Summer Workshop on the Dynamic Brain

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&
Christof Koch, Allen Institute for Brain Science

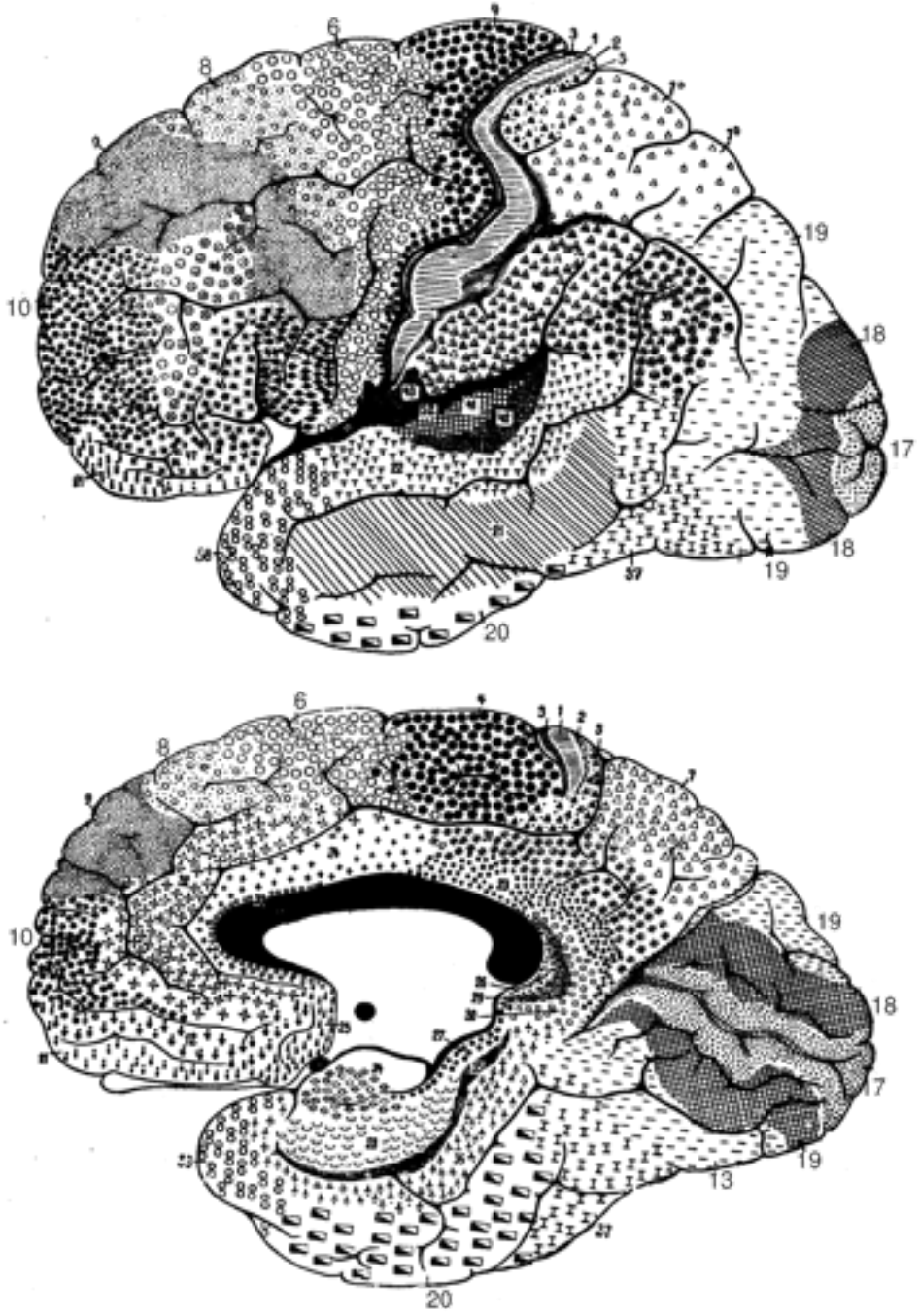
Course Directors

August 25th 2014

A Rapid Sensory-Motor Behavior

Computing in the Brain

- Six million cone photoreceptors, each modulated up to 25 Hz with a signal-to-noise ratio of 100 (< 7 bits) --> Process ca. 10^9 bits/sec of visual information (Pitkow & Meister 2014)
- 50 words/min typing, 6 letters per word, 2 bits/entropy per letter in English --> Generate ca. 10 bits/sec of motor information (Pitkow & Meister 2014)
- Highly trained visuo-motor routine (Logan & Crump 2009)
- The same visuo-motor system can be rapidly deployed to ride a bike, pick up a fork and eat, or recognize Jennifer Aniston
- All done with $86 \cdot 10^9$ neurons, firing about 10^{12} (trillion) action potentials/sec
- How does this happen? How is the brain so flexible? How can the brain rapidly learn? How is intelligence instantiated?



Brodmann's Areas

My cortico-thalamic system

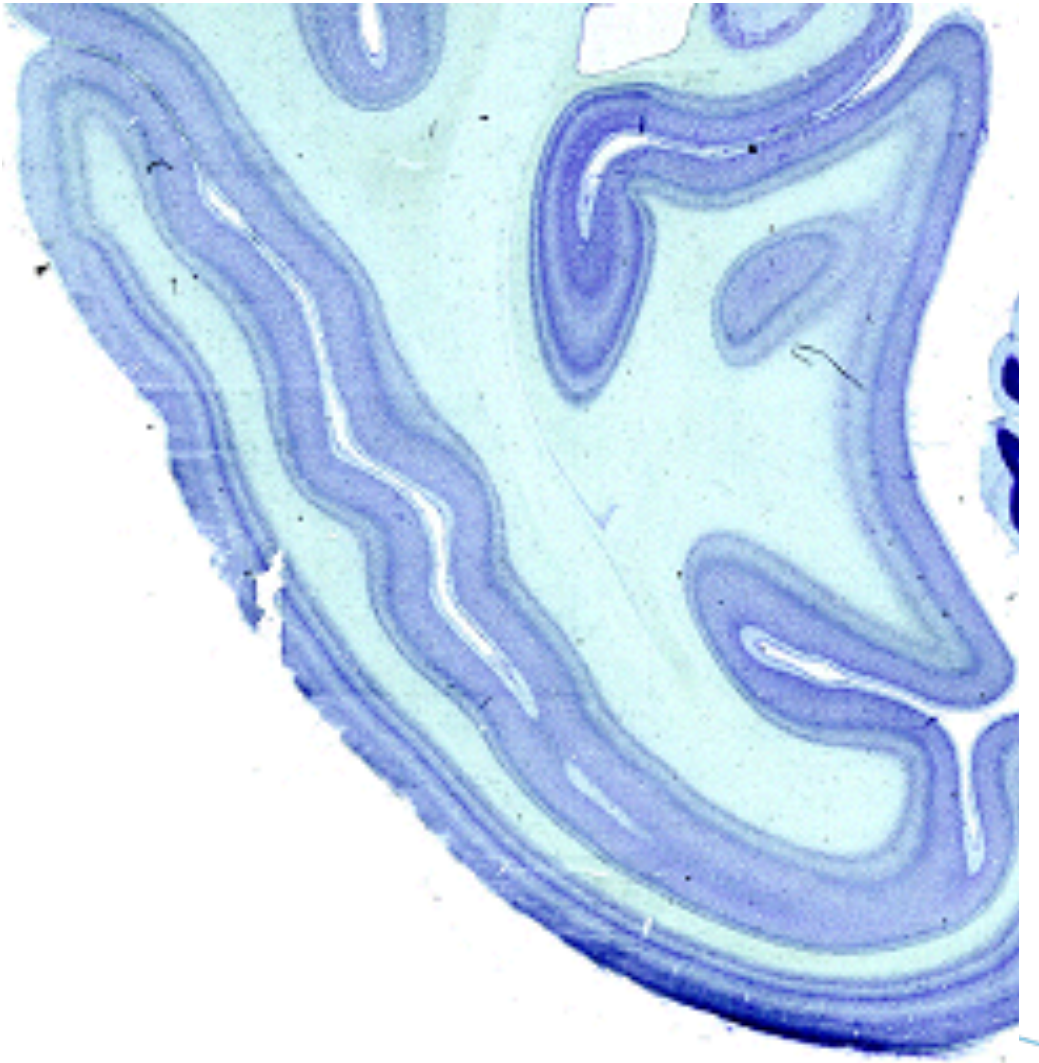
Human Neocortex
Some Numbers to Remember

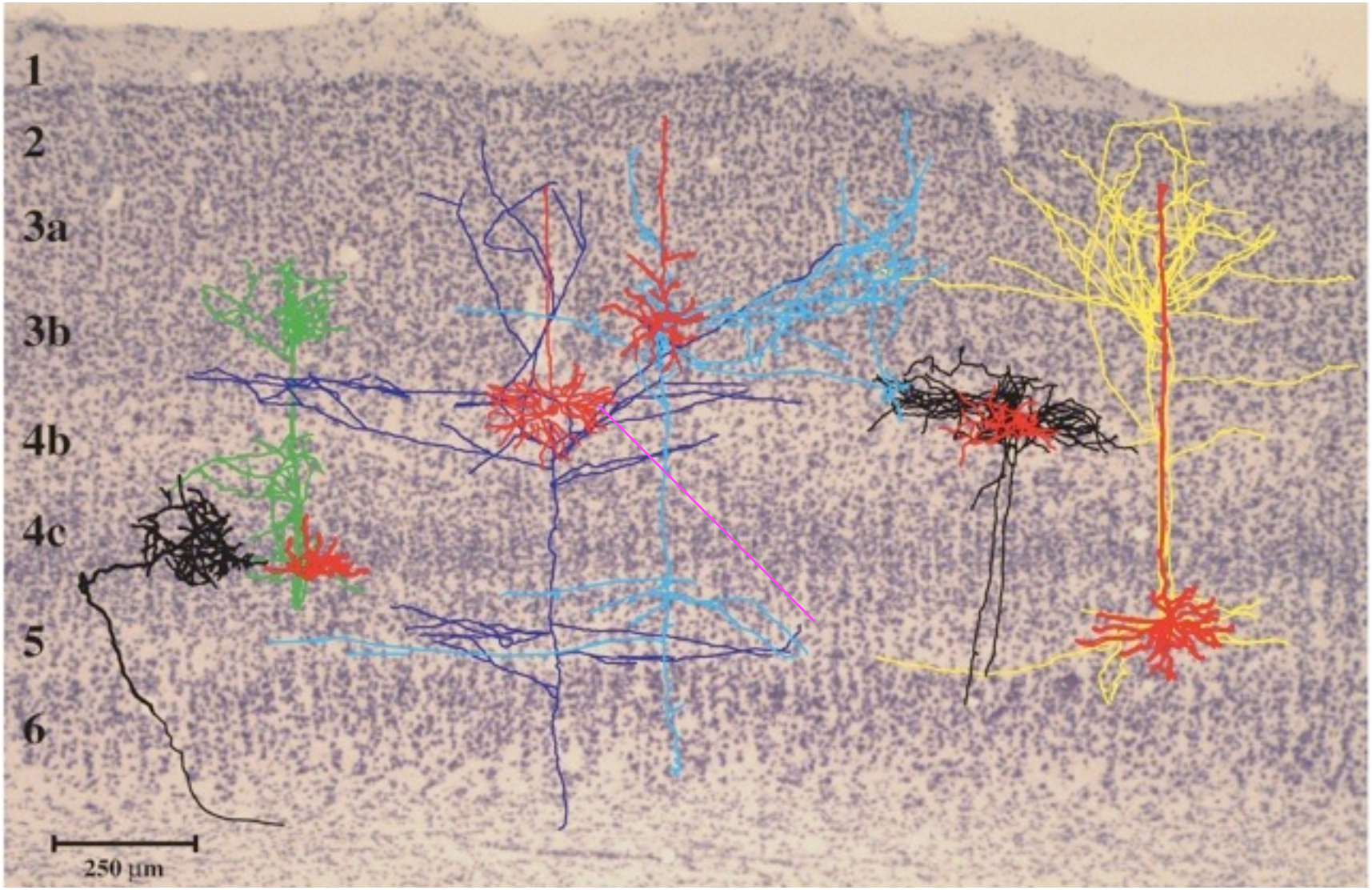
- 1,500 +/- 300 grs (4 brains)
- 86 +/- 8 Billion NeuN cells (range 79 - 95 B) and 85+/- 10 non NeuN cells
- Cortex - 16 +/- 2 B neurons (19%)
- 69 +/- 7 B cerebella neurons
- < 1% of neurons in the remainder (basal ganglia, diencephalon, brainstem)
- Cortex consist of two 2-3 mm thick sheets, 35 cm in diameter
- Estimated cortical cell density of ca 100,000 /mm^2
- Estimated 200 trillion synapses in cortex

S. Herculano-Houzel

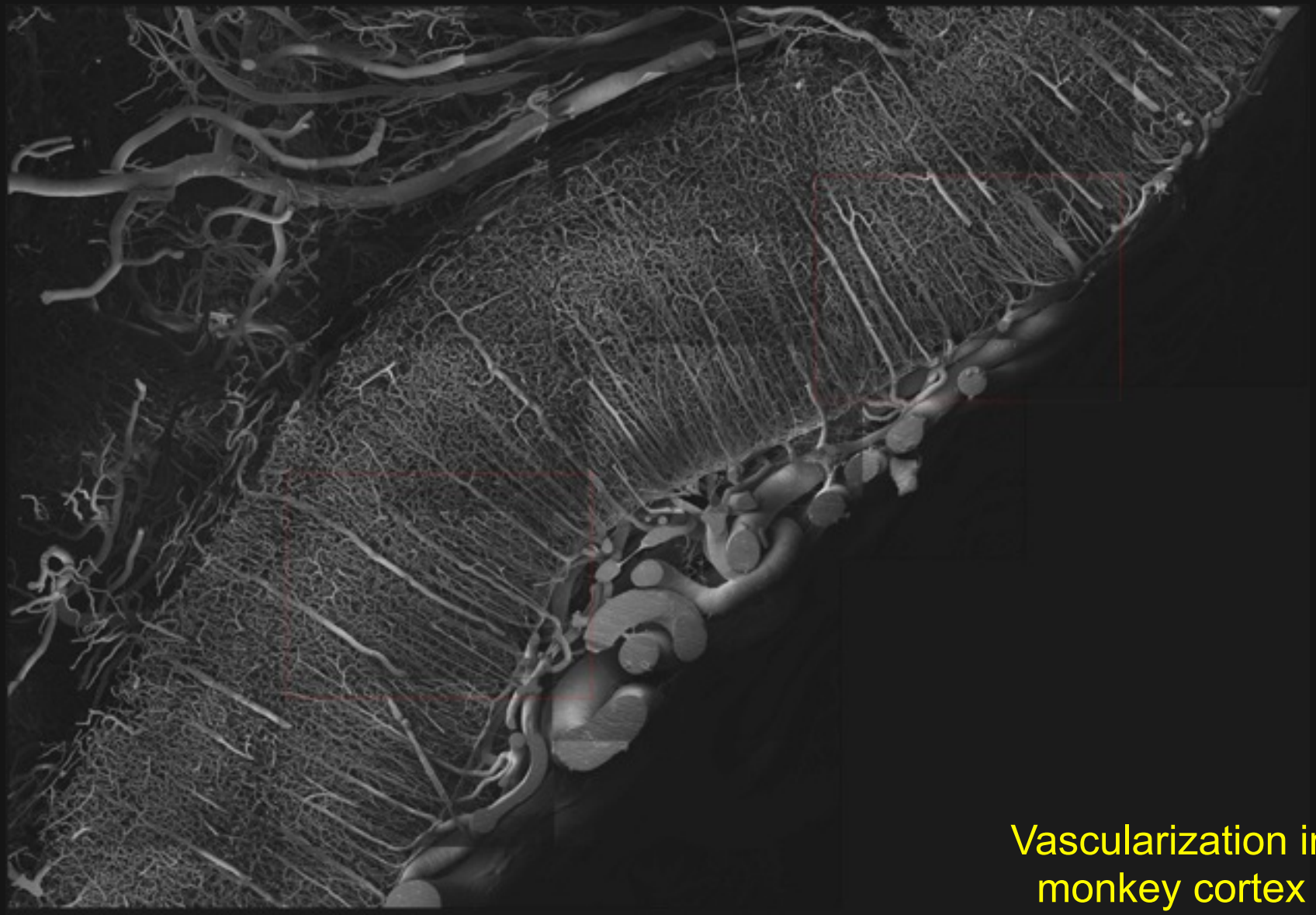
Why Study Neocortex?

- Cortex is a planar 2+e-D computational tissue
- Varies 10^5 in surface areas across mammals
- Relative uniformity (translation invariant) across cortical surface
- What is the canonical, columnar operation performed by cortex that makes natural intelligence so robust and flexible?

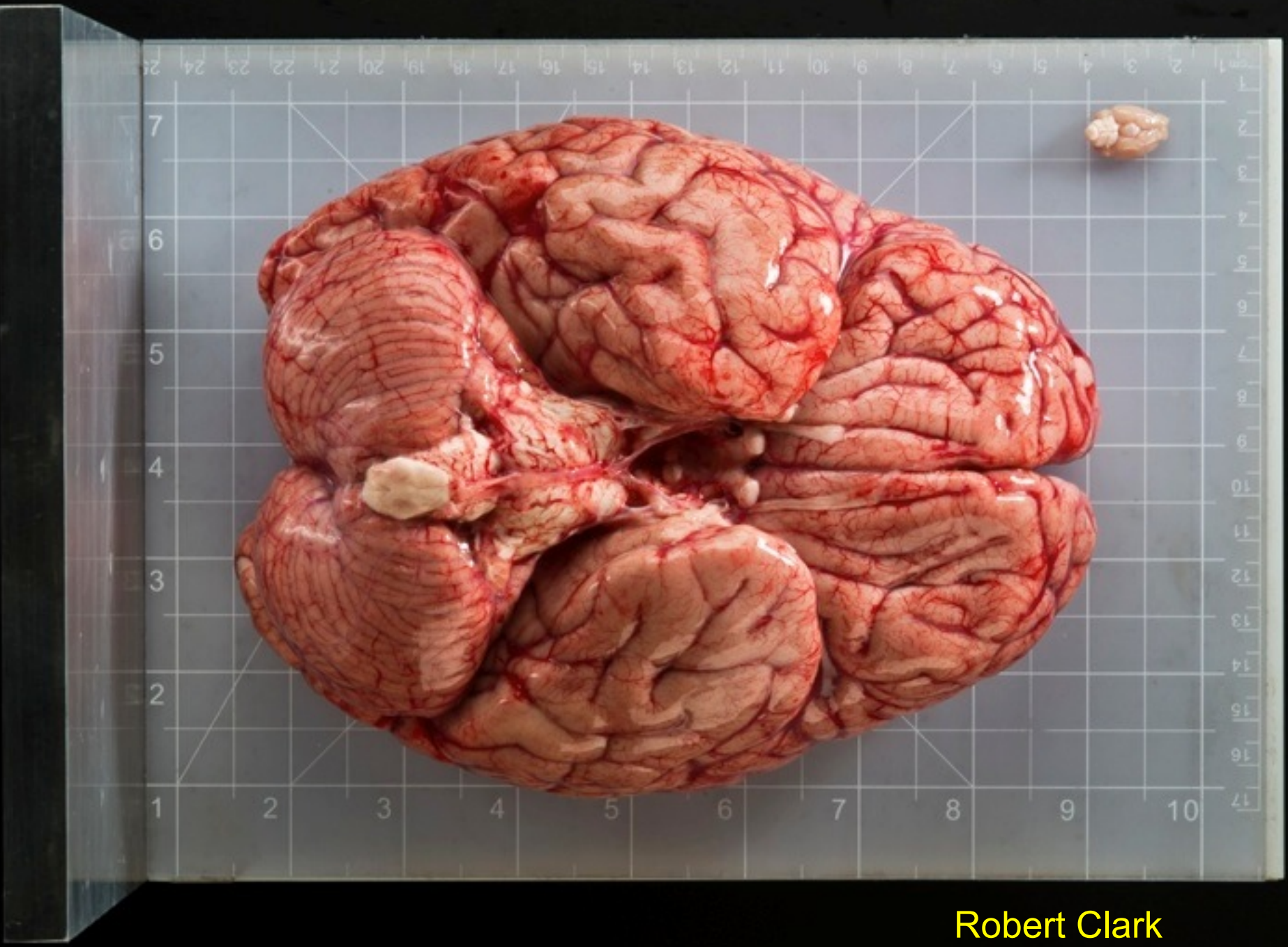




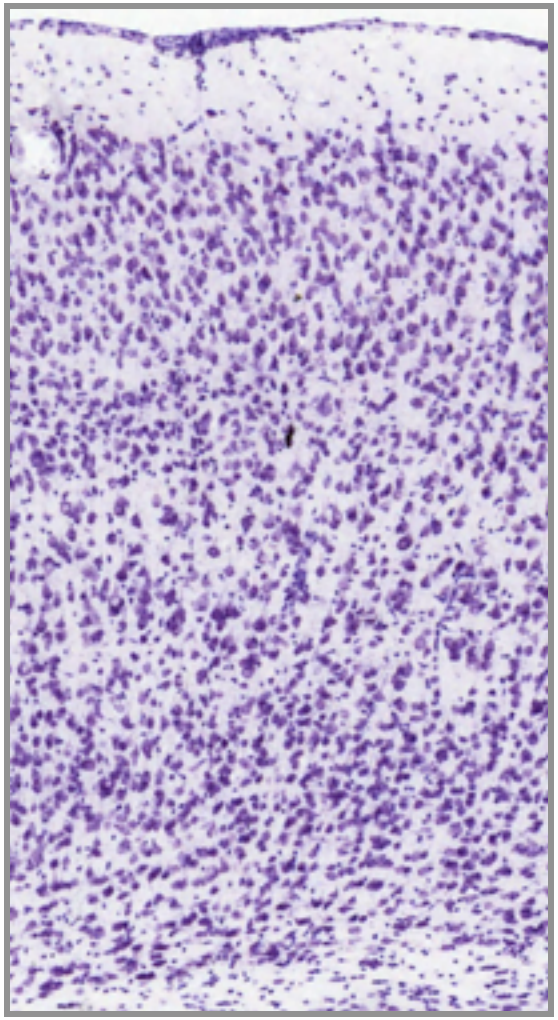
Callaway (2003)

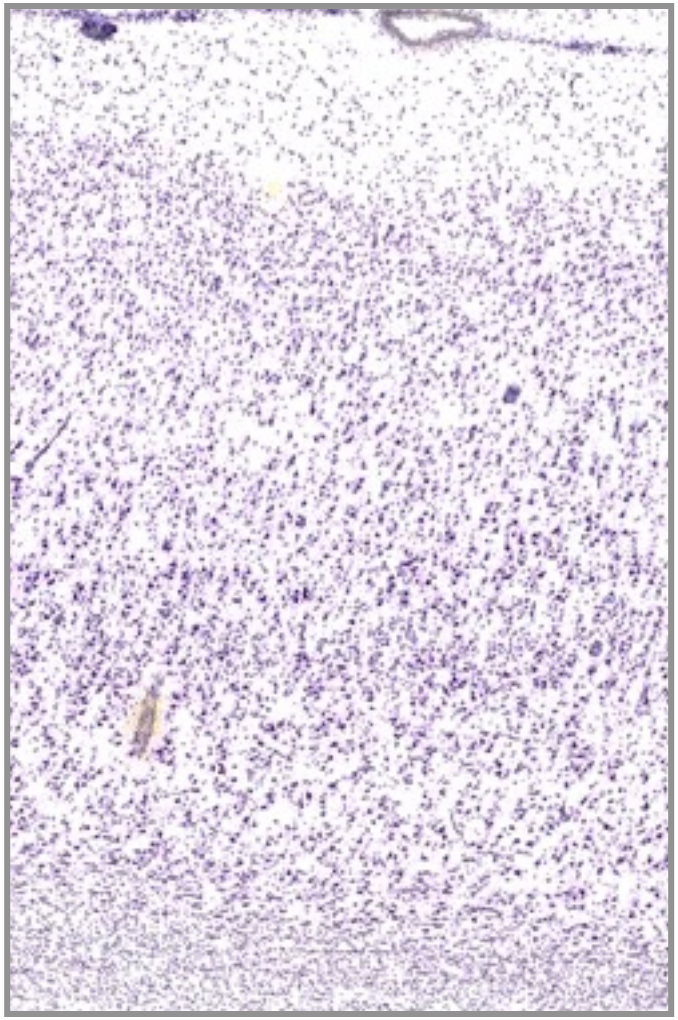


Vascularization in
monkey cortex
Weber *et al (2008)*


Robert Clark

Temporal Neocortex





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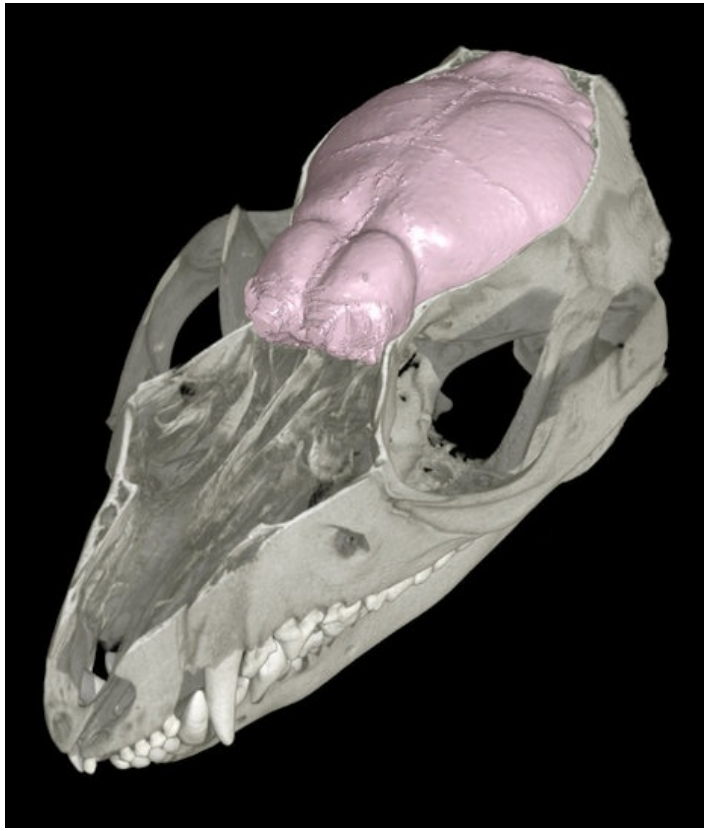
The oldest mammal - *Hadrocodium wui*

Luo, Crompton & Sun *Science* 2001



Rowe, Macrino & Luo *Science* 2010

Goals for the Workshop

- We want this to be an intellectually intense two week long experience
- Not primarily a lecture course but project-based, but hands-on summer school with neuro-biological data
- We need your feedback on how to improve this course for 2015 and beyond
- We would also like to have your feedback on how to improve the data resources and products of the Allen Institute for Brain Science

The Challenge

- Brains consist of a very large number (10^8-10^{11}) of highly heterogeneous cell types (~10^3), interacting with 10^3-10^4 others, across a spectrum of spatio-temporal scales (ms-years; μm - cm)
- We don't have a list of the cellular components
- Difficult to simultaneously record from more than 0.001% of them
- No accepted standards for relevant phenomenon - spikes, 40 Hz oscillations, synchrony, sharp wave
- No central unifying projects
- O(10,000) laboratories with different questions, methods, protocols & standards heading off exuberantly in all directions
- Universities are not set up for large-scale, systematic efforts
- Limited interactions between experiments, modeling & theory

T nce

- An indepen , founded in 2003, suppor
- 160 staff in
- Culture betw ssed on large project ght interactions a
- Ten year pr vel observatories
- 2014 Budge
- Made possi Allen

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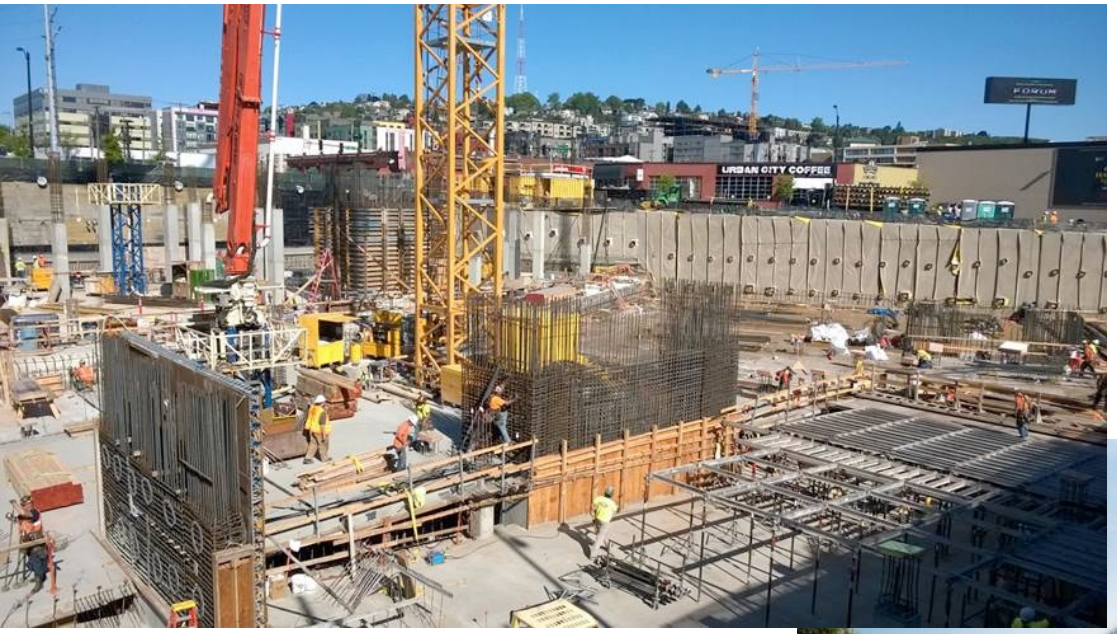
“These days, I'm disinclined to invest in completely open-ended research. I've learned that creativity needs tangible goals and hard choices to have a chance to flourish.”

Paul Allen

New Building



270,000 ft^2 building in South Lake Union by September of 2015

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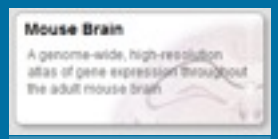
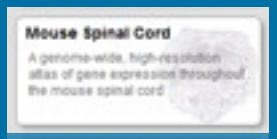
Allen Institute - Online Public Resources
www.brain-map.org

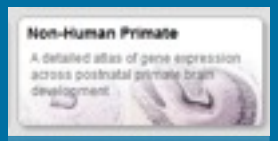
- 45,000 unique visitors/month
- >1 million microscope slides
- > 10,000 engineered mice
- > 3 PB of data
- >350 million gene expression measurements in human and mouse brain



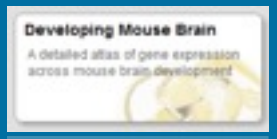
December, 2004



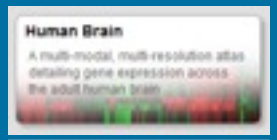
July, 2008



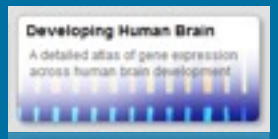
October, 2009



November, 2008



May, 2010



October 2010

October 2011

2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

All data are

- publicly accessible via API as soon as they pass QC
- freely available without any commercial restrictions
- accessible 1-2 years prior to any publications

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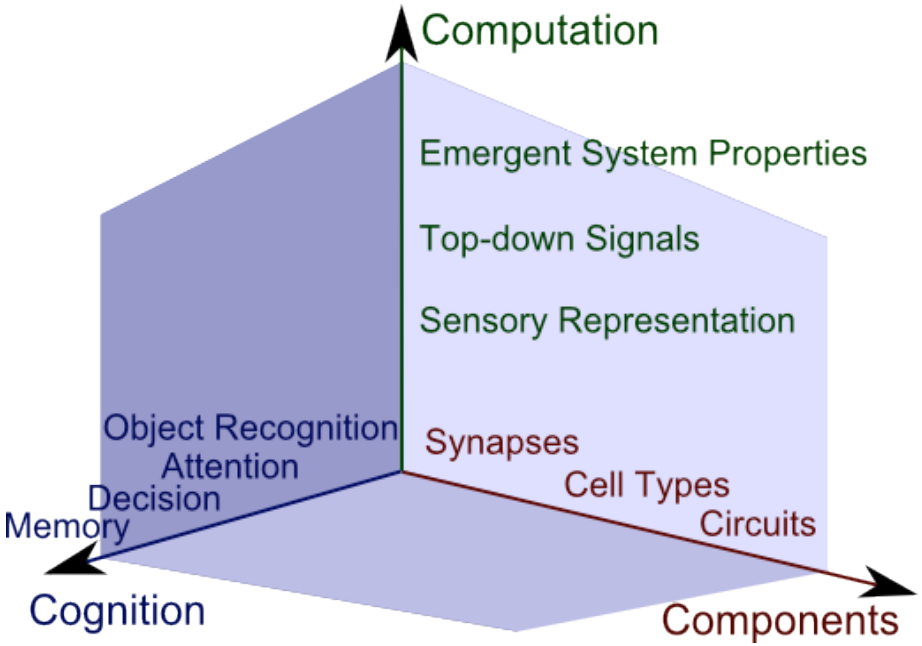
Understanding Complex Biological Systems



Components

- What are the characteristics that define functionally distinct synapses?
- What are the characteristics that define functionally distinct cell types?
- What are the characteristics that define functionally distinct ‘canonical’ circuits or circuit motifs?

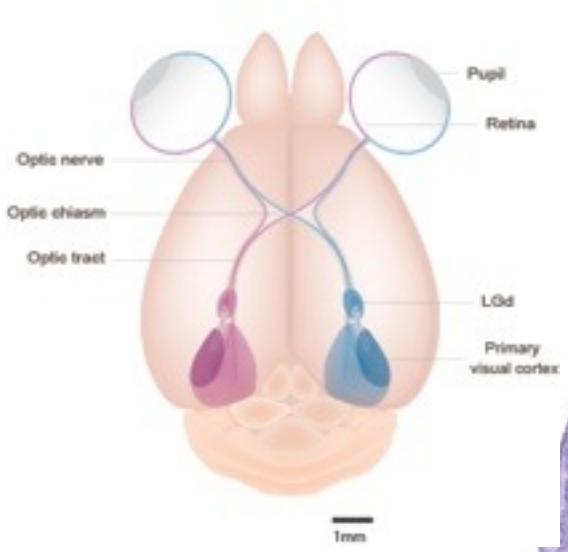
Computation

- How is sensory information represented and processed in the cortex?
- How are top-down signals routed and how do they affect sensory processing?
- What computations do the different synapses, neuronal cell types and circuits implement?

Cognition

- What are the neuronal mechanism of selective visual attention?
- What are the neuronal mechanism of feature integration and invariant object recognition?
- What are the neuronal mechanism of learning?

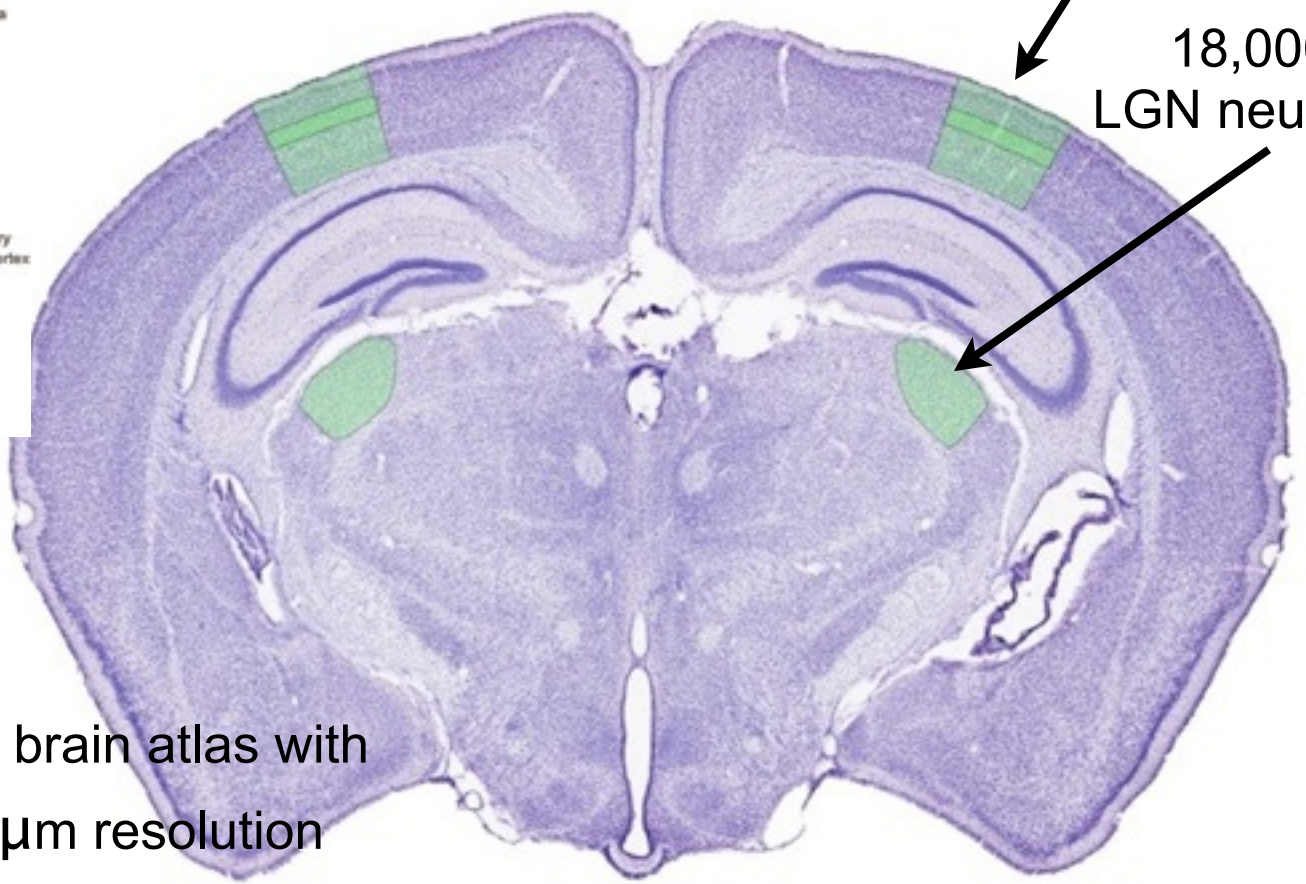
Mouse Cortico-Thalamic Visual System



14 million
cortical neurons

360,000
V1 neurons

18,000
LGN neurons



Build true 3-D mouse brain atlas with

10 µm pixels and 50 µm resolution

45,000 retinal
ganglion cells

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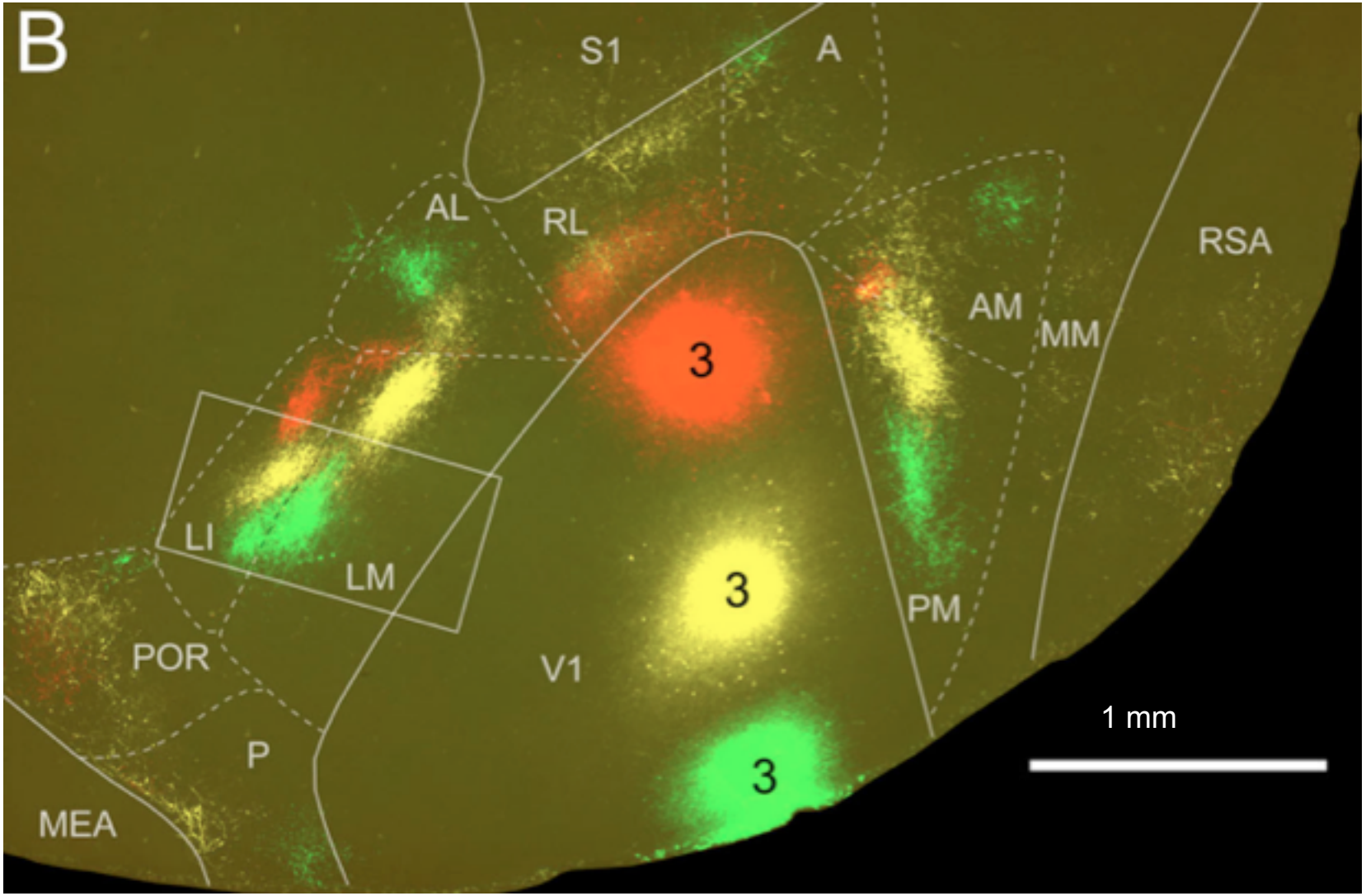
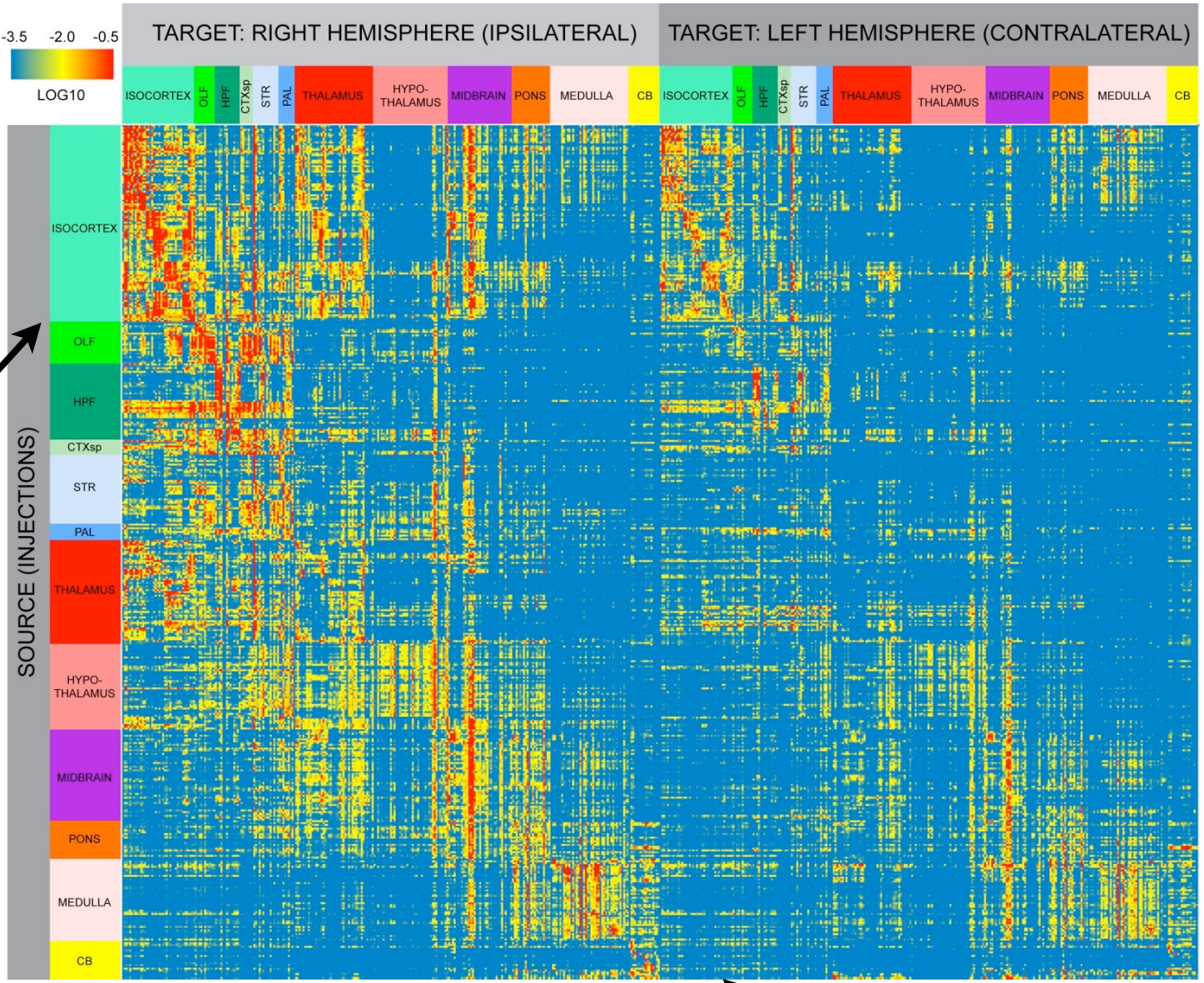
Mouse Visual Cortex



Wang & Burkhalter (2007)

Connectivity Matrix for the Entire Mouse Brain



An injected brain region in one of 495 mice

One of 295 brain regions

Oh et al. *Nature* 2014

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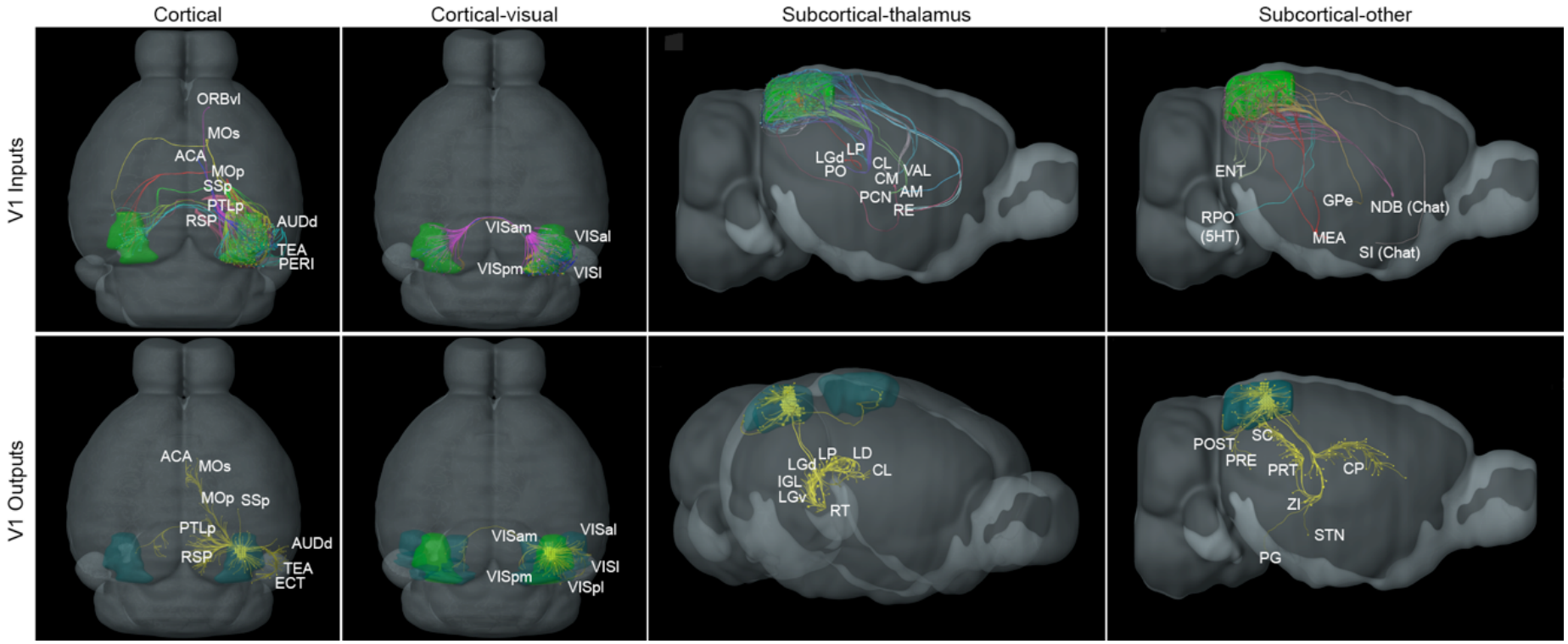
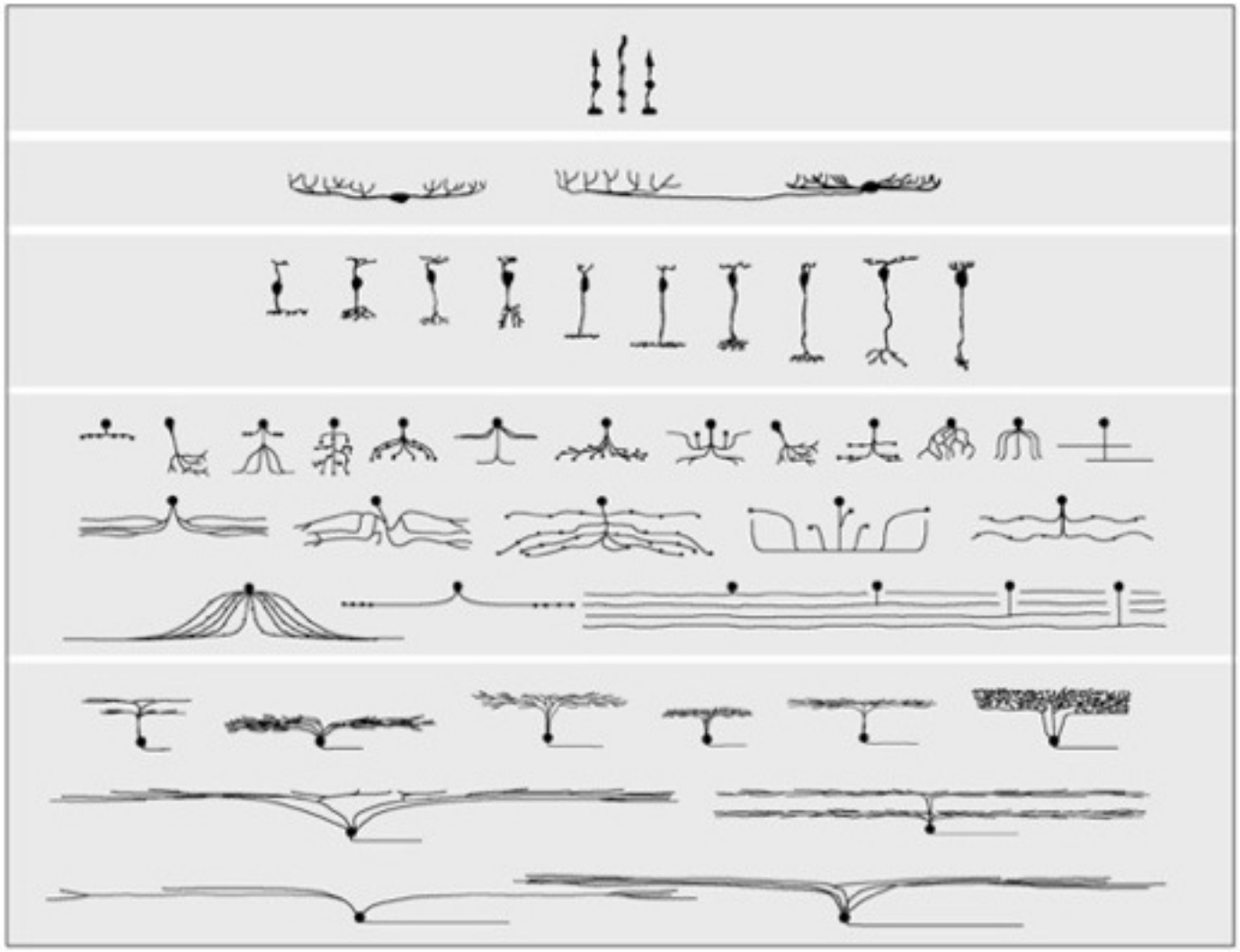
Primary Visual Cortex



Julie Harris

We're now executing on the Next-Gen Connectivity Atlas, a much higher resolution, retro- and antero-grade, connectivity atlas of the visual system, including retinal outputs and layer-specific information

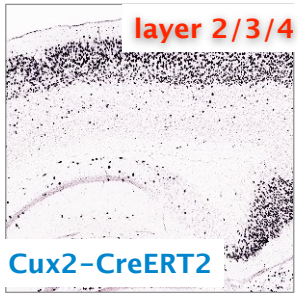
Retinal Cell Types

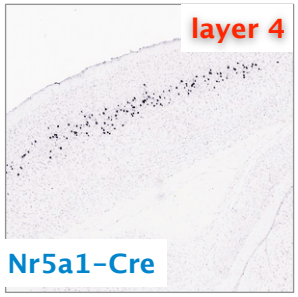


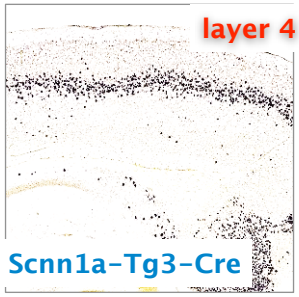
Masland (2001)

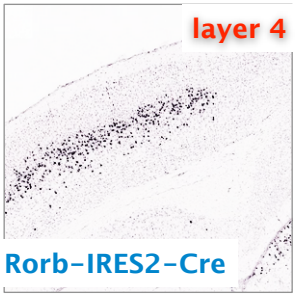
Genetic Markers via Cre Lines

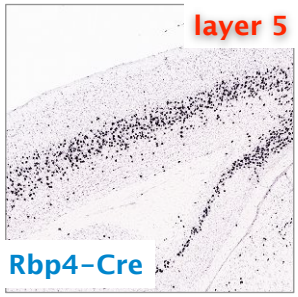
Excitatory neurons

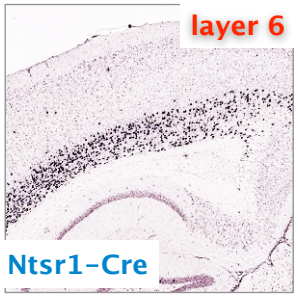


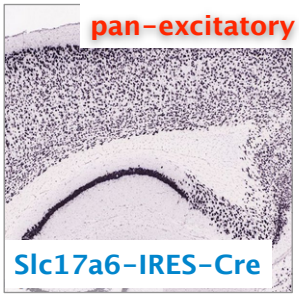






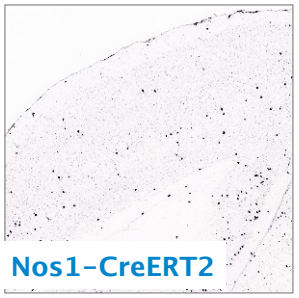


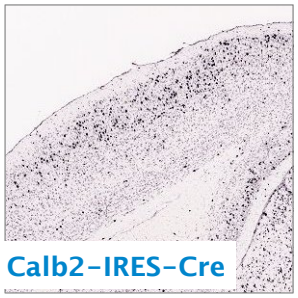


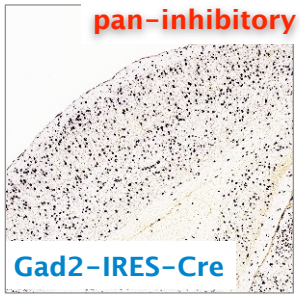


LGN

Inhibitory neurons







Htr3a-Cre in progress

Madisen, Harris & Zeng

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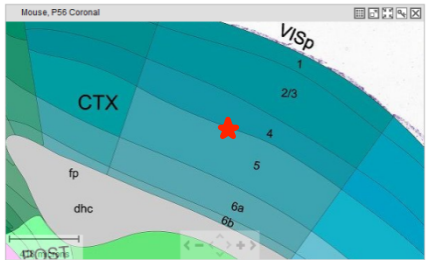
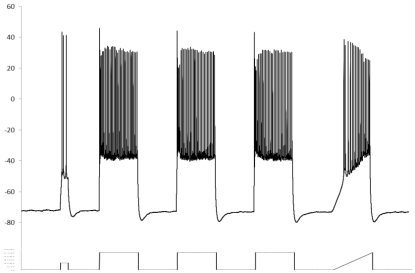
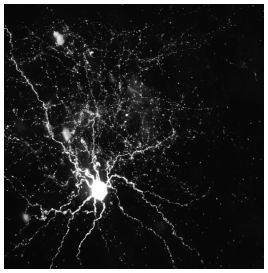
In vitro Single Cell Characterization

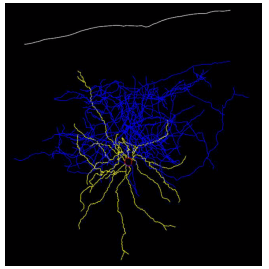


Metadata
(Common Coordinate System)

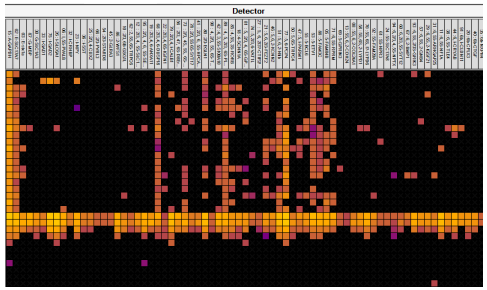


Electrophysiology





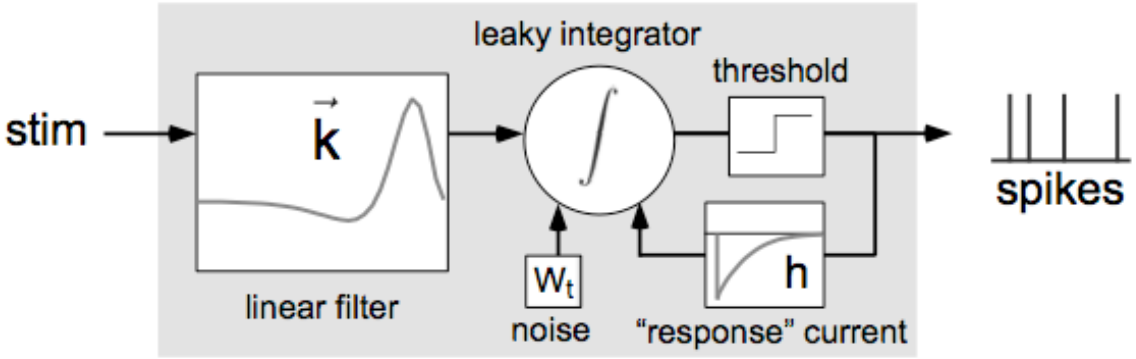
Morphology

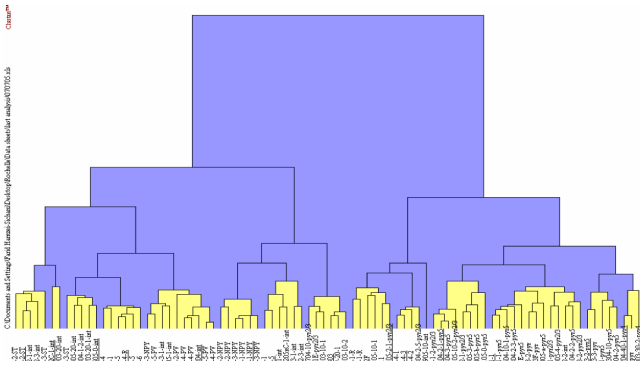


Fitting GLIF/GLM Models

mRNA transcripts

Data-driven taxonomy of cell types





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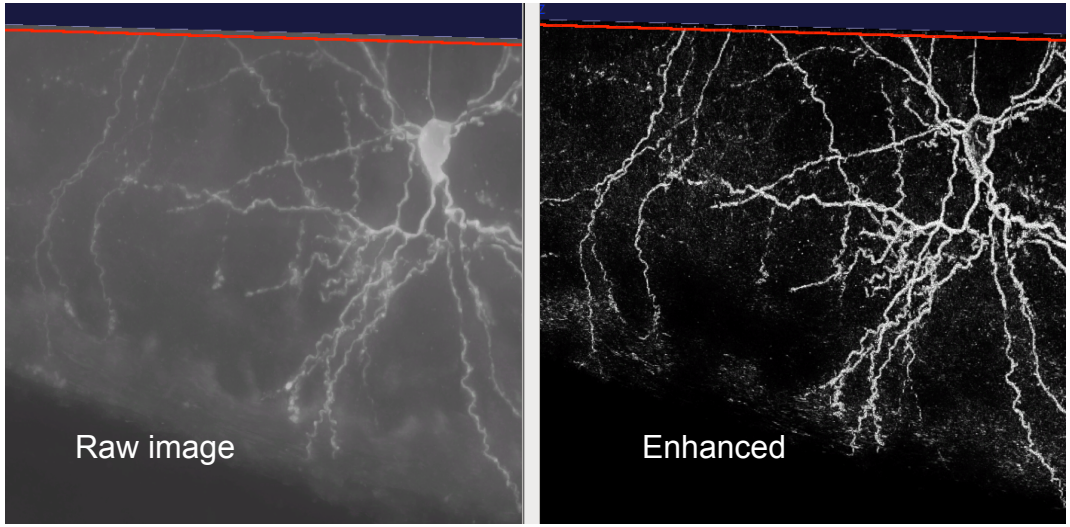
Towards Automatic Neuronal Reconstructions via Vaa3D

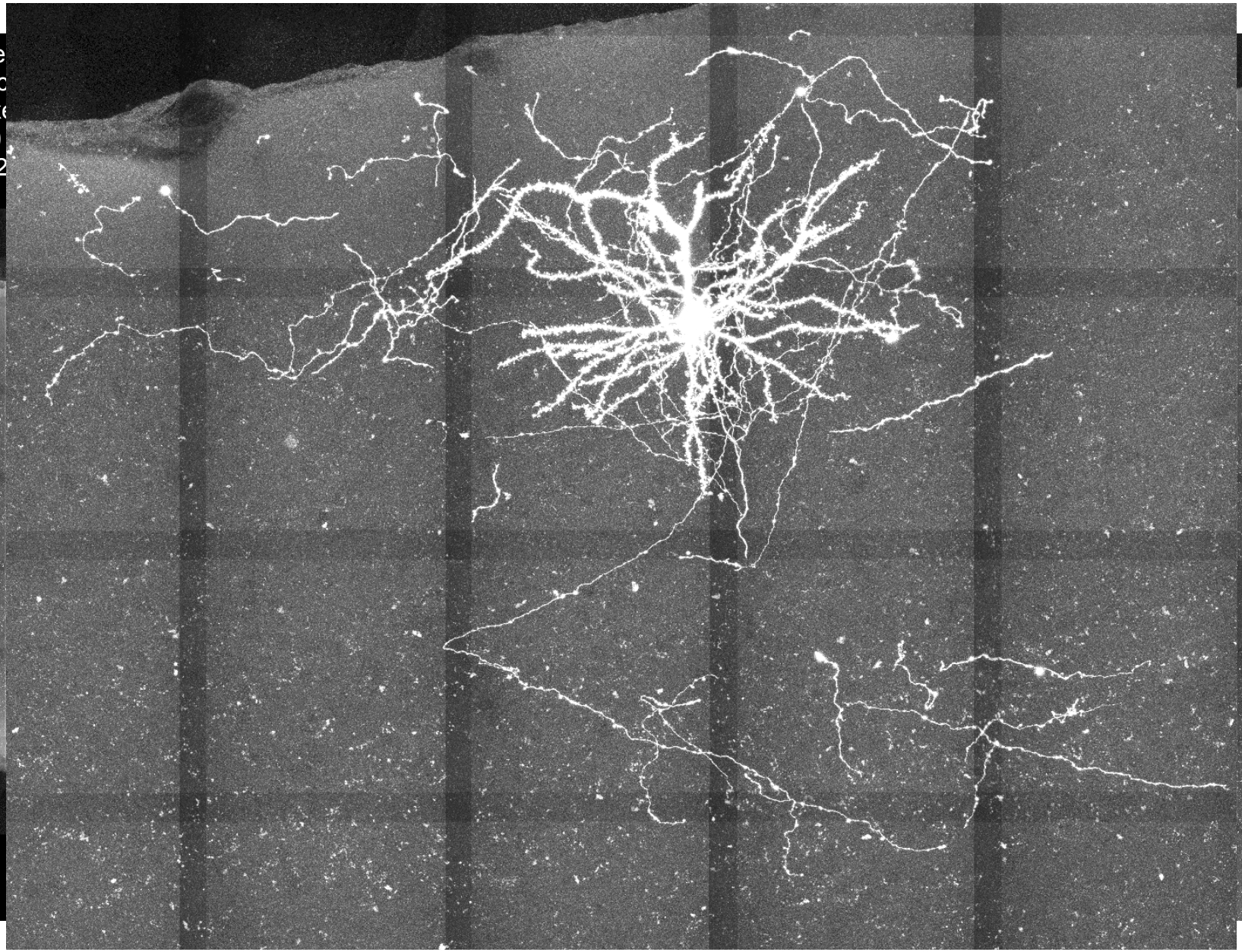
Software is deployed for 3D visualization of large (10-20GB) data sets massive (100GB-3TB) image data sets (TeraFly) and for manual and semi-automatic neuronal reconstruction



www.Vaa3D.org

Peng *et al. Nature Biotech.* (2010)
Peng *et al. Nature Protocols* (2014)

- laye
- Elec
- Voxe
- 160
- 53.2



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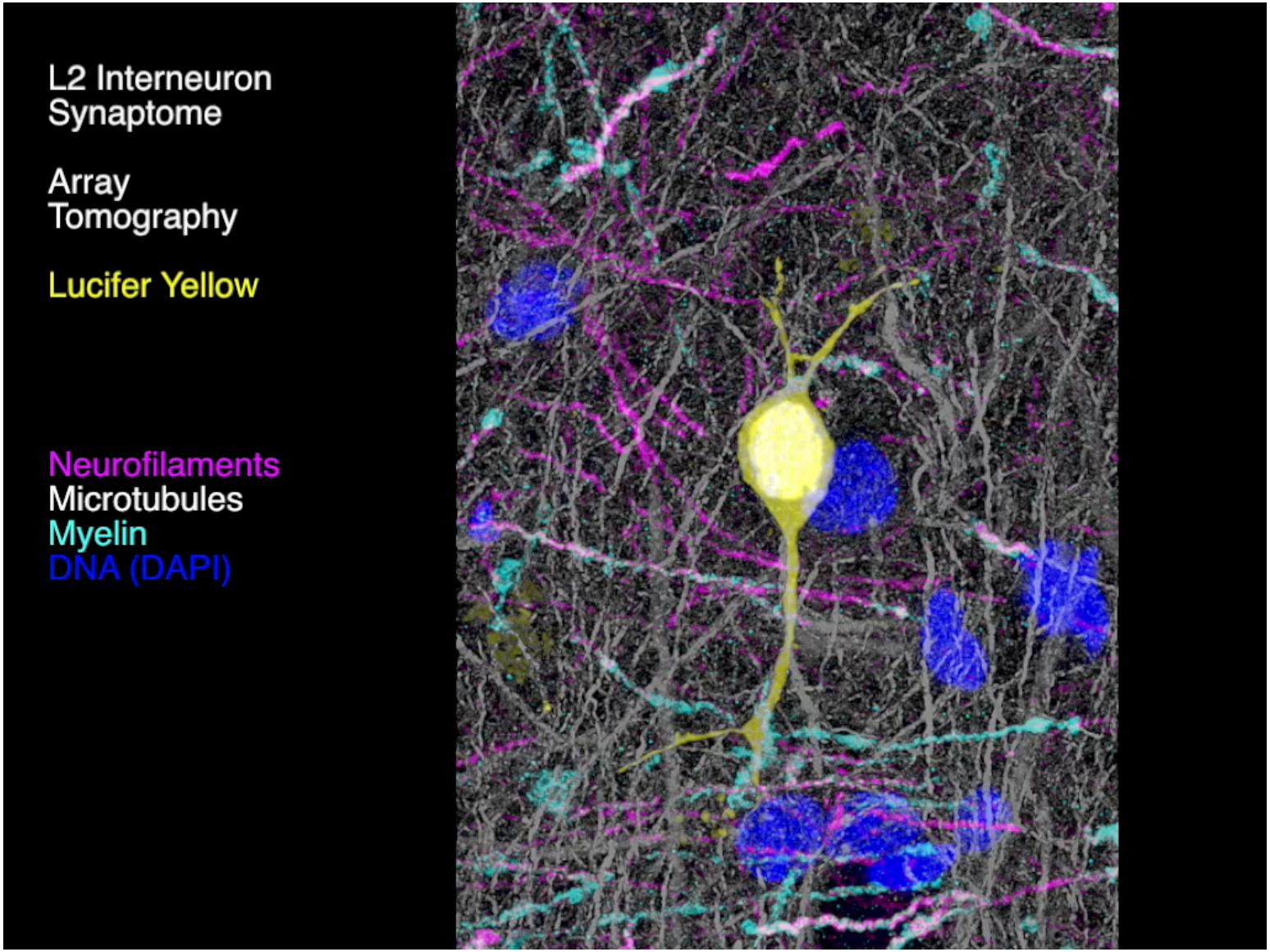
Peng & Zhou

Synaptomes



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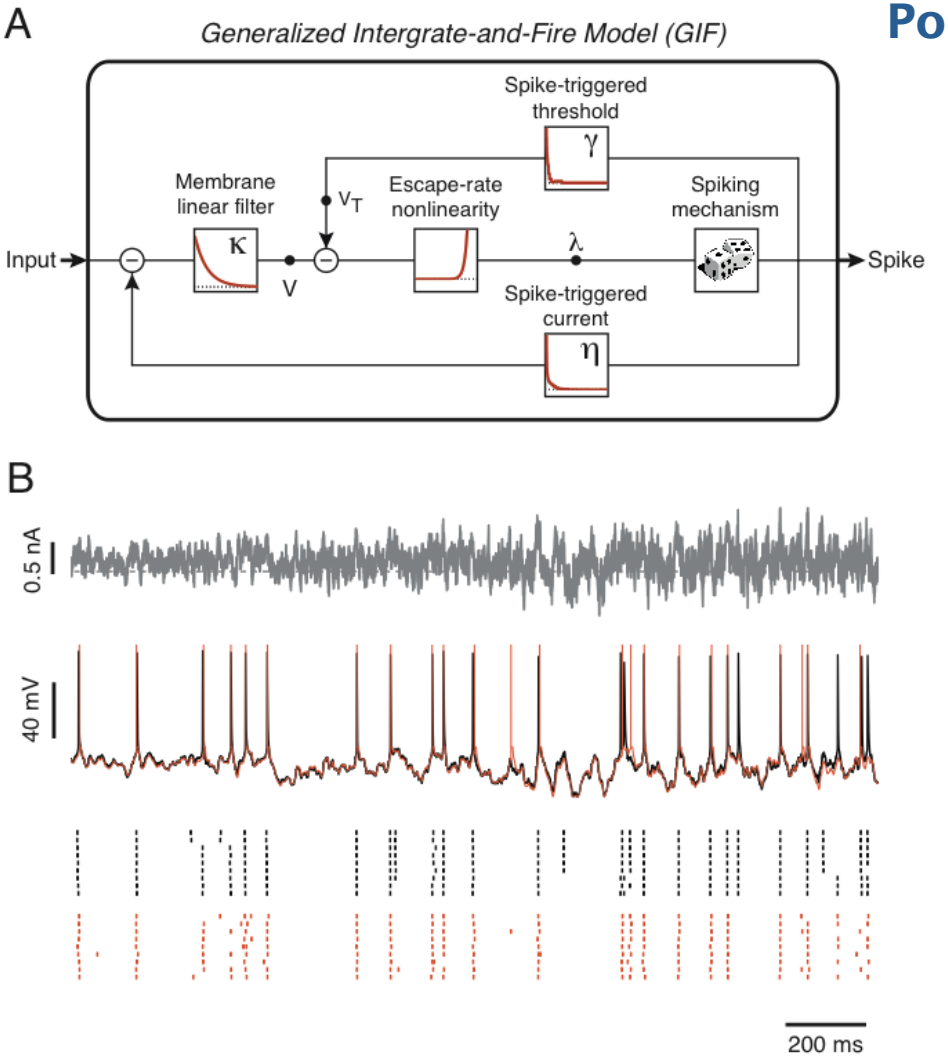
Array Tomography - Stephen Smith

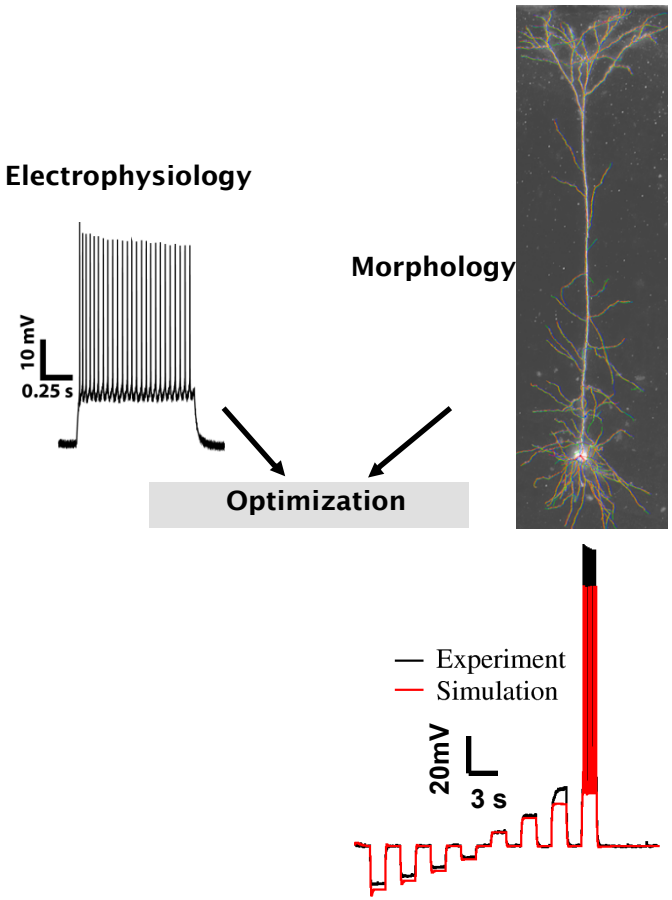
Automatic Model Fitting of Neurons

Mensi, Pozzorini, Hagens, Naud, Koch & Gerstner

Point Neurons



Spatially Extended Neurons



Mihalas, Anastassiou, Teeters & Arkhipov

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Observatories

- Ground-based telescope with 30 m effective mirror - consisting of 492 adjustable hexagonal mirrors (10x resolution than Hubble)
- Planning started in 2003, first light in 2018
- Estimated cost $1 Billion
- We want to do something similar in the mouse with methods that are

➡Standardizable

➡Reproducible

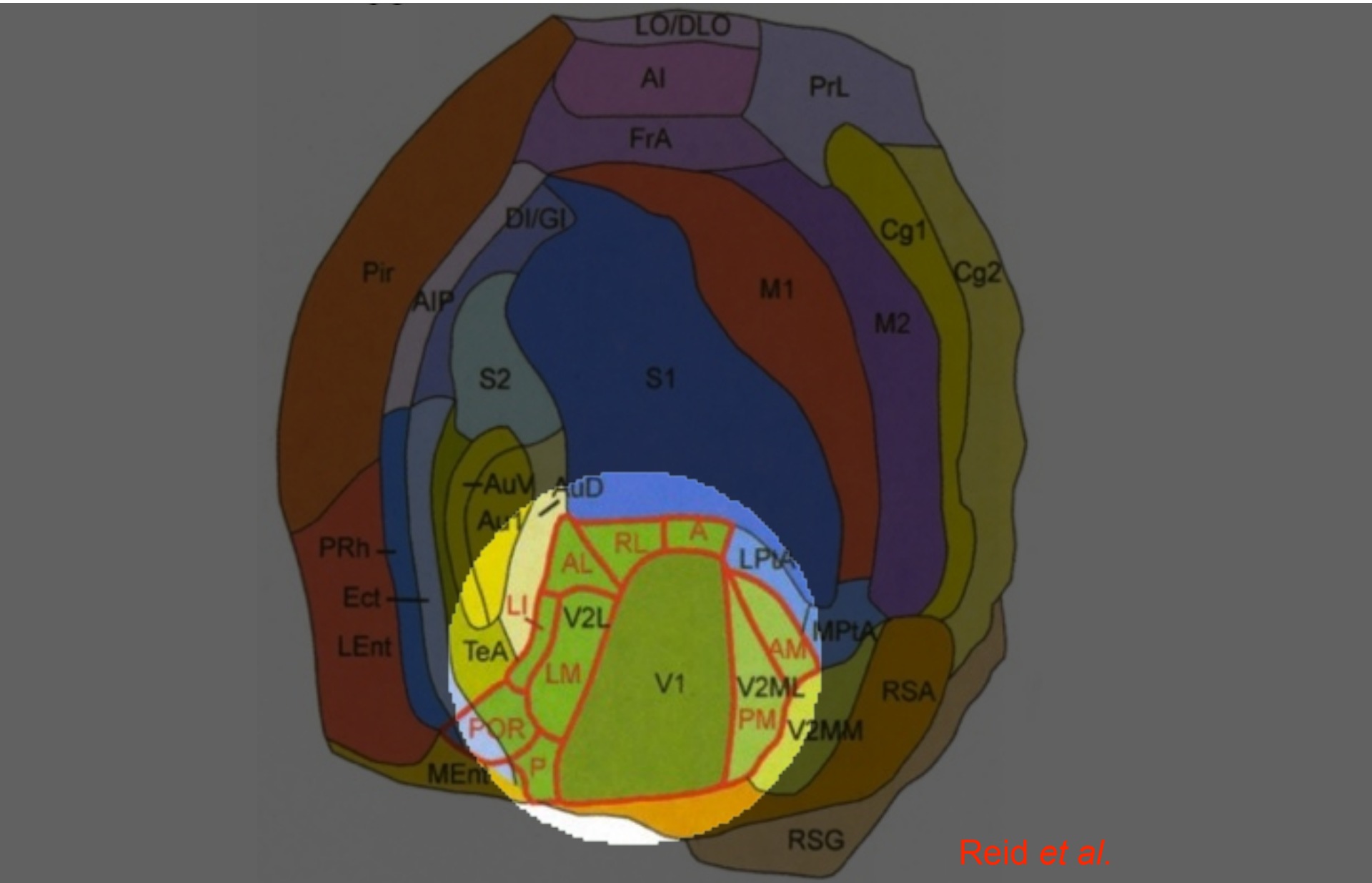
➡Accurate

➡Scalable

Record Cellular Activity in Behaving Mice

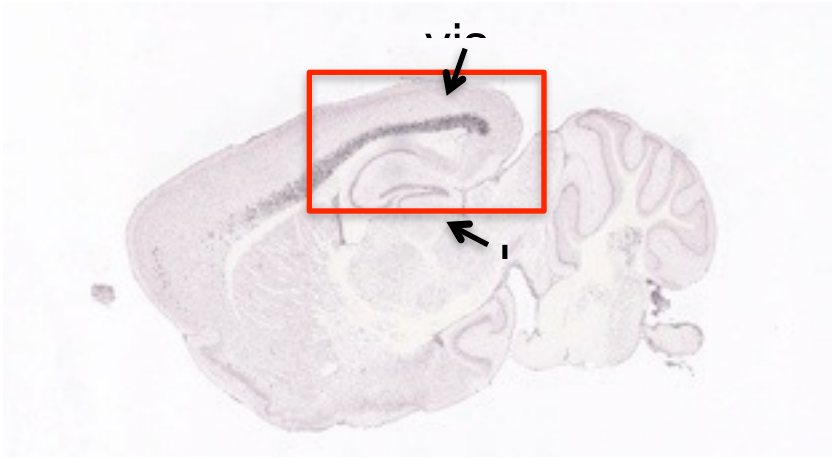
Shawn Olsen, unpublished

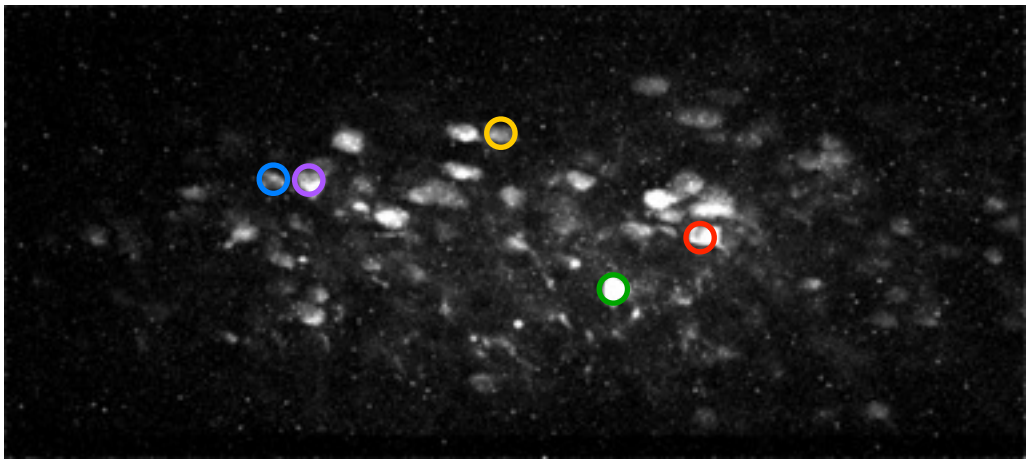
Observe Spiking Activity in Behaving Animals



Reid *et al.*

Measuring Activity in Specific Neural Populations



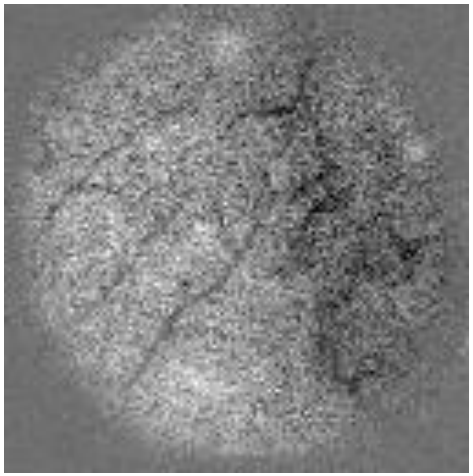


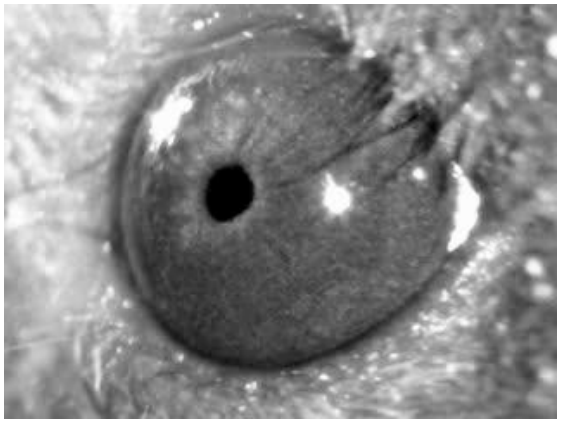
FLEX-GCaMP6s injection in V1

Ntsr1-Cre Layer 6 line

Garner, Cheng & Reid

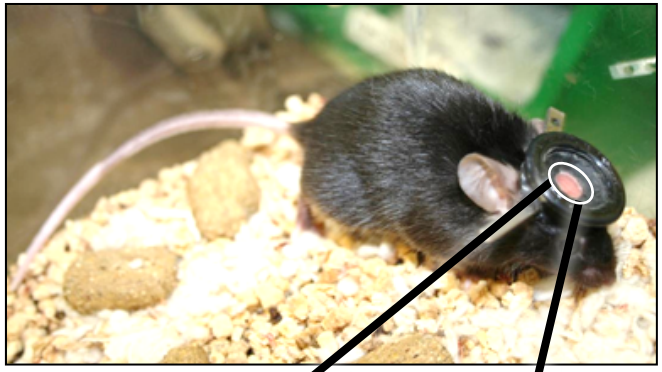
Whole Field Fluorescent Imaging for Retinotopic Mapping

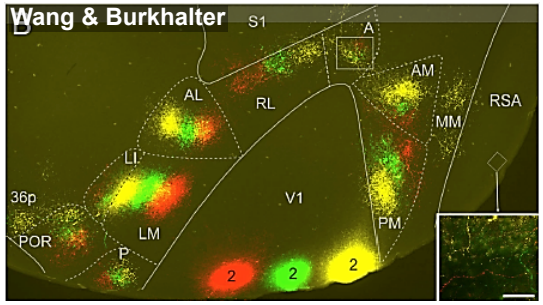


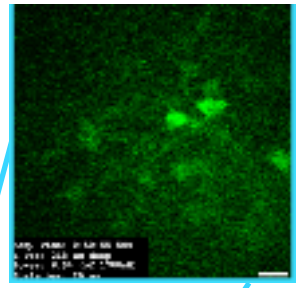


Zhuang, Waters, Garrett, Ollerenshaw, Groblewski, Williams & Danskin

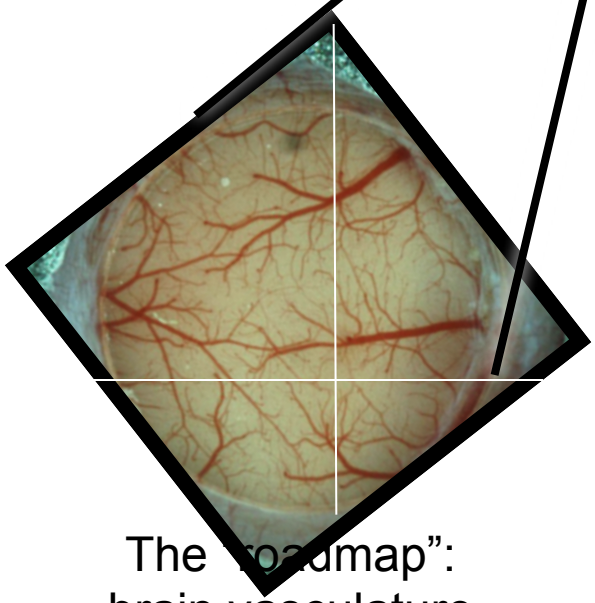
Cortical Activity Map Pipeline



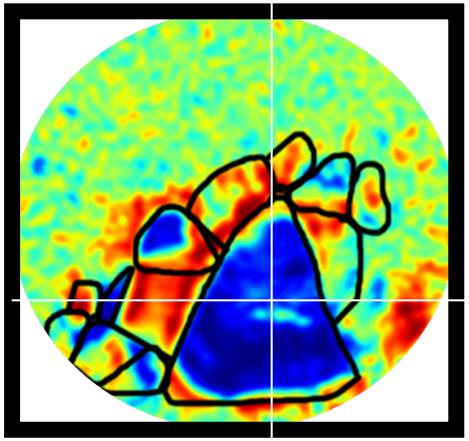




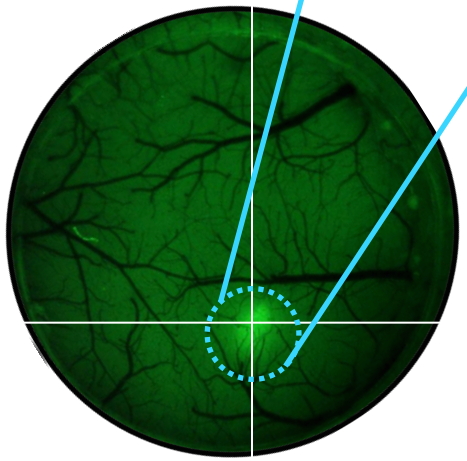
Cellular activity



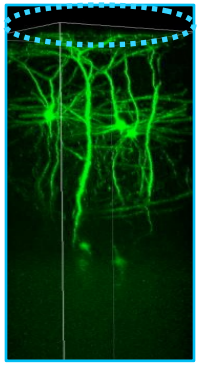
The "roadmap":
brain vasculature



Brain activity:
reflectance
measured from
bloodflow



Localizing cells
with fluorescent
markers



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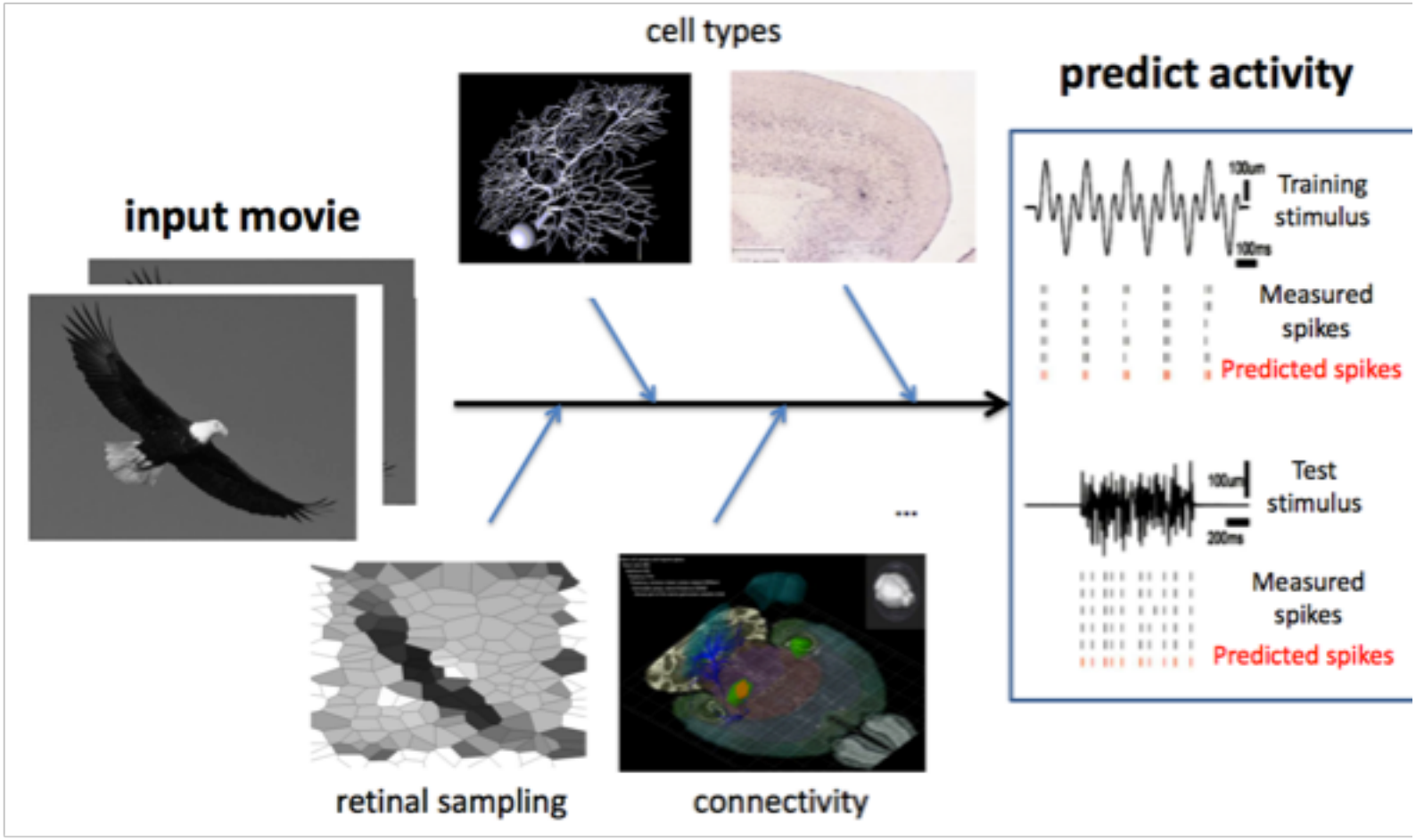
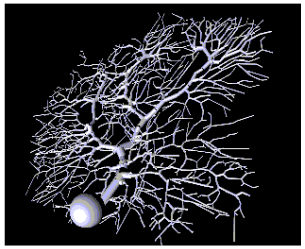
Bernard

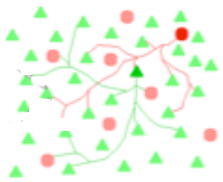
A Neuronal Grand Challenge

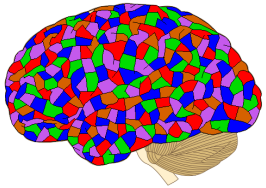


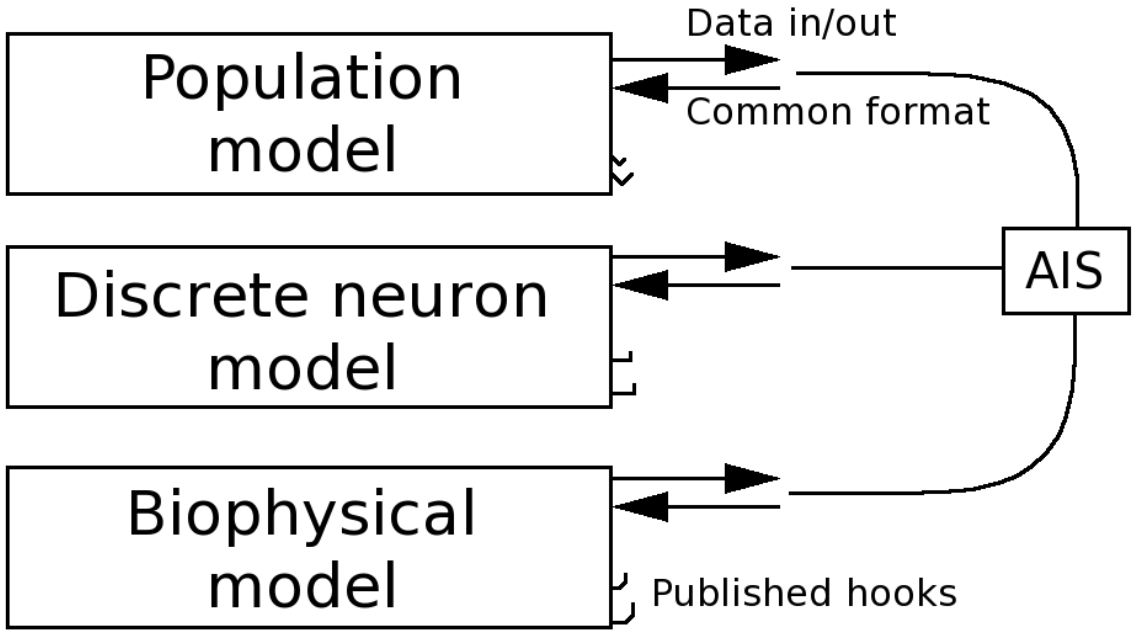
Integrated Simulator: Neuron, Brian, and DiPDE

- Can send information between 3 different simulation platforms
- Platforms jointly controlled by a joint time-stepping controller



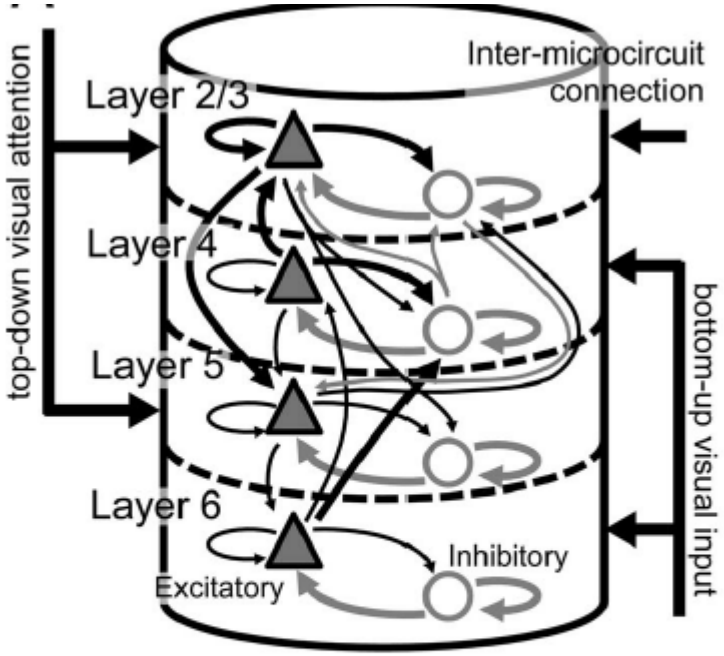


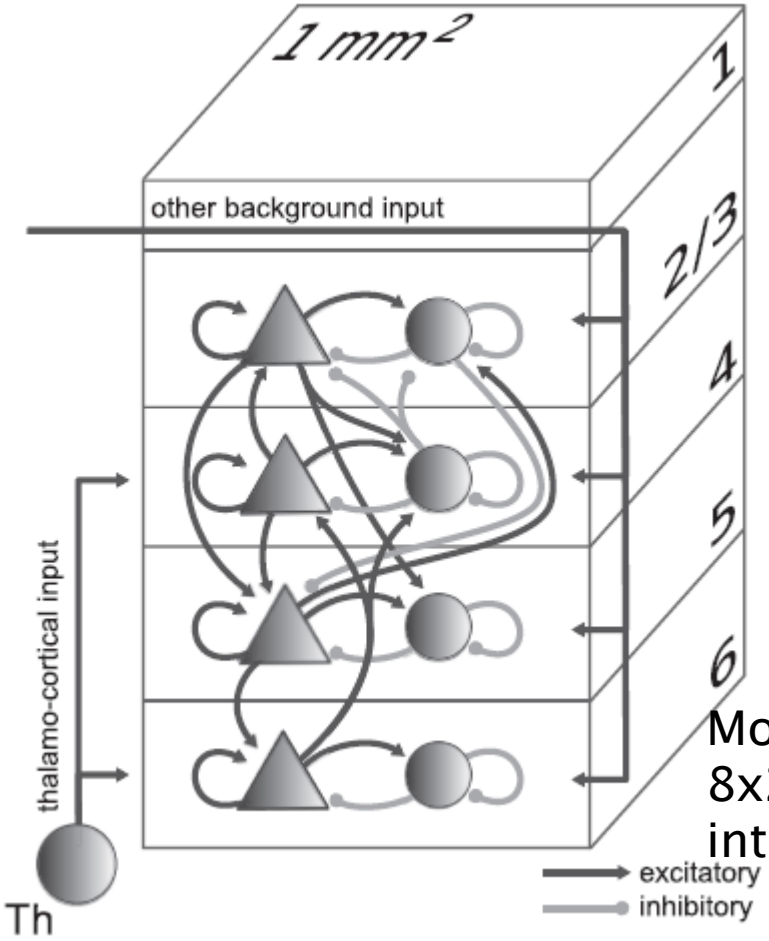




Mihalas, Cain & Iyer

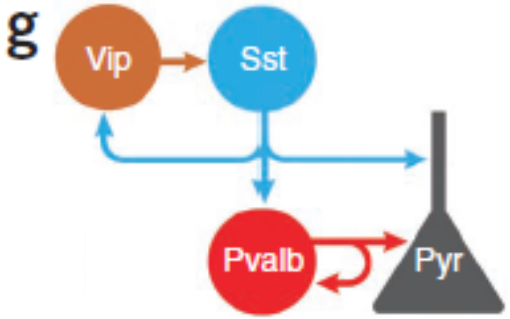
Wagatsuma *et al.* 2012





Potjans & Diesmann 2011

Move from 80,000 LIF (300M synapses) to 8x20,000 LIF model with 3 types of inhibitory interi



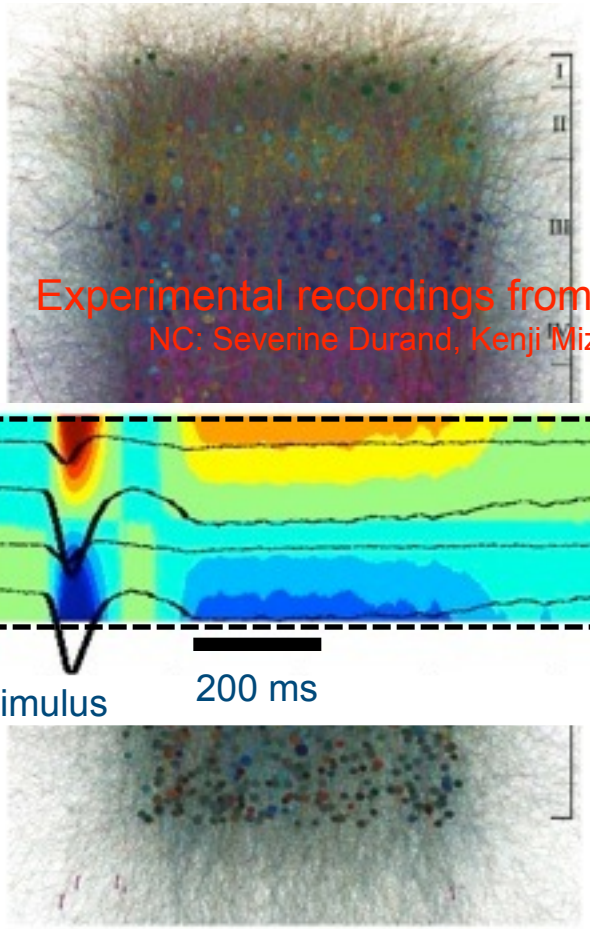
Pfeffer et al. 2013

Lee & Mihalas

Cellular-Level Modeling of the Local Field Potential

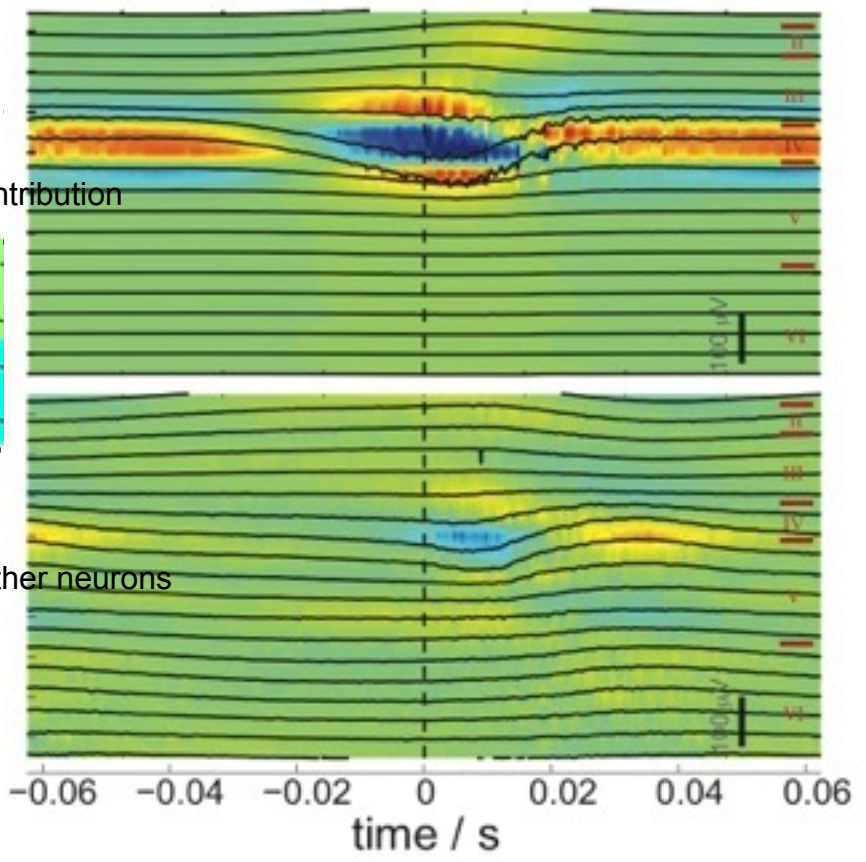
Thalamic input into layer 4
10 Hz spike drive modulation

Traces: Local field potential (voltage)
Color: current source density



L4 PC contribution

Rest of all other neurons



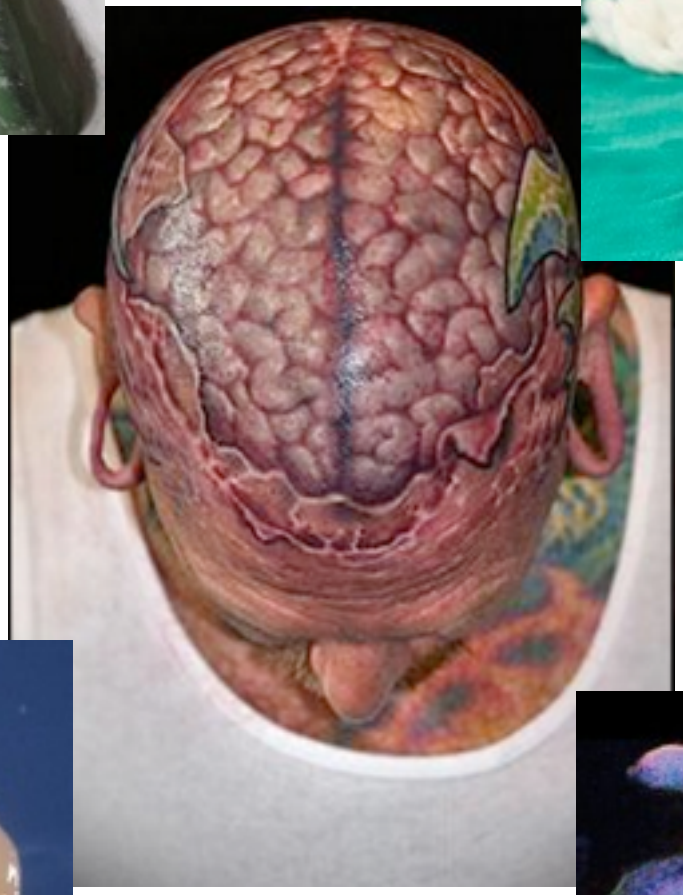
With BBP

Reimann, Anastassiou, Perin, Hill, Markram & Koch, *Neuron* 2013

Human Cellular Physiology

Post-mortem brain for molecular atlasing

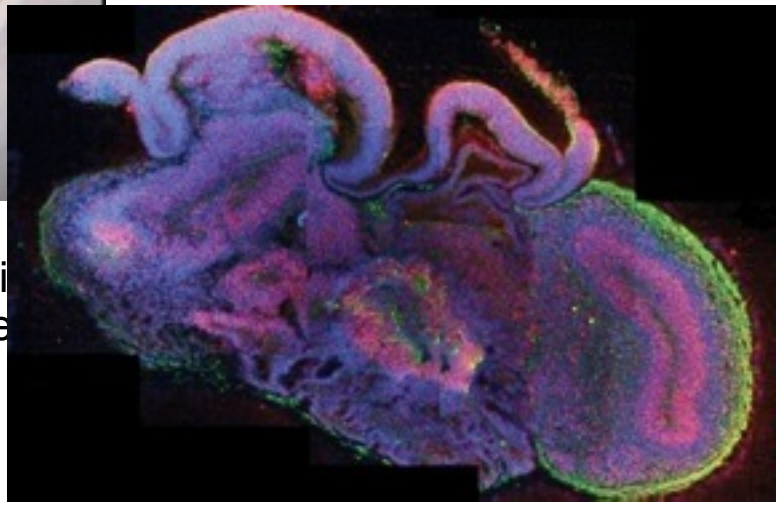
Excised brain tissue



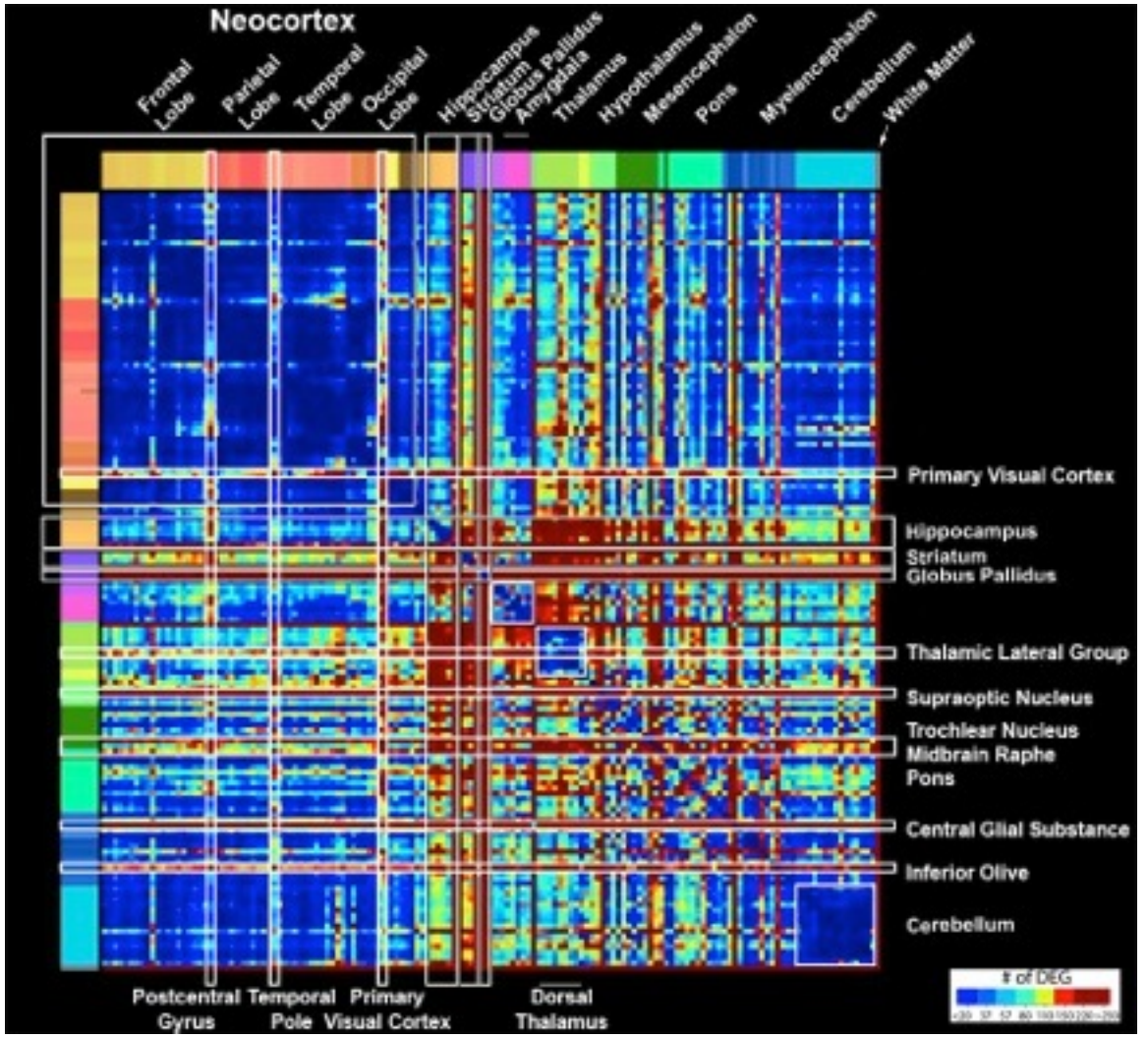
Fetal brain tissue

n brain tissue under four di
pture the working of the he

Human stem cell derived neurons



Transcriptional Atlas of the Adult Human Brain



- Differential gene expression between regions across 6 brains
- 50M data points
- Gene expression levels in cortex & cerebellum are remarkably homogeneous
- Different from anatomical (Brodmann) view
- 30% of genes are differentially expressed in the brain between human and mice but only 5% between human and monkey

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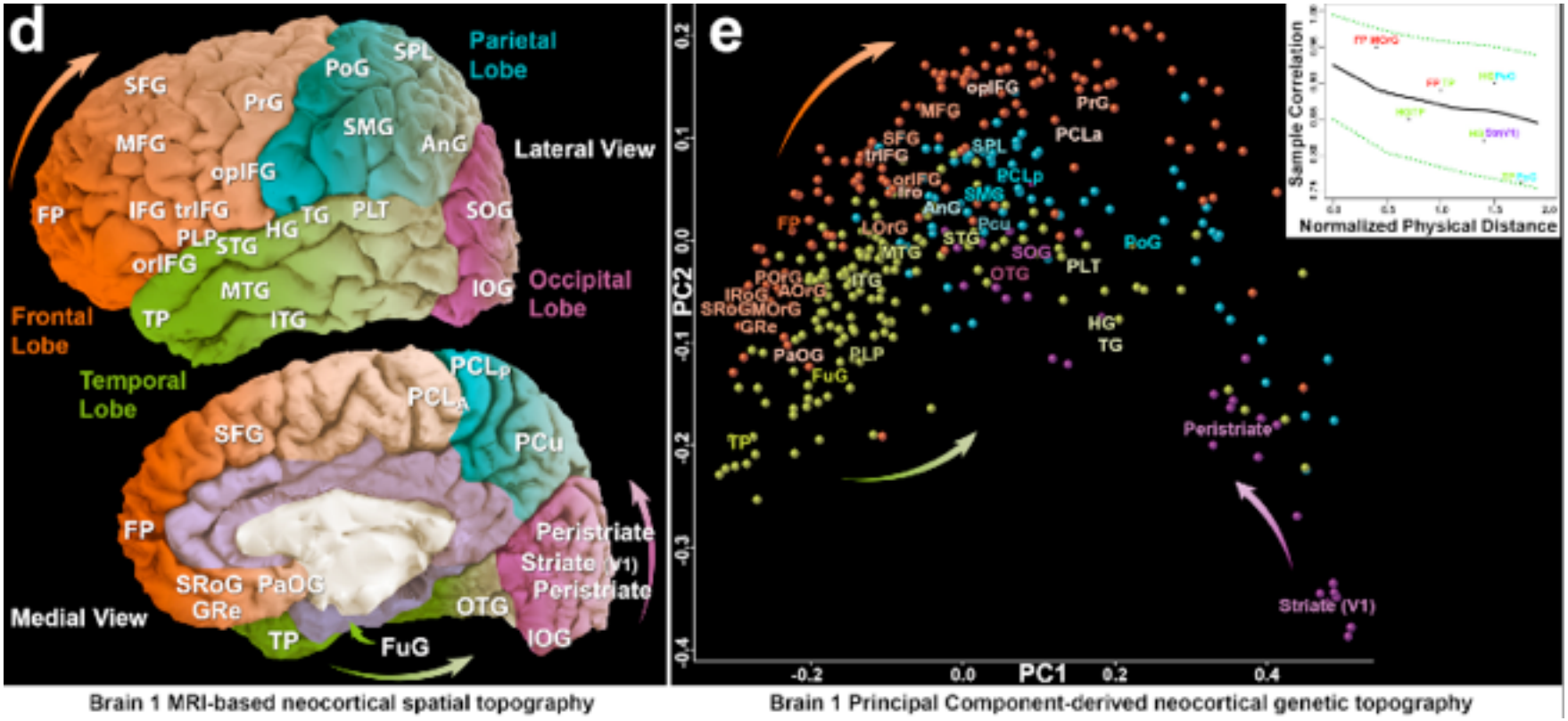
Hawrylycz *et al. Nature* 2012; Lein & Hawrylycz *Scientific Am.* 2014

Cortex is Relative Homogeneous



Brain 1 MRI-based neocortical spatial topography

Brain 1 Principal Component-derived neocortical genetic topography

The closer two cortical locations are, the more similar their gene expressions

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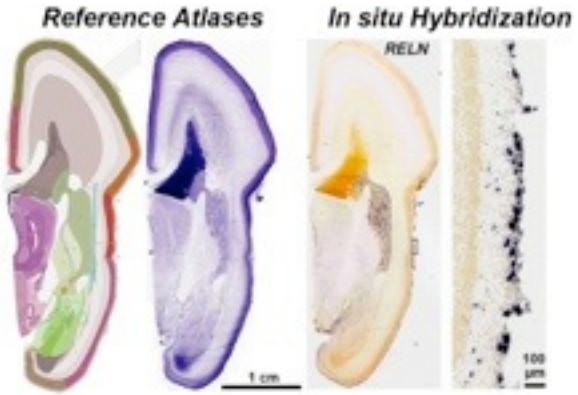
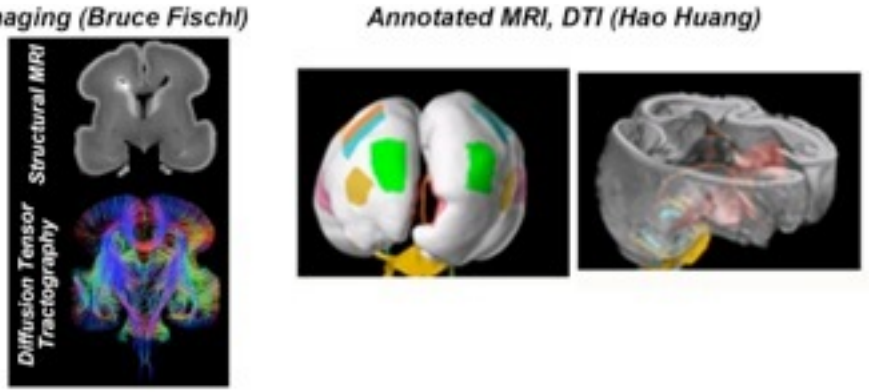
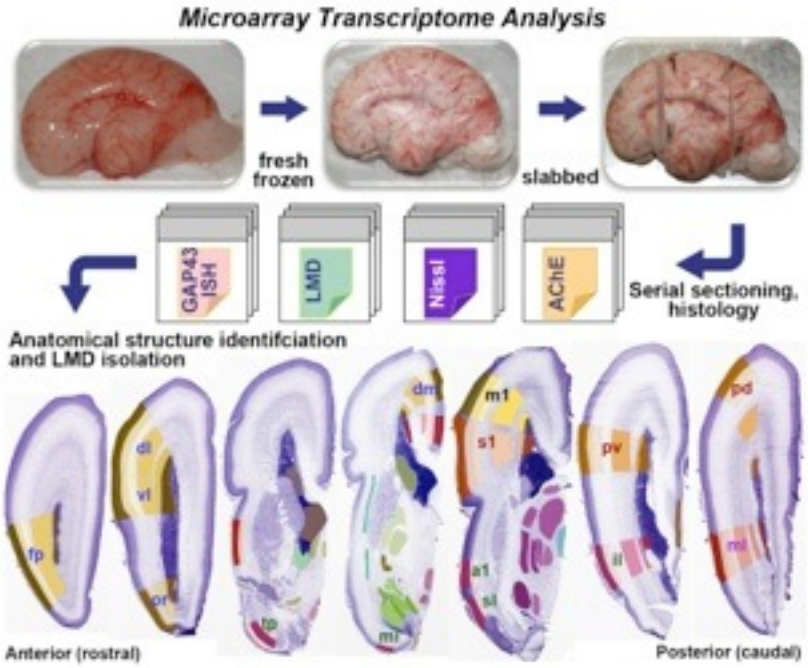
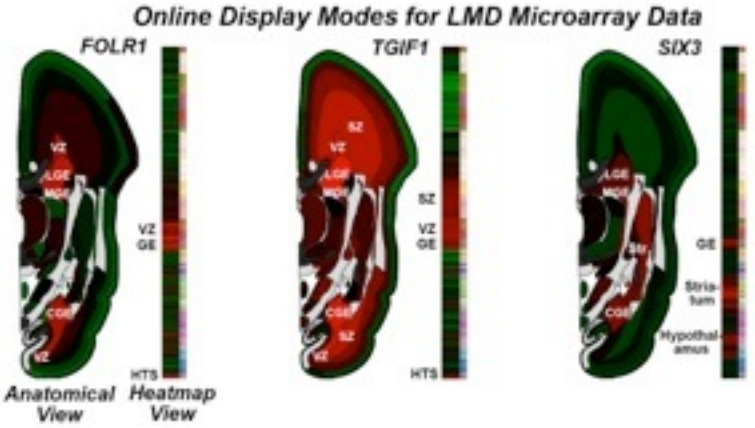
Hawrylycz *et al. Nature* 2012

Transcriptional Atlas of the Prenatal Human Brain







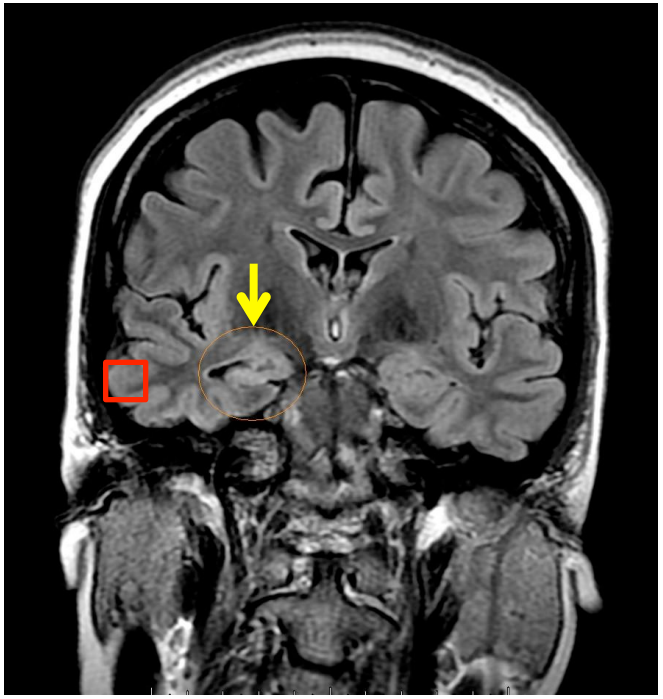


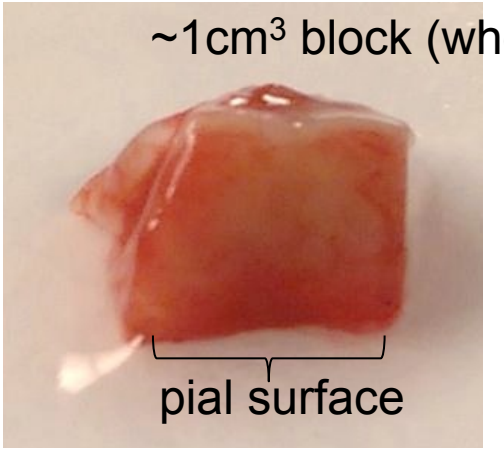
Maximizing precious resources:
6 prenatal specimens yielded ~1200 microarrays,
2 reference atlases and 6400 ISH slides

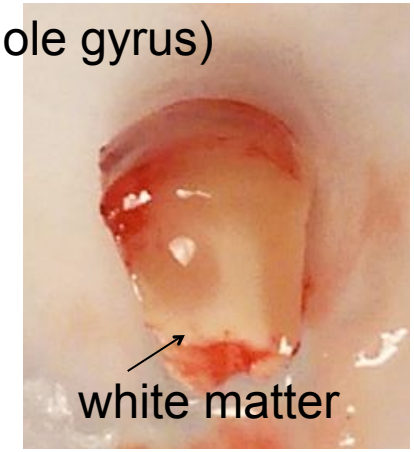
BRAINSPAN
ATLAS OF THE DEVELOPING HUMAN BRAIN

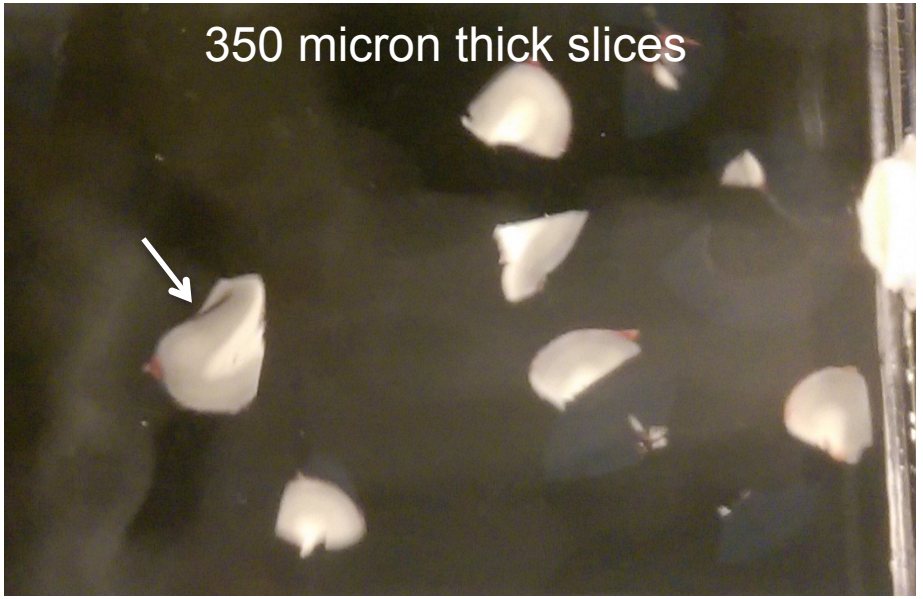
Miller et al. *Nature* 2014

In vitro Single Cell Characterization in Humans









- Lateral temporal lobe resection
- Medial temporal lobe pathology
- Transport from OR to Institute & slicing <30 min after resection

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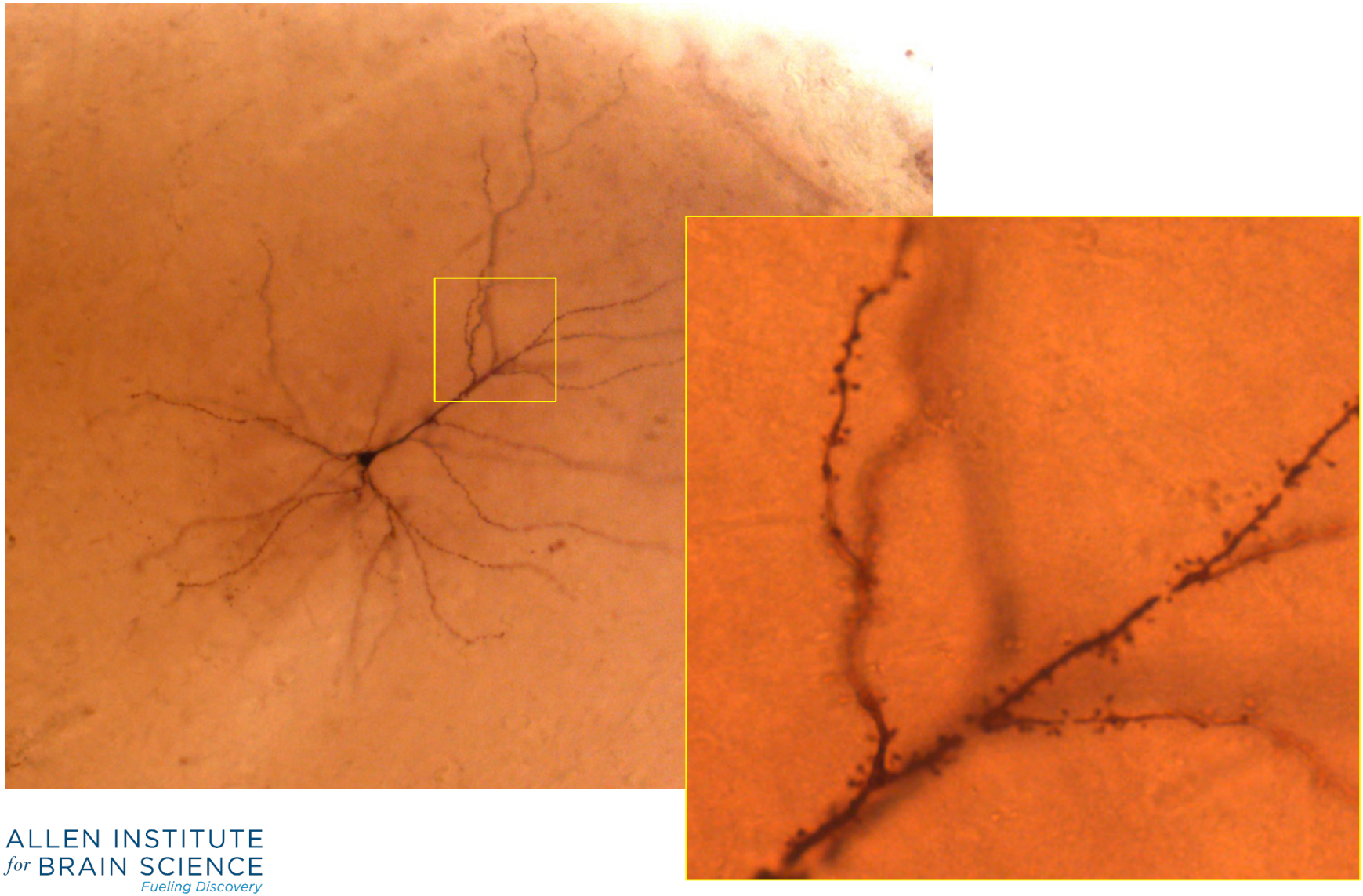
Lein & Ting

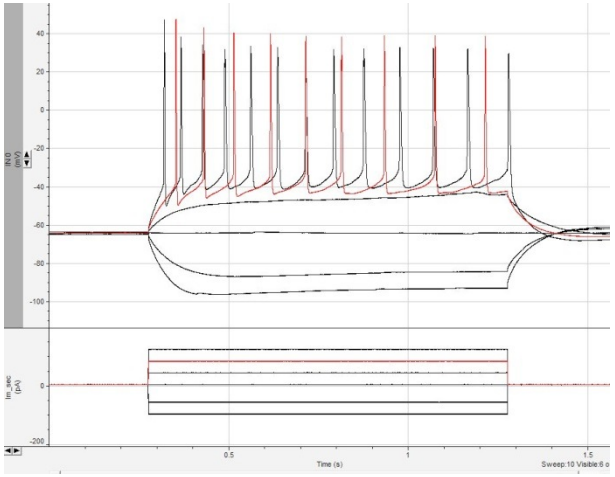
Surgery by Dr. Jeff Ojemann/Harborview

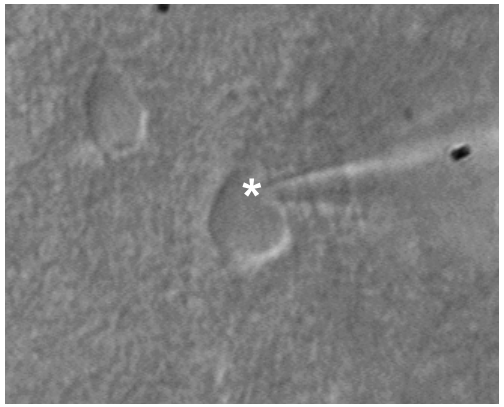
Morphological recovery of Biocytin-filled human cortical layer II pyramidal neurons



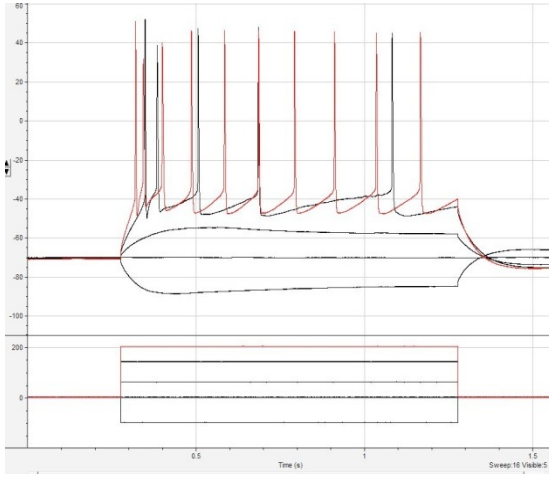
Sampling the Diversity of Human Cell Types

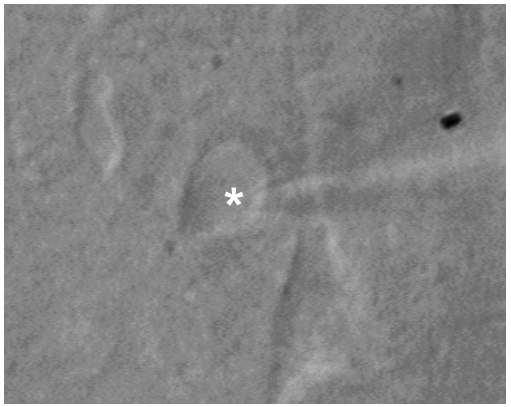
Layer II pyramidal neuron



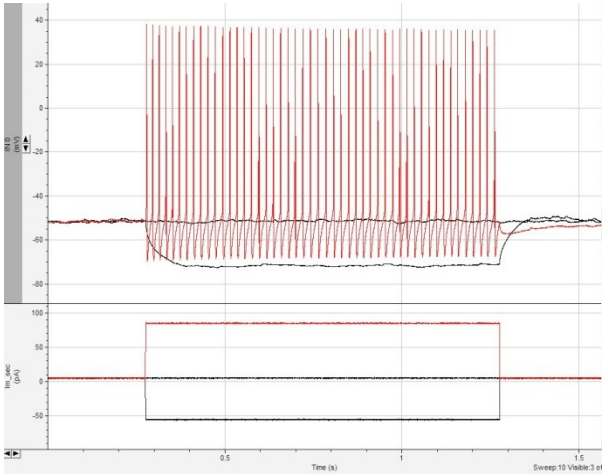


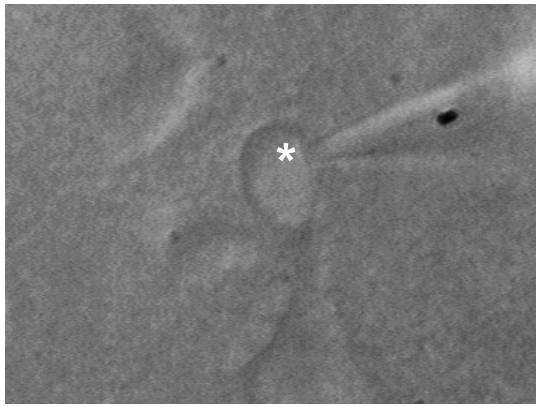
Layer V pyramidal neuron





Layer V fast-spiking interneuron





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Lein, Ting, Teeters & Mihalas

Big Science Comes to Neuroscience

These are plans for a large (250+ scientists, technologists & engineers), high throughput, 10 years effort under one roof whose fruits will continue to be freely & publicly shared via dedicated web-tools. These plans come with unique challenges

- The need to focus on a few large-scale projects
- The need to integrate distinct anatomical & physiological methods, modeling and theory ==> virtuous loop to achieve synergy
- The need to harness the creativity and drive of individual investigators while emphasizing the team aspect
- Experiment in the Sociology of Neuroscience

Acknowledgements - Paul & Jody Allen

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