Technologies for controlling neural circuit dynamics

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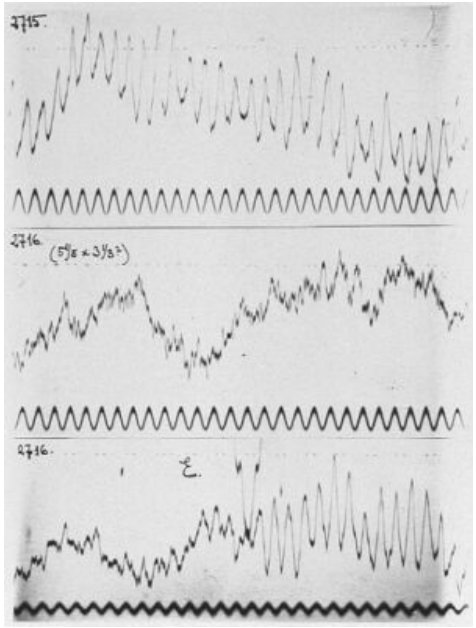
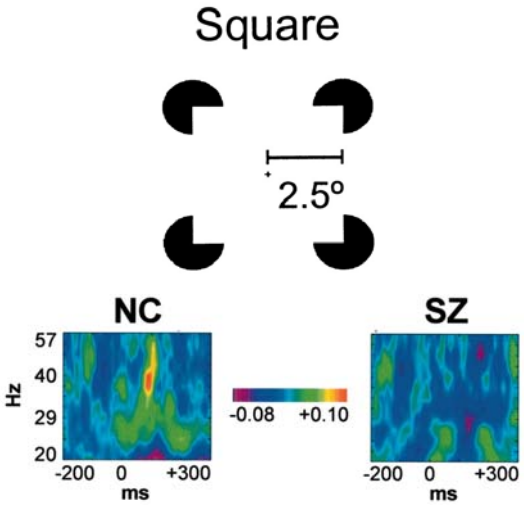
The Landscape of Neural Circuit Computations and Dynamics

The brain continuously computes in a dynamic fashion, utilizing densely-wired sets of heterogeneous cells distributed across the 3-dimensional brain



Hans Berger, 1928



Spencer et al., 2003

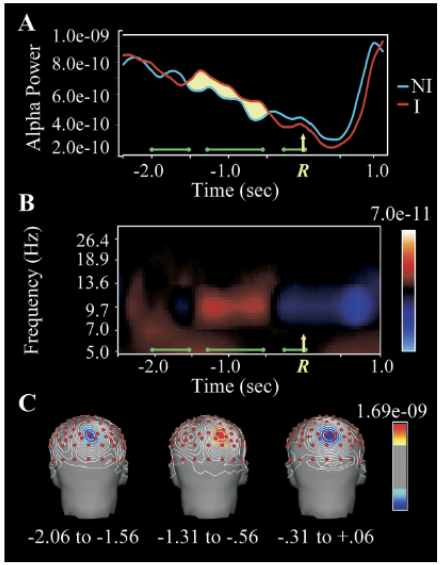
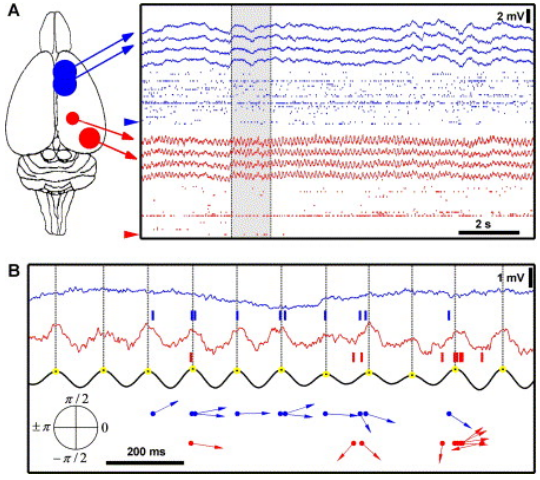


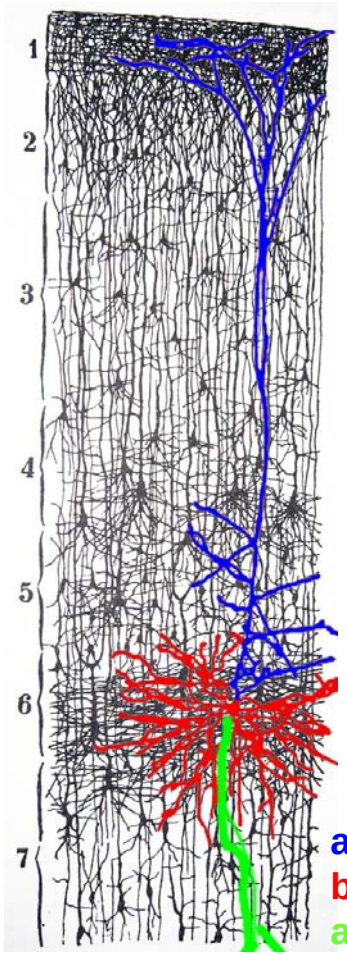
Figure 5. Alpha-Band Power for Insight and Noninsight Solutions

Jung-Beeman et al., 2004



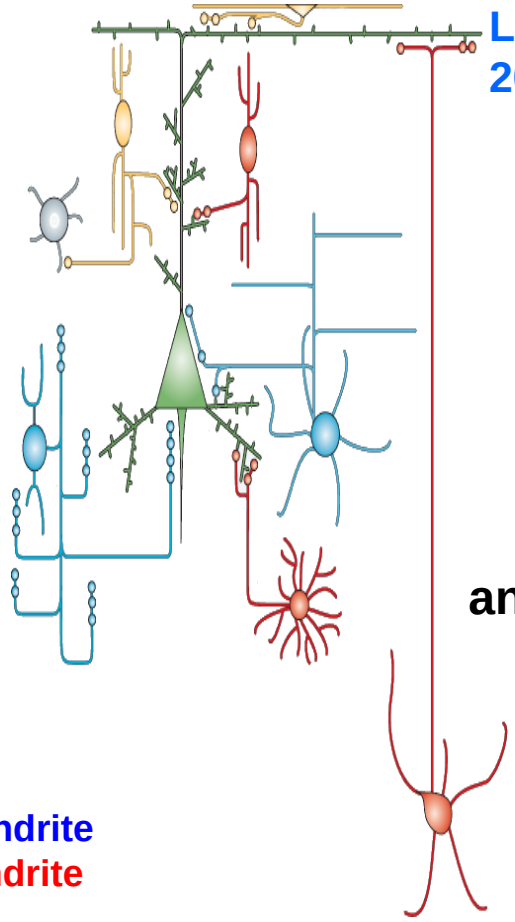
Siapas and Wilson 2005

Activity patterns emerge from actions of component circuit elements;
Disorders often involve disruptions of specific circuit elements



Ramon y Cajal 1899

apical dendrite
basal dendrite
axon



Lewis et al. 2005

Basket cells in schizophrenia;

Dopamine neurons in Parkinson's;

Specific interneurons and pathways in epilepsy;

...

Towards systematic brain dynamics analysis

1. Develop better **technologies** for systematically controlling and observing neural circuits

   As **precise** as possible: a technology pipeline towards the future.

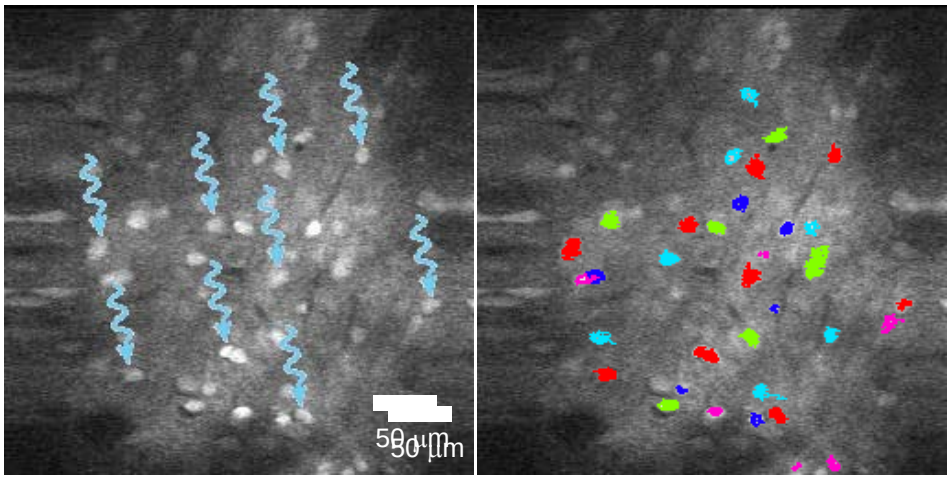
2. Use these tools to understand the **principles** of how neural circuits perform computations, become corrupted by disease, and generate behavior

   Find the patterns of activity **necessary and sufficient** for achieving specific behavior or correction of pathology

   Computational modeling of the links between circuit elements and emergent dynamics is essential

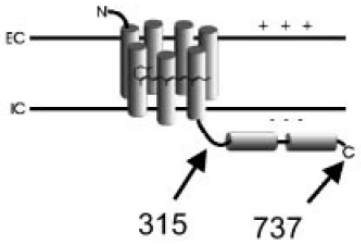
Fundamental limits of existing stimulation technology

- Electric, Magnetic fields
  - Can't focus or aim far from the source
  - Stimulation will affect all cells in the driven volume (e.g., excitatory, inhibitory, and modulatory)
- Light: can be very focal



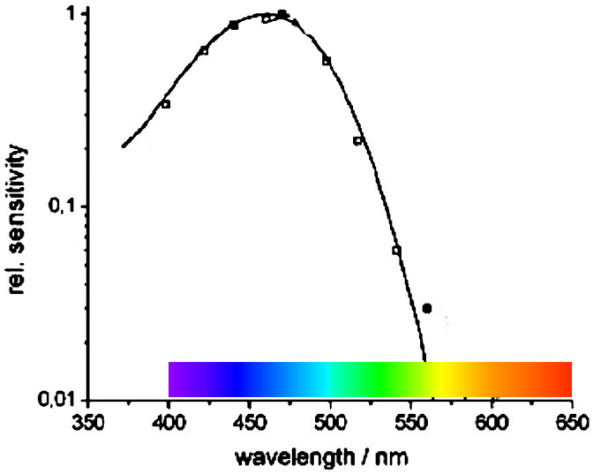
Channelrhodopsin-2 (discovered by Nagel et al., 2003)

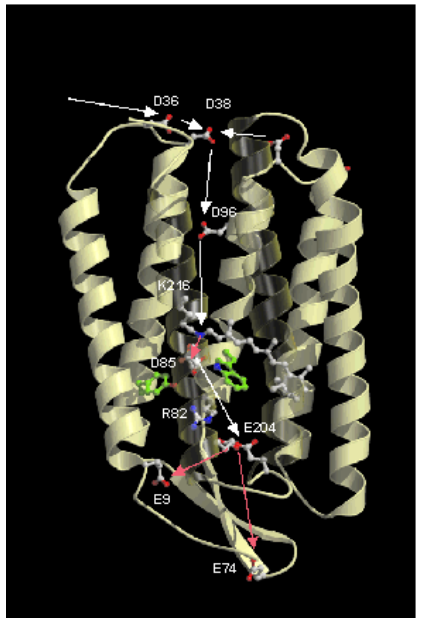
Found in a species of **green algae**
Core protein is **315 amino acids** long



Nagel et al., 2003

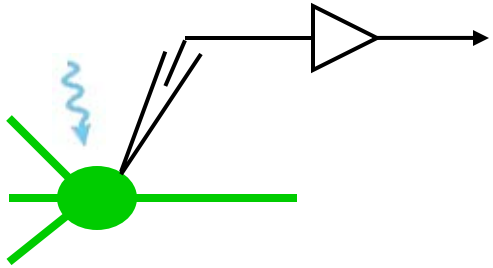
Driven by **blue light** **(~10 mW/mm²)**



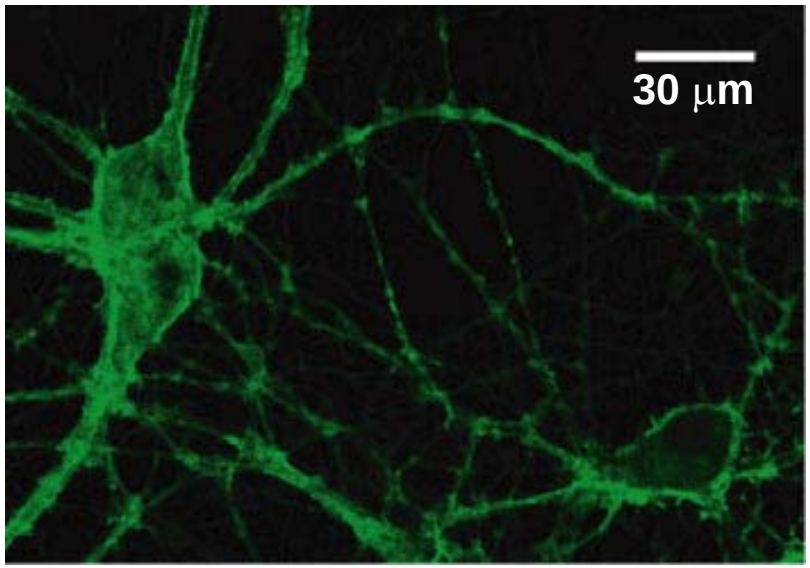


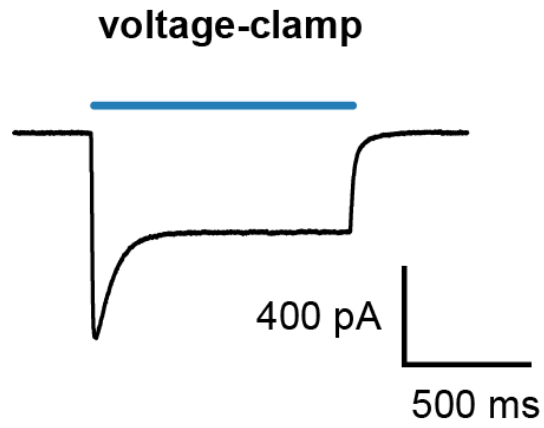
Strong homology to the 7-tm protein bacteriorhodopsin ⇑
Conducts **cations** (**Na^+**, **K^+**, etc.) when gated by light

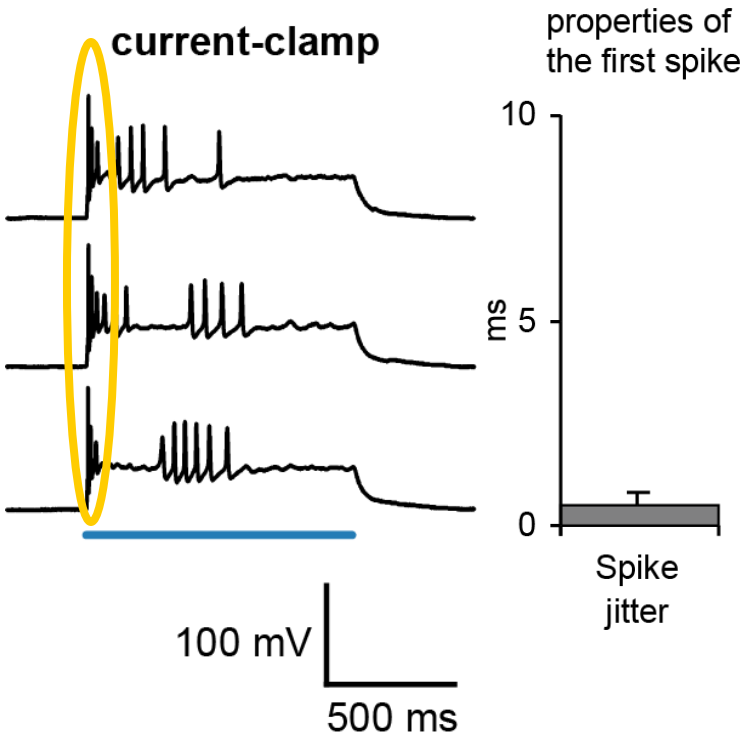
Targeting channelrhodopsin-2 to neurons



Fused with yellow fluorescent protein (YFP), and expressed in neurons:

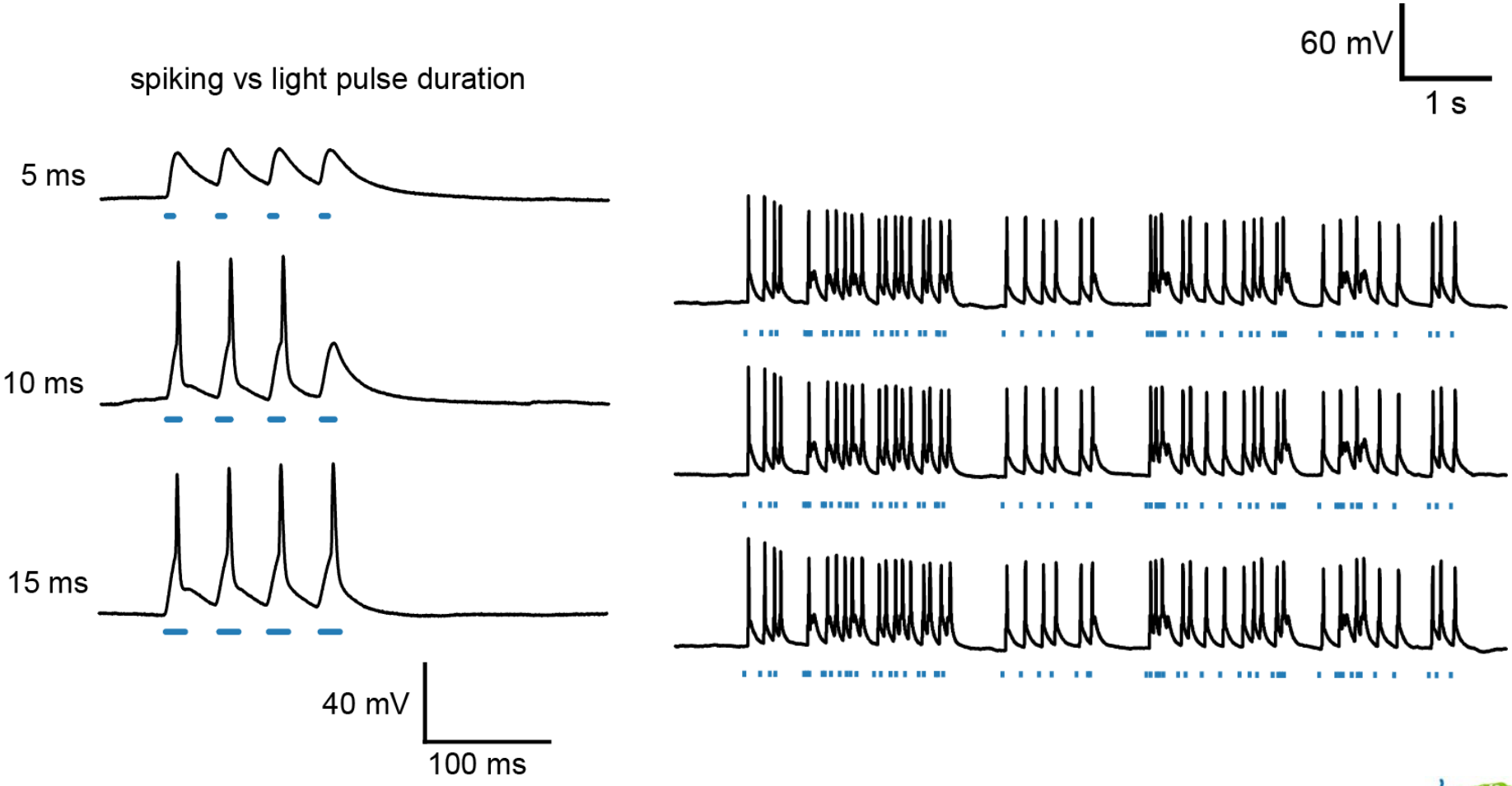




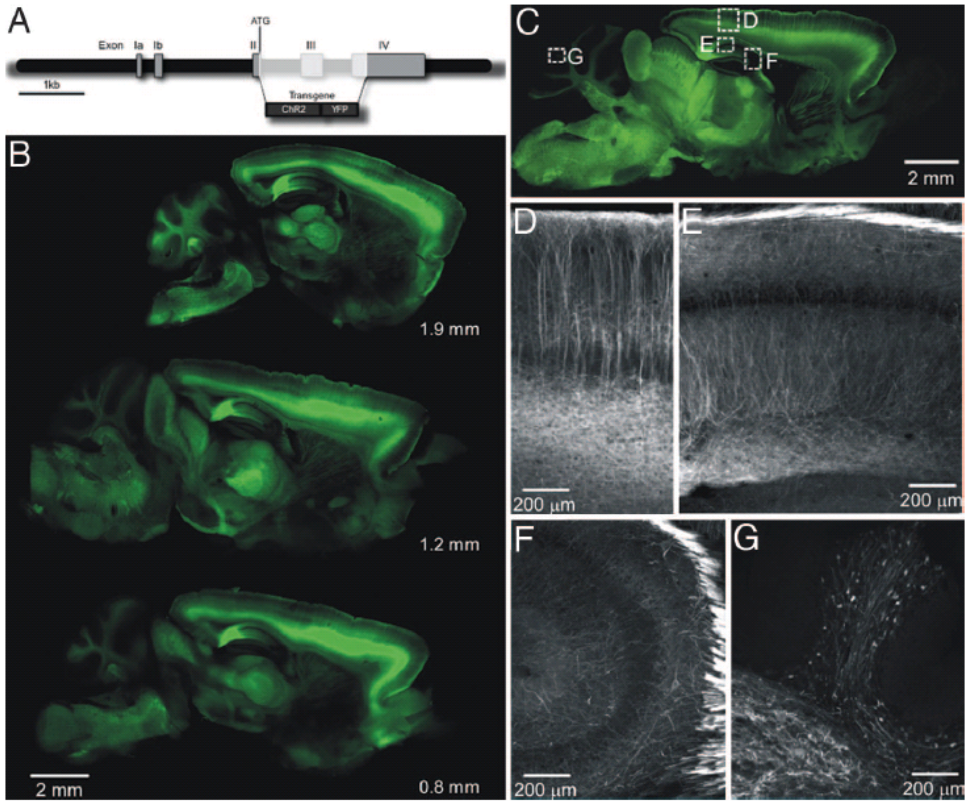


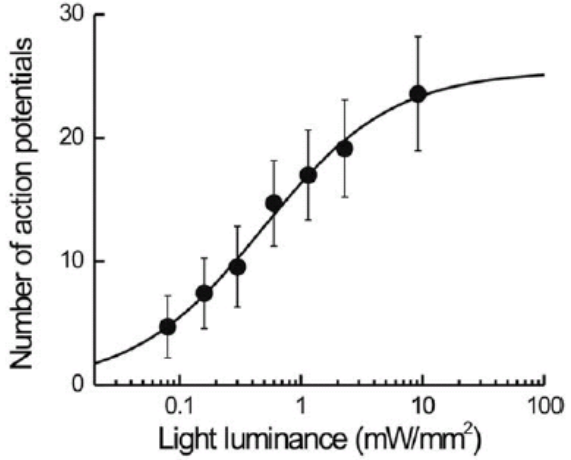
Boyden et al. (2005) *Nat. Neuro.* 8(9):1263-8.

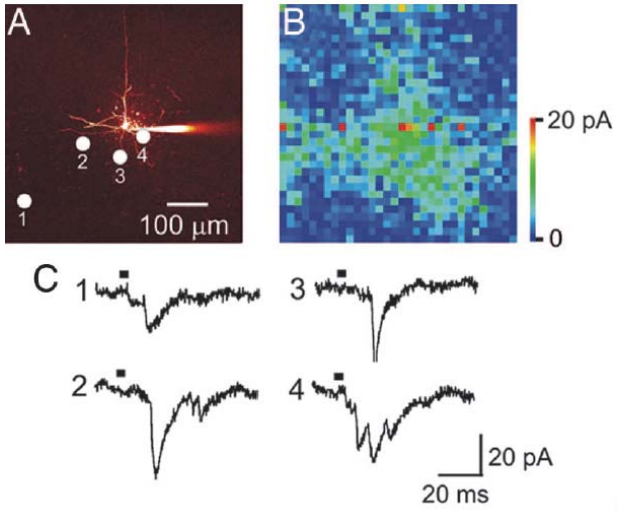
Reliable light-evoked spiking



Mapping circuits using transgenic mice: well-tolerated, no need for supplementation



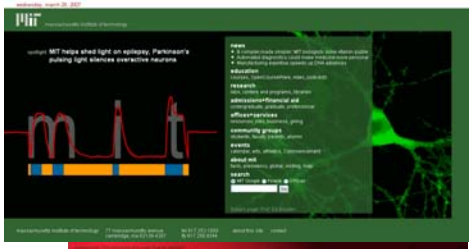




Wang, … Boyden, … Feng, Augustine (2007) *PNAS* 104(19):8143-8148.

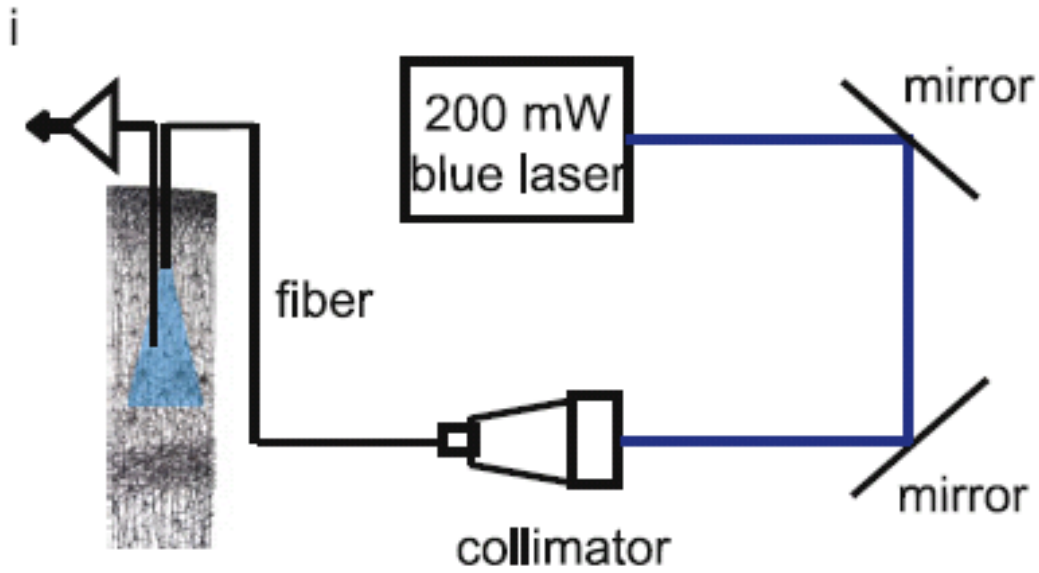
ChR2 use widespread in the basic-science world

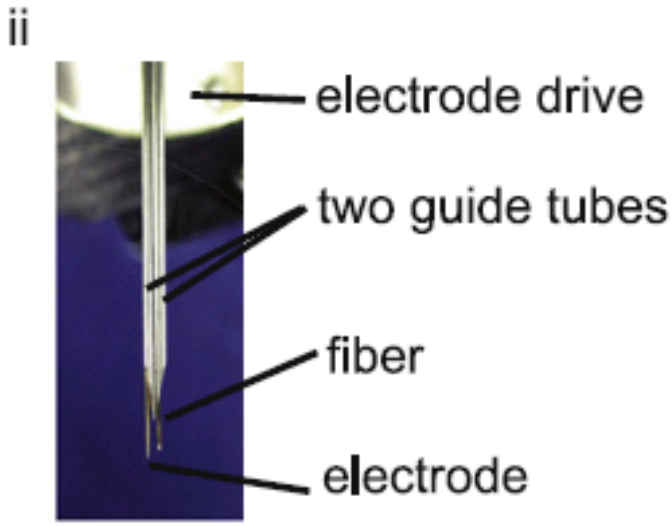
- Easy to use, no extra reagents required for many species, light levels reasonable
- Flies
- Worms
- Chick
- Gene-gun organotypic slice culture
- Mouse brain slice
- *In vivo* mouse
- Safe for up to 1-1.5 years



"It is the best thing that has happened in neuroscience in a good long time."

Blue light evokes neural spiking in the primate brain
Using CaMKII promoter

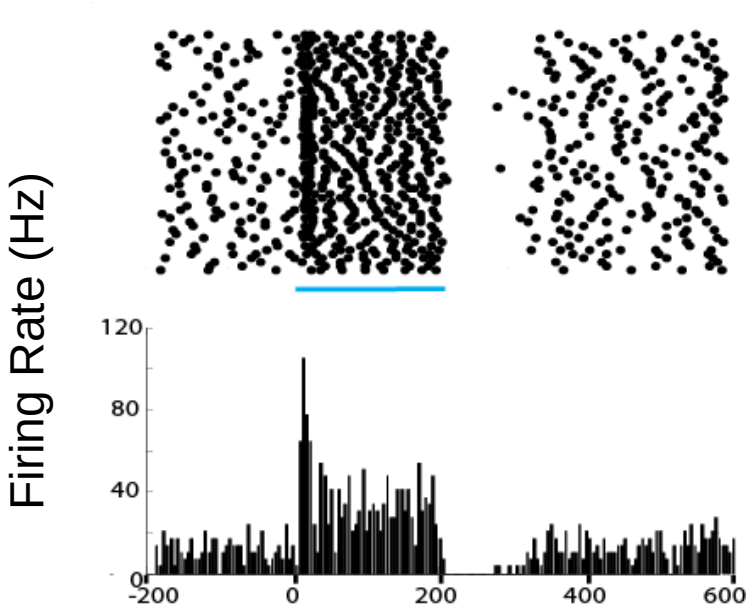


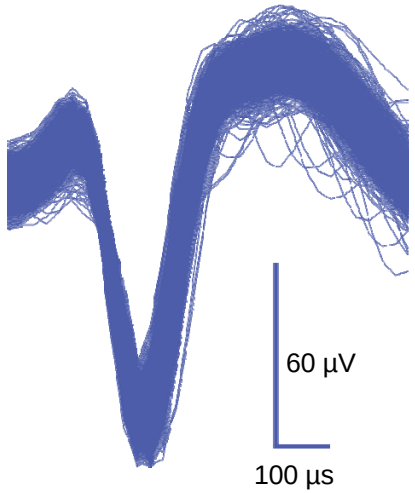


Han et al., *Neuron,* 2009

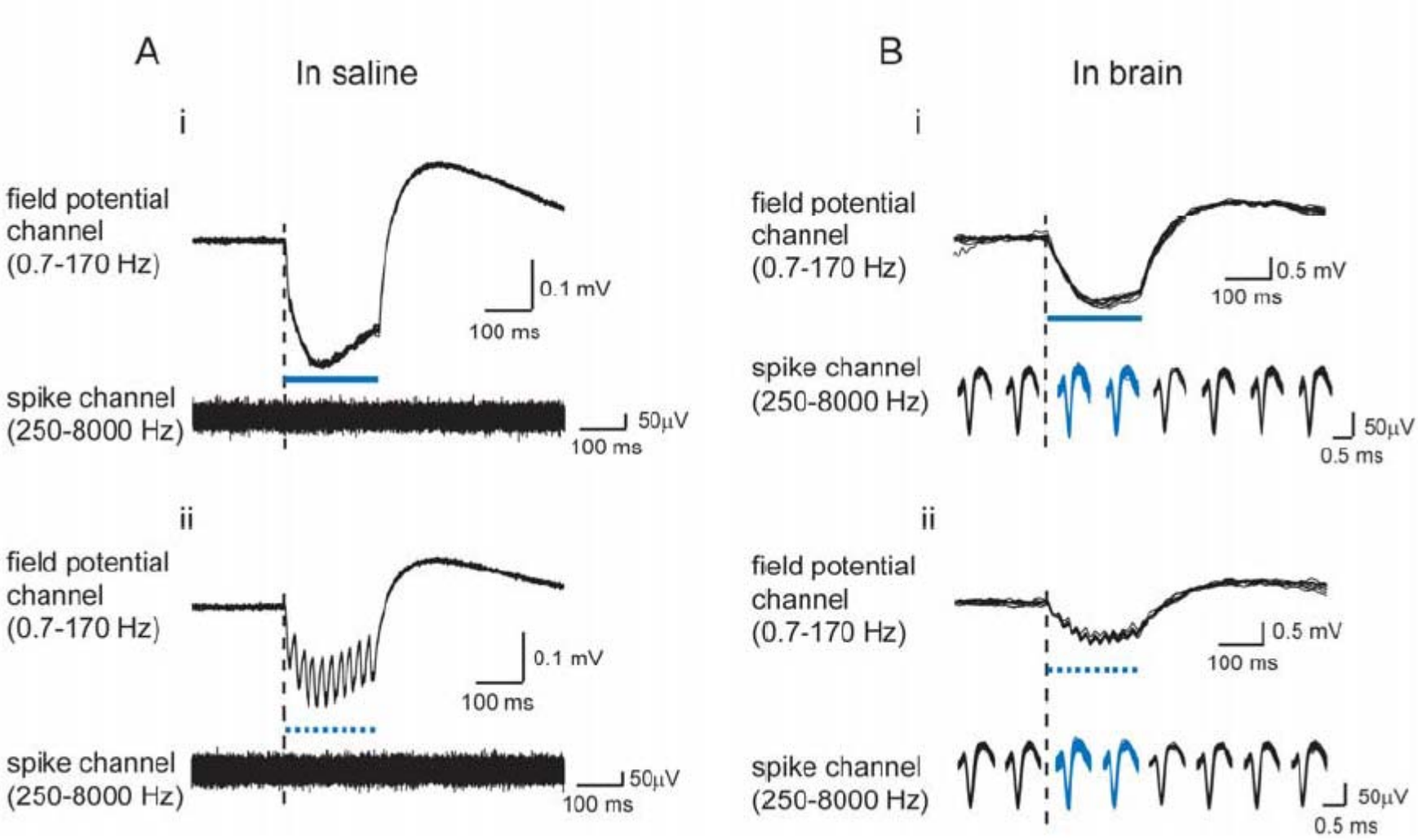
(collaboration: Xue Han, Ann Graybiel, Bob Desimone)

Spiking: within a 1 mm radius of the light, get activation

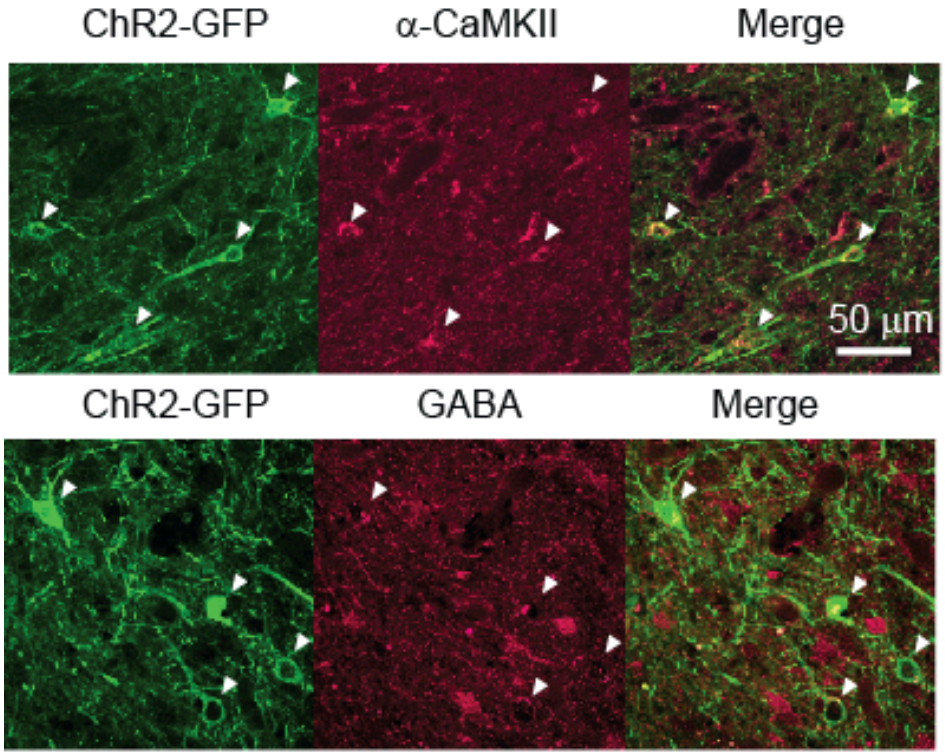


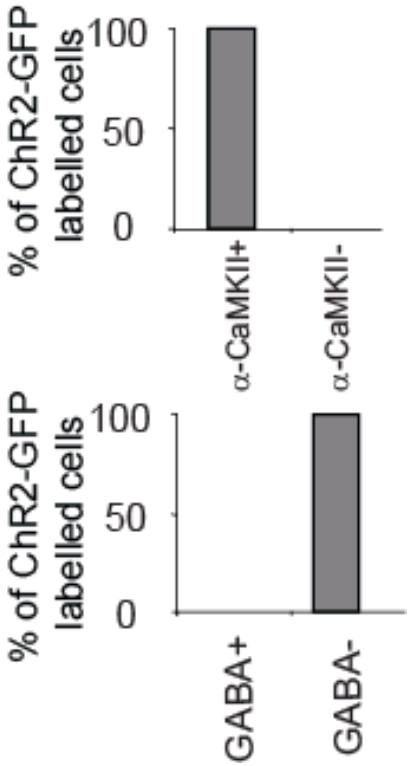


Artifacts: not great for recording LFPs



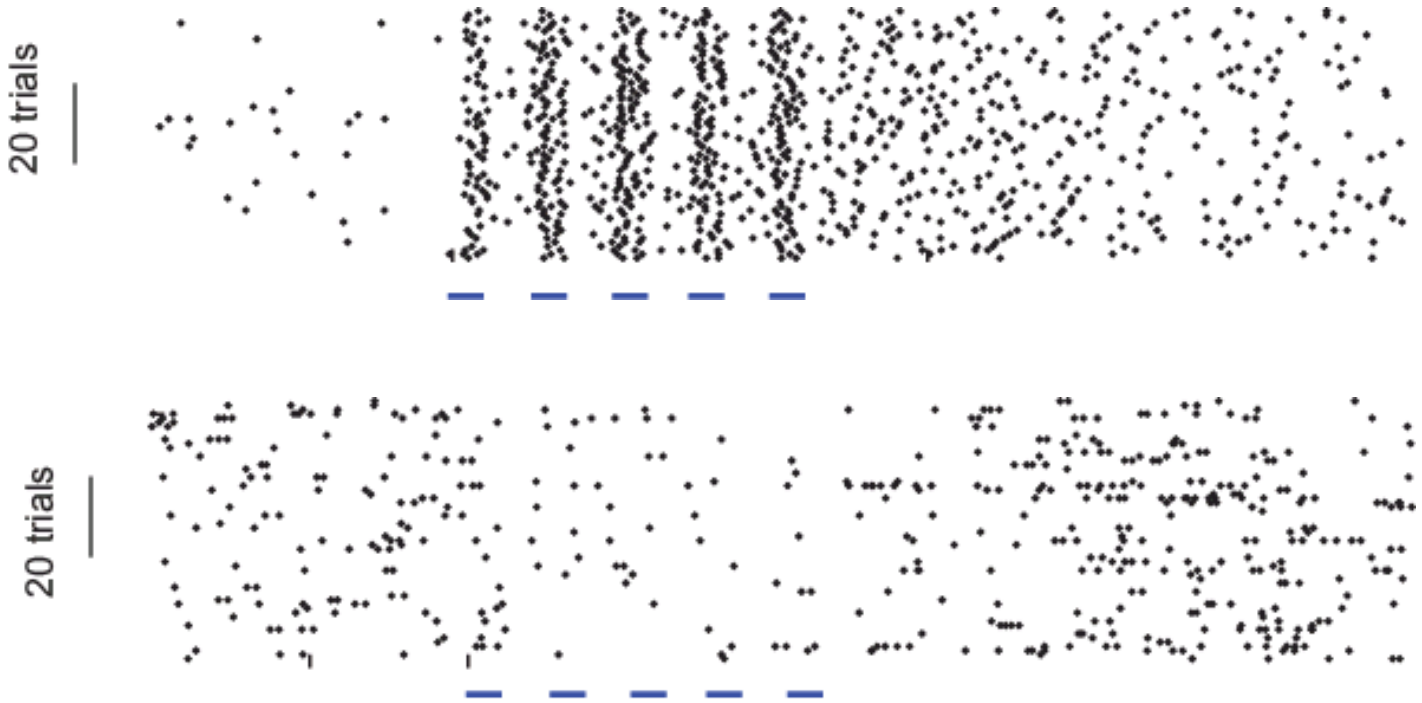
Cell specificity in primates



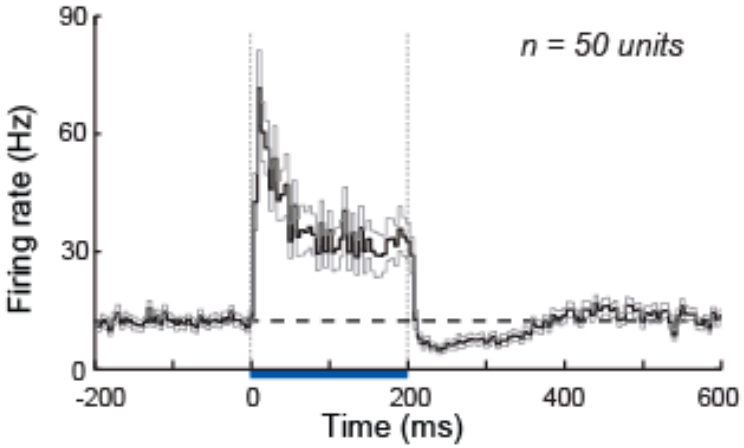


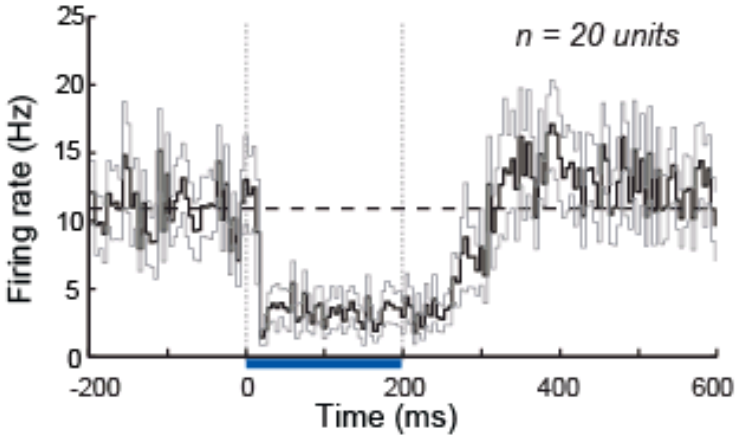
Towards principles of controlling neural circuits: Driving excitatory neurons can result in reliable neural suppression

- Two neurons on the same electrode:

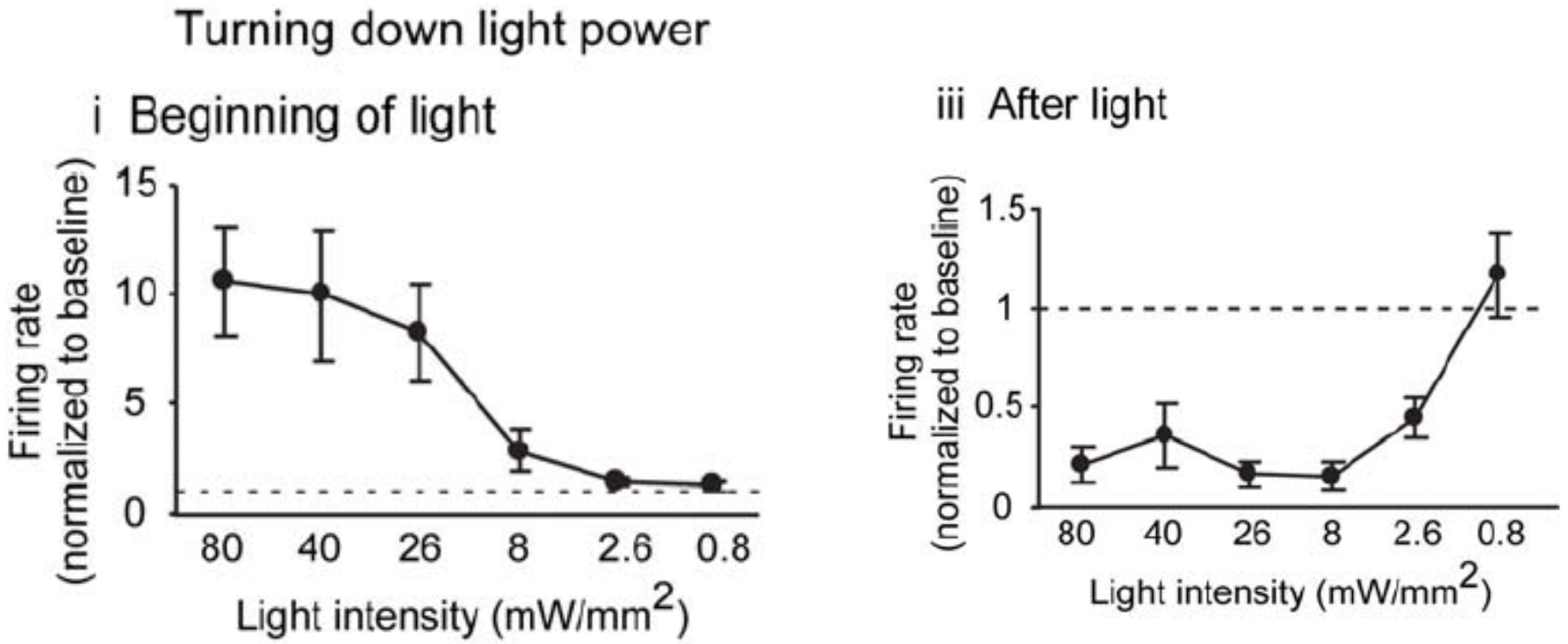


Excited and suppressed units are both found, when excitatory neurons are activated

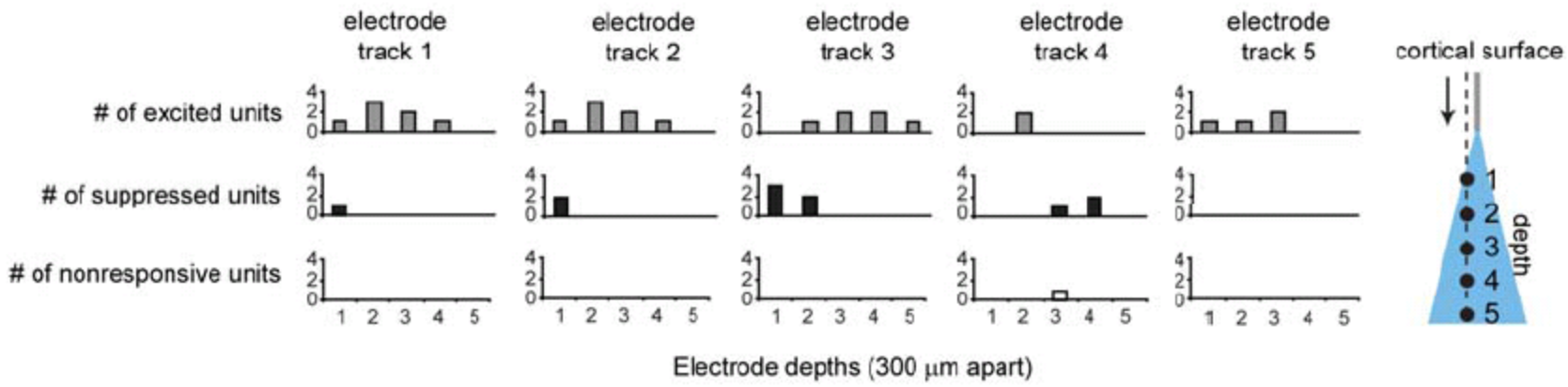




Inhibition is more sensitive to light than excitation

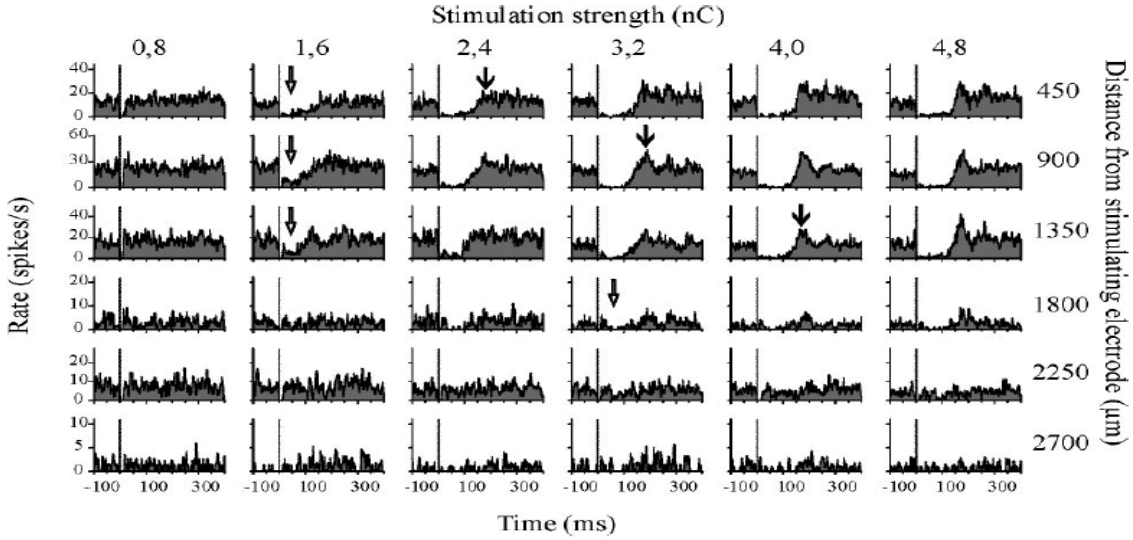


ChR2 in cortex generates “center-surround” activations?



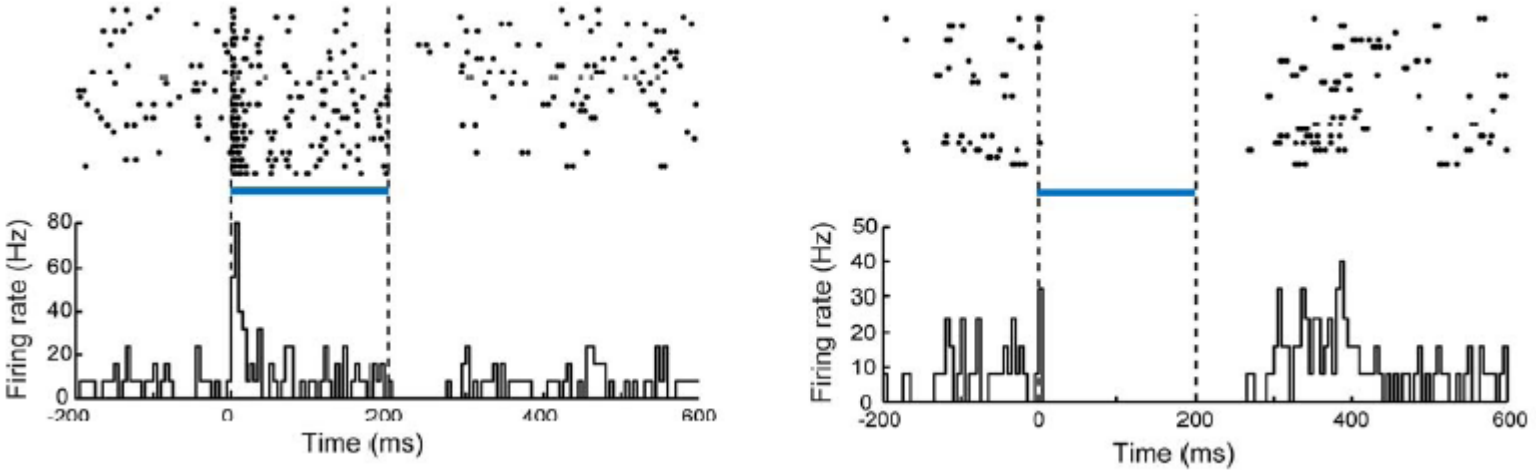
Using cell-type specific control to understand the meaning of neurostimulation

- Electrical stimulation: has heterogeneous effects on neurons
  - Example: some neurons can be completely silenced by electrical stimulation
  - Engaging interneurons? Direct silencing?



(Butovas and Schwarz, 2003)

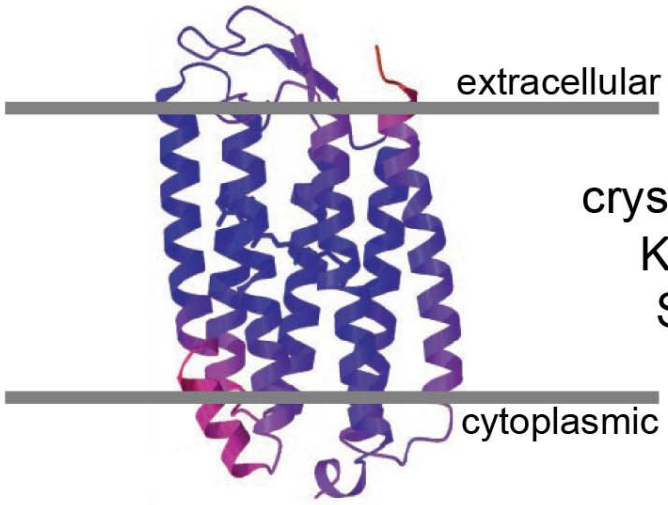
In mice too



- Not seen in previous cortical ChR2 studies using anesthetized mice?
  - Hypothesis: awake state may prime network dynamics for such silencing; anesthetized state may alter network dynamics

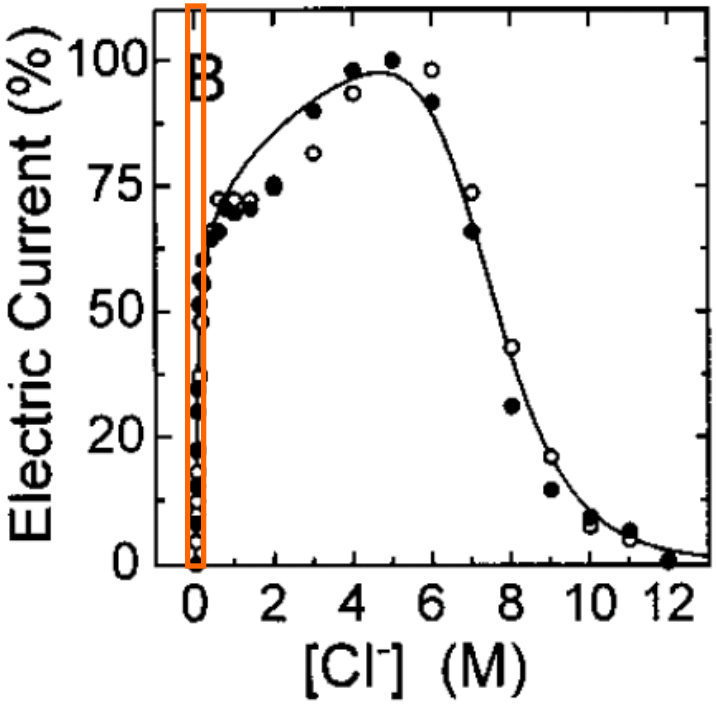
Yellow-light optical neural silencing

- Halorhodopsins: Light-activated **chloride pumps** from archaebacteria
  - A ‘microbial,’ **type-1 opsin** (like ChR2) – binds all-trans-retinal
  - Discovered ~1980’s; **crystallized** ~2000

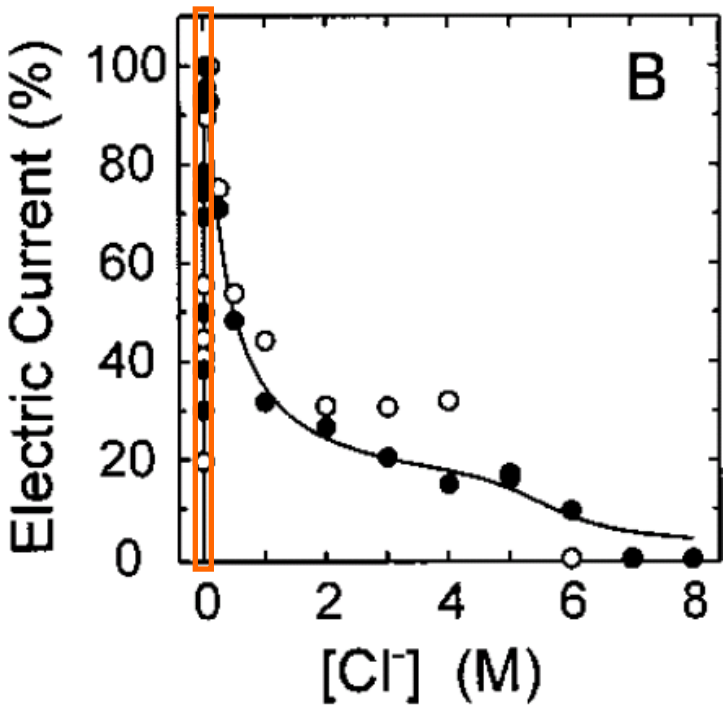


crystal structure reported in
Kolbe..Oesterhelt (2000)
Science 288:1390-1396

A halorhodopsin that works at mammalian chloride levels



Halorhodopsin from *H. salinarum*

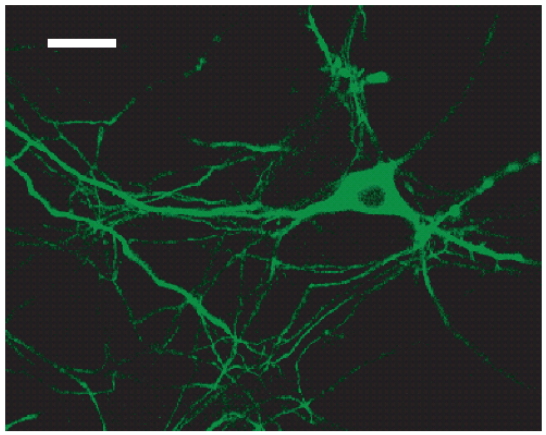


Halorhodopsin from *N. pharaonis*
(Halo, NpHR)

Okuno et al., 1999

Mammalian codon-optimized halorhodopsin (‘Halo’) expresses well

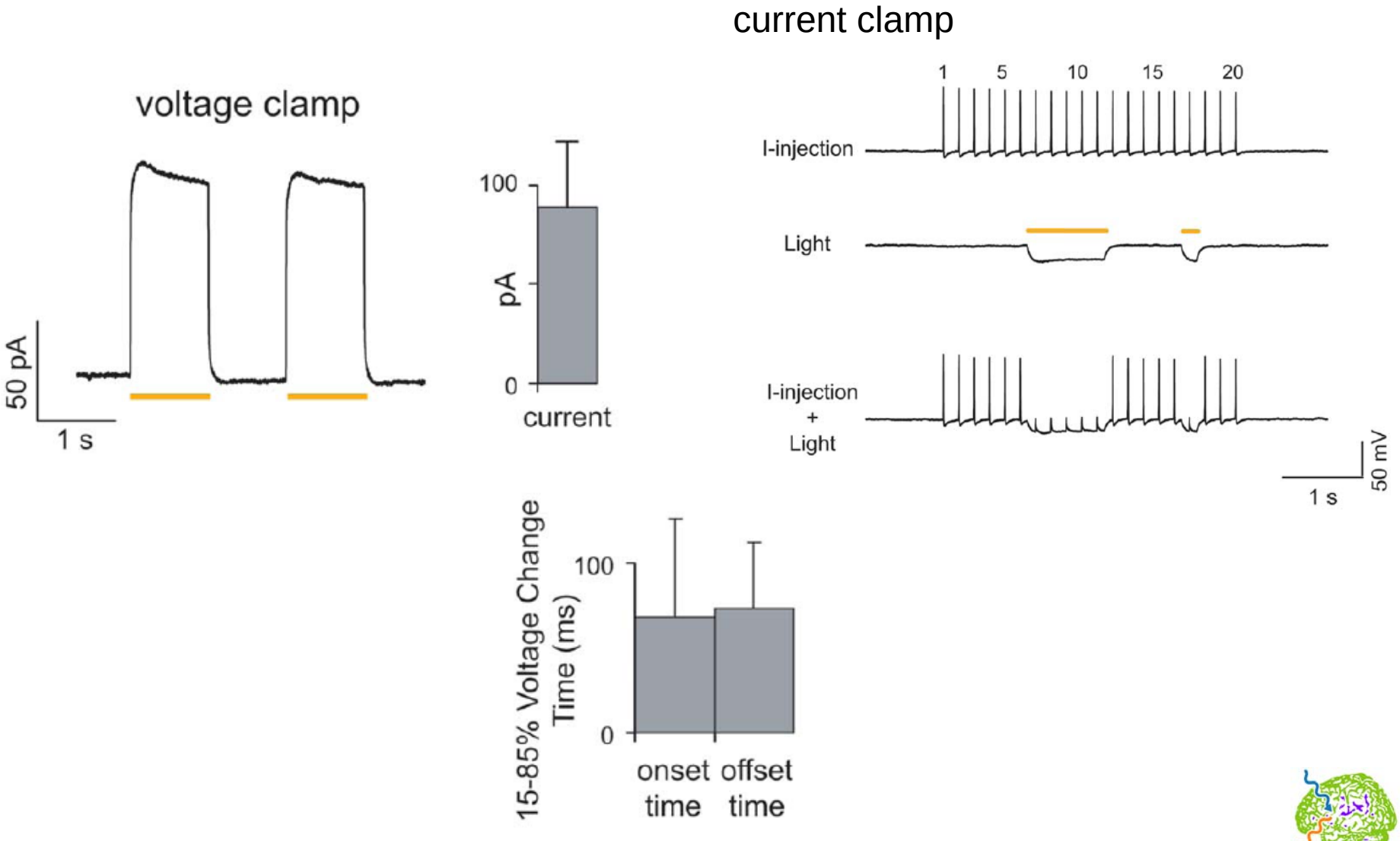
codon-optimized N. pharaonis halorhodopsin (Halo), fused with GFP, and expressed under the CaMKII promoter



cultured hippocampal neurons

Han and Boyden, 2007

Halo mediates fast hyperpolarizing currents



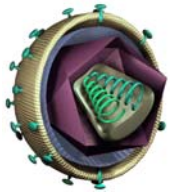
Improving neural silencing

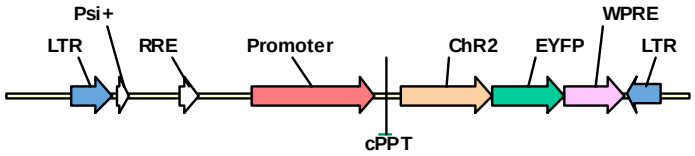
Chow et al., submitted

- Unbiased screening for variants that yield higher currents
  - Others have improved trafficking somewhat but boosts currents only 50-75% (e.g., eNpHR)
  - We began an unbiased screen, and identified variants capable of **3x-6x** higher currents than original halorhodopsin

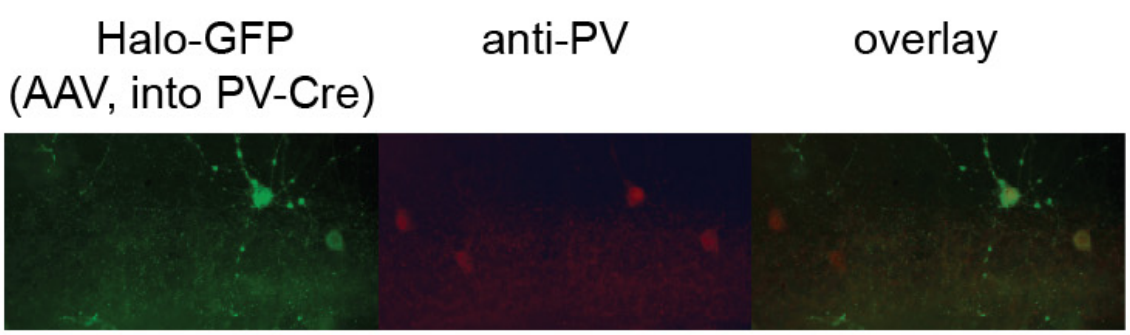
Targeting different neurons of hippocampus, cortex

- Lentiviruses, adeno-associated viruses
  - Can tune the promoter





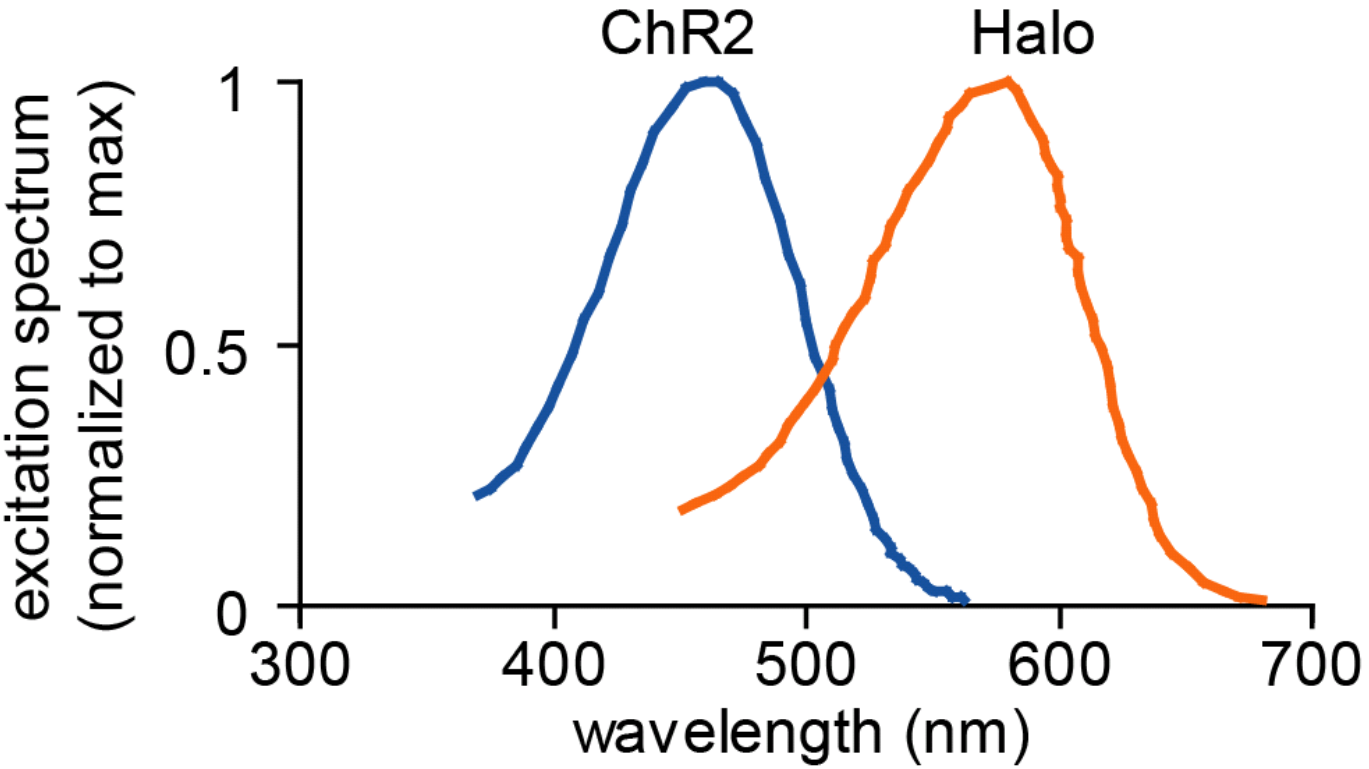
- Lots of Cre mice
  - Dopamine, serotonin, parvalbumin, etc.
- Administer a floxed-stop vector via virus injection (Josh Huang, Scott Sternson)
  - Cause ChR2 or Halo to be expressed by cellular subtypes



Ideally, what you have is an "Informational Lesion"

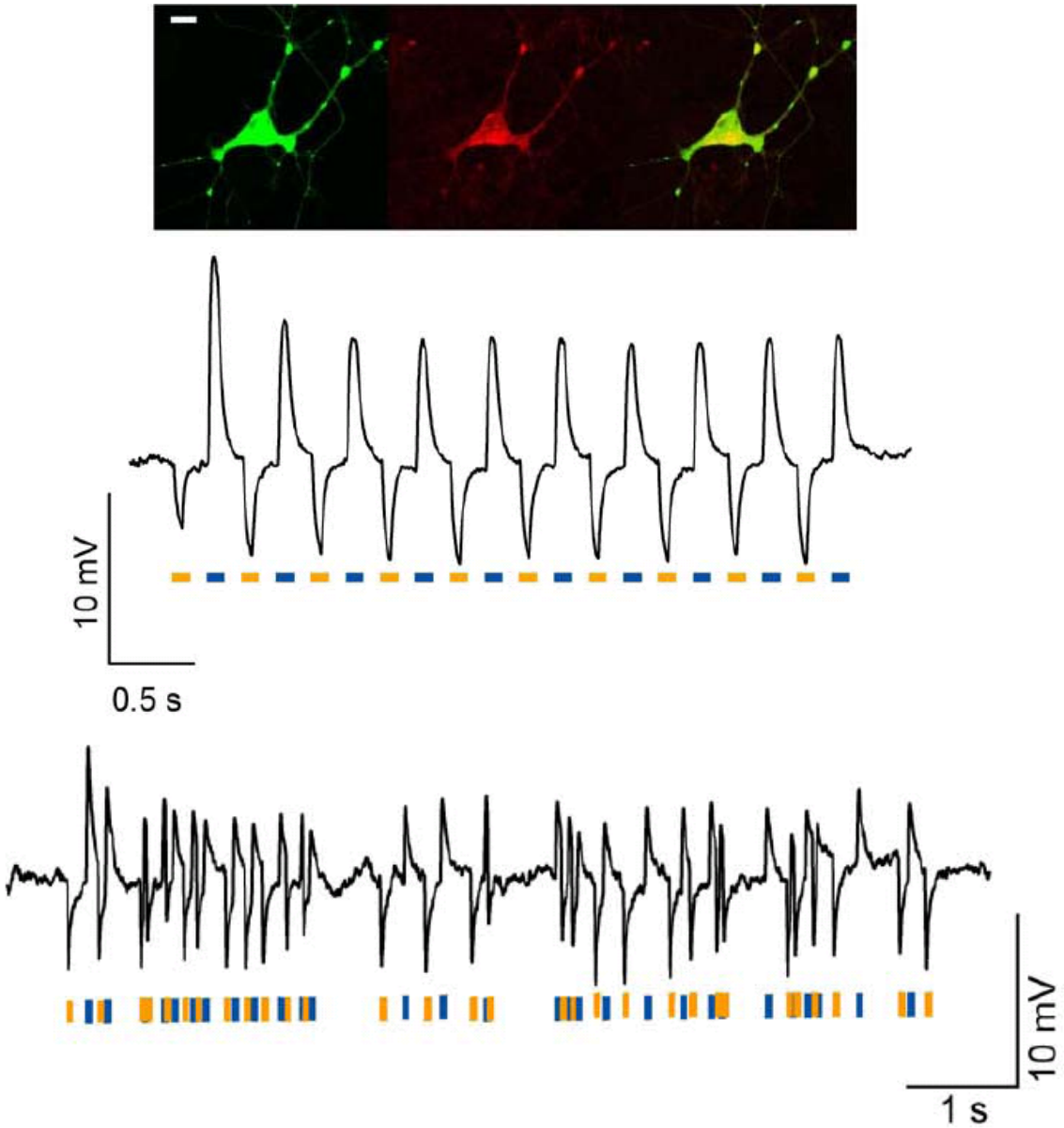
- Get rid of the correlated information, but leave the basic functions going
  - If you silence everything, you might drive the system out of its normal functional range
    - Example: shut down a tonically firing inhibitory neuron (i.e., Purkinje cell), then other neurons may exceed their normal dynamic range
  - A few examples
    - Bicuculline in locust olfactory system (Laurent)
    - Tonic agonist + phasic antagonist (Bao, Chen, Thompson)

Multiple-color bi-directional control

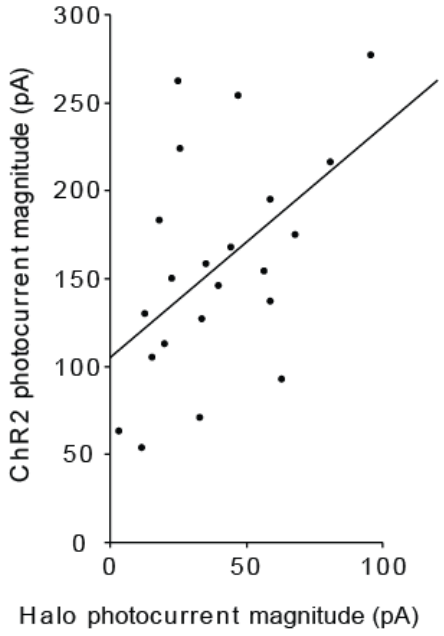


Digitized from **(Nagel et al., 2003)** **(Duschl et al., 1990)**

Fusion proteins between ChR2 and Halo

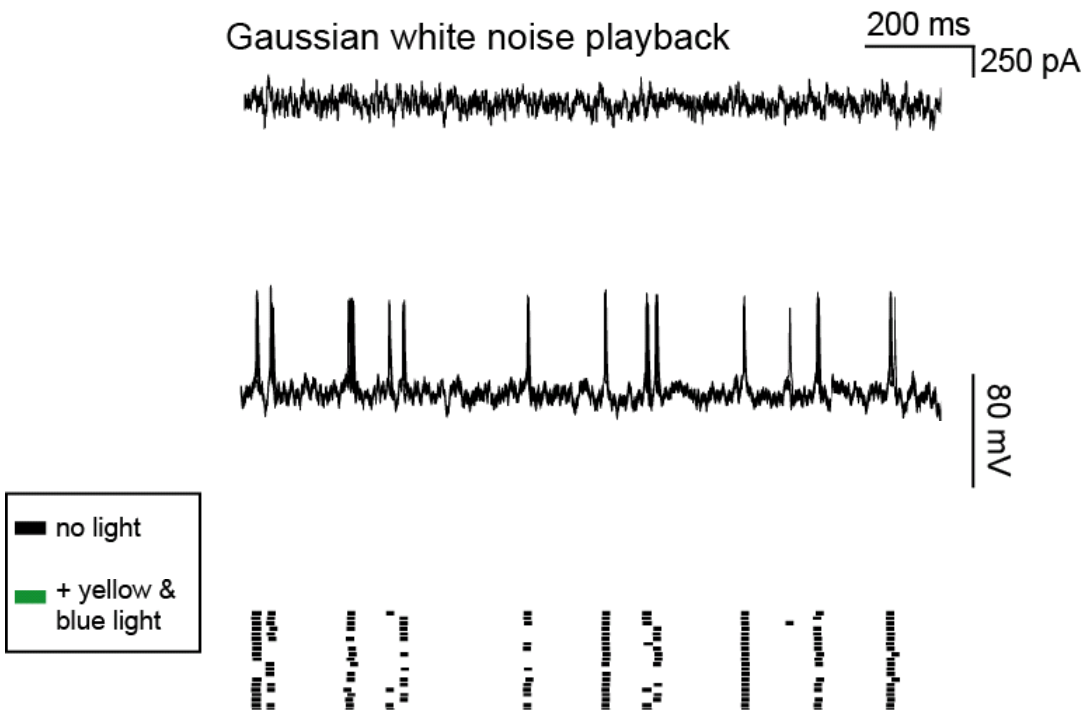


Fusion protein,
Self cleaving protein
Foot/mouth disease
Virus (Han et al., submitted)

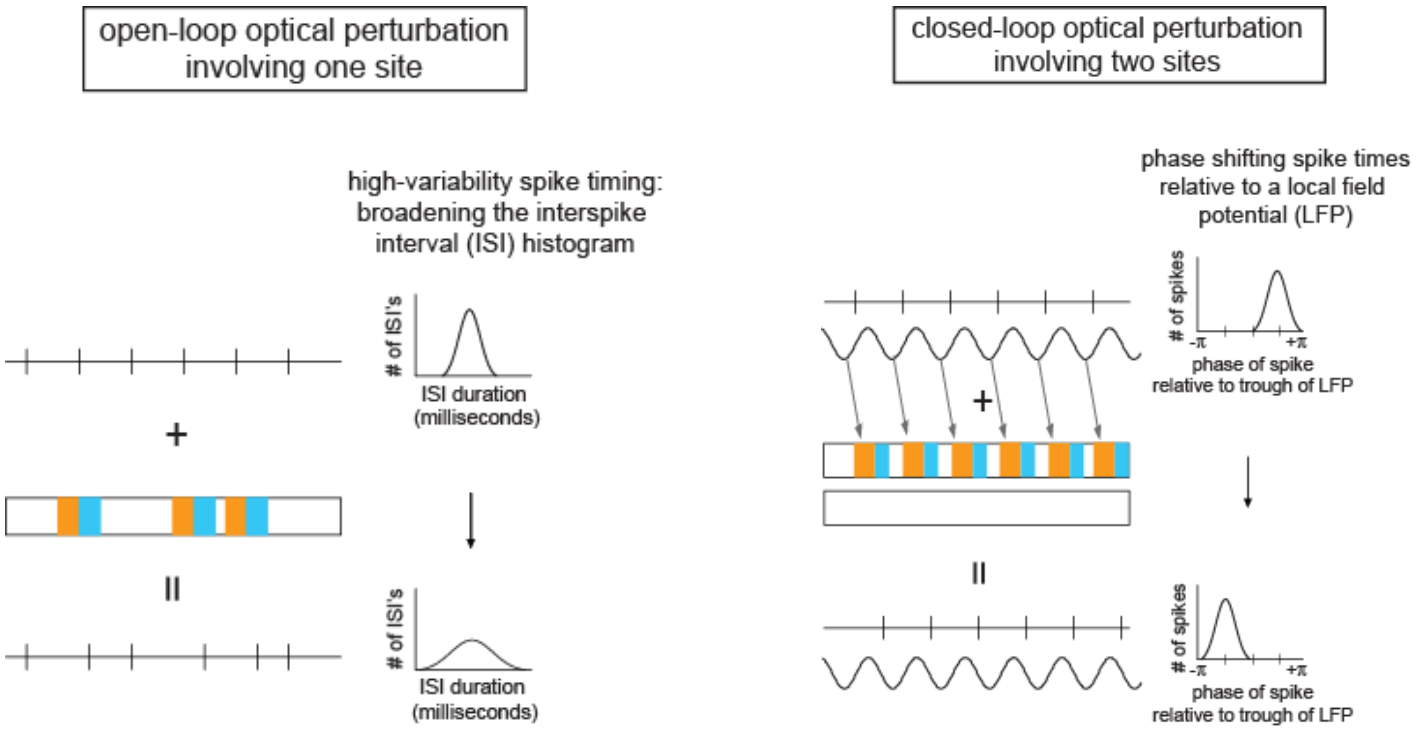


r ~ 0.5

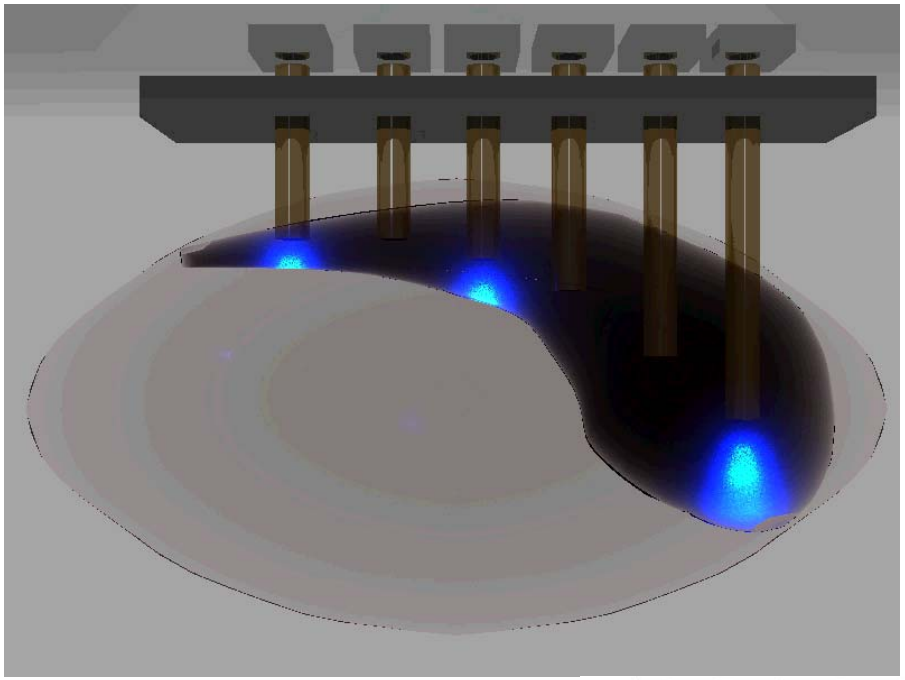
Manipulation of neural coordination

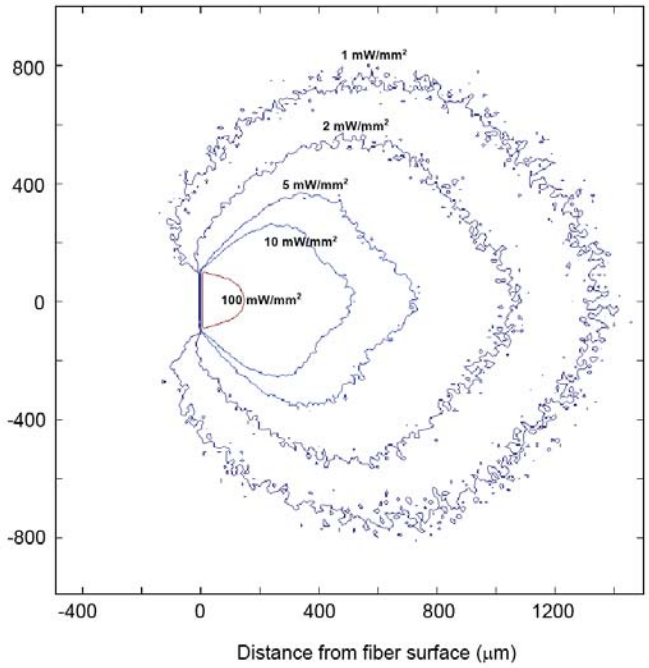


New experimental concepts



Optical fiber arrays: for targeting entire circuits





A potential clinical path?

- Neuromodulation: precision without side effects
  - ~250,000 people implanted with cochlear implants, deep brain stimulators, spinal stimulators, other stimulators
- Optical control could be made very cell-specific and targeted, improving therapy even further
  - Adeno-associated viruses (AAV) have been used in >600 people in 48 clinical trials without a single serious adverse event due to the virus

Therapeutic impact: need new principles to guide therapy

Neurological & psychiatric disorders

1.5 billion sufferers worldwide of disorders such as stroke, depression, addiction, epilepsy, pain, Parkinson's,…

> **$1 trillion** annual worldwide cost

To augment cognition

Improve memory, happiness, creativity, intelligence,…

Strategies for doing so:

Drugs

Neuromodulation

Surgery

Talk therapy, software

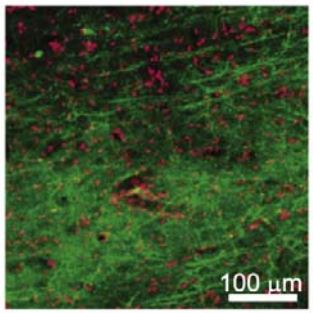
Need more systematic tools.

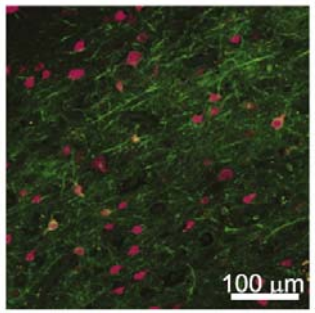
Treating blindness: before

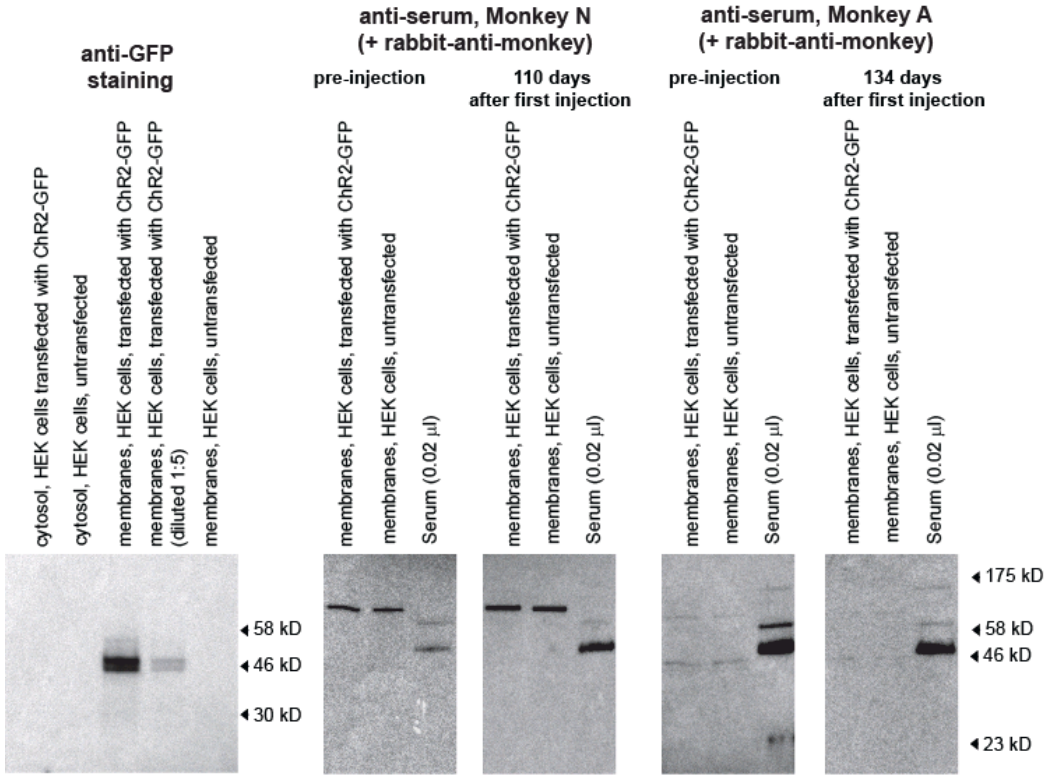
Treating blindness: after

Evaluating safety for translational use

- Early days, but cells appear to be healthy for many months, in primate brain







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