Minding the Gaps in Neuroscience:Enabling Great Science to Become Great Medicine

William Mobley

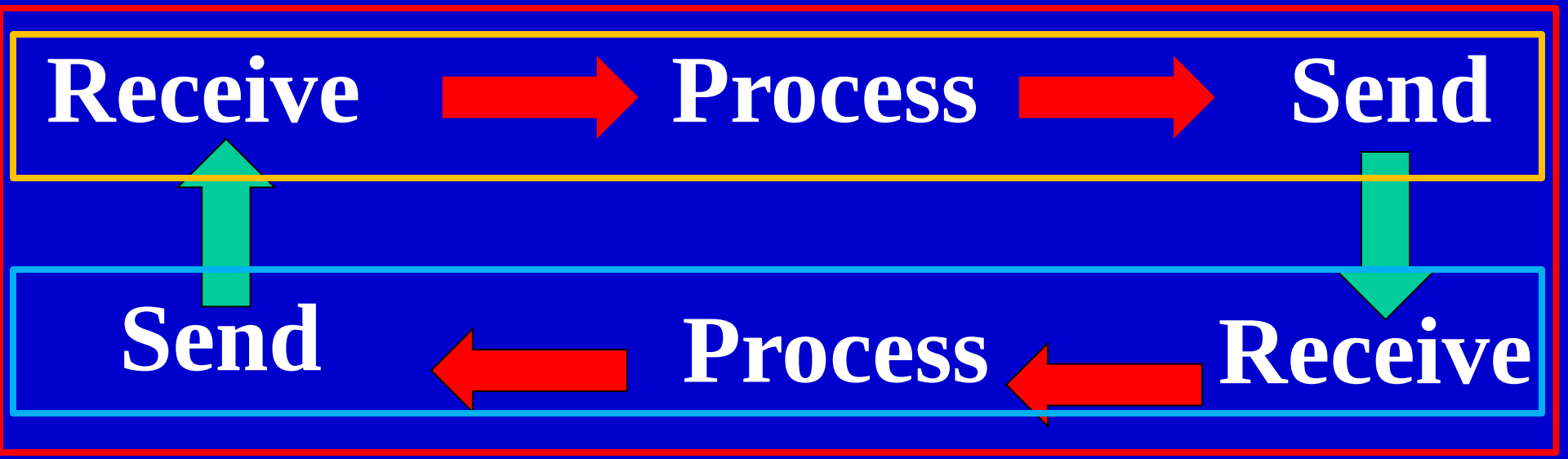
University of California San Diego

The Brain -
This Three Pound Gem Is
The Most Powerful Information Tool
In The Known Universe

The Brain-
Functions to Receive, Process and Act Upon Information

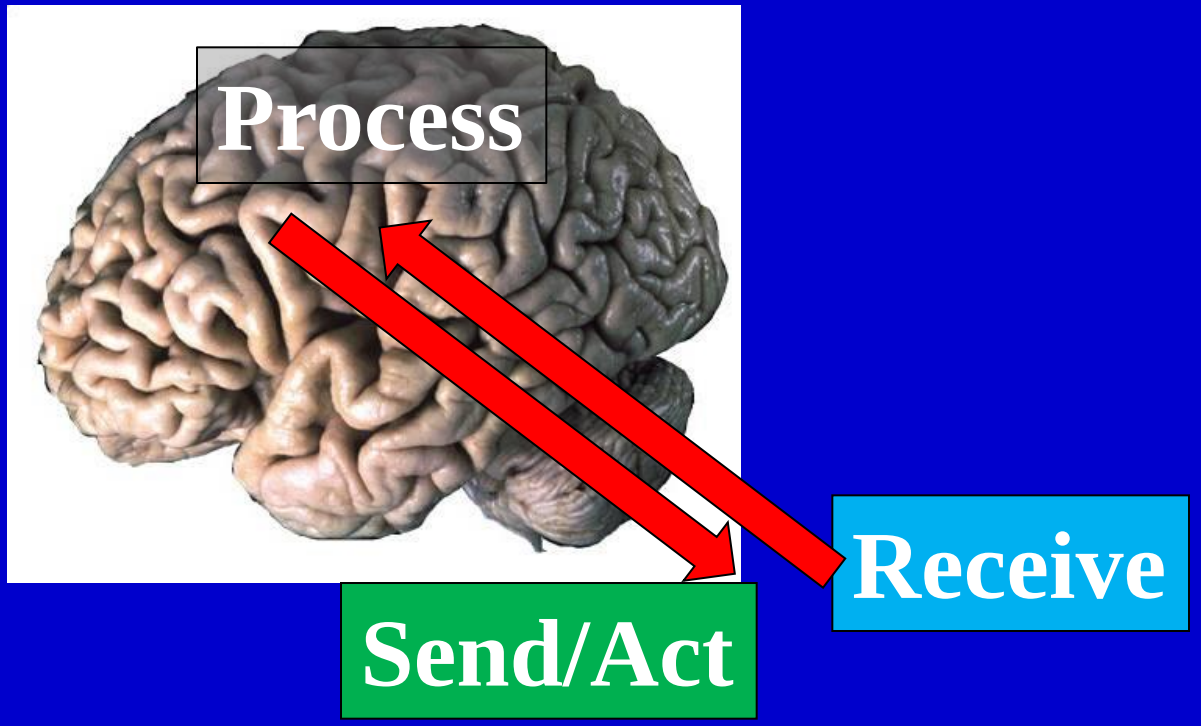
Receive → Process → Send

Brains Share Information in Context



To Understand the Brain Is The Most Important Human Undertaking

We Can Transform Our World If We Can: Decipher How The Brain Receives, Processes and Acts Upon Information



Receive: in spite of sensory loss or distraction.

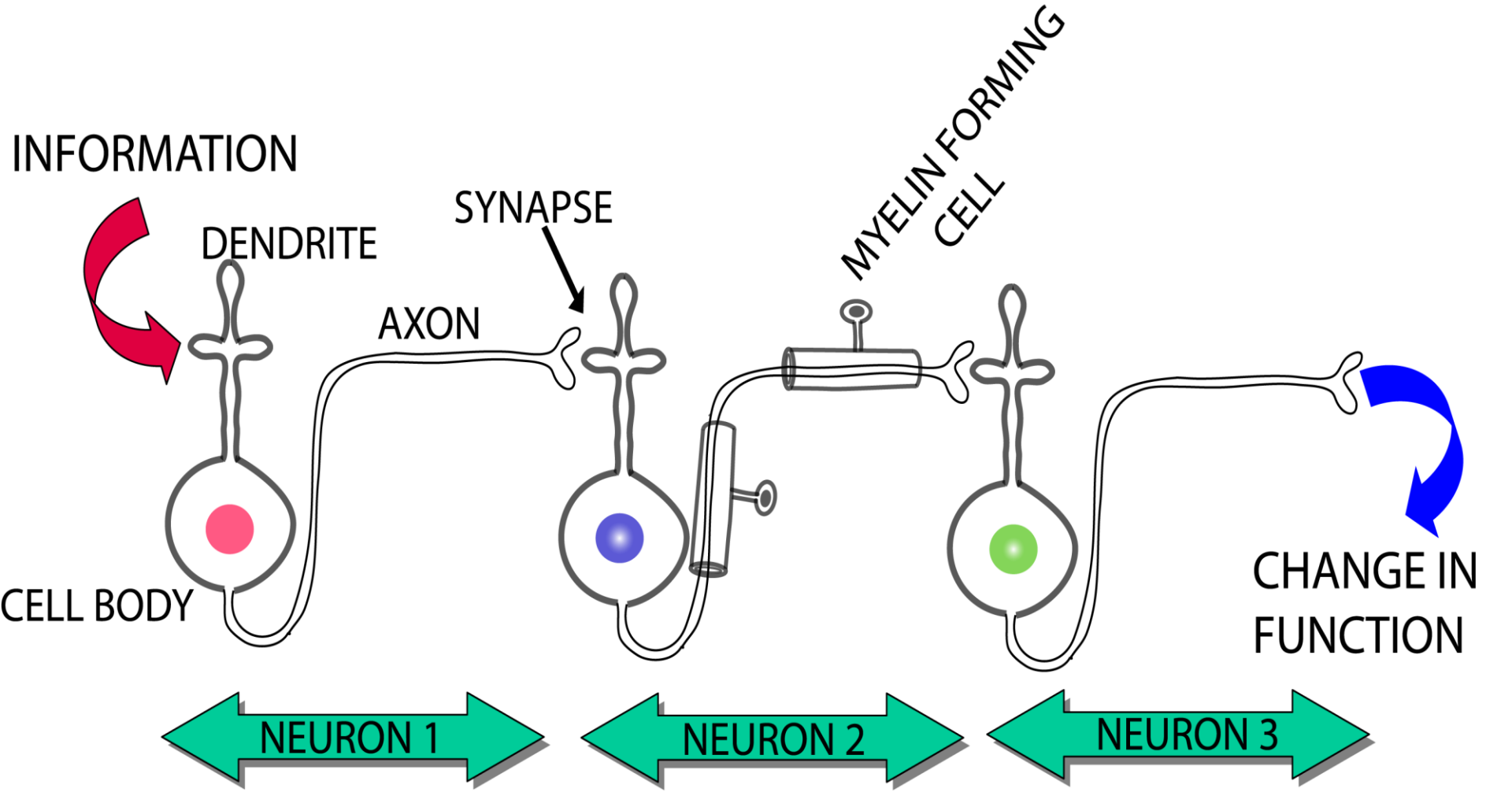
Process: even during stress or in old age.

Send/Act: even when power is diminished.

Deciphering the Brain

Brain function is written in the structure and function of neural circuits.

NEURONAL CIRCUITS MEDIATE ALL BRAIN FUNCTIONS

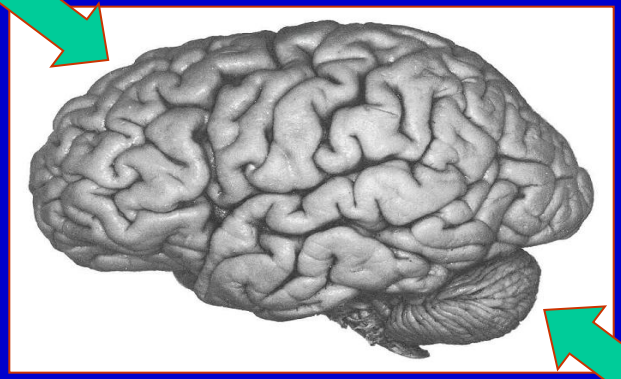


Deciphering The Brain Requires That We Learn:

-how neural circuits assemble and operate,
-how learning modifies circuits,
-how circuits create behavior,
-how circuit disorders impact the brain.

Deciphering Neural Circuits: Working Across Scales To Understand Brain Function

Cognitive function



Circuit function

Molecular and cellular function

Playing the Brain Scales

- Length – nanometers to meters (10^9)
- Time – milliseconds to decades (10^9)
- Complexity – the structure and function of single molecules to higher order processing of brain signals
- Development – conception to old age
- Health Status – well to ill
- Disease profile – from development to dysfunction to degeneration
- Context – discovery to delivery

Linking the Scales and Scaling the Links

For success, we need to:

- create ***new technologies*** to decipher the basis of circuit dysfunction,
- establish ***strong collaborations*** between physicians and colleagues in the physical sciences, engineering, behavioral sciences and education,
- discover new ways to ***repair/replace circuits***,
- create a ***culture that speeds translation*** of great science into great medicine.

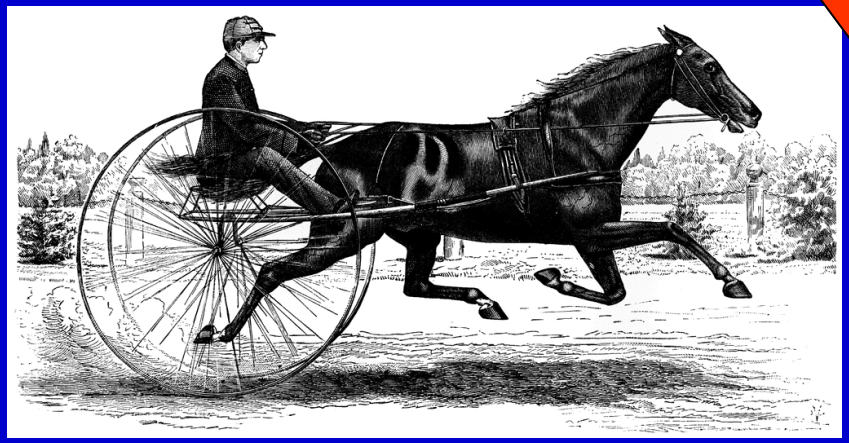
Basic Science Advances Are Key to Success in Helping People

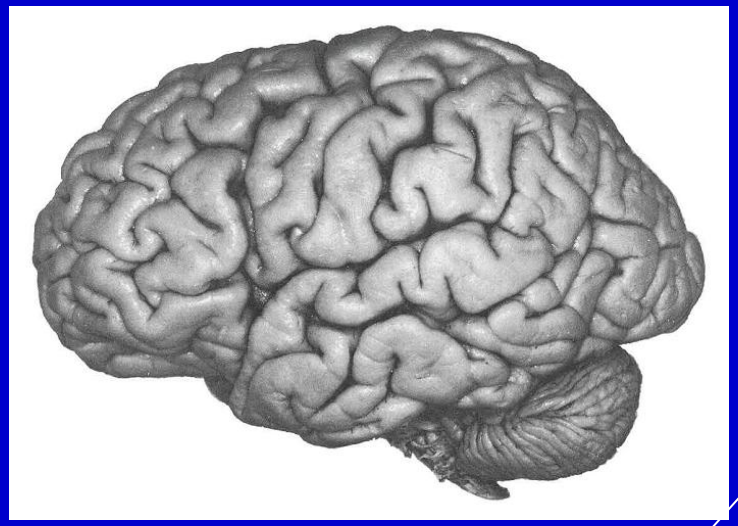
- **In the last 20 years we have gone from:**
  - Biochemical studies on crude homogenates ***to precise definition of molecular and synaptic complexes***
  - Imaging fixed tissue ***to live-imaging of neurons***
  - Recording single neurons ***to watching entire circuits***
  - Surgical lesions ***to precise genetic control of circuits***
  - Observing function ***to real-time modulation of function***
  - Few tools for studying people ***to a wealth of methods***

Basic Science Advances: Enable A 100-fold Increase in Signal Detection

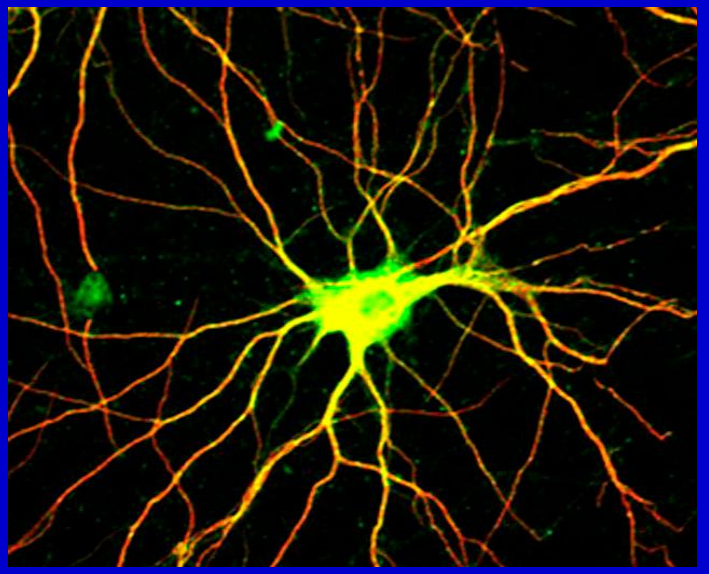
1 HP

500 HP





Theory



Cognition/ Behavior

Function- Circuits

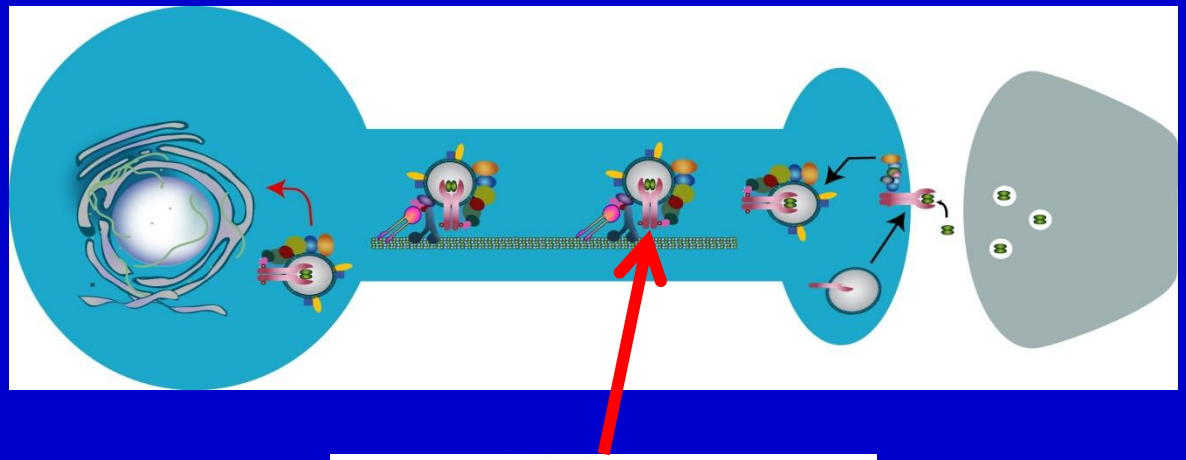
Structure- Circuit

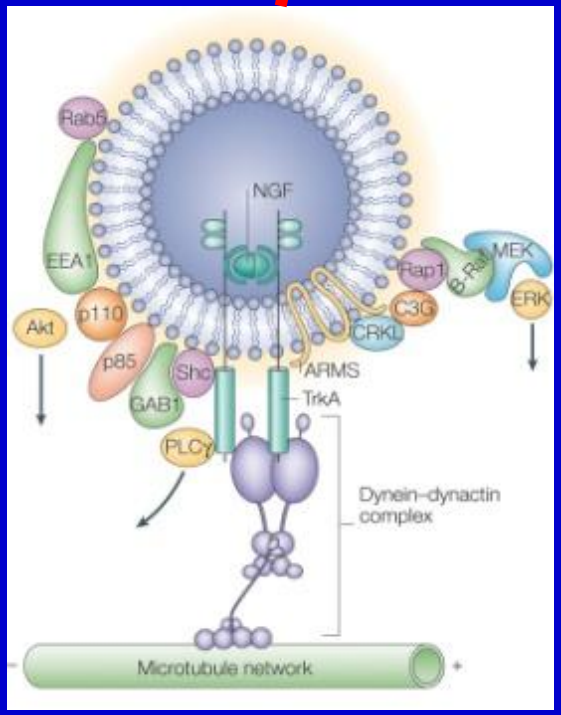
Function- Neurons/ Synapses

Structure- Molecular/ Cellular

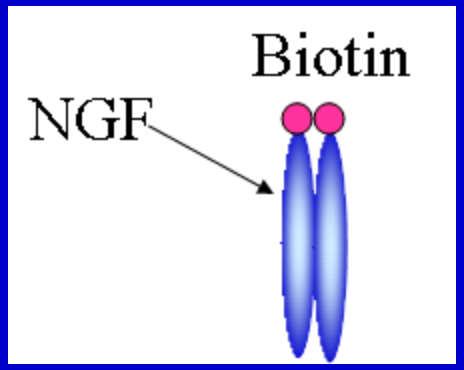
Dynamic Modeling of Circuits Across Scales

Signaling Endosomes Carry Trophic Signals

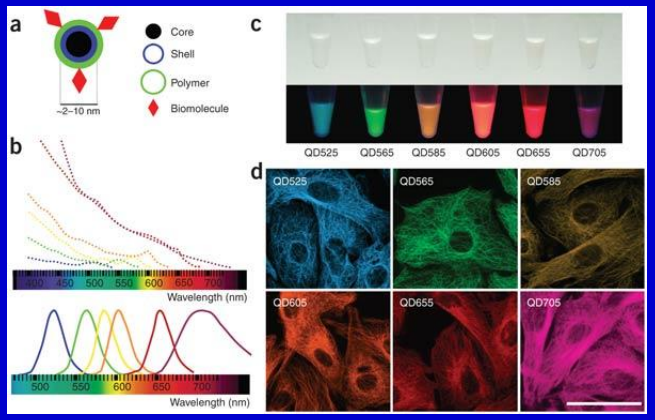




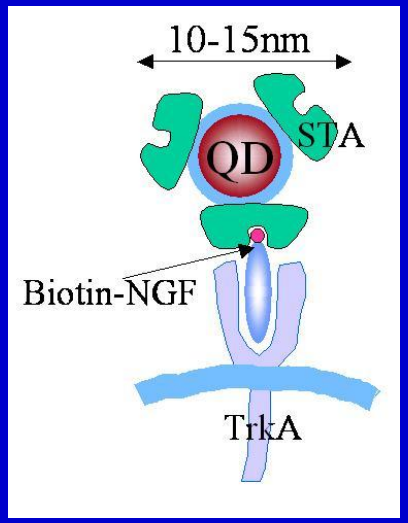
Tracing Endosomal Traffic: Quantum Dot Labeled NGF



+

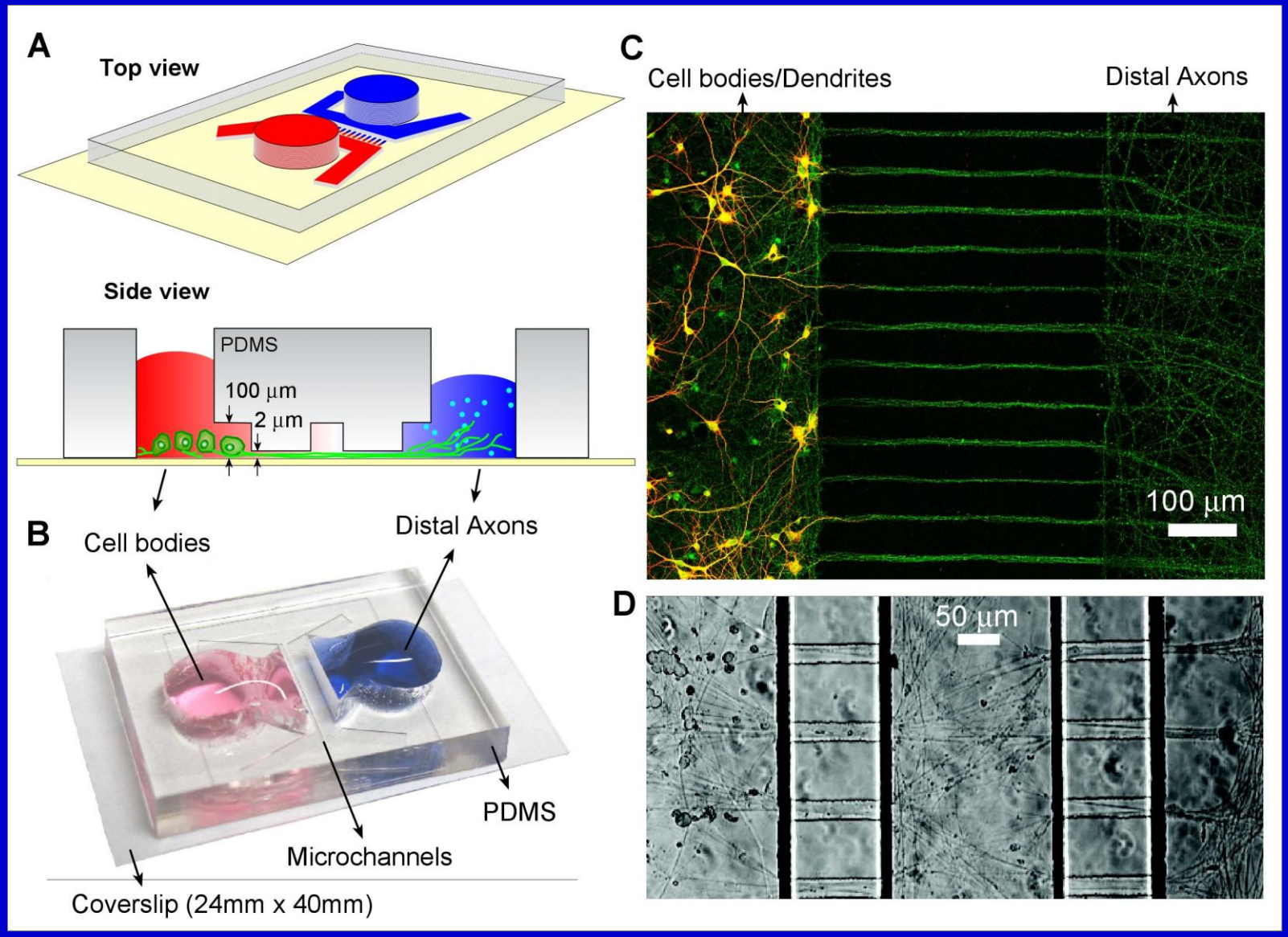


=



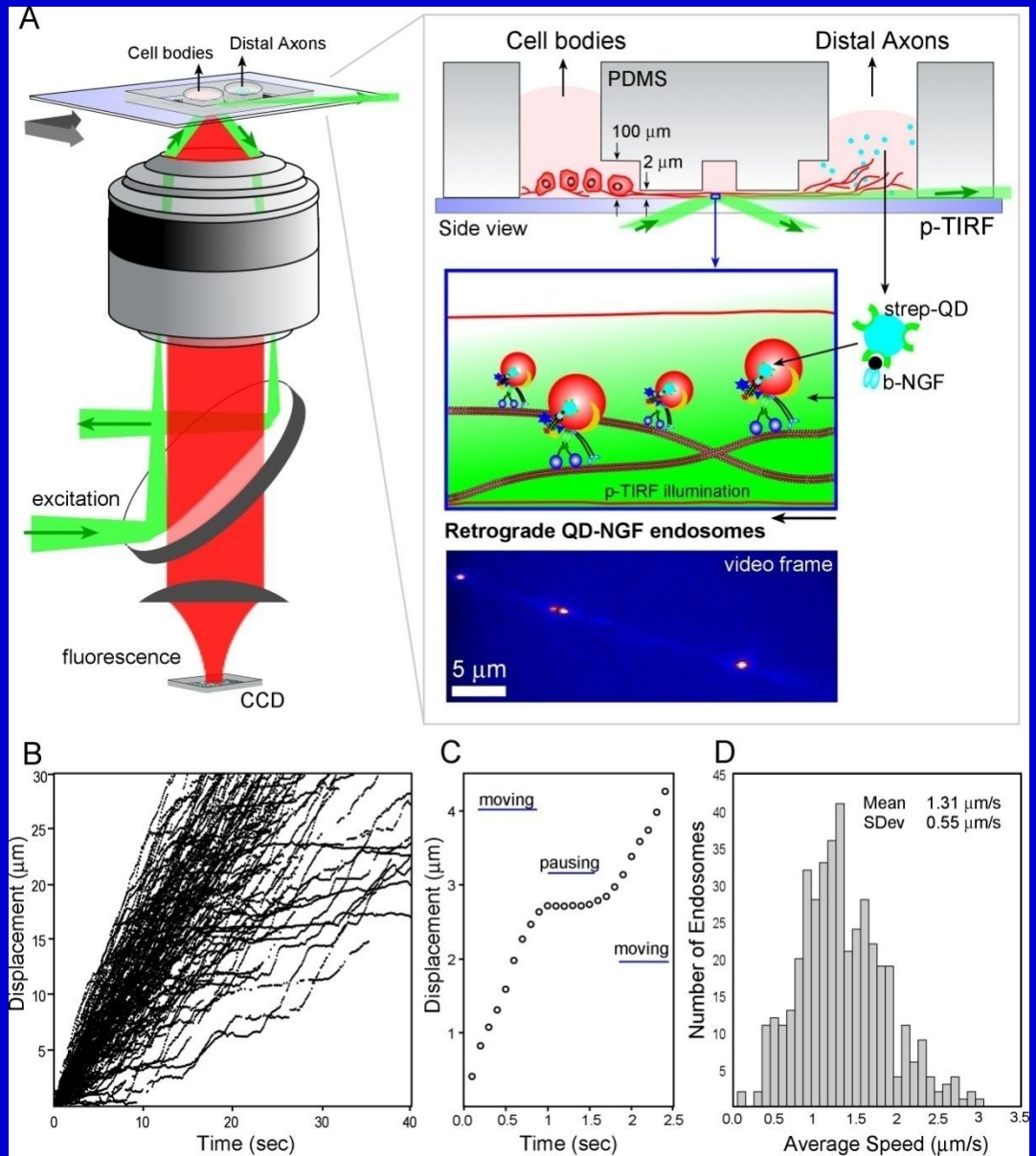
Biotin-NGF + **Streptavidin-Qdot** = **Qdot-NGF**

Separting Axons from Cell Bodies



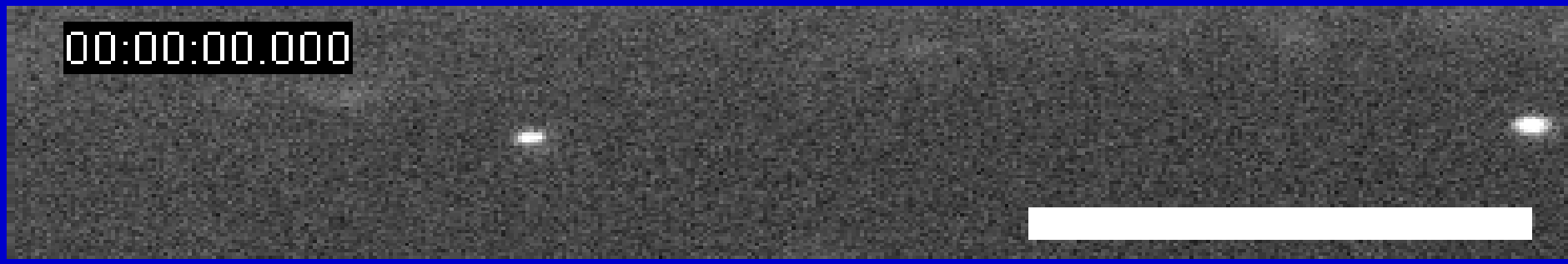
Chowdary, Che, Cui. Ann Rev Phys Chem, 2012

Watching Traffic in Real-Time

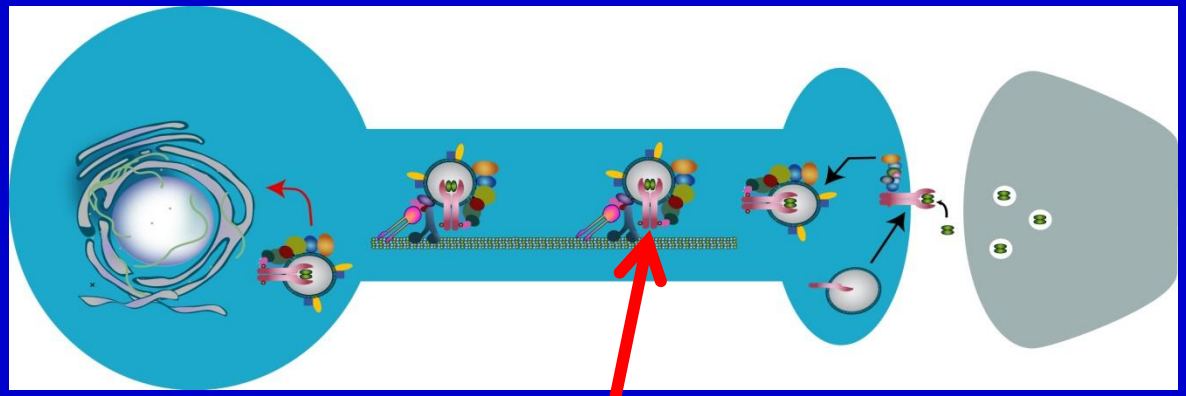


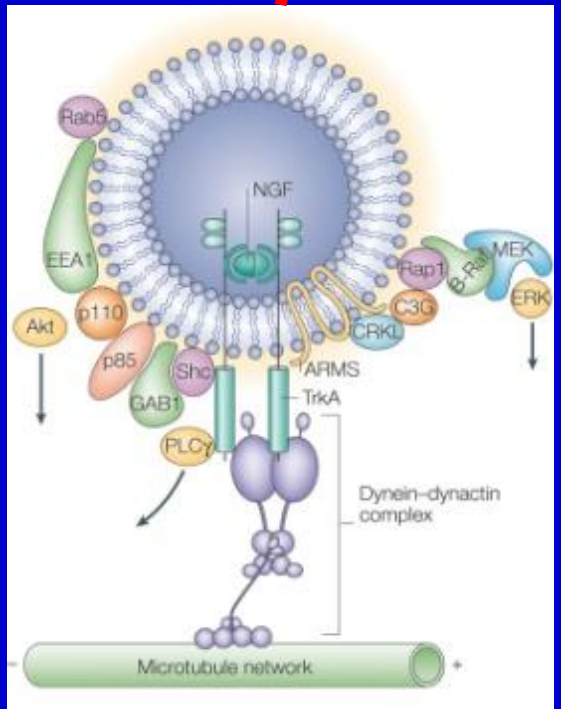
Qdot-BDNF Transport in Hippocampal Neurons

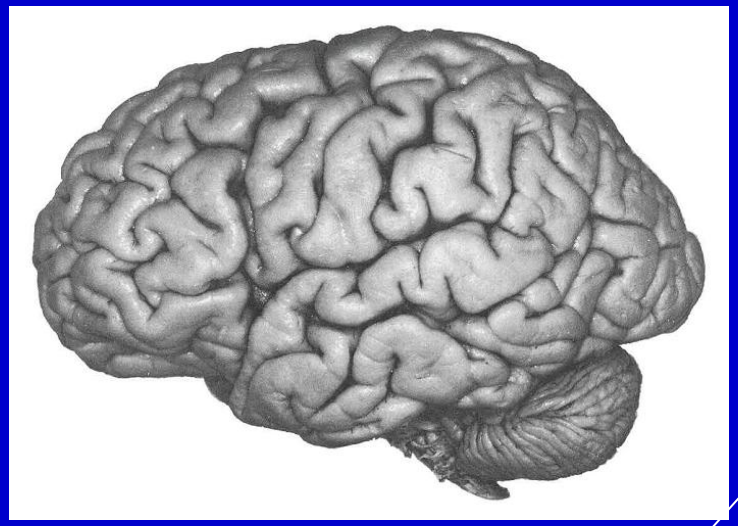
Retrograde



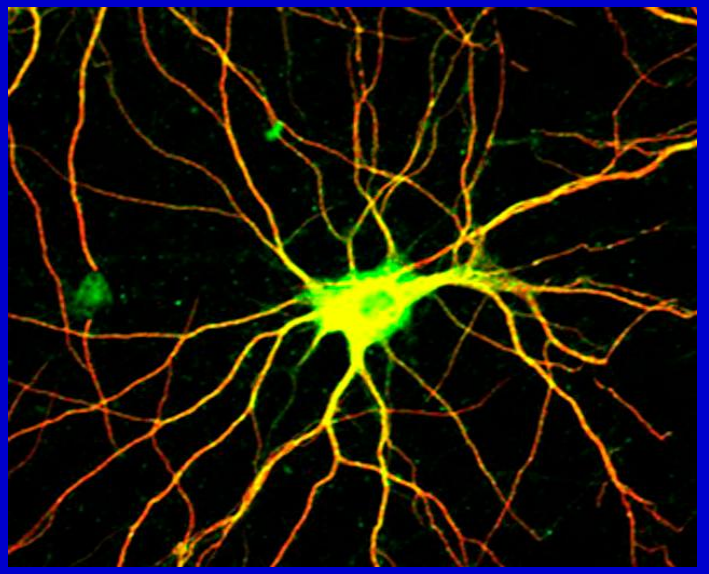
Disrupted Trafficking of Signaling Endosomes May Contribute to Dementia







Theory



Cognition/ Behavior

Function- Circuits

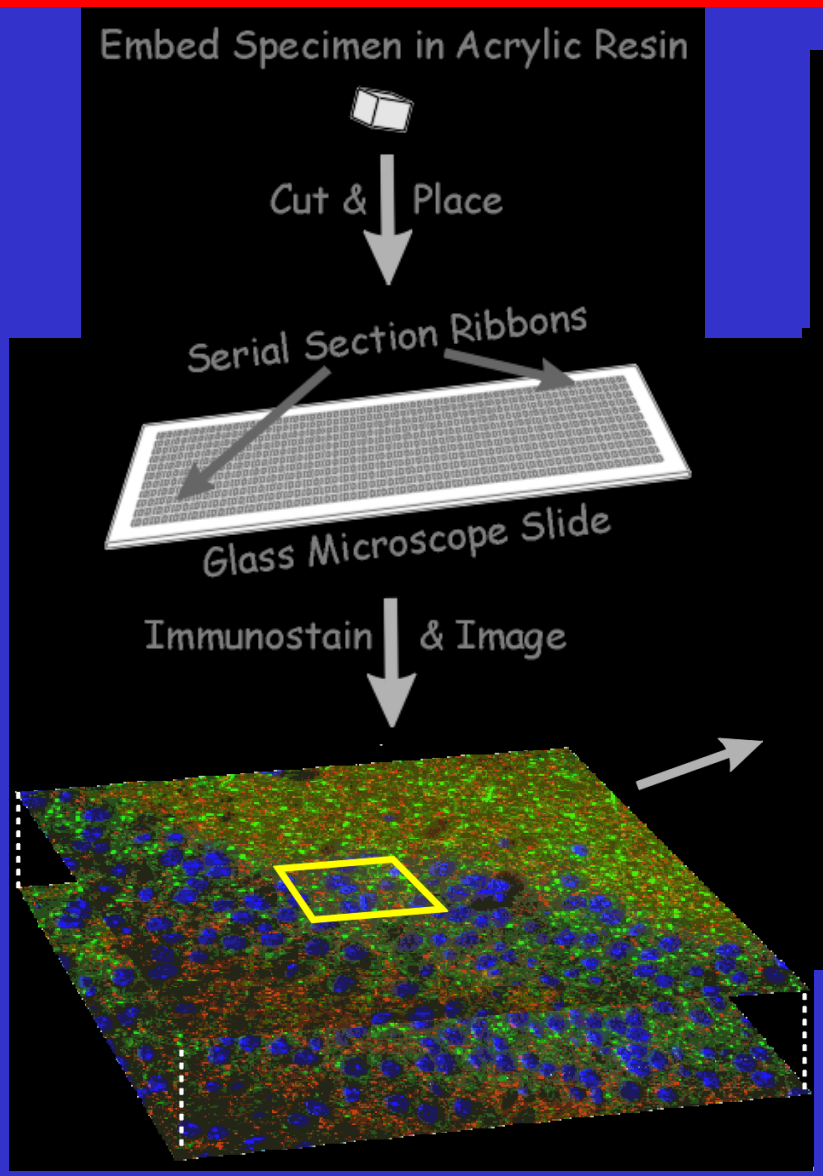
Structure- Circuit

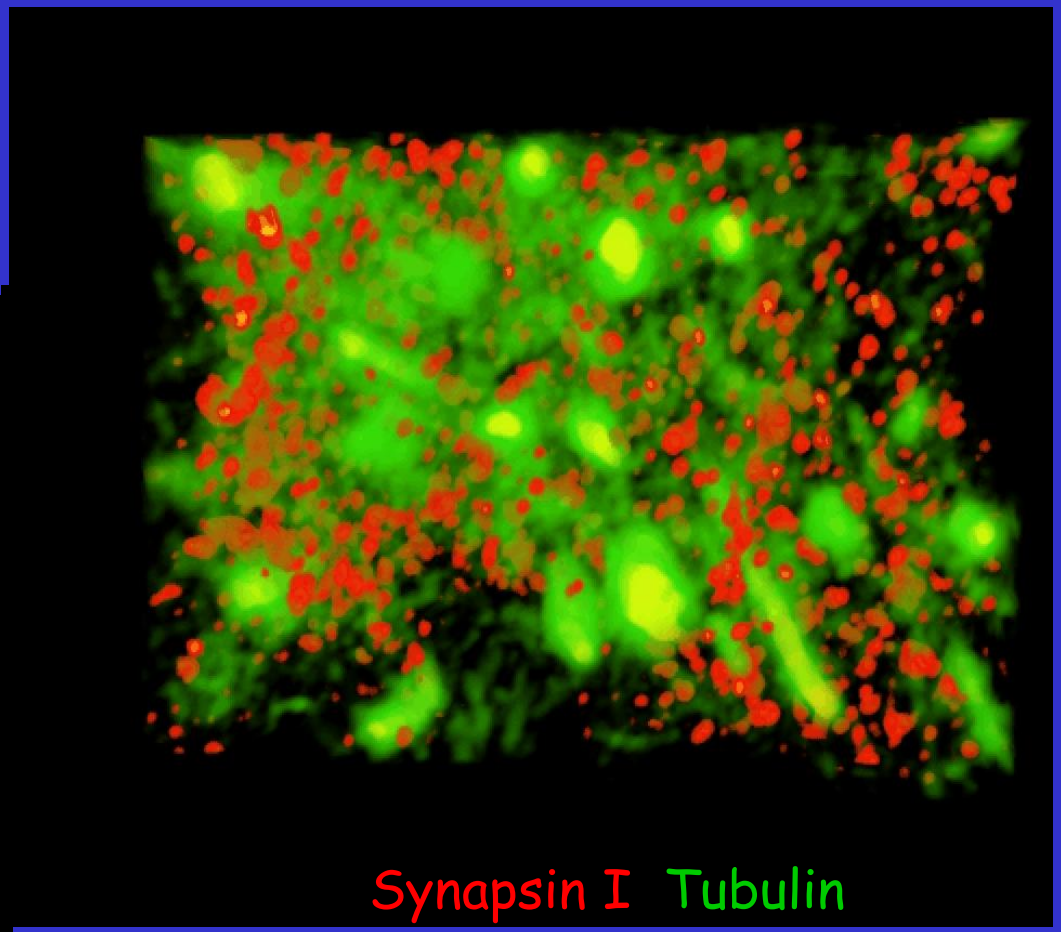
Function- Neurons/ Synapses

Structure- Molecular/ Cellular

Dynamic Modeling of Circuits Across Scales

Array Tomography: A Means to Image the Molecular Basis of Circuits

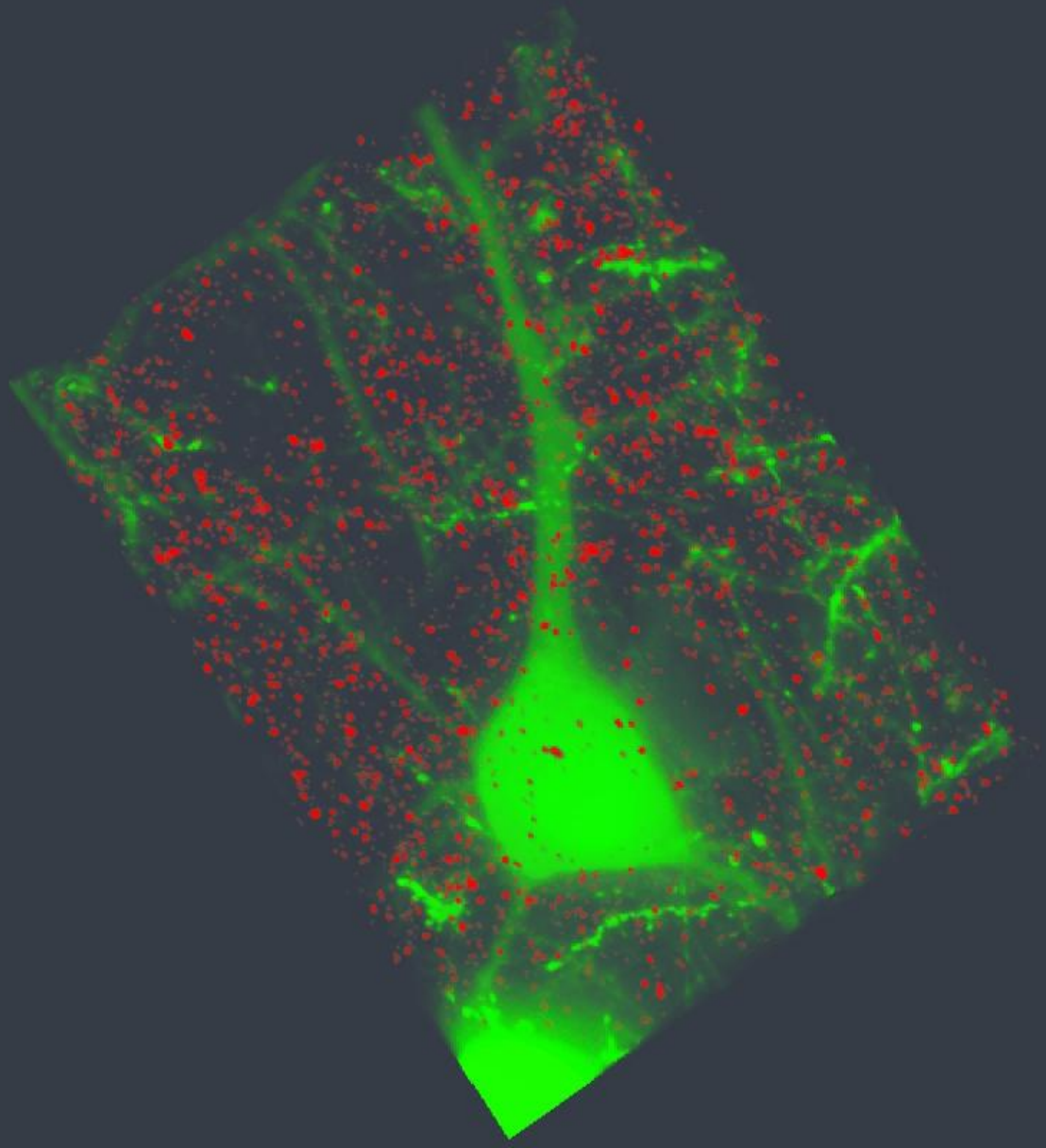


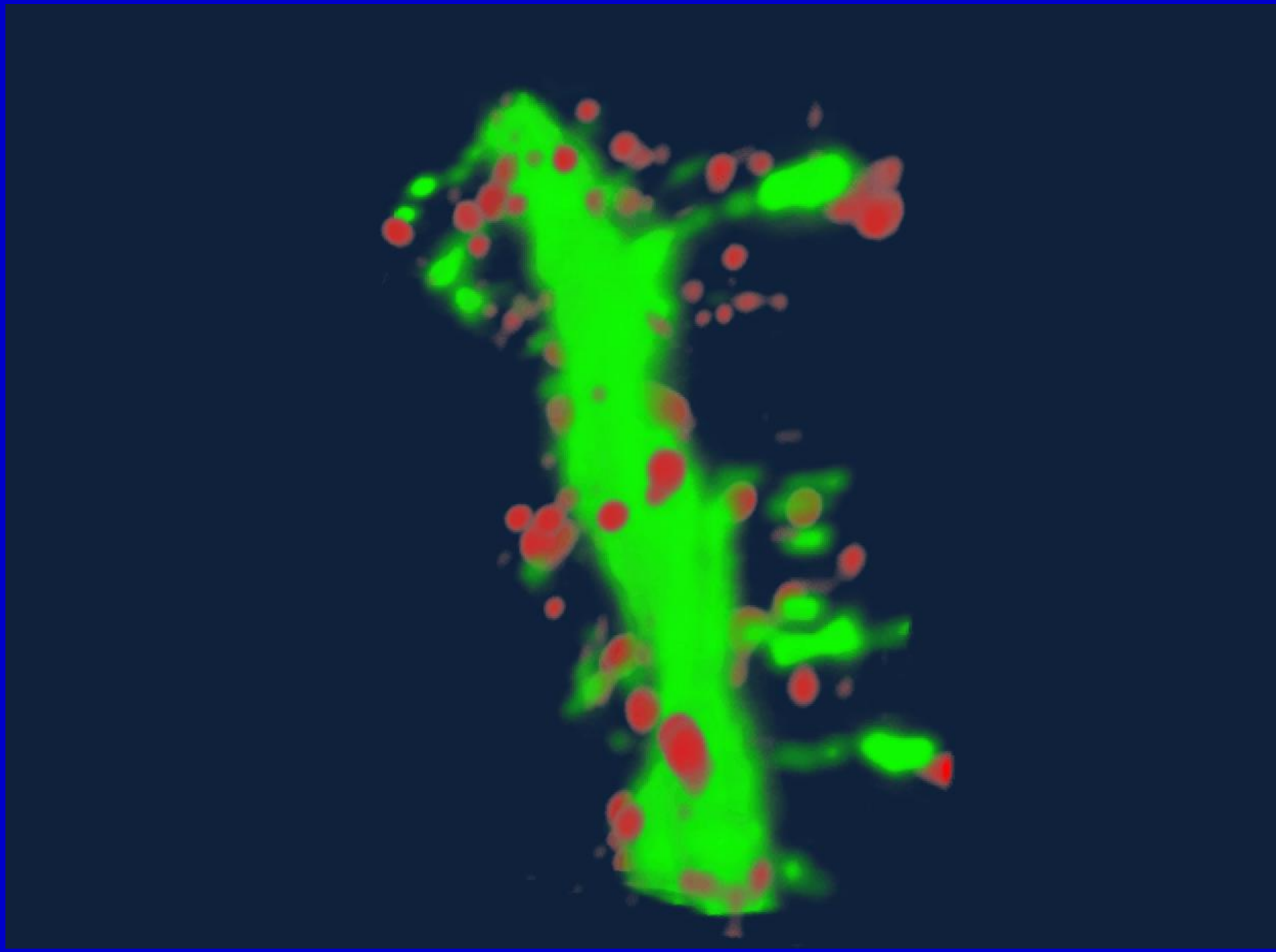


Synapsin I Tubulin

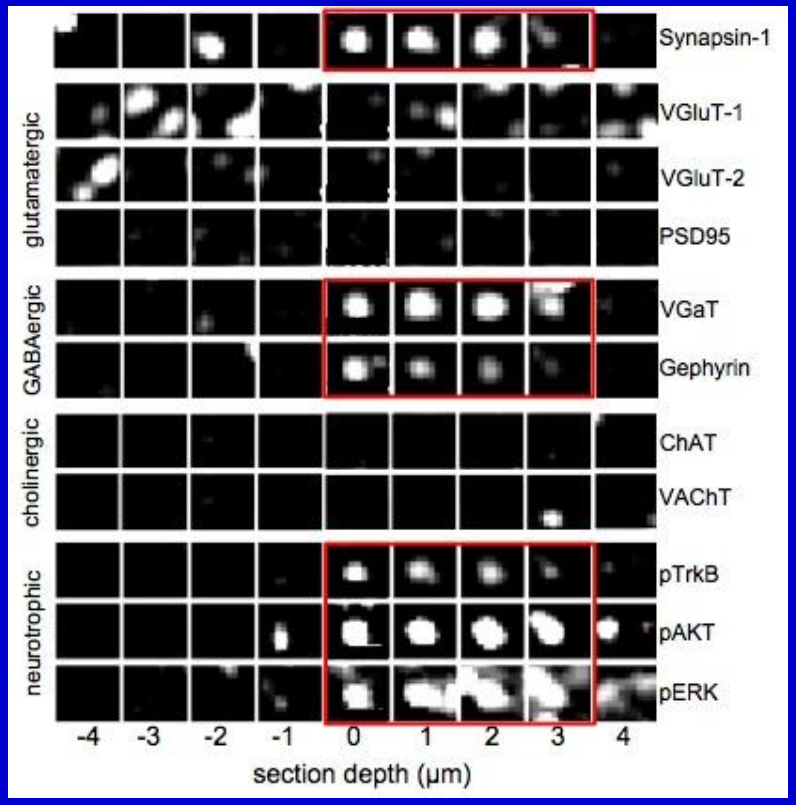
Kristina Micheva

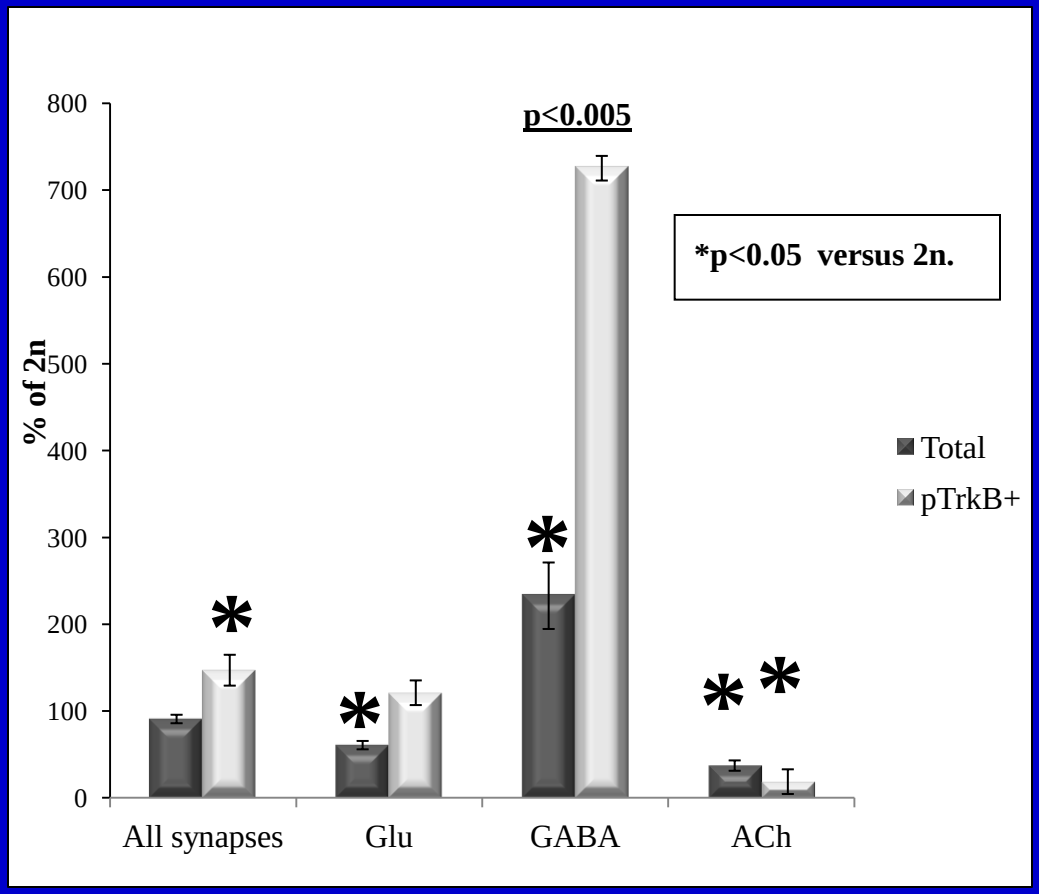
Stephen Smith





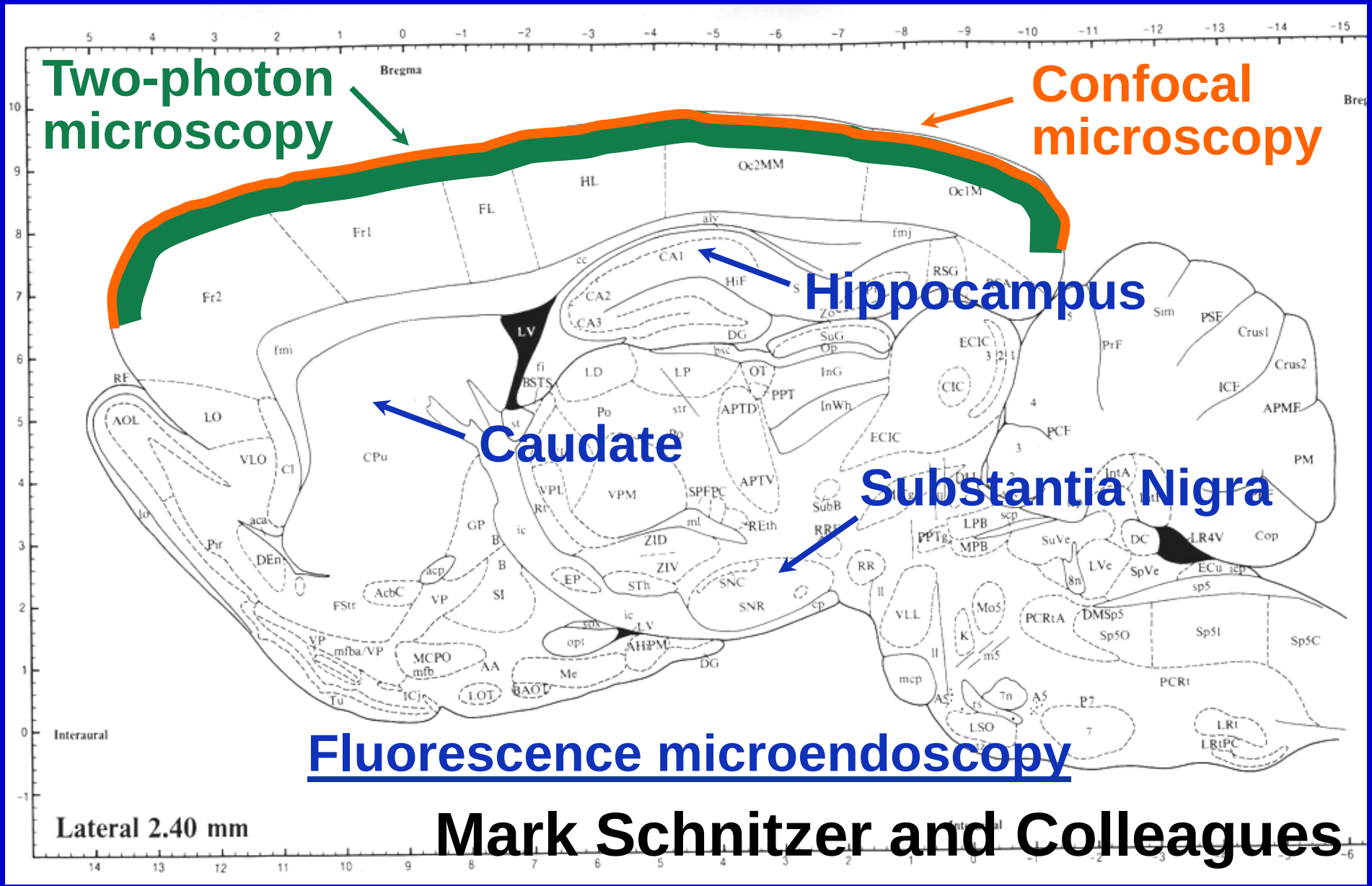
Automated Synapse Classification in Cortex of a Mouse Model of Down Syndrome





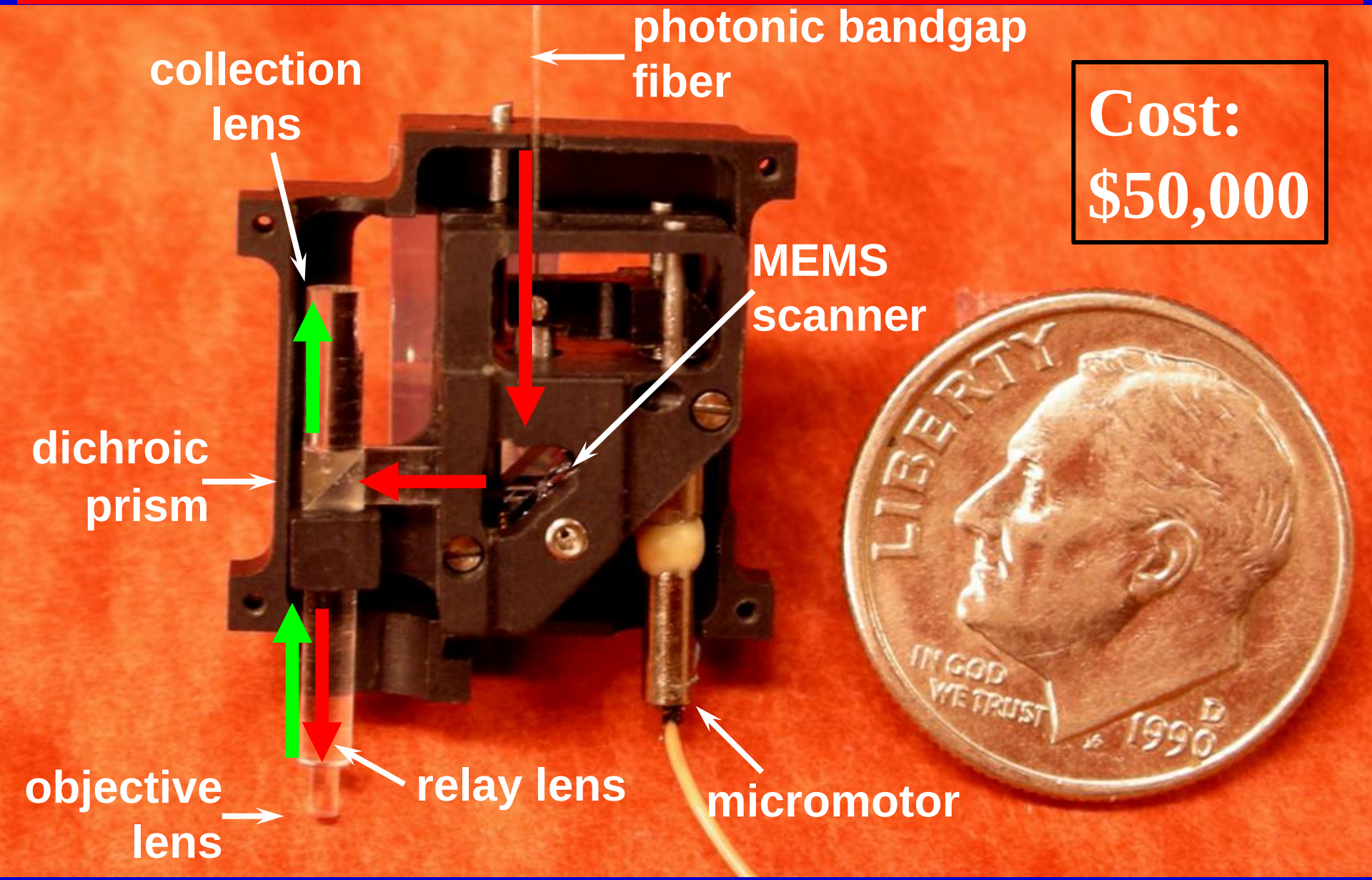
80K-150K Synapses Classified by a Machine Learning Algorithm

Imaging Circuits In Vivo



Mark Schnitzer and Colleagues

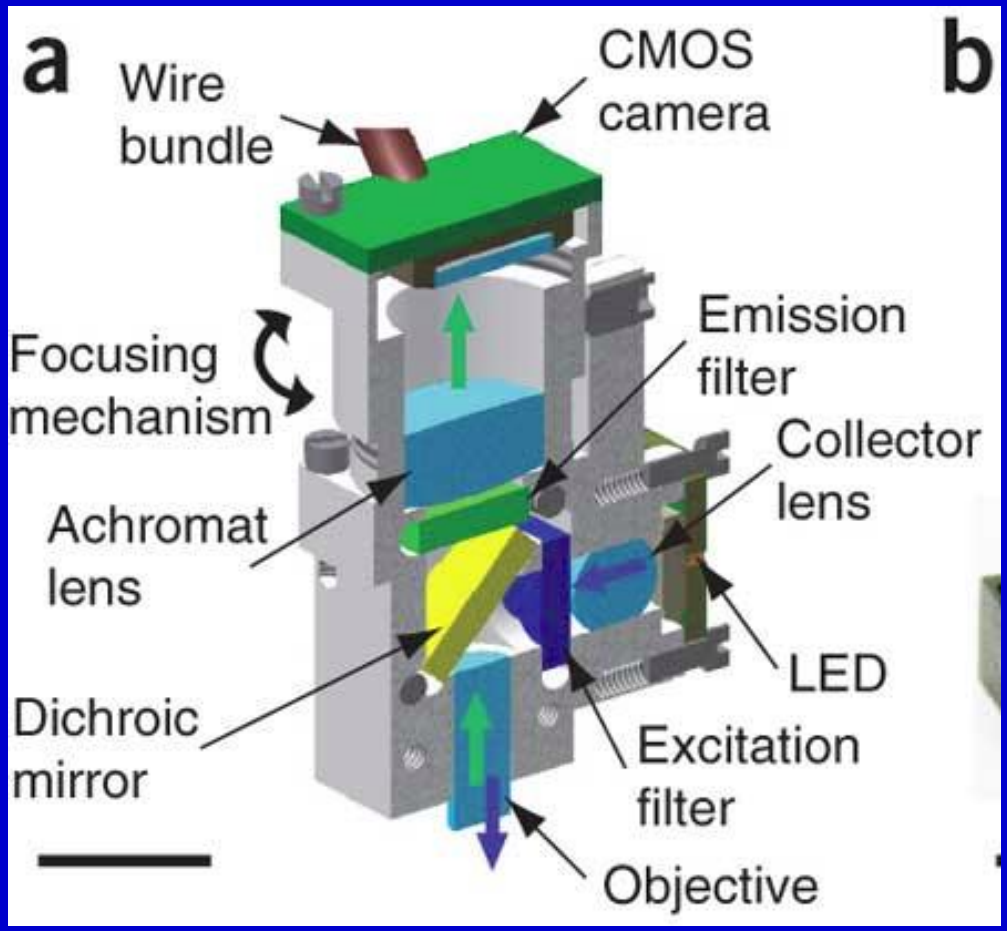
Two-Photon Imaging Device



Cost: $50,000

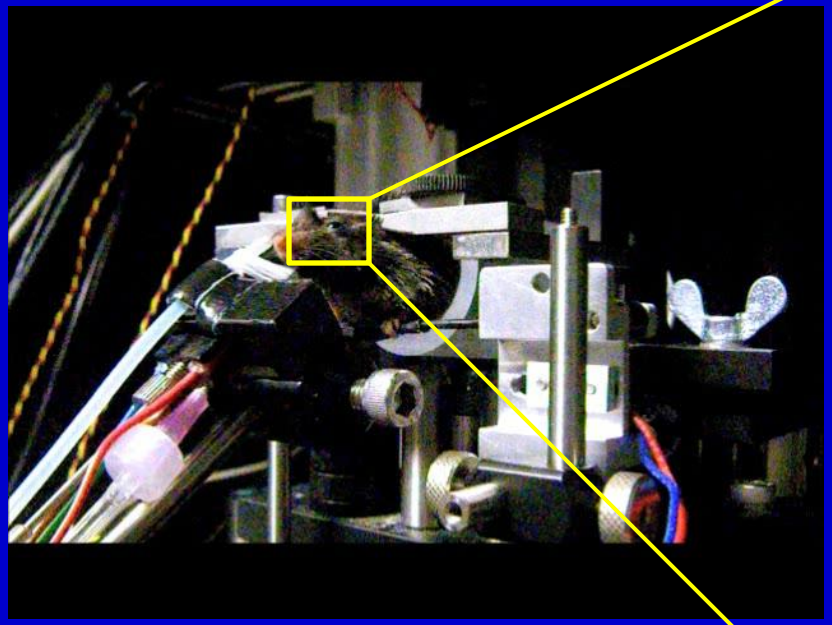
A Microscope That Weighs Less Than 2 gm And Fits In Your Wallet

And costs ~$5.00

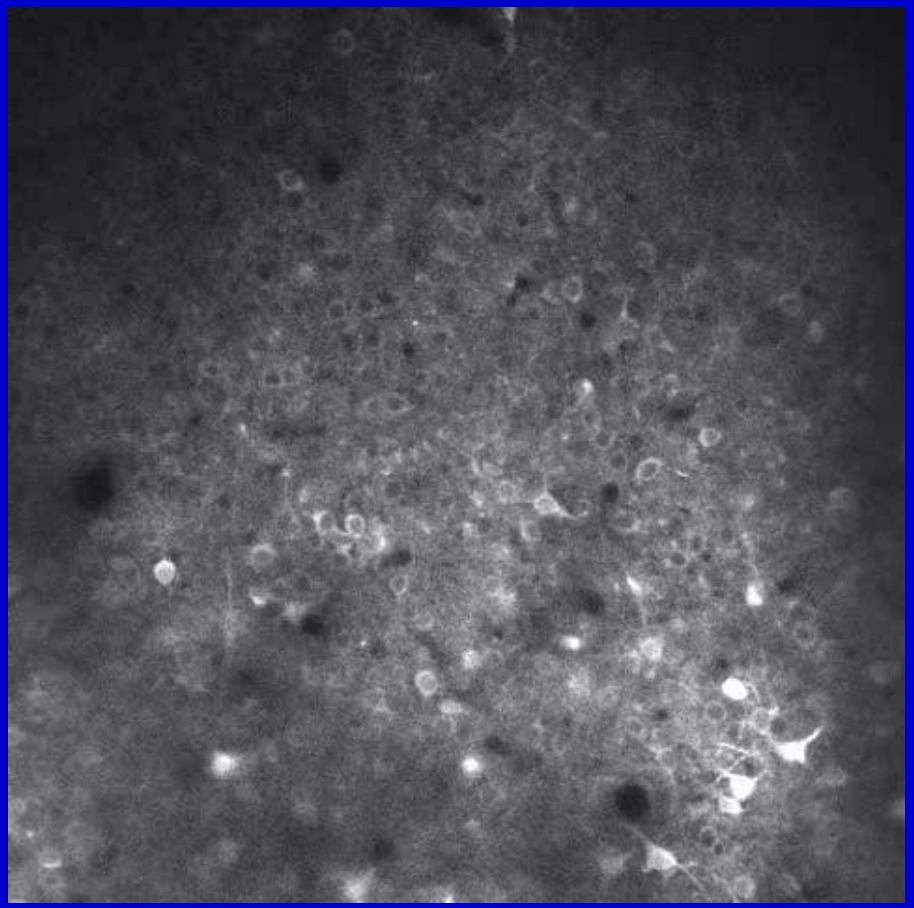


Mark Schnitzer and Colleagues

Imaging Function of Neurons in Circuits in Behaving Mice

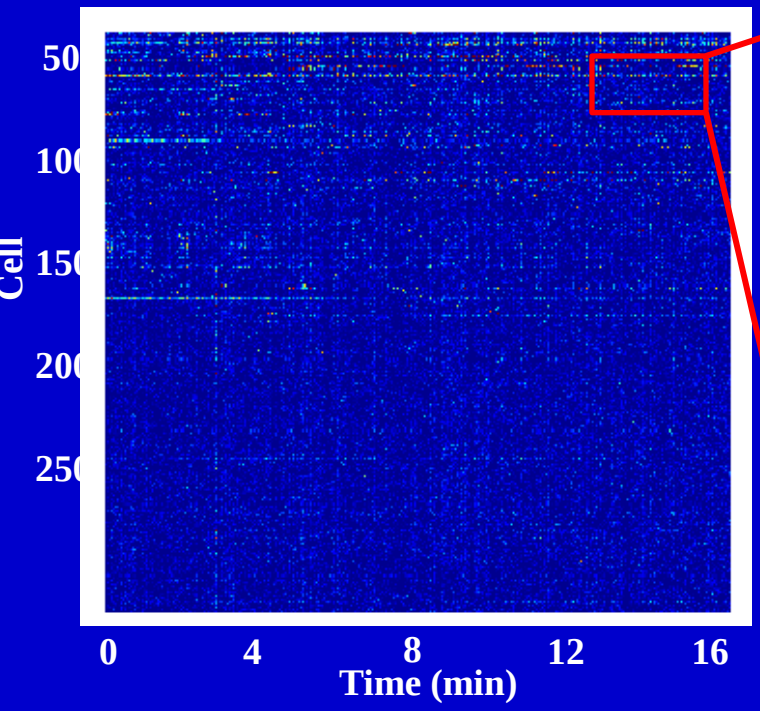


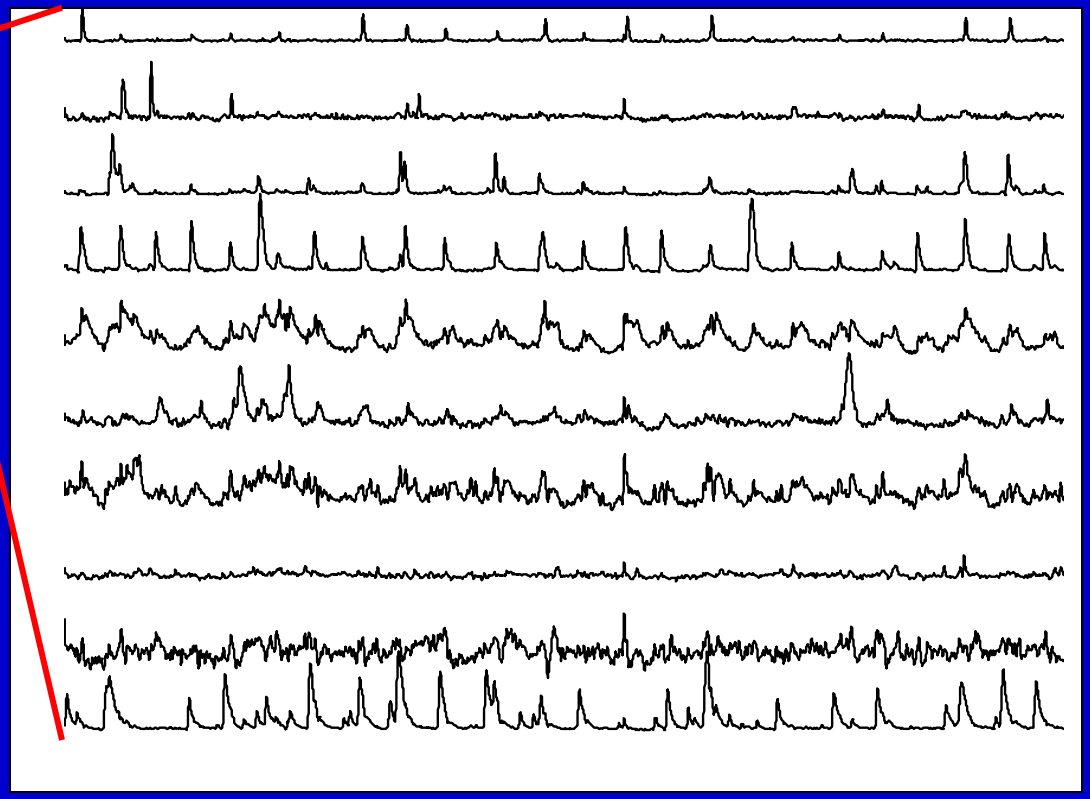
(Real time)



(10x real time)

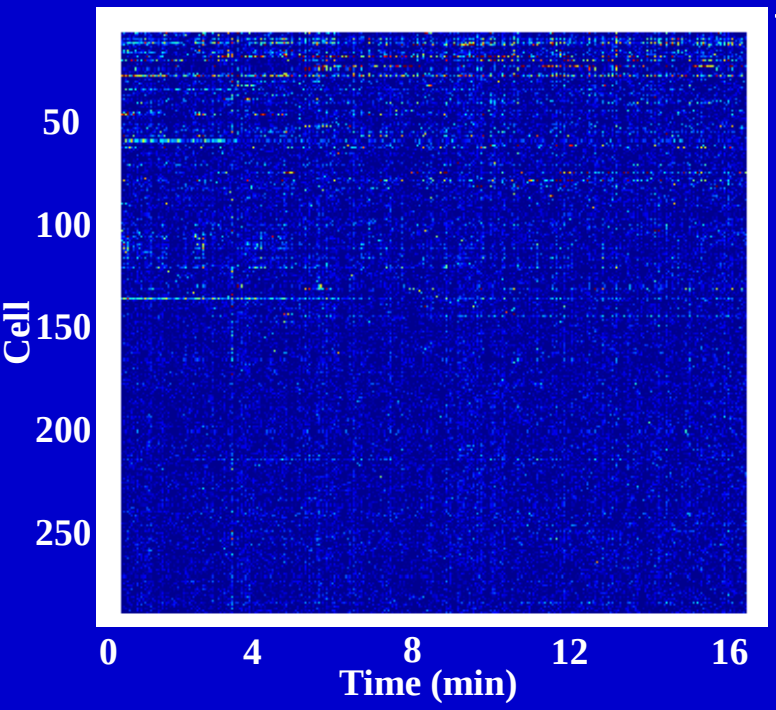
Recording of Ensemble Activity During Behavior





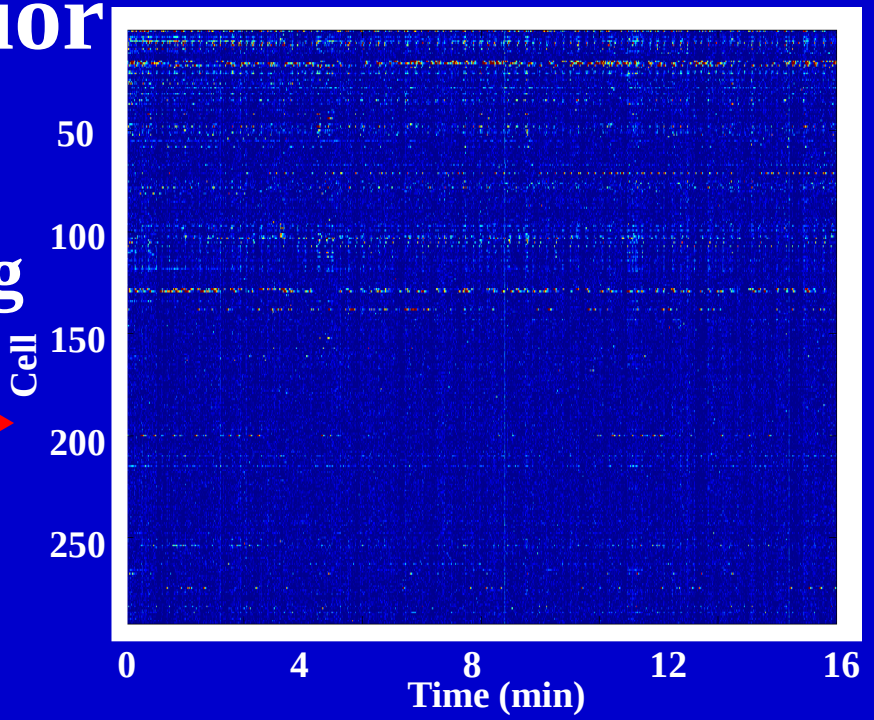
- Activity of hundreds of neurons can be visualized simultaneously in awake, behaving animals

Recording of Ensemble Activity During Behavior



Day1

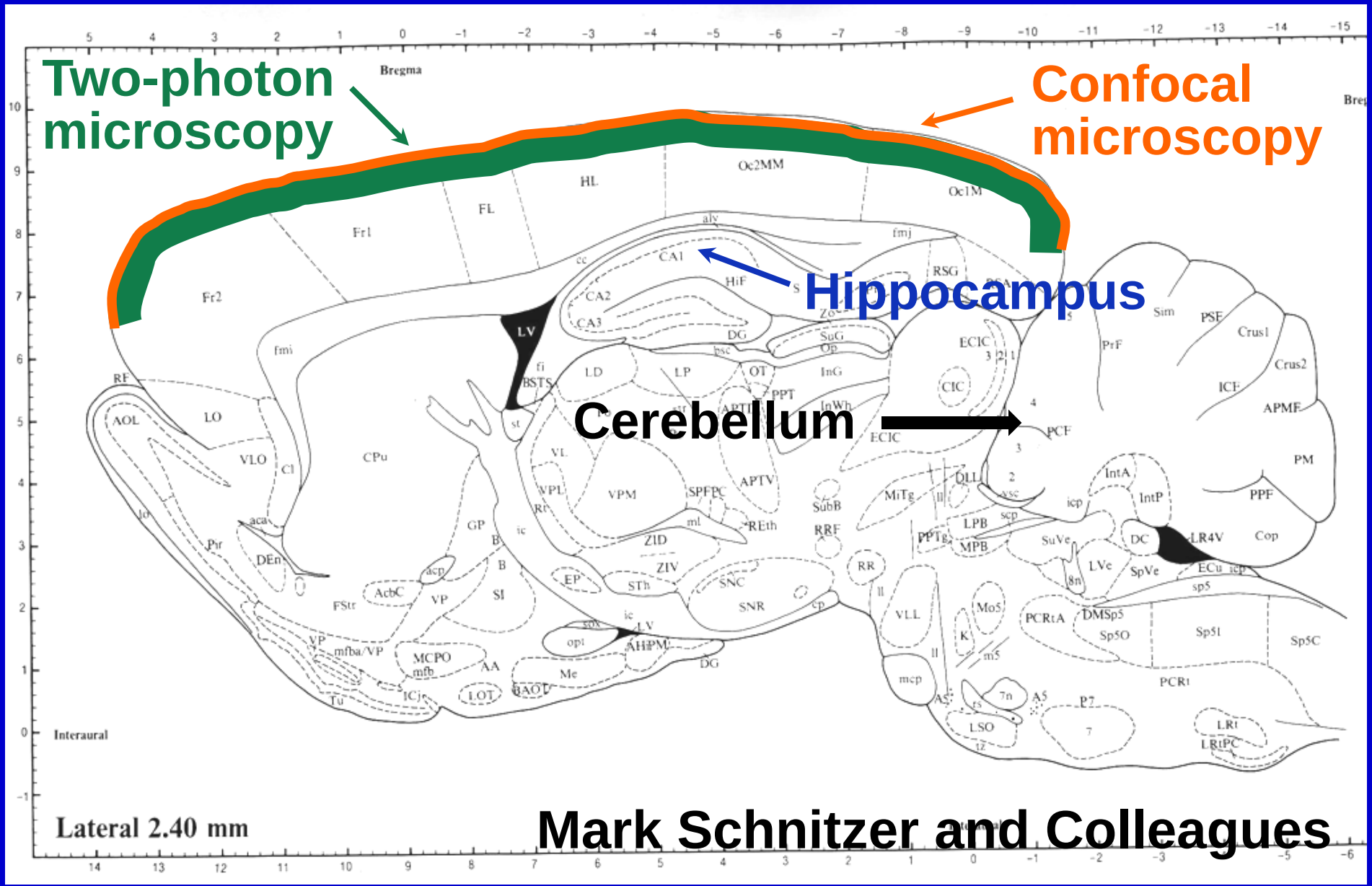
learning



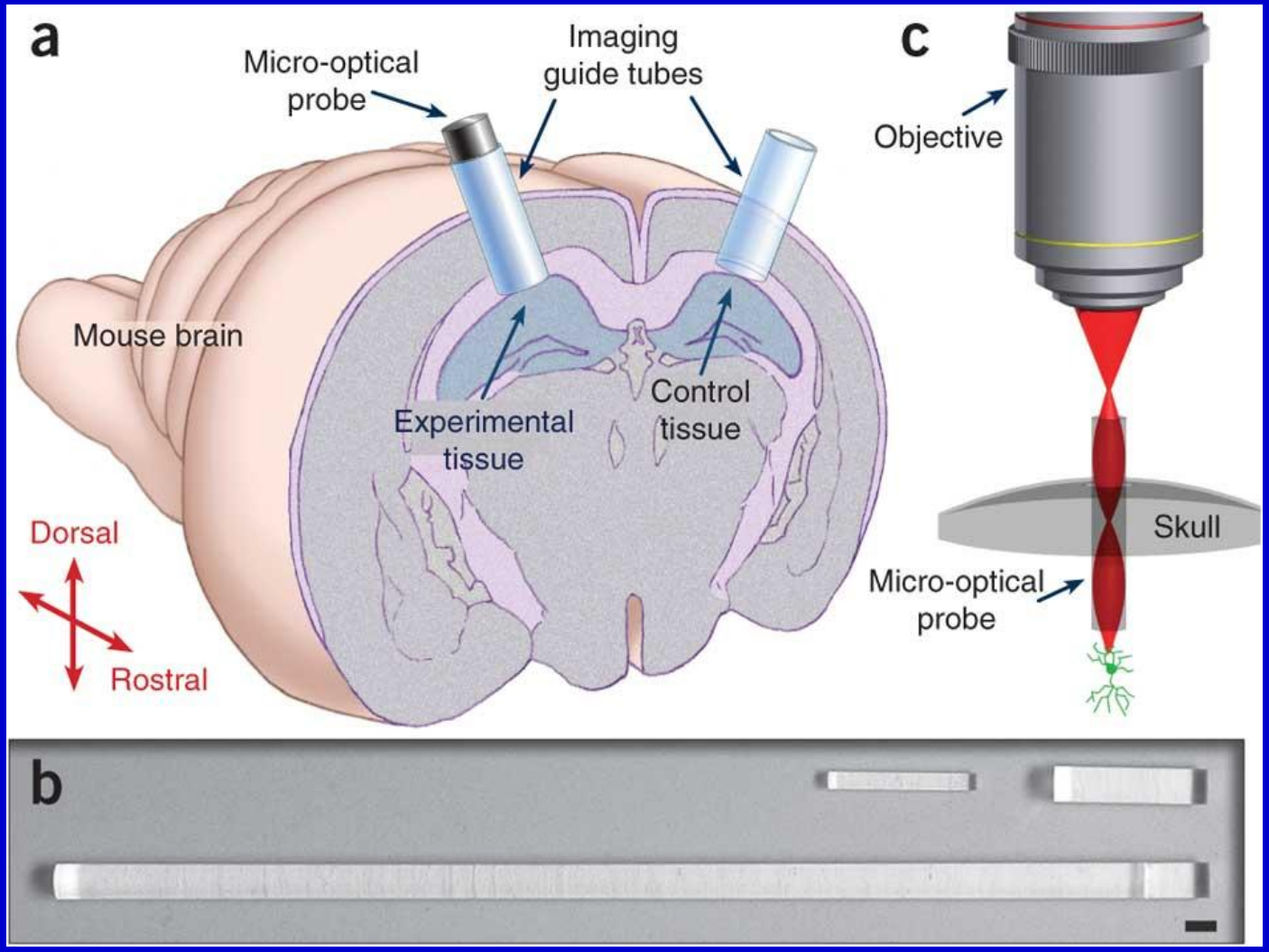
Day14

- Longitudinal imaging allows identification of changes in ensemble activity during learning

Imaging Circuits In Vivo

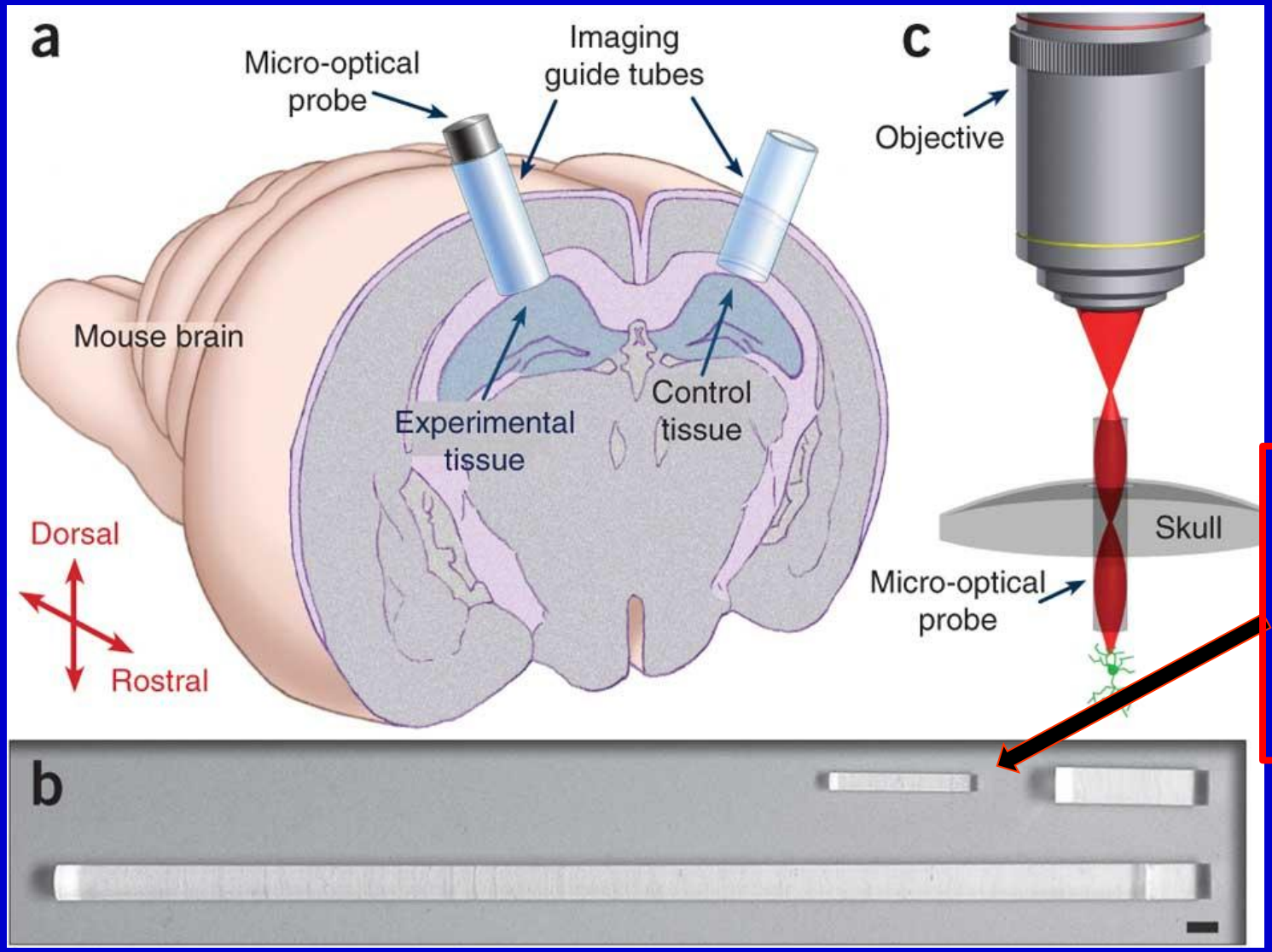


Looking Deeply Into the Brain



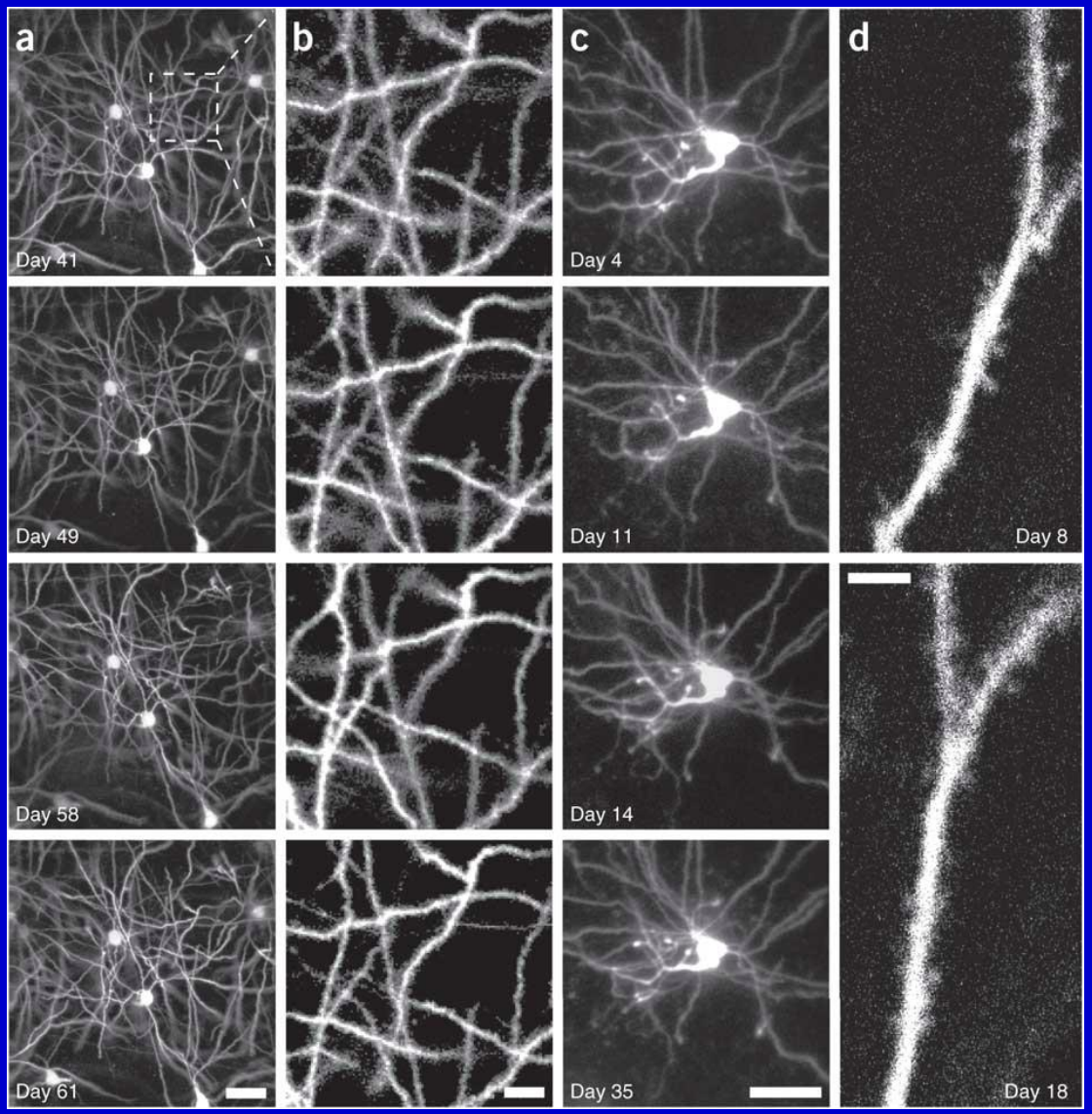
Mark Schnitzer and Colleagues

Looking Deeply Into the Brain



0.02 Inch Dia.

Imaging Circuit Structure Over Time



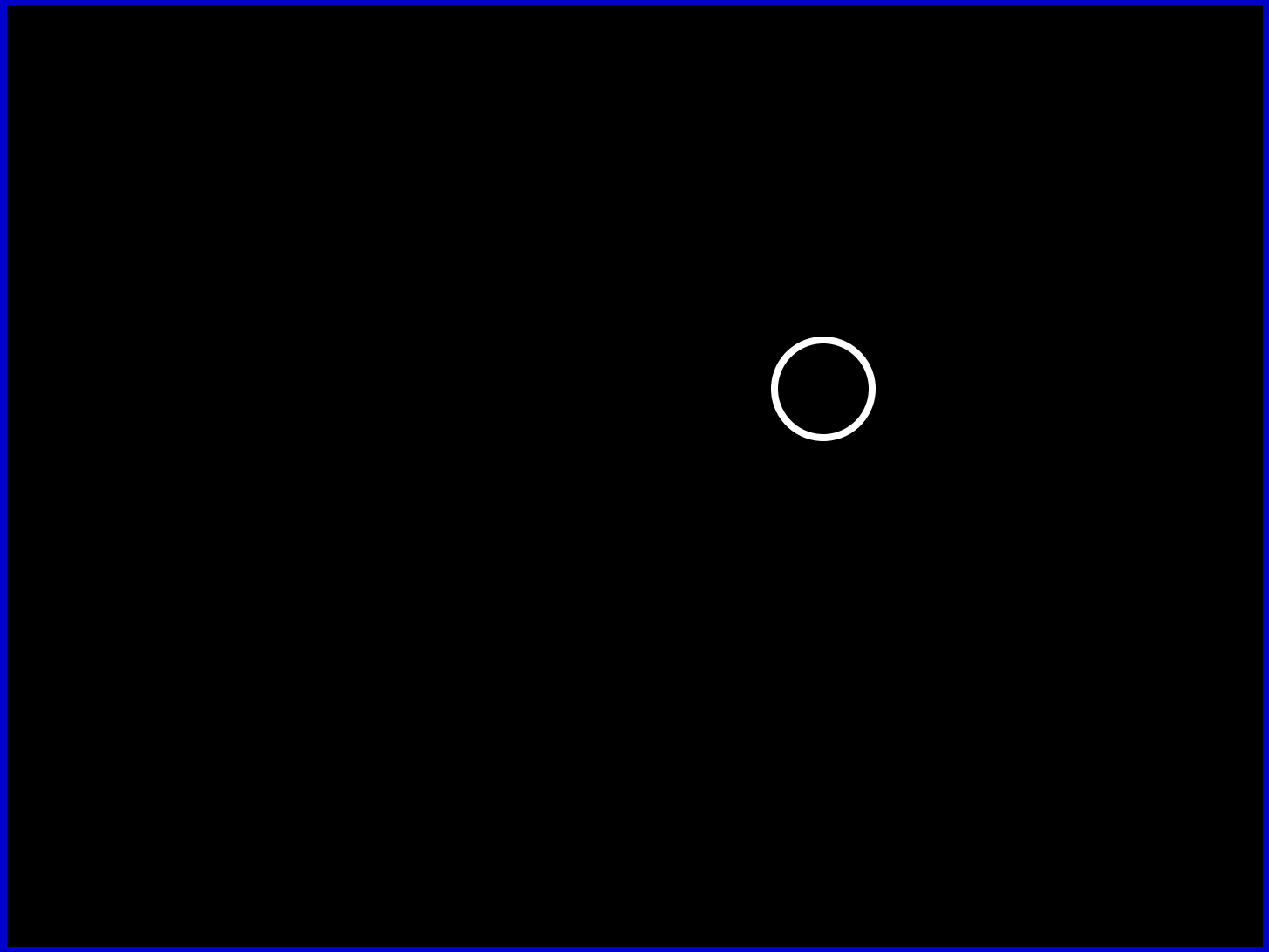
Mark Schnitzer and Colleagues

Real Time Measures of Blood Flow in Hippocampus

nm.2292-S3.mov

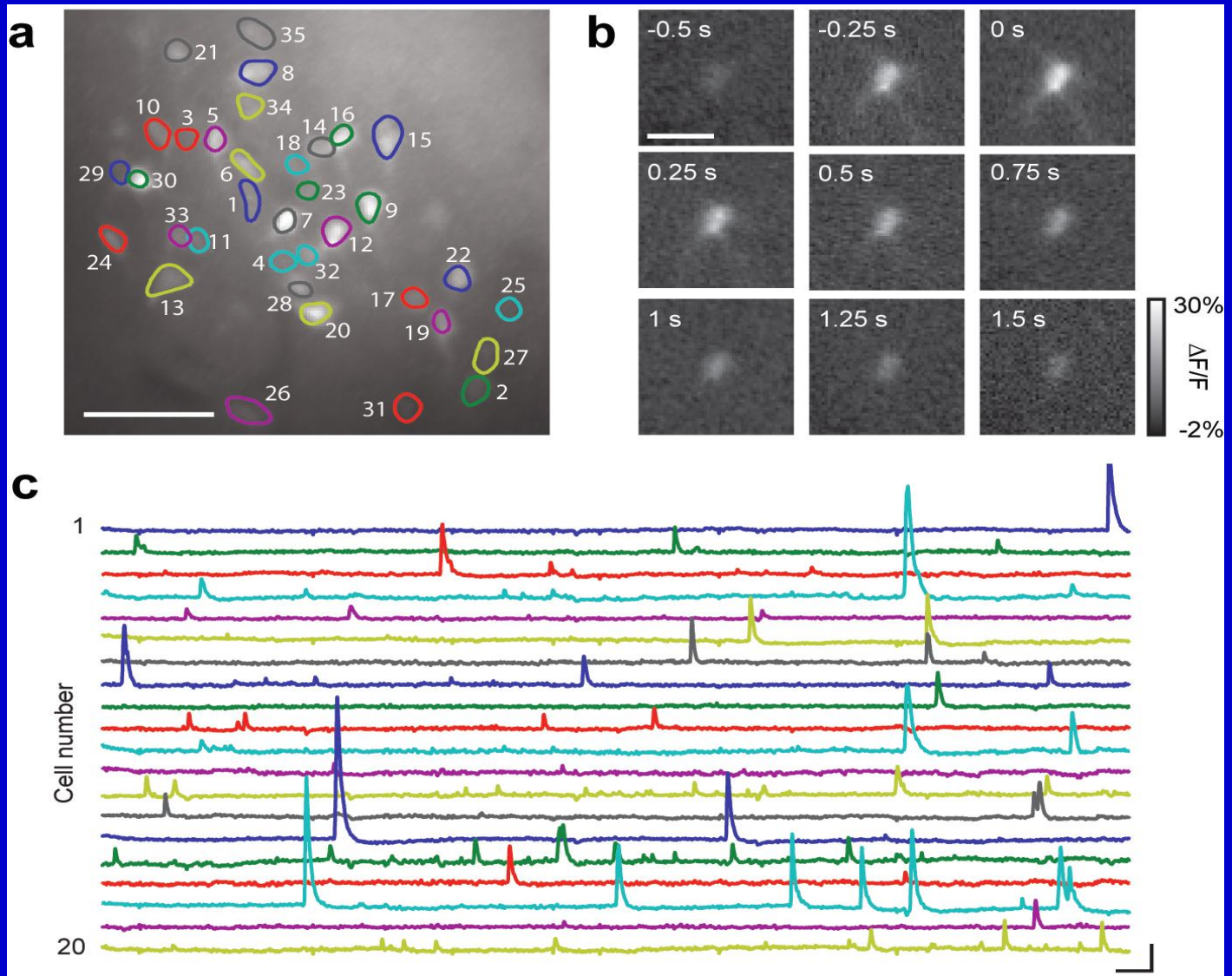
Mark Schnitzer and Colleagues

Imaging the Hippocampus Live



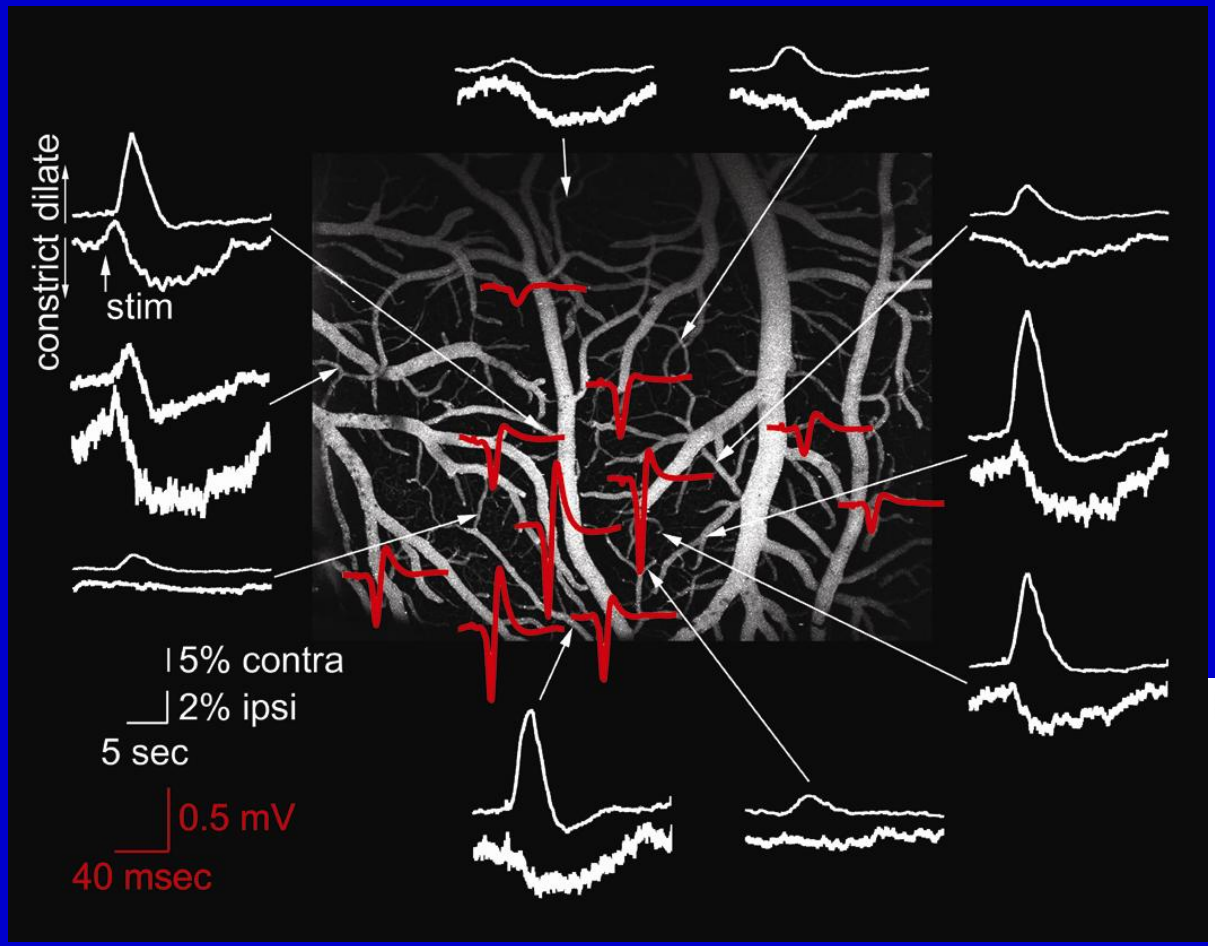
Schnitzer and Colleagues

Imaging Circuit Function Over Time

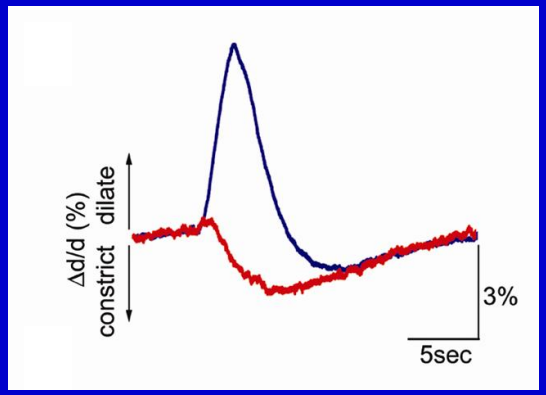


Schnitzer and Colleagues

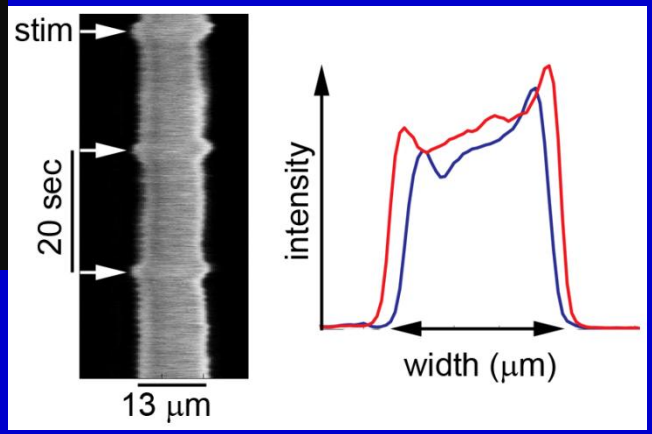
Exploring the Neuro-Vascular Link



Average



Line-scan

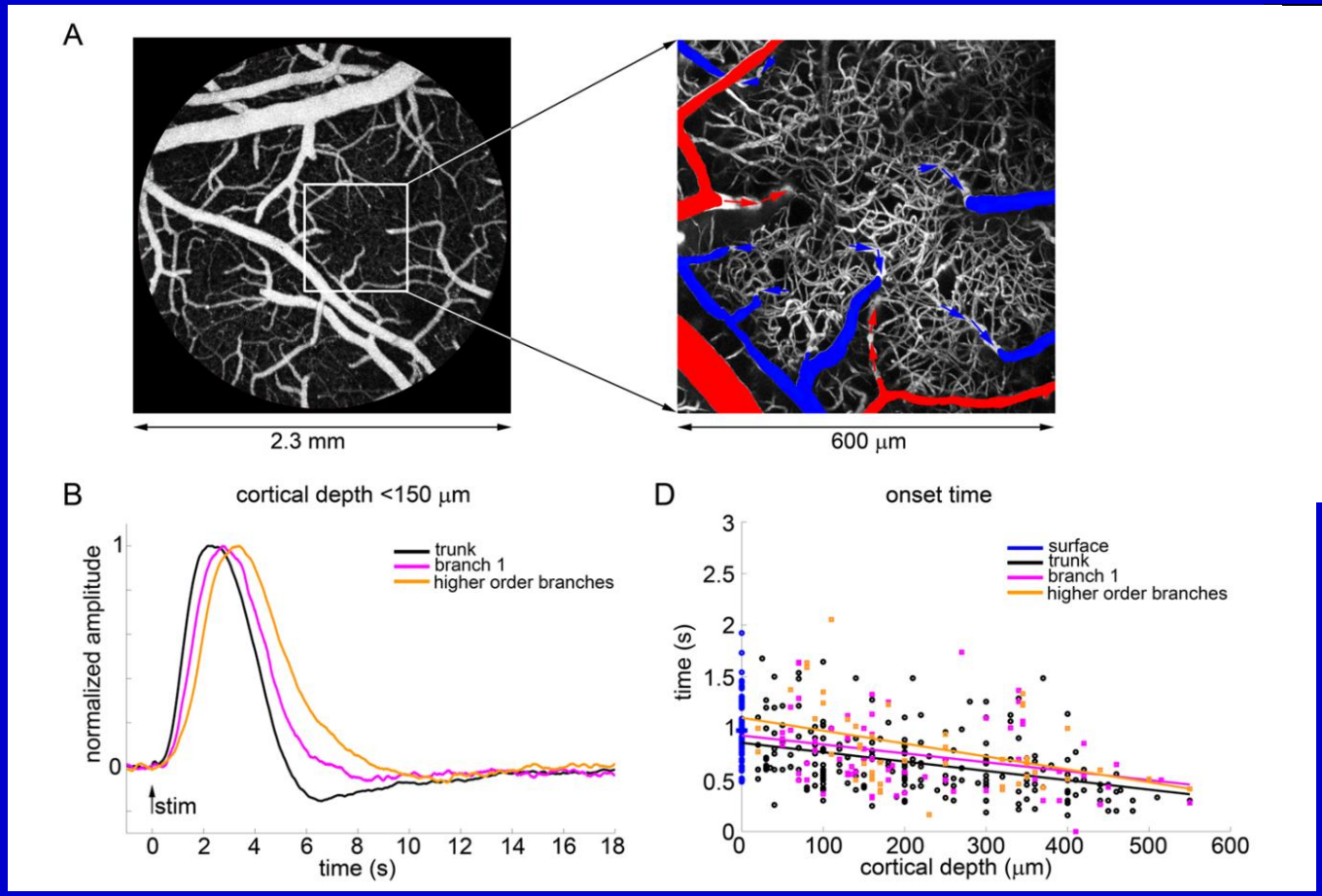


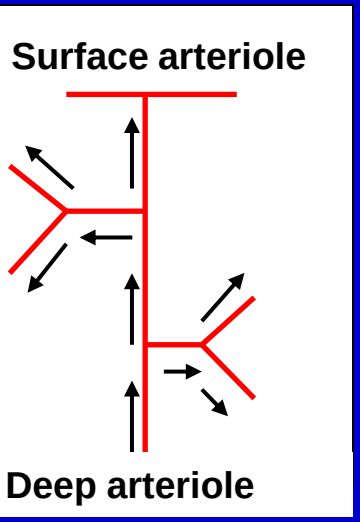
Neuronal excitation - *vasodilatation,*
Neuronal inhibition - *vasoconstriction*

UC San Diego
School of Medicine

Devor et al., JNeurosci 2007, 2008

Stimulus-Induced Vasodilation: Fast, Propagates Upstream along Trunks, Invades Lateral Branches



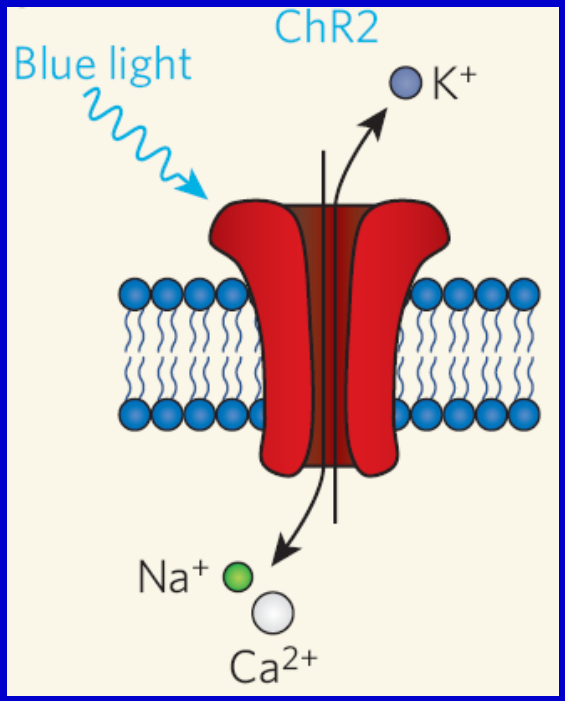


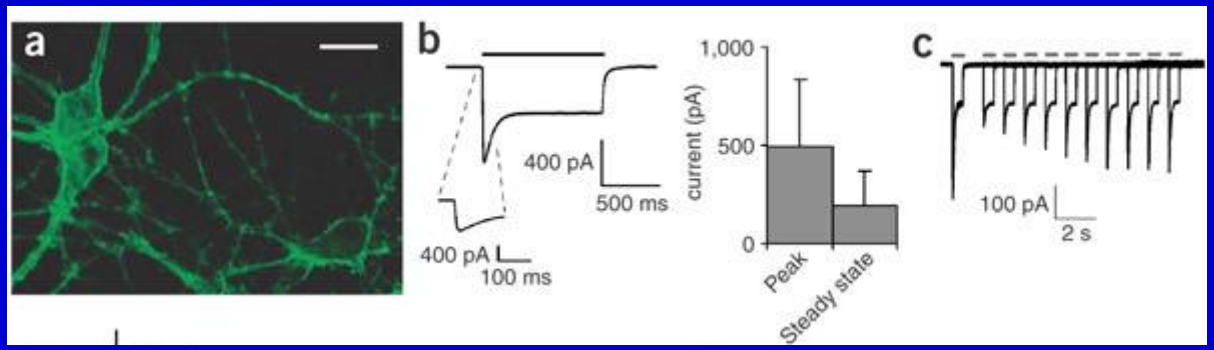
UC San Diego School of Medicine

Tian et al., PNAS 2010

Modulating Circuit Activation

Optogenetics – Allows millisecond-timescale, genetically targeted optical control of activity.

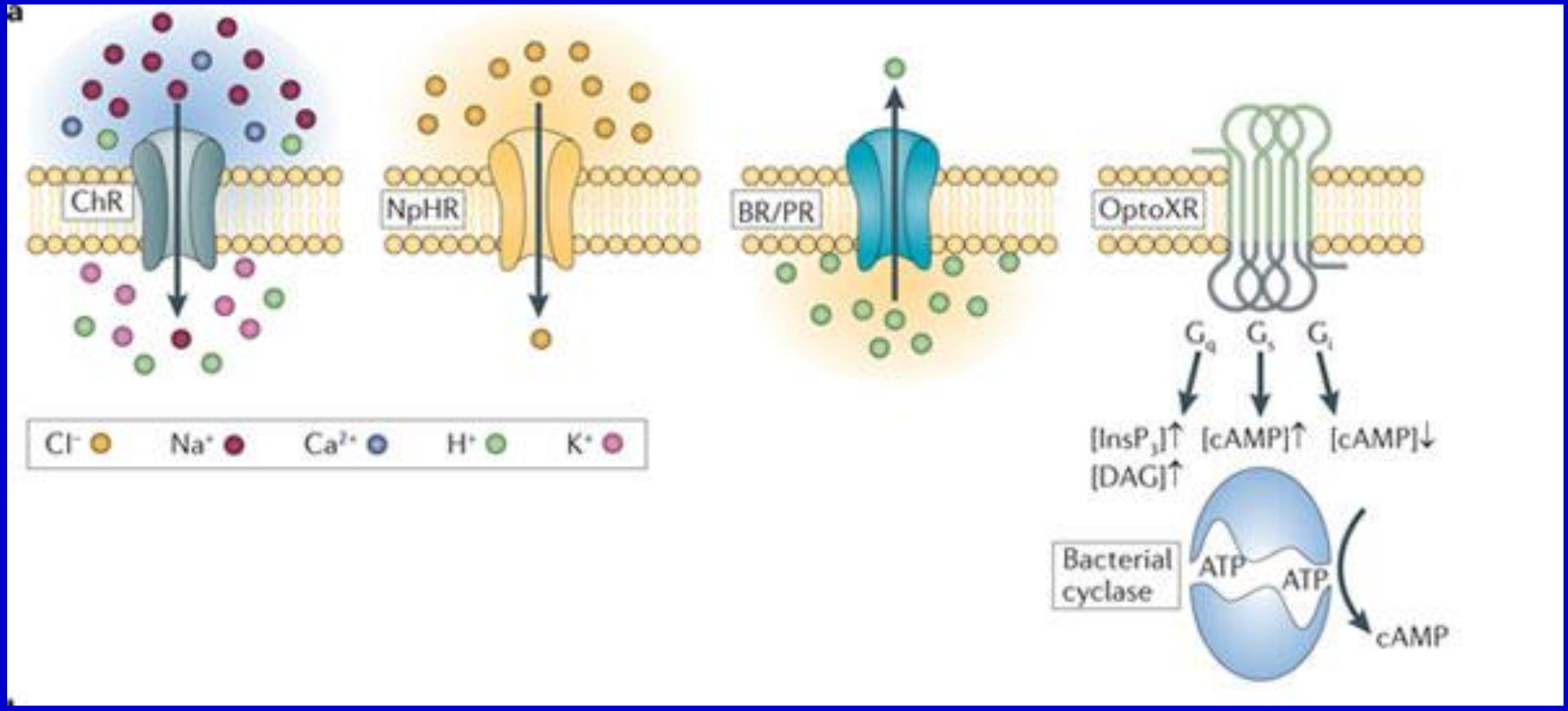




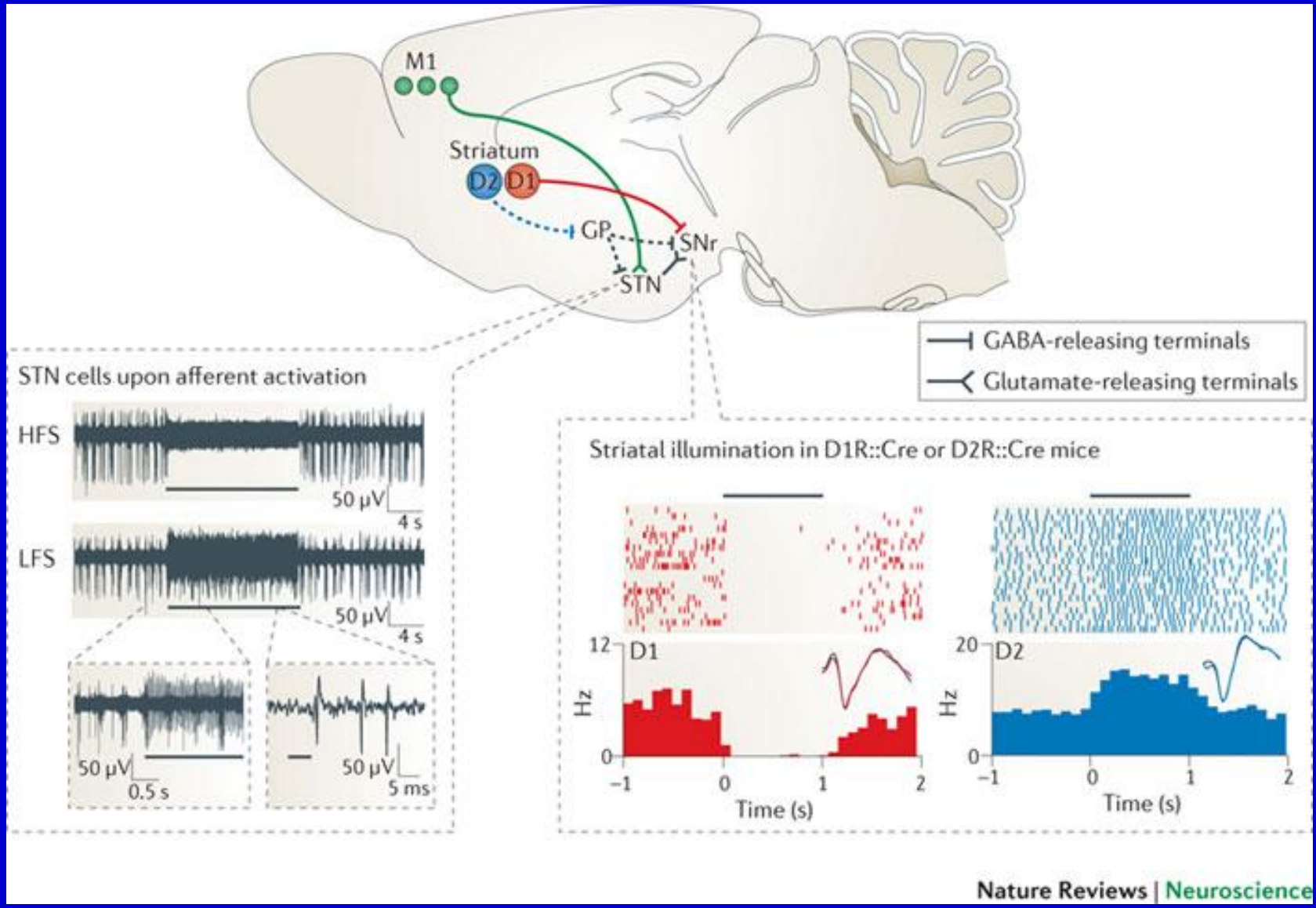
This tool enables light-driven control of neuronal firing within circuits with precise temporal and spatial resolution.

Karl Deisseroth and Colleagues

A Growing Toolbox for Optogenetics



Selectively Stimulating Circuits



Karl Deisseroth and Colleagues

Deciphering Circuits in Humans: Toward a World Without Human Brain Disorders

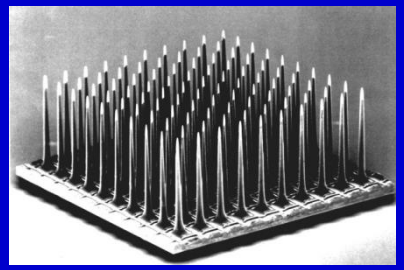
Basic Science Research Promises to:

- Help understand normal human brain function
- Inform us about human brain disorders
- Teach us how to diagnose brain disorders
- Provide insights needed to treat them, and
- Ultimately, allow us to prevent them

But What About Tools for Human Studies?

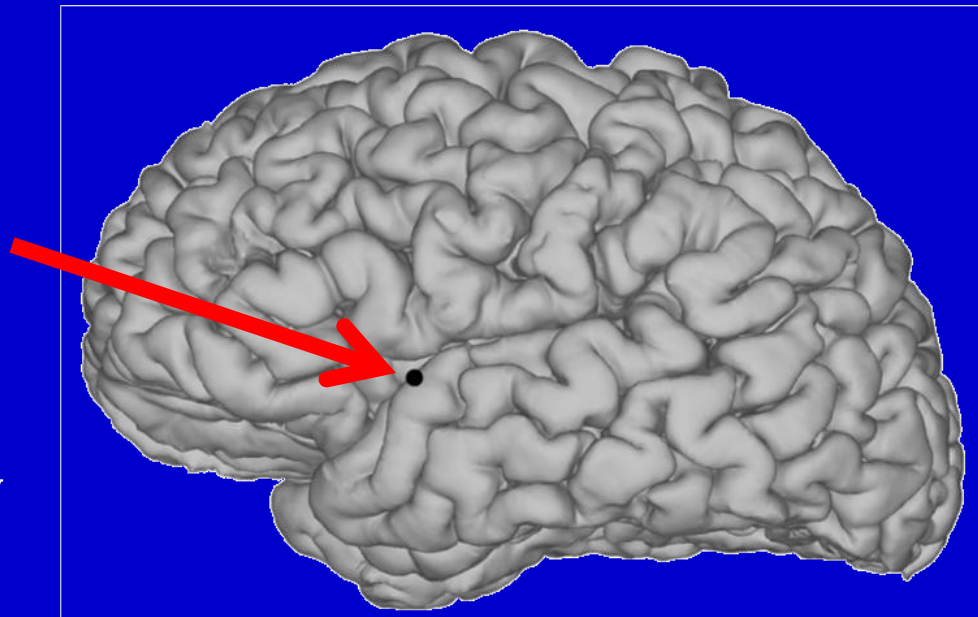
Speech Processing in Humans

- What is the locus of speech processing?
- Role of anterior superior temporal lobe?
- What features do single units encode?
- Do phonemes exist as constructs?

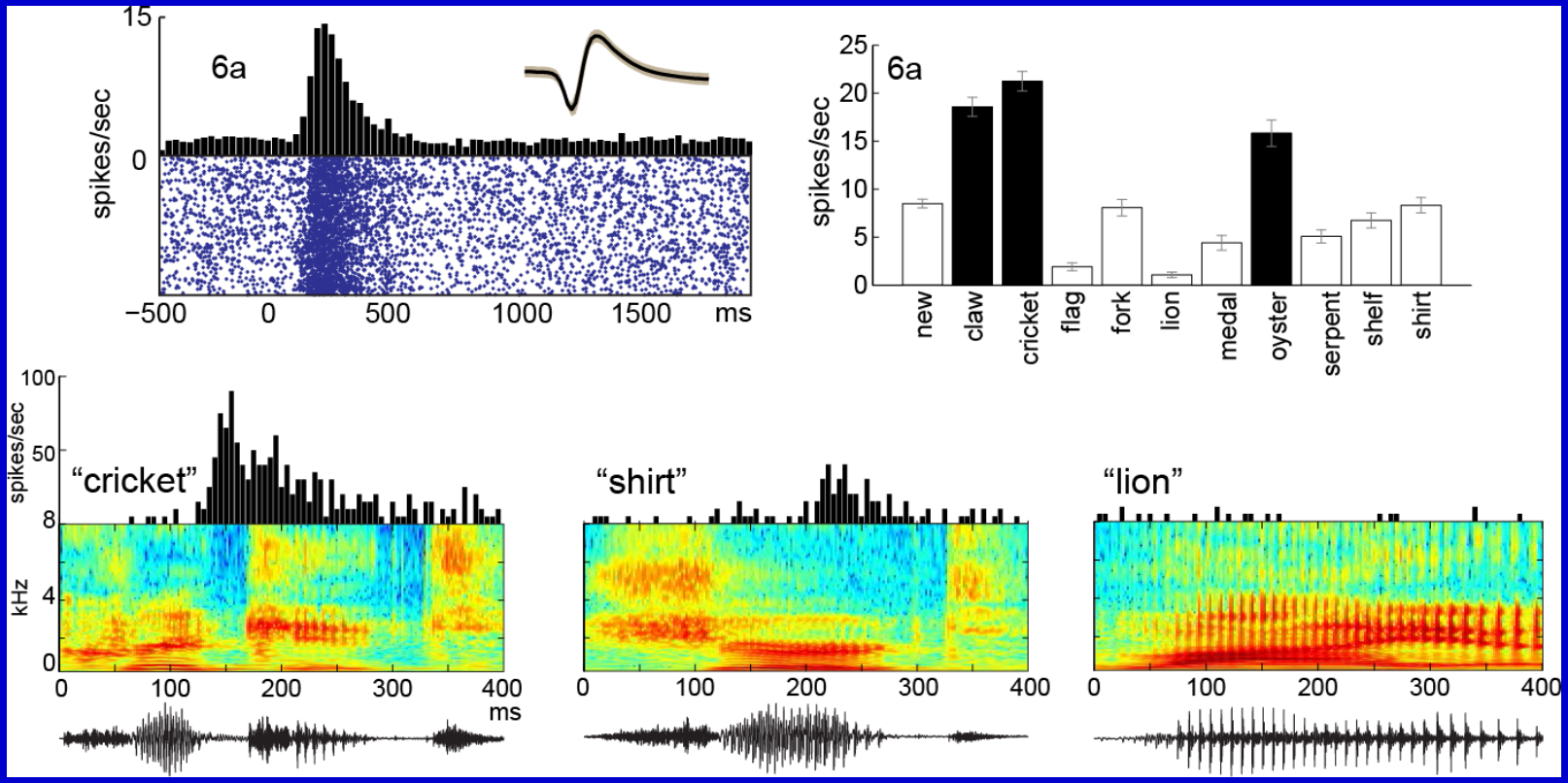


2mm

Electrode Array

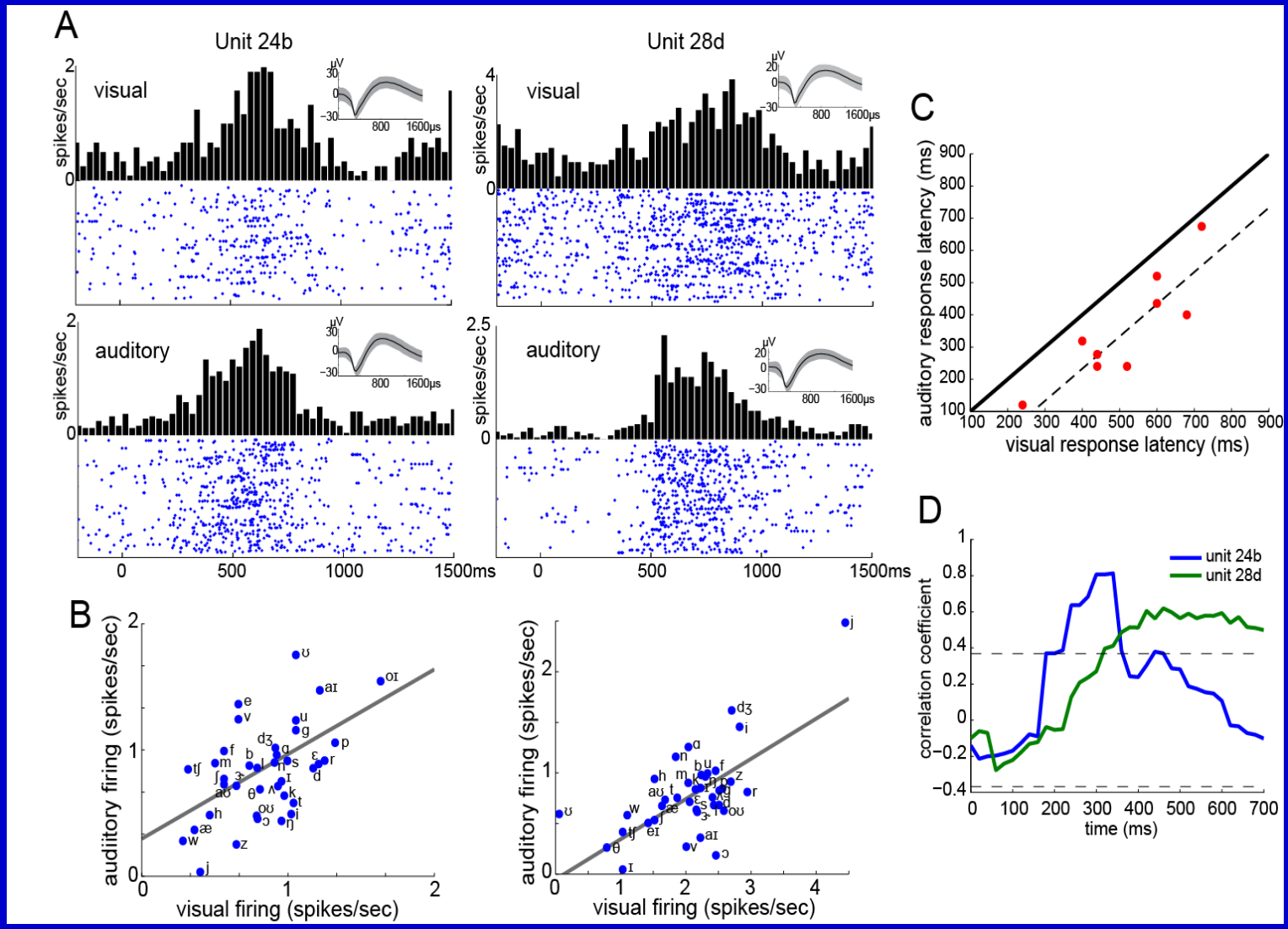


Single Units Fire to Specific Words



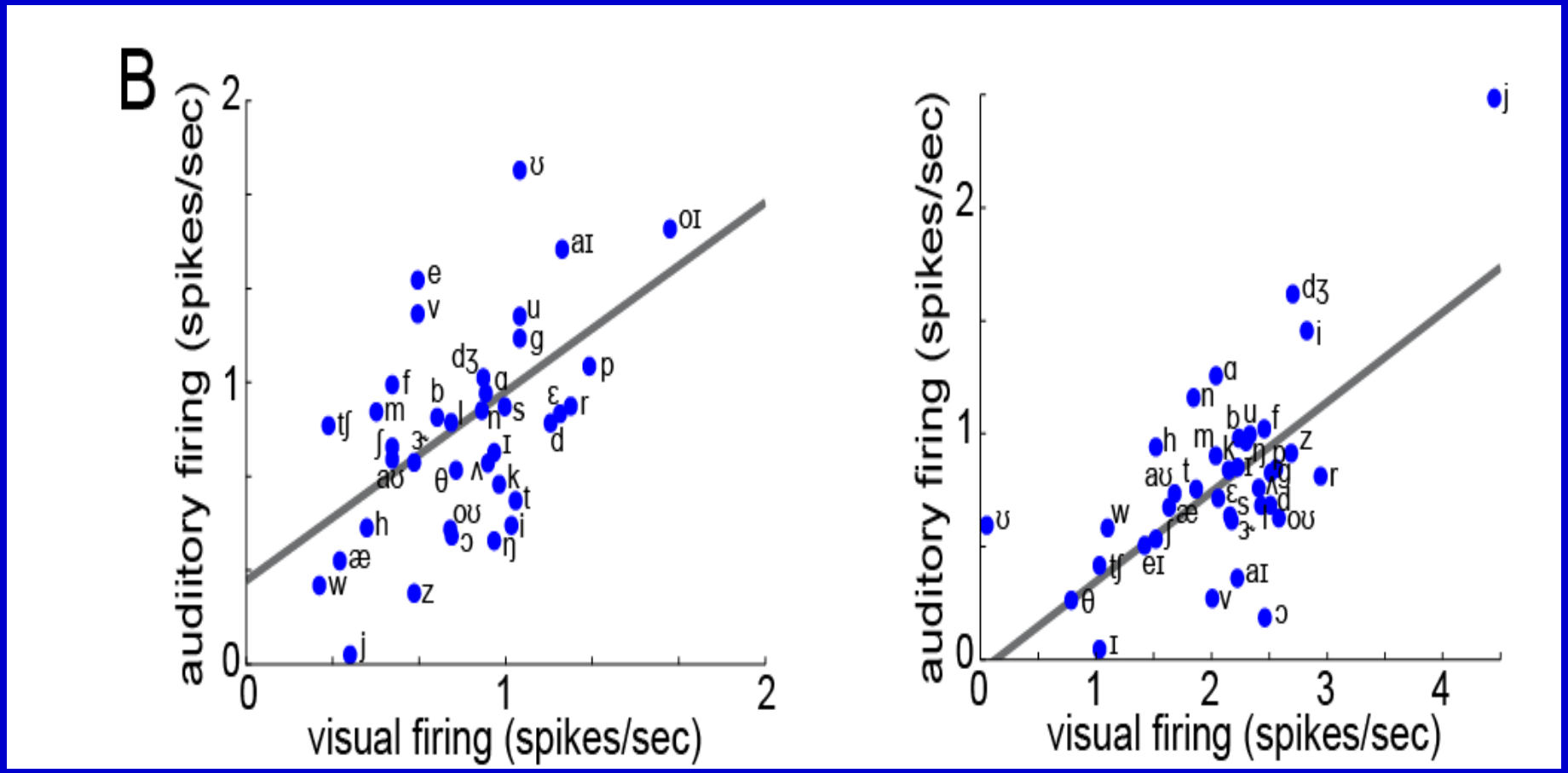
Chan et al. (2012) *in preparation*

Single Units Fire to Specific Phonemes and its Associated Letter



Chan et al. (2012) *in preparation*

Single Units Fire to Specific Phonemes and its Associated Letter



Chan et al. (2012) *in preparation*

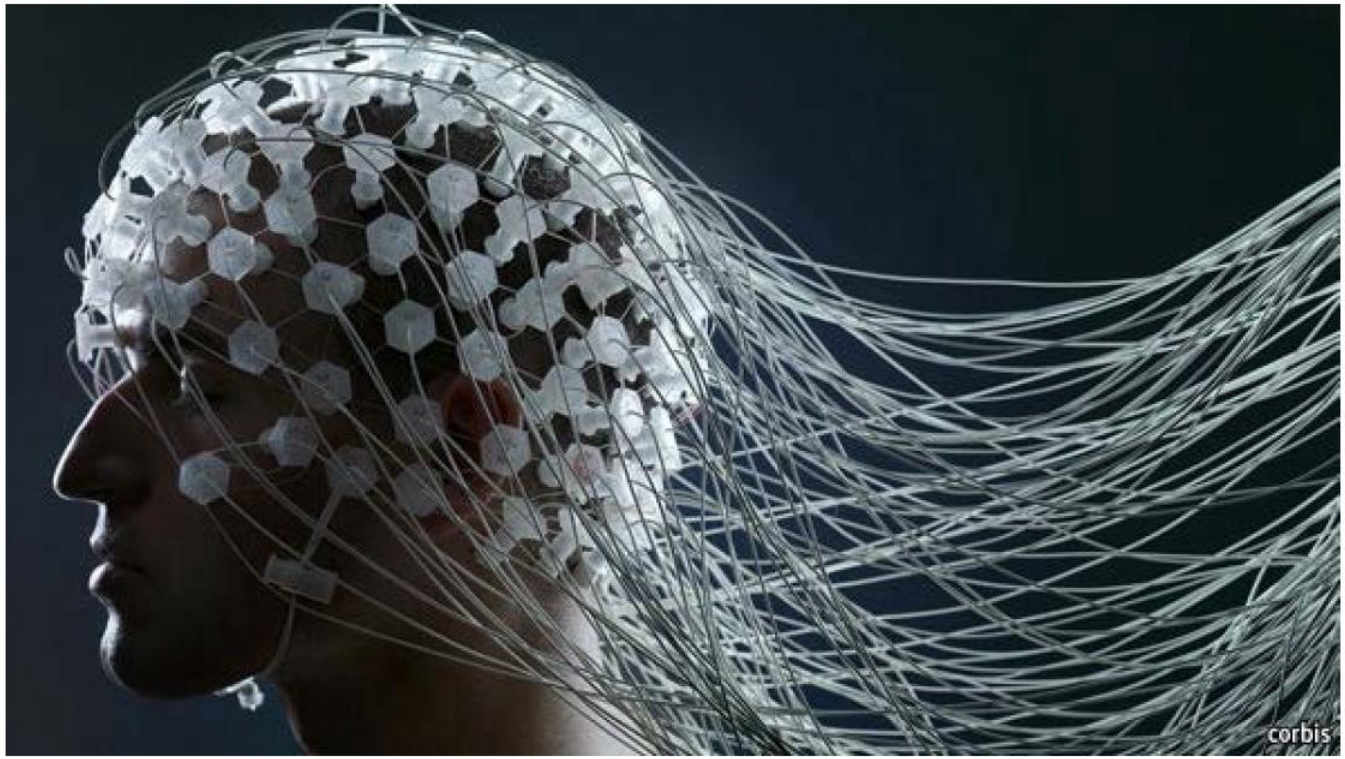
The Economist

Brainwave controllers

Put your thinking cap on

Consumer electronics: Once the stuff of fables, hoaxes and science fiction, controlling things via thought alone is fast becoming a reality

Sep 3rd 2011 | from the print edition



The Economist

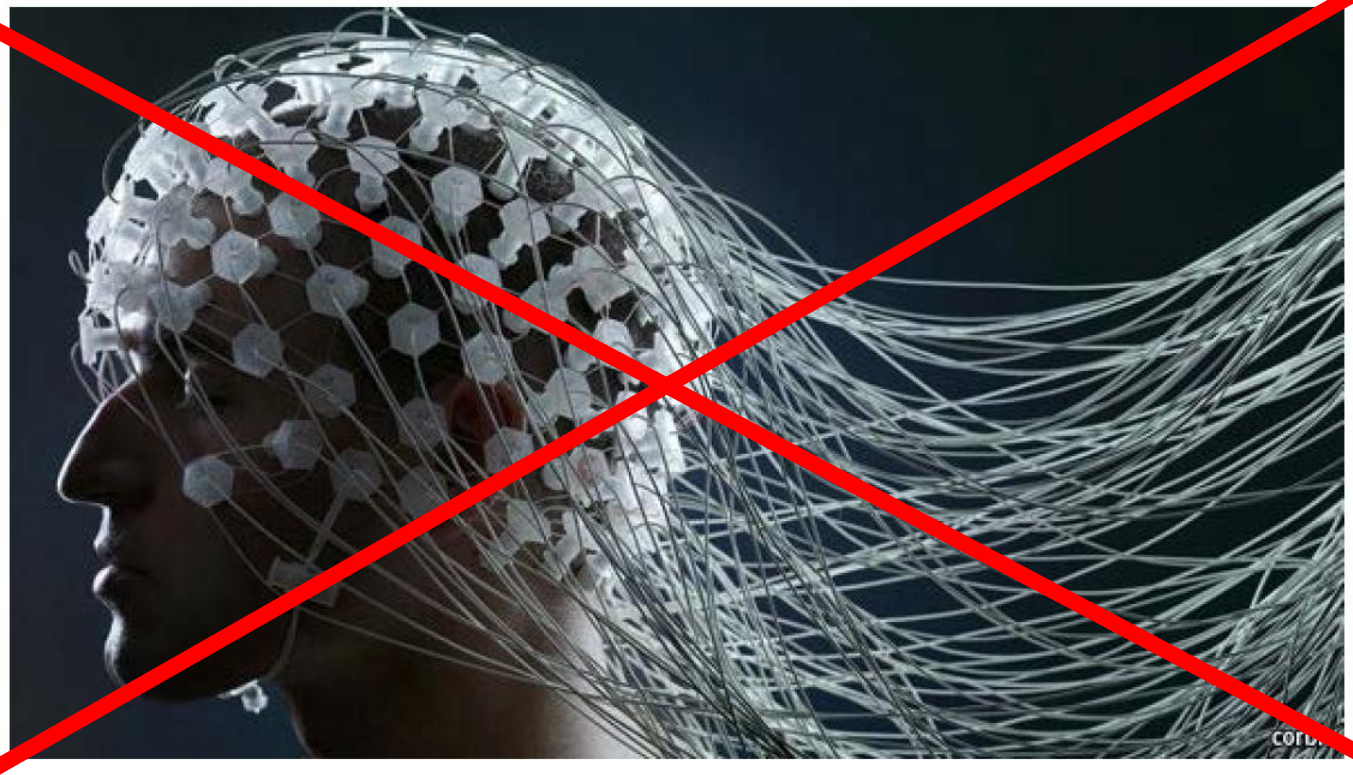
Technology Quarterly: Q3 2011

Brainwave controllers

Put your thinking cap on

Consumer electronics: Once the stuff of fables, hoaxes and science fiction, controlling things via thought alone is fast becoming a reality

Sep 3rd 2011 | from the print edition



Watching Brain Connectivity- Live

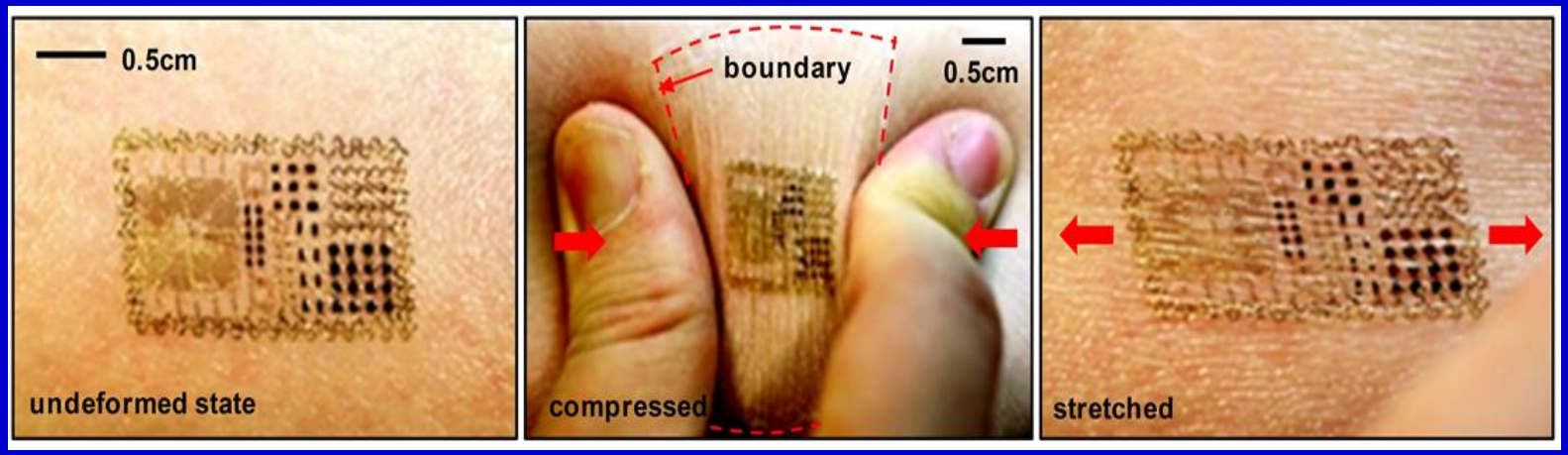
The Economist

Brainwave controllers

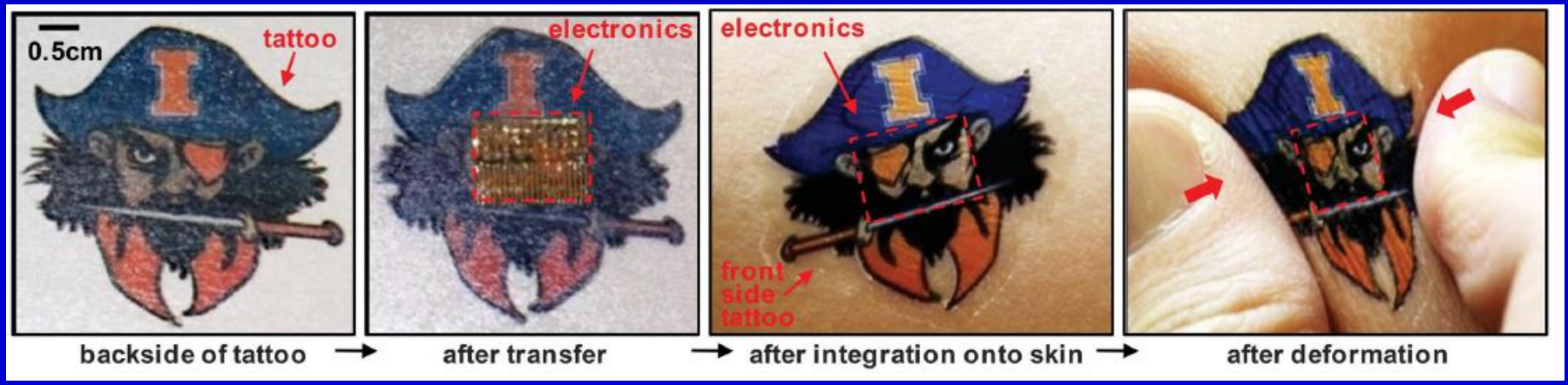
Put your thinking cap on

Consumer electronics: Once the stuff of fables, hoaxes and science fiction, controlling things via thought alone is fast becoming a reality

Ultra-thin, Ultra-light, Flexible Electronics

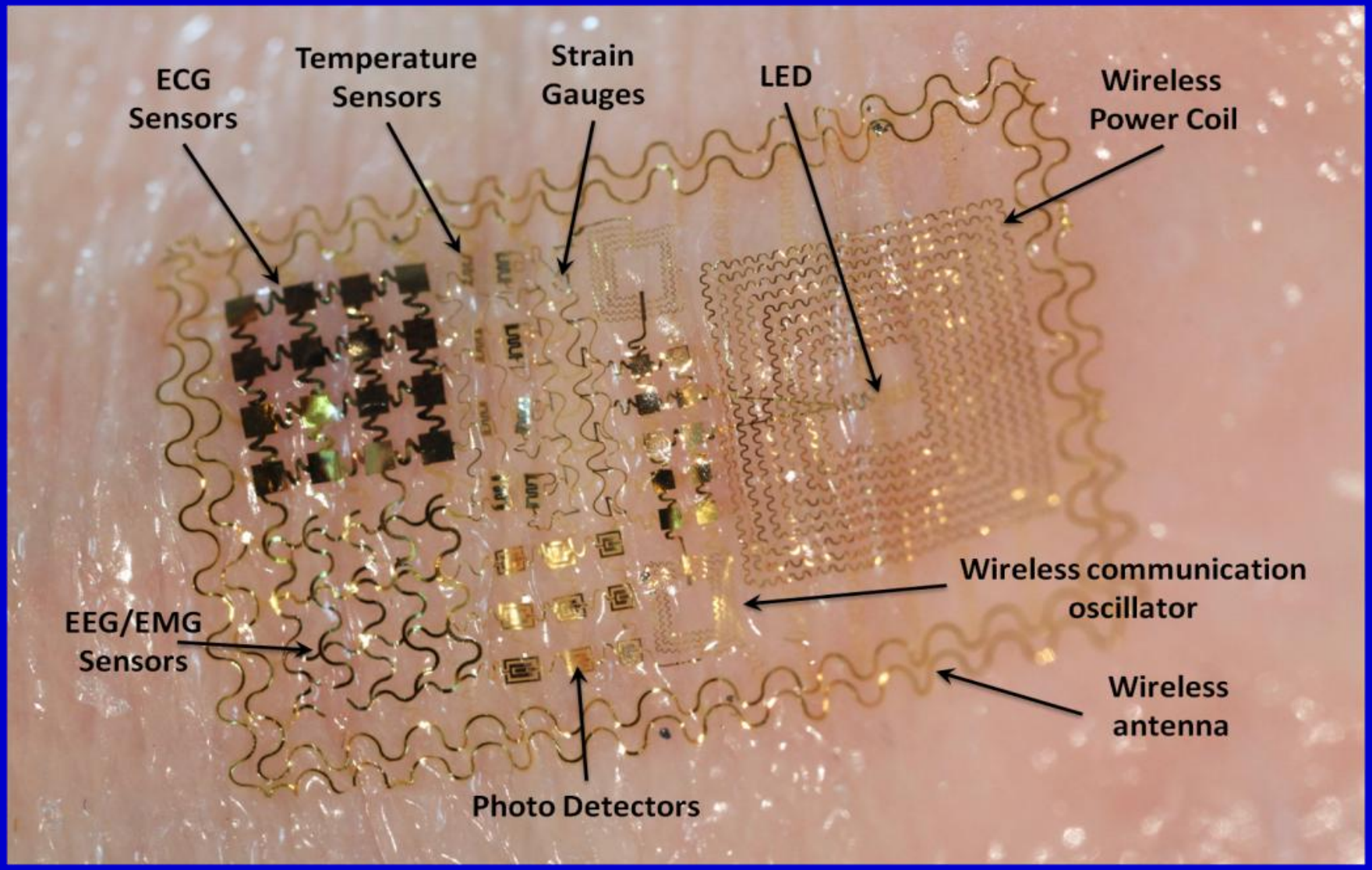


'electronic temporary disposable tattoo'



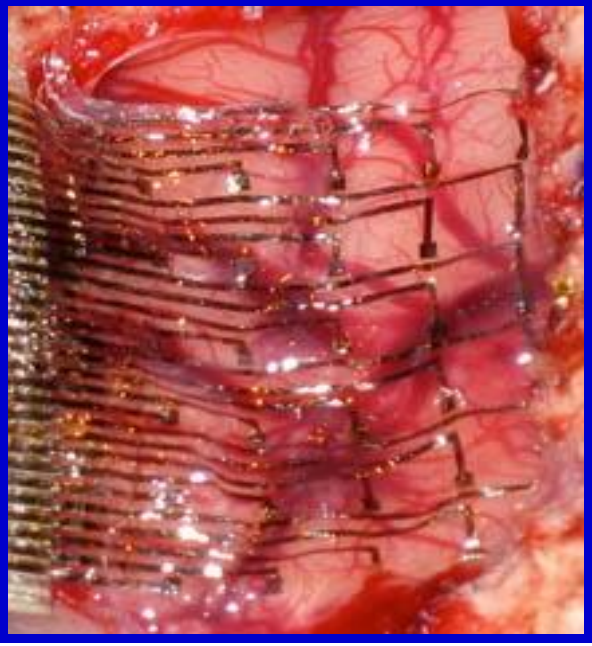
Kim et al., Science, 2011

A Sensor with Many Capabilities

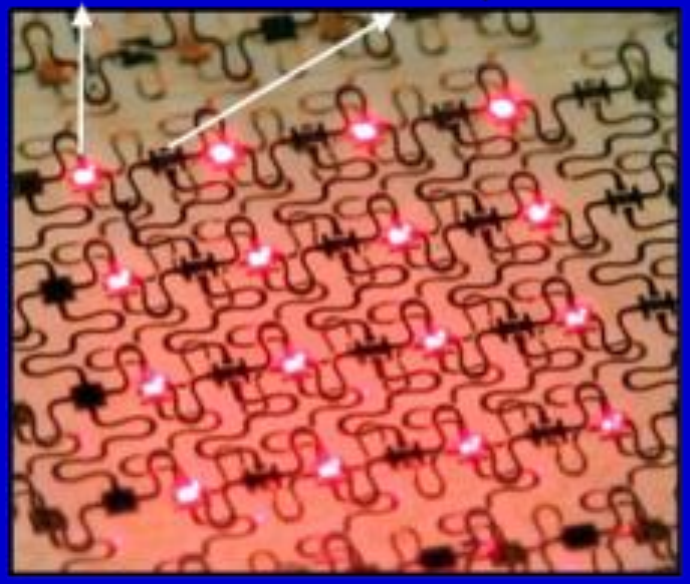


Kim et al., Science, 2011

New Directions:
Beyond Skin and Beyond Sensing



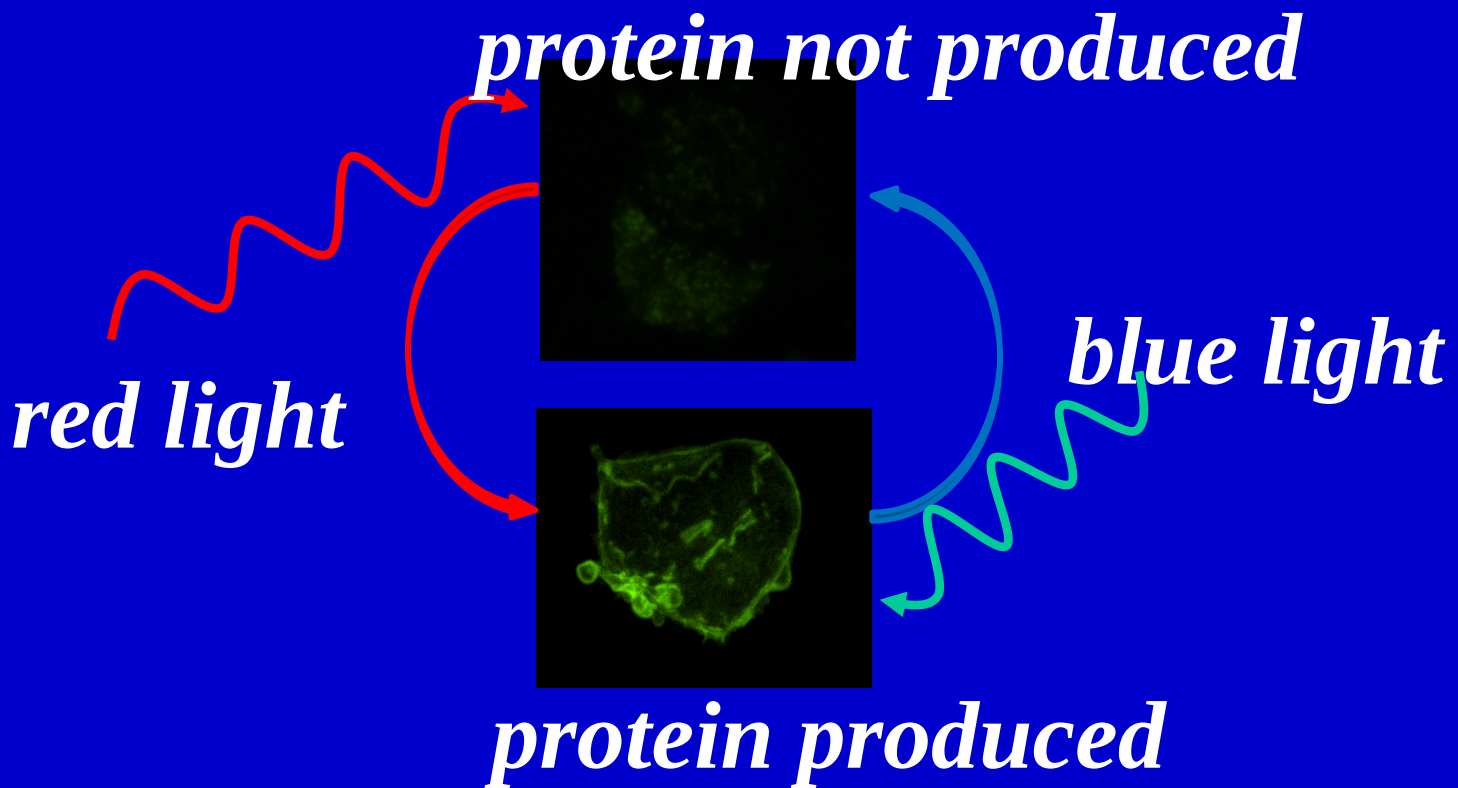
Directly Applied to
the Brain Surface



Integration of LEDs
of multiple colors

Todd Coleman and Colleagues

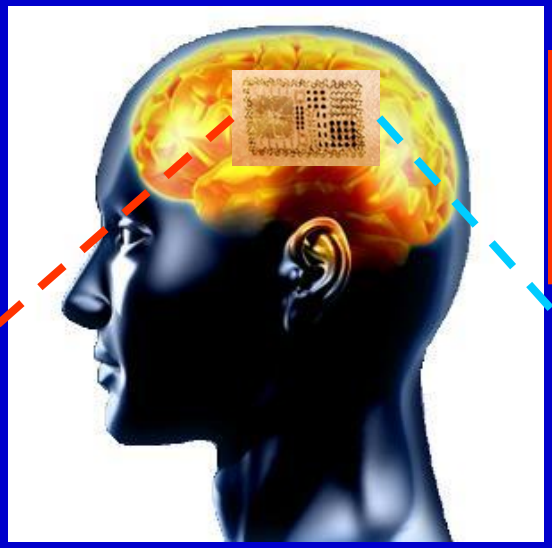
Future Use of Sensors to Modify Neurons and Circuits?



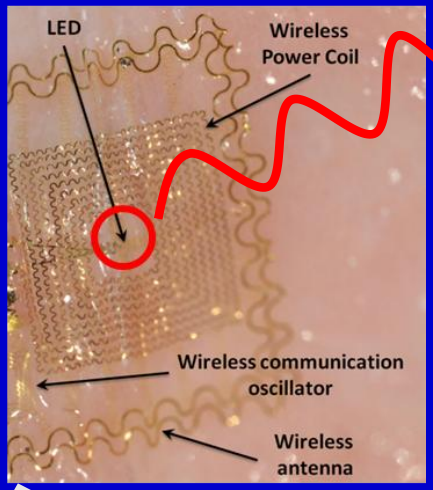
Recent Results in Culture: Todd Coleman and Colleagues

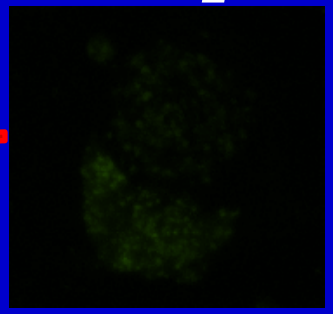
A Tool to Modify Brain Function?

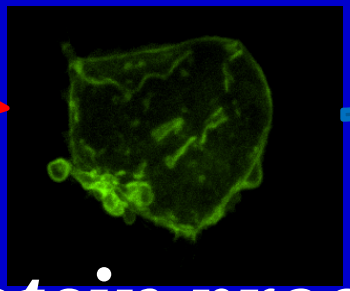
Start/stop delivery

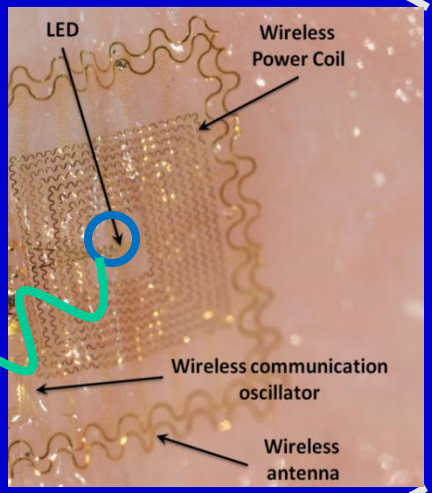


protein not produced







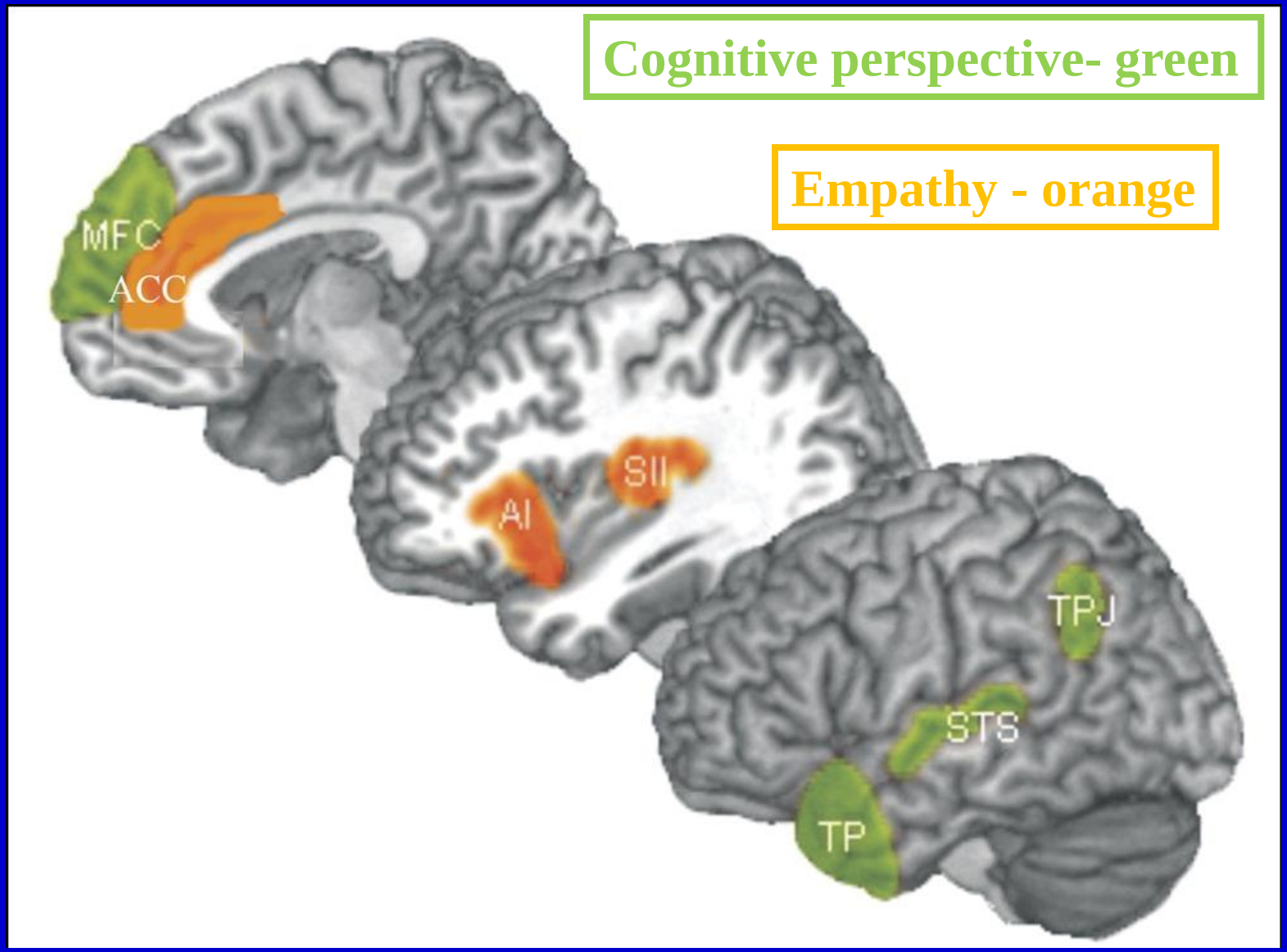


protein produced

Basic Science Advances Are Key to Success in Helping People

- **In the next 20 years we could**:
  - Define the genes responsible for normal brain function
  - Detail the many circuits responsible for most aspects of brain function
  - Define the molecules that mediate essential aspects of brain function
  - Create tools that allow us to understand the fundamental causes of neurological disorders, and
  - Apply these insights to alleviate or prevent suffering in millions of Americans

Exploring the Neural Basis of Empathy



Hein and Singer, Curr Opin N'biol, 2008

To Understand The Brain Is The Most Important Human Undertaking

We Can Transform Our World If We Decipher How The Brain Receives, Processes And Acts Upon Information