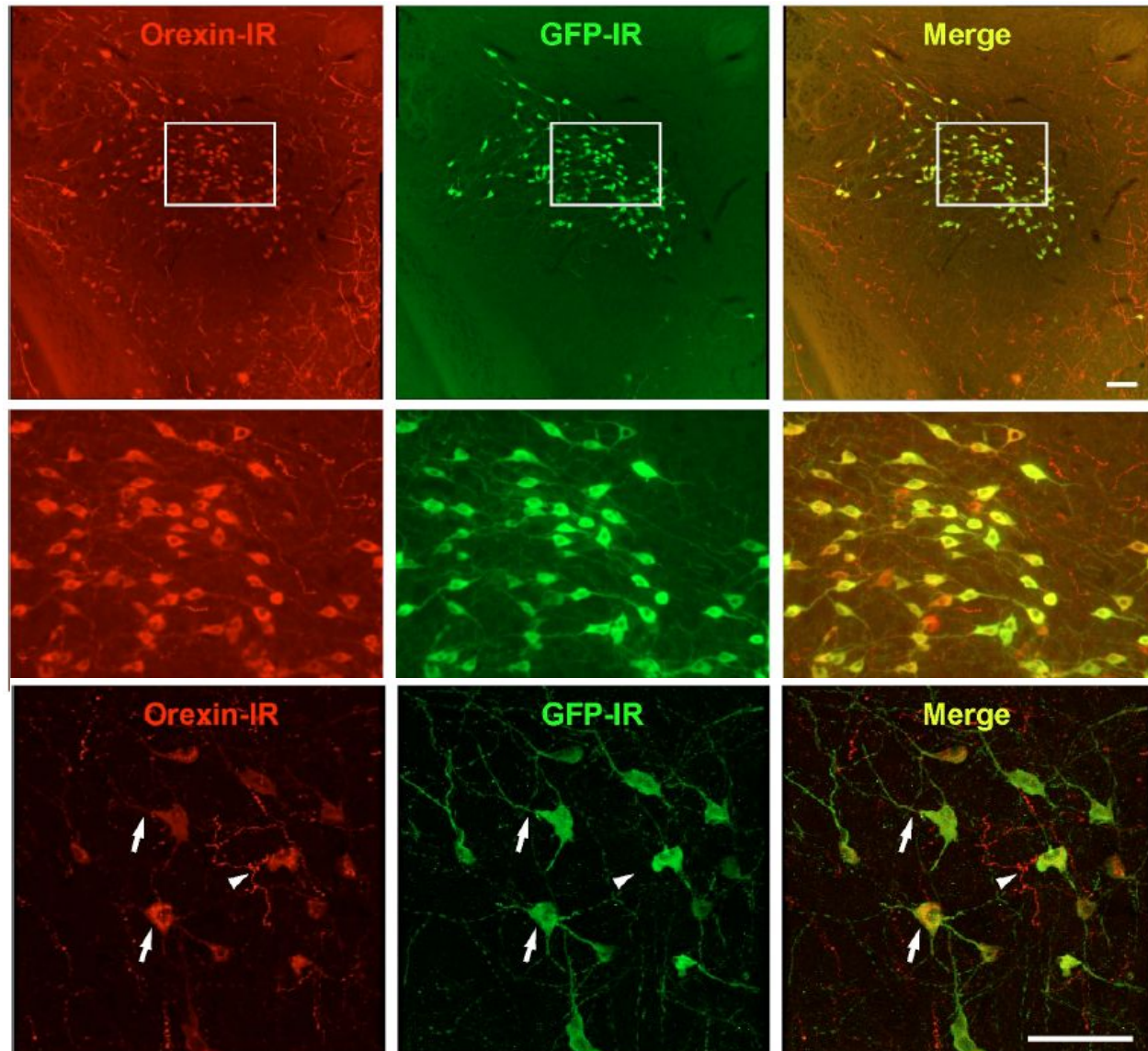
Three major optogenetic molecule classes: microbial opsins, seven-transmembrane proteins, binding endogenous all-trans-retinal



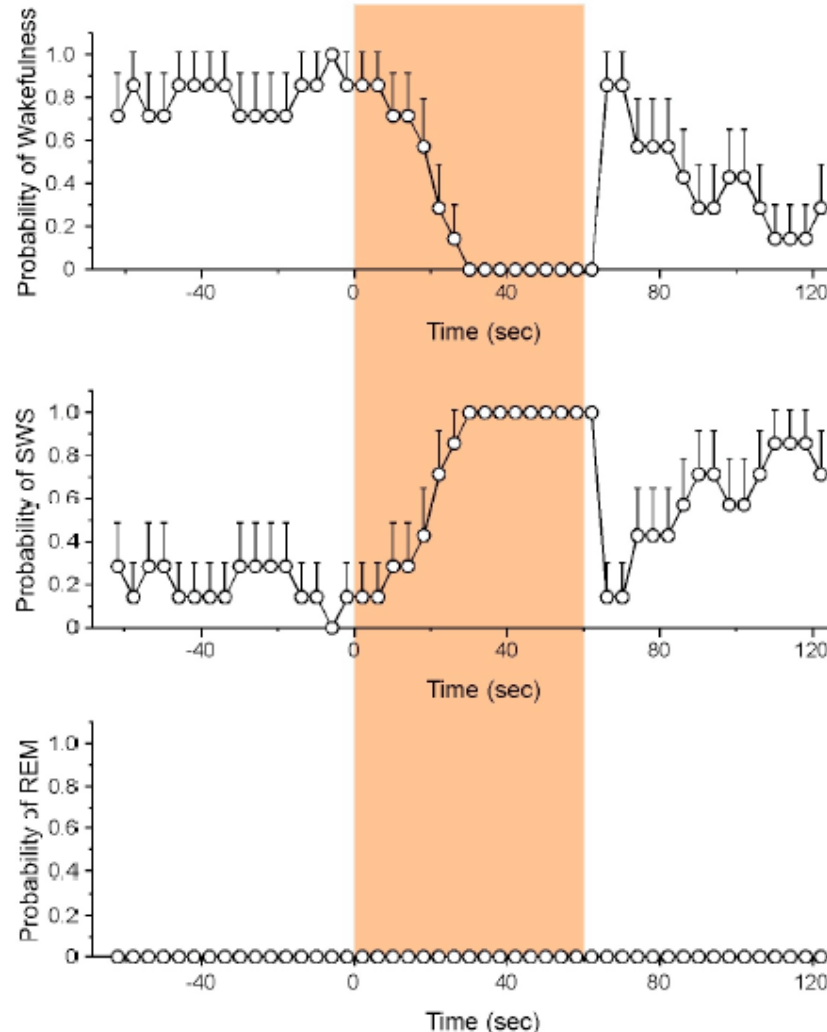
Boyden (2011) *Faculty of 1000 Biology Reports* 3:11.

Sequences, plasmids, links to DNA/virus providers, at <http://syntheticneurobiology.org/>

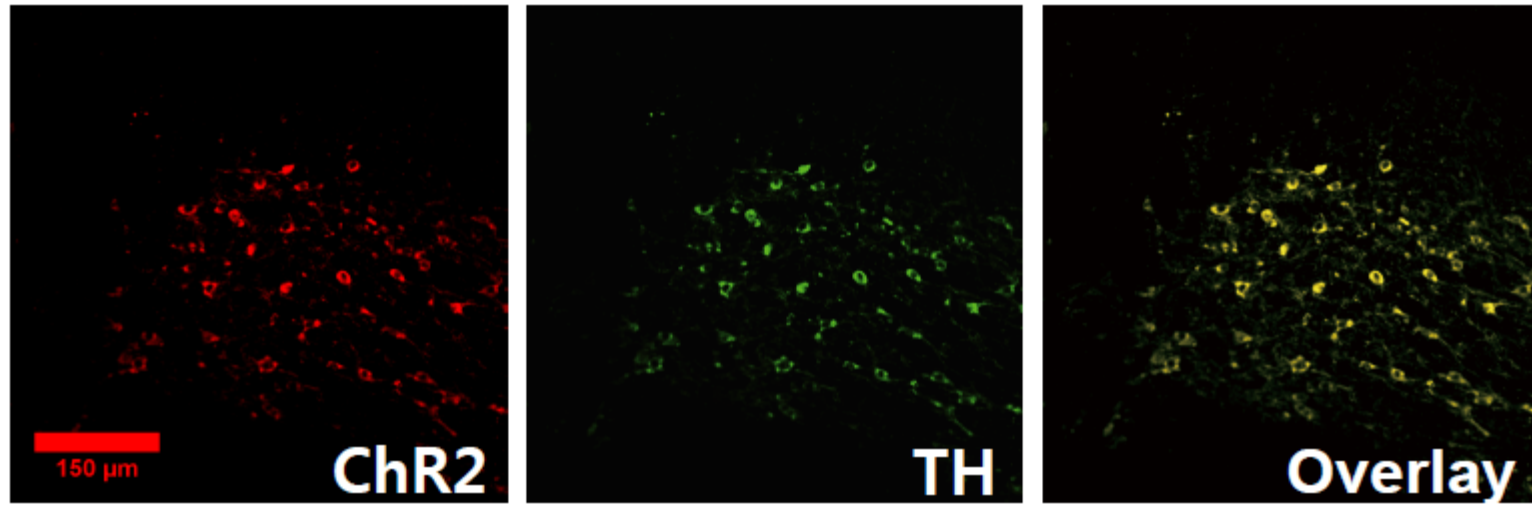
Transgenic mice expressing original-N. pharaonis halorhodopsin, tagged with GFP, in hypocretin neurons



Light silences the neurons, resulting in slow-wave sleep



DAT-Cre + AAV-FLEX-ChR2- tdTomato



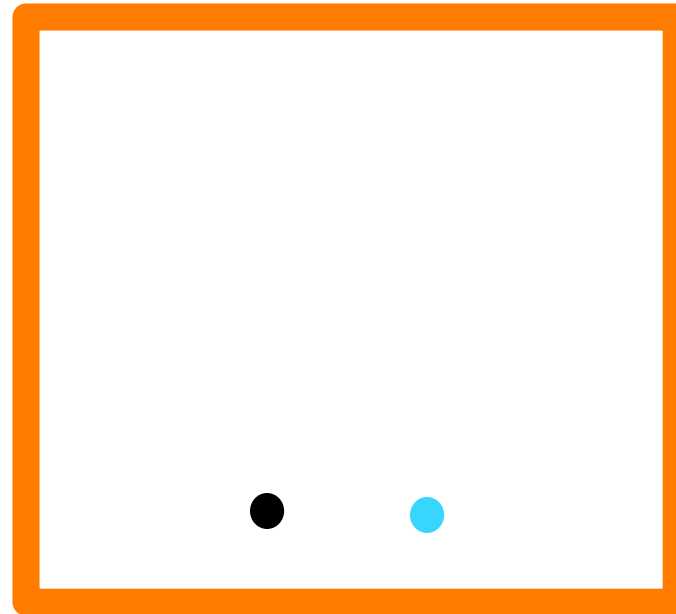
Finding circuits in the brain that can mediate reward

Dopamine

neurons:

implicated in reward and addiction, but largely through pharmacological and electrical means

Is a brief activation of them sufficient to drive

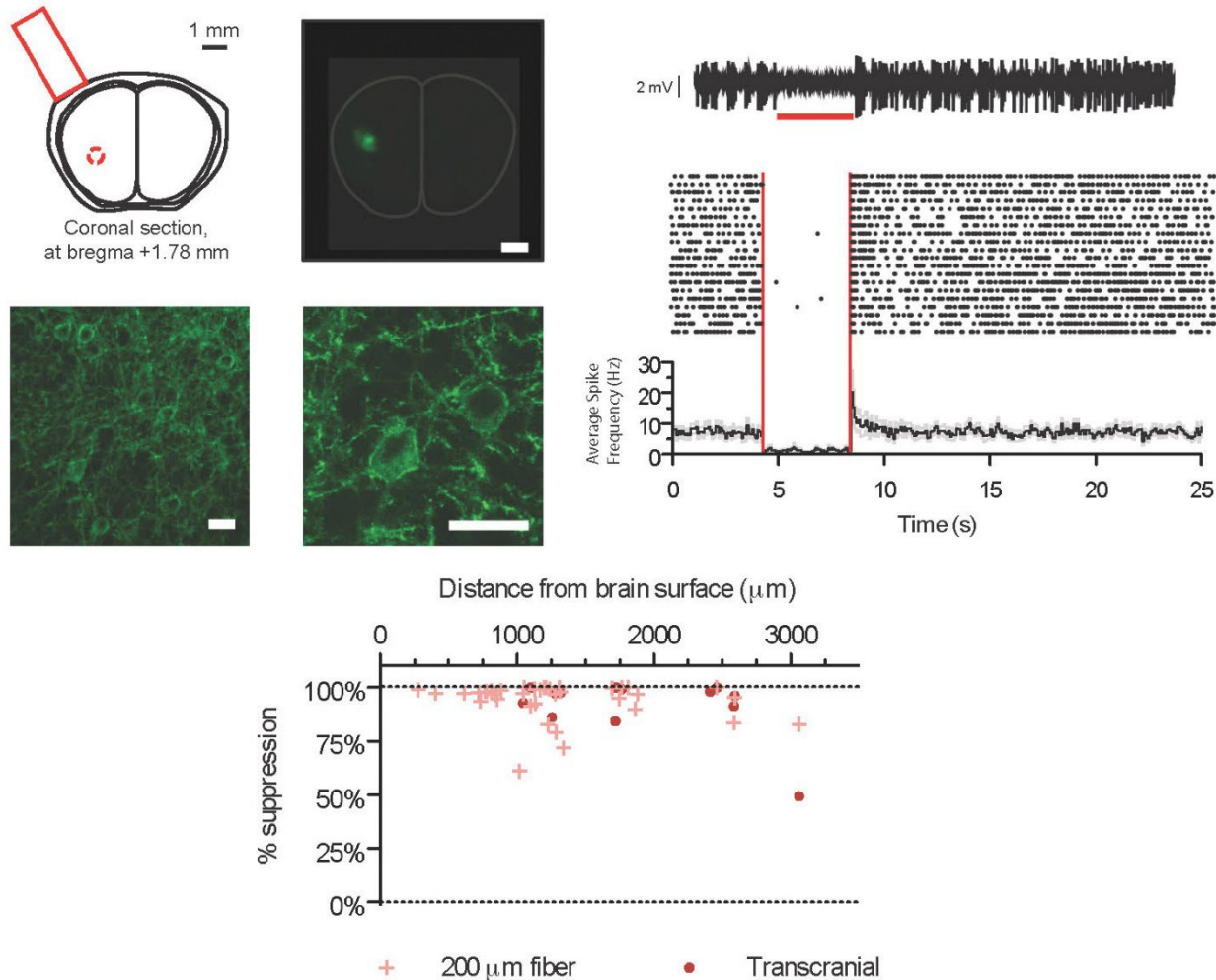


no light
stimulation

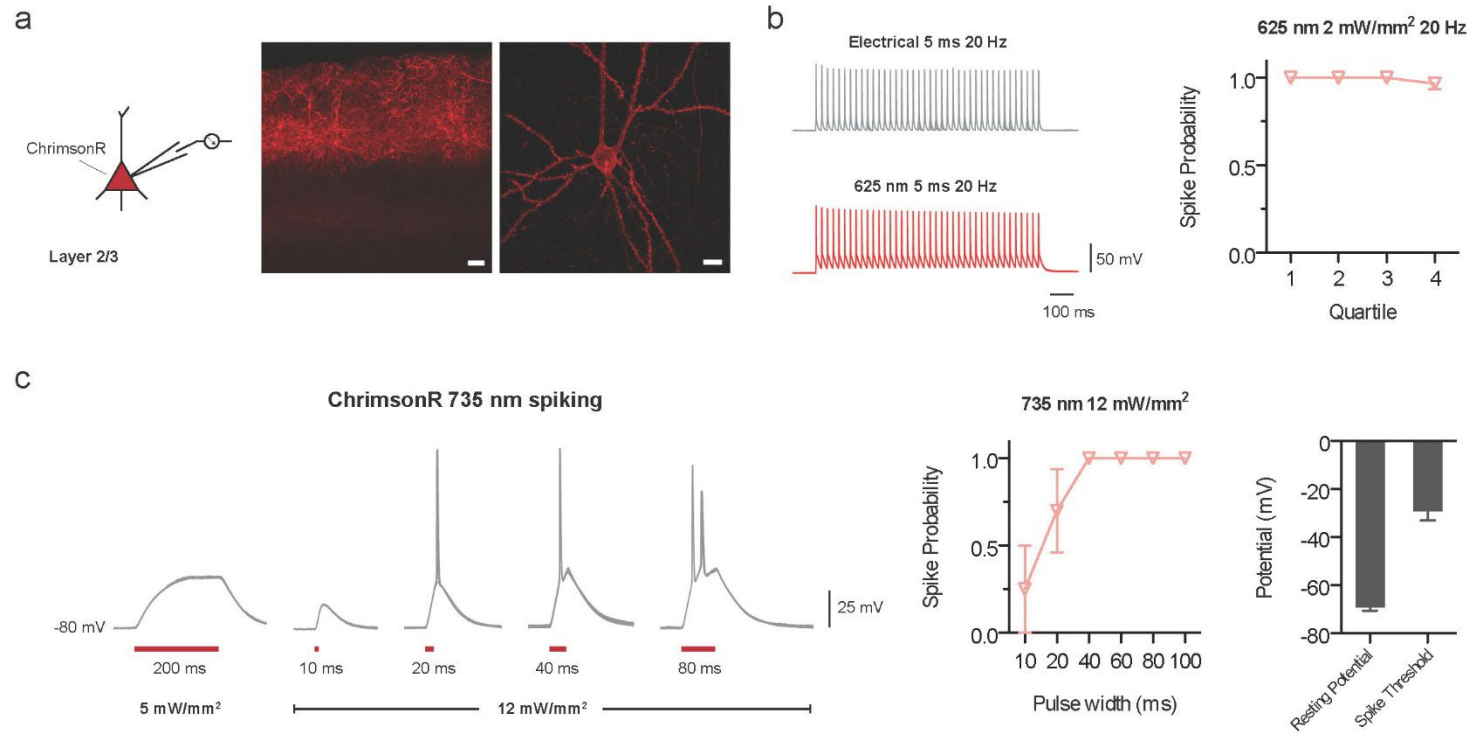
light
stimulation



Noninvasive optogenetic neural silencing: Jaws



Chrimson: quasi-infrared neural stimulation



~250,000 people have implanted electrical stimulators

~600 people have safely undergone gene therapy with AAV (first one approved in Europe)

Pre-clinical testing of light control reagents under way

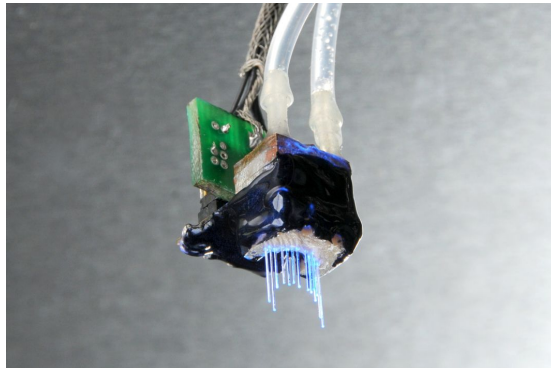
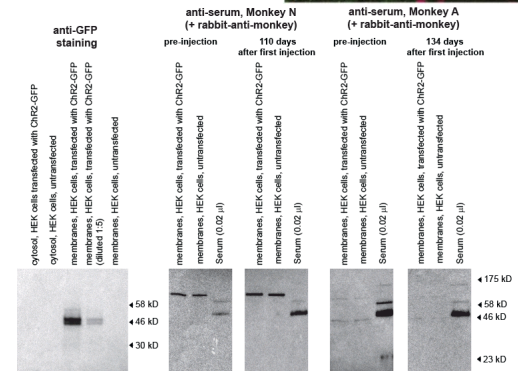
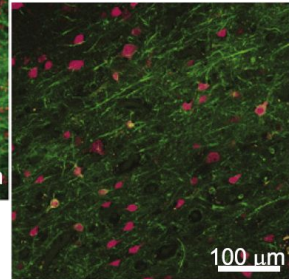
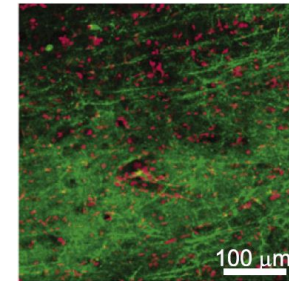
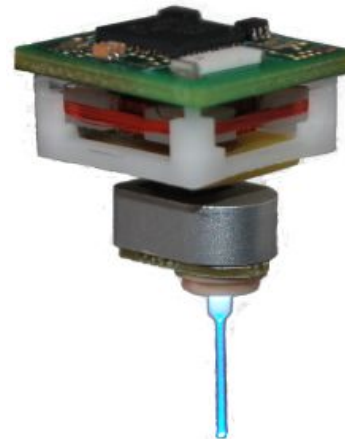
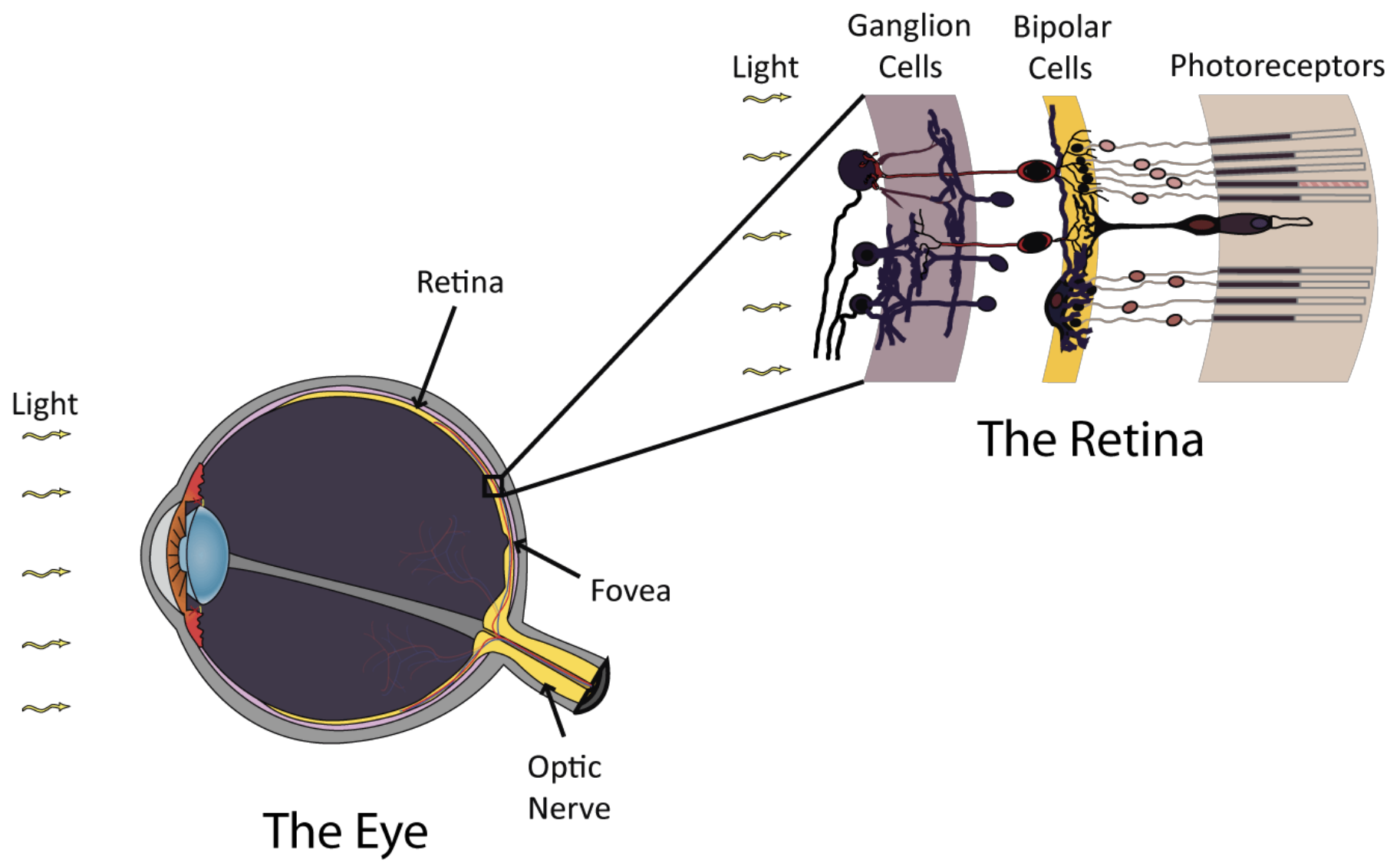
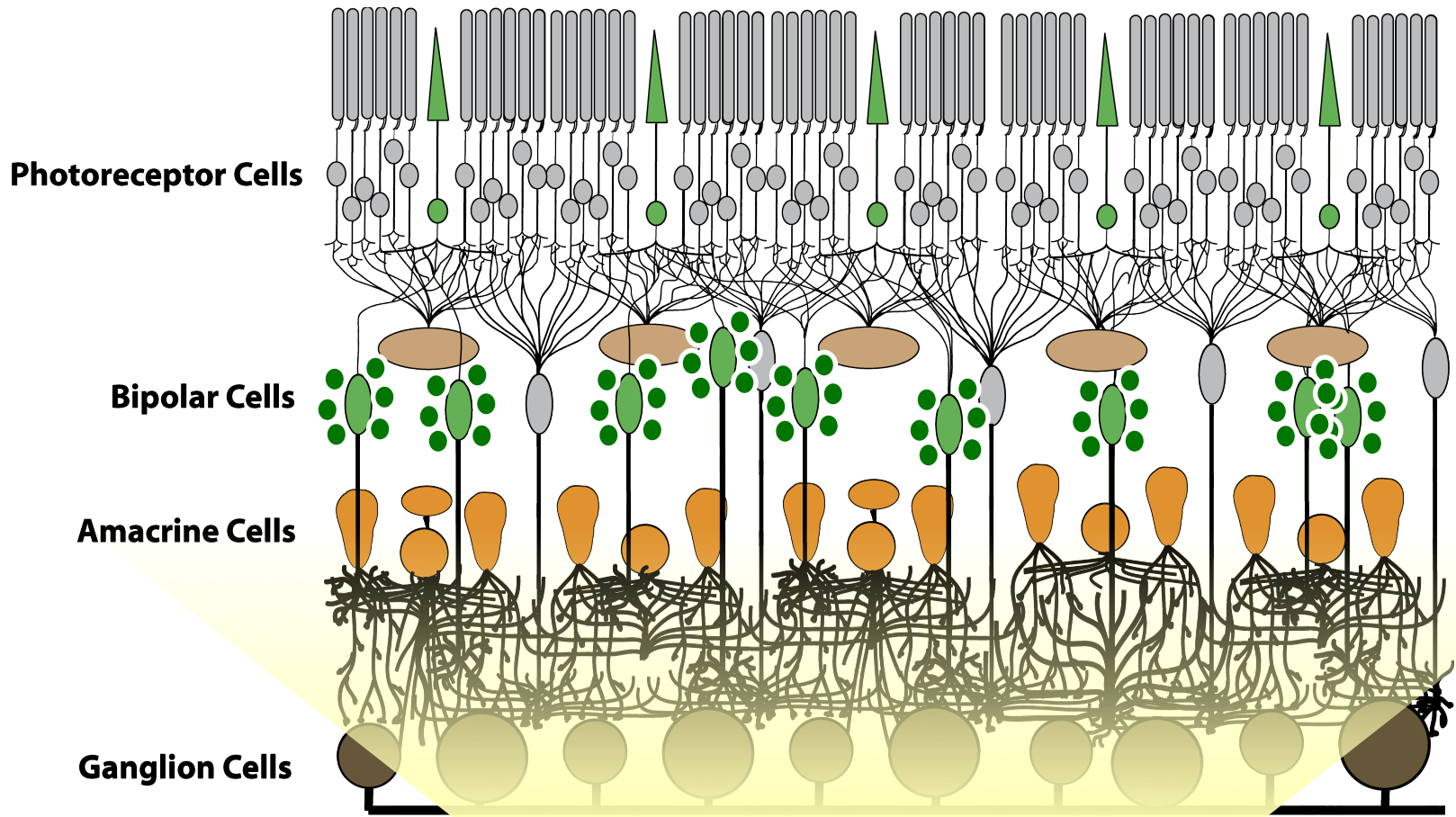


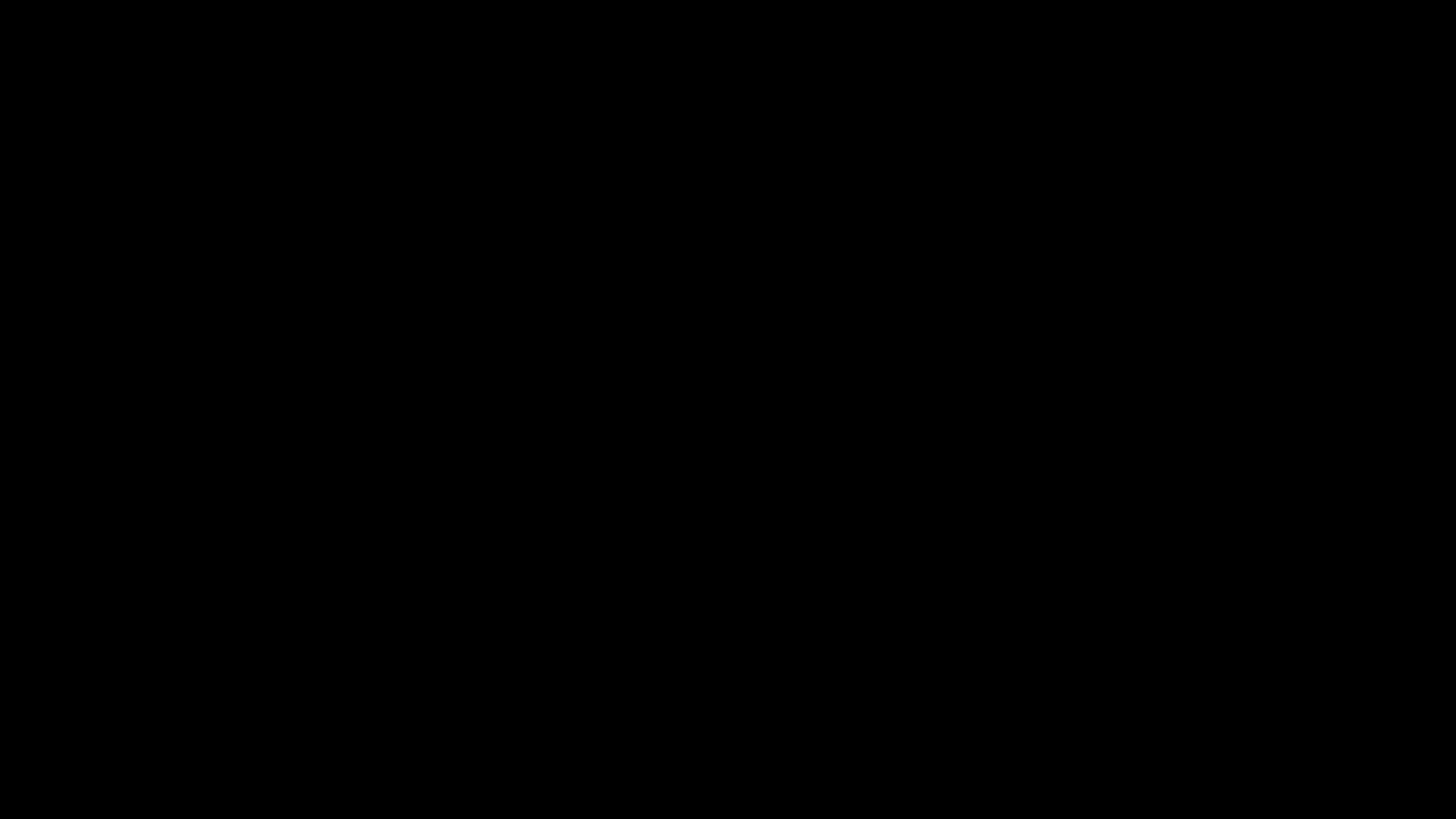
photo credit Justin Keena, Keenaphoto.com

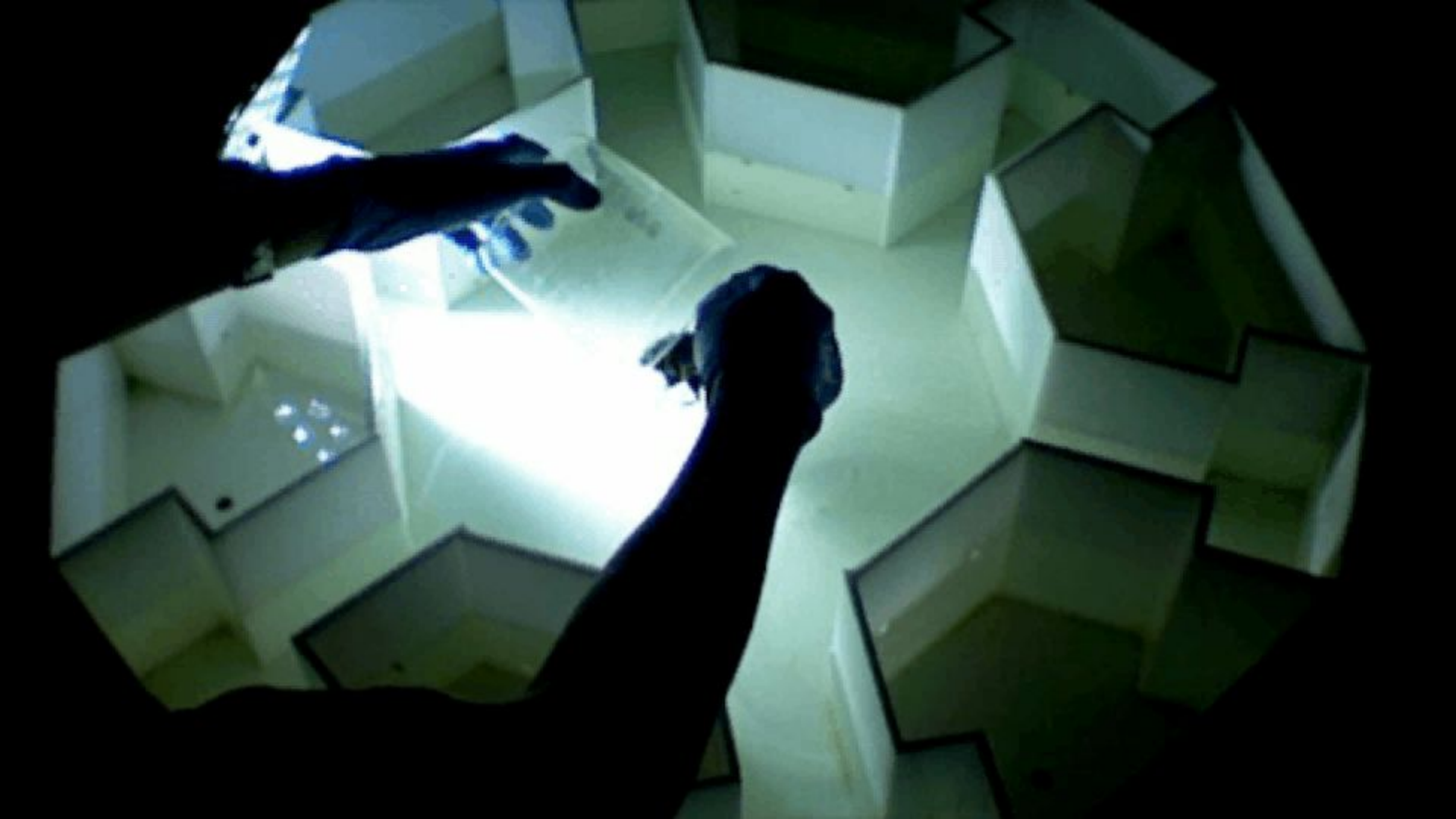






artesy of Cyrus Arman





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In vivo Robotics: Craig Forest, Hongkui Zeng
Microscopy: Alipasha Vaziri, Peter So, Ramesh Raskar
Neural modeling: Christoph Borgers, Fiona LeBeau, Miles Whittington, Nancy Kopell
Neural recording: George Church, Keith Tyo, Konrad Kording, Leafabs
Opsin engineering: Adam Cohen, Beijing Genomics Institute, Ernst Bamberg, Gane Wong, Jess Cardin, Kay Tye, Martha Constantine-Paton, Michael Melkonian, Patrick Stern, Robert Campbell, Vivek Jayaraman, Yingxi Lin
Opto-fMRI: Ann Graybiel, Chris Moore, Itamar Kahn, Nancy Kopell, Randy Buckner
Optogenetic hardware: Clif Fonstad, Ferro Solutions Inc., Joseph Jacobson, Kendall Research Systems, Rahul Sarpeshkar, Steve Wasserman
Polymerase engineering: George Church, Keith Tyo, Konrad Koerding
Primate work: Ann Graybiel, Bob Desimone, Bob Wurtz, Roderick Bronson, Wim Vanduffel
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Synthetic Neurobiology Group

<http://syntheticneurobiology.org/>

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