Project MindScope

Exploring Cortex in a High-Throughput Manner with Experimental and Computational Techniques

Christof Koch

Allen Institute for Brain Science

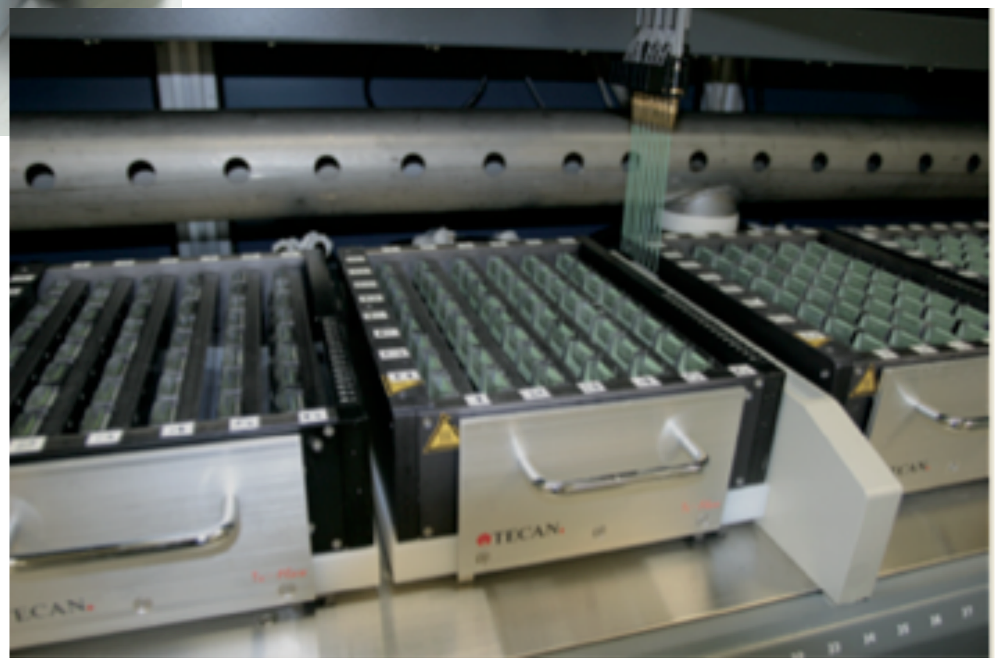
February 25th 2013

ALLEN INSTITUTE *for* BRAIN SCIENCE
Fueling Discovery

The Allen Institute for Brain Science

- An independent, non-profit research organization, founded in 2003, working to support basic research in the brain sciences
- Dedicated to making tools and information readily available to the scientific community
- 210 staff (50 PhDs)
- 75,000 sq ft across 3 buildings in Freemont/Seattle
- Not a traditional, PI-driven research institution
- Not an extramural funding agency
- Generate high quality, standardized brain-wide atlases of gene distributions using ISH and Microarrays for adult & developing mouse, adult & developing monkey, and adult and developing human brain
- Generated 3.2 million tissue sections, >1 PB of image data, 200 million gene expression measurements

The Allen Institute for Brain Science



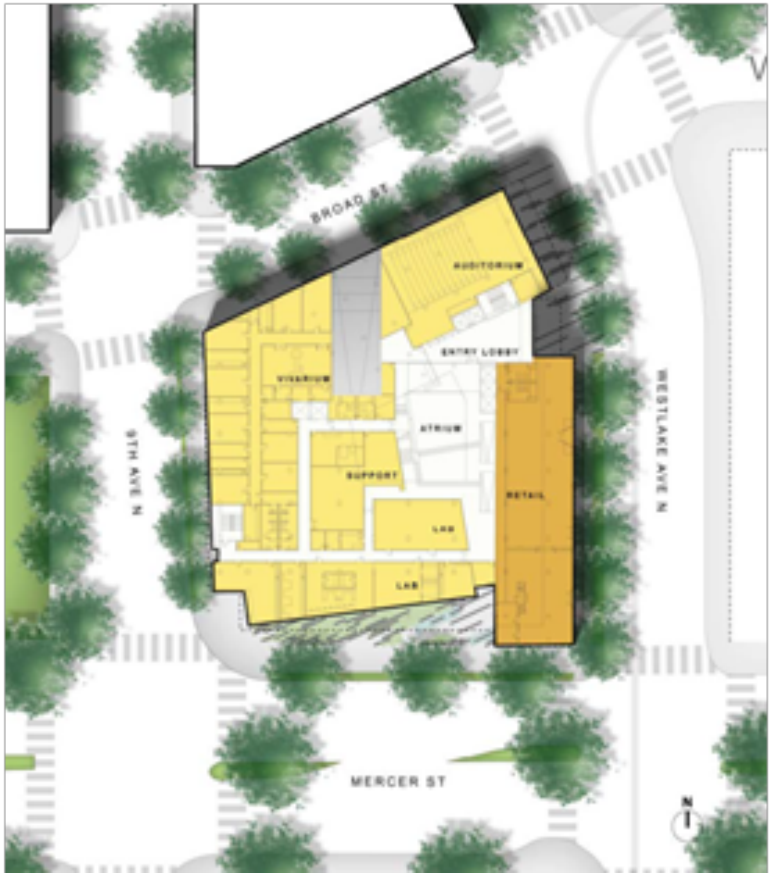
Observatories of the mind

An ambitious project to map the mouse brain at the Allen Institute for Brain Science is a huge undertaking that may unify neuroscience, argue **Christof Koch** and **R. Clay Reid**.

Neuroscience is a splintered field. Some 10,000 laboratories worldwide are pursuing distinct questions about the brain across a panoply of spatio-temporal scales and in a dizzying variety of animal species, behaviours and developmental time-points. At any large neuroscience meeting, one is struck by the pace of discovery, with 50,000 or more practitioners heading away from each other in all directions, in a sort of scientific Big Bang.

Although this independence is necessary, it has prevented neuroscience from entering a more mature phase, which would involve developing common standards and collaborative projects. Neurophysiologists are more likely to use each other's toothbrushes than each other's data and software; physiological results are hoarded and rarely made accessible online; molecular compounds and transgenic animals are shared only after publication. All of this has made comparisons across laboratories difficult and has slowed progress.

At the Allen Institute for Brain Science in Seattle, Washington, we and our colleagues are initiating an experiment in the sociology of neuroscience — a huge endeavour that will involve several hundred scientists, engineers and technicians at the institute. Philanthropist Paul G. Allen, who founded the institute in 2003, has pledged US$300 million for the first four years of an ambitious ten-year plan that will accelerate progress in neuroscience, bringing his total commitment so far to $500 million. Our goal is to attract the best young scientists and build a series of 'brain observatories', with the aim of identifying, recording and intervening in the mouse cerebral cortex, the outermost layer of the brain. Unlike the telescopes that peer at remote events in space ▸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MindScope - The Team

- Allan Jones - CEO
- Clay Reid - Neural Coding
- Hongkui Zeng - Cell Types
- Michael Hawrylycz - Modeling, Analysis & Theory
- Chinh Dang - Technology
- Stefan Mihalas, Hanchuan Peng, Ali Cetin, Anton Arkhipov, Shawn Olsen and more investigators to come
- 16 post-doctoral scientists
- Advisory Committee - L Abbott, D Anderson, G Buzsaki, E Callaway, J Maunsell, M Meister (chair), M Stryker, D Tank & G Tononi
- All of it made possible by the unprecedented generosity of Paul Allen

Astronomical Observatories

- Ground-based telescope with 30 m primary mirror - consisting of 492 adjustable hexagonal mirrors
- Spatial resolution with adaptive optics is 10x superior to Hubble
- Planning started in 2003, first light in 2018
- Estimated (2009) cost $1 Billion
- We want to do something similar with methods that are

➡Standardizable

➡Reproducible

➡Accurate

➡Scalable

MindScope - Mission

We seek to understand the computations that lead from photons to behavior by observing and modeling the physical transformations of signals in the cortico-thalamic visual system within a few perception-action cycles (< 2 sec). We want to catalogue and characterize the cellular building blocks of the cerebral cortex, their dynamics and the cell-type specific, structural ($w_{\alpha,\beta}$) and functional ($w_{i,j}$) connectomes. We want to know what the animal sees, how it thinks, and how it decides. We want to map out the murine mind in a quantitative manner.

The vision - *MindScope* focuses enormous in-house resources and the labor of 250+ scientists, engineers & technicians onto the most complex piece of organized matter in the known universe - the mammalian cortico-thalamic system. The aim of *MindScope* is to discover and understand the canonical computations performed by neocortex. Knowledge gained through *MindScope* will impact both science and the clinic.

The challenge - *MindScope* must be more than the union of its parts. It has to achieve synergy.

Some 10 years objectives -

Exhaustively characterize cortico-thalamic cell types at the single cell level and their cell-type specific (genetic; $w_{\alpha,\beta}$) and functional ($w_{i,j}$) connectomes

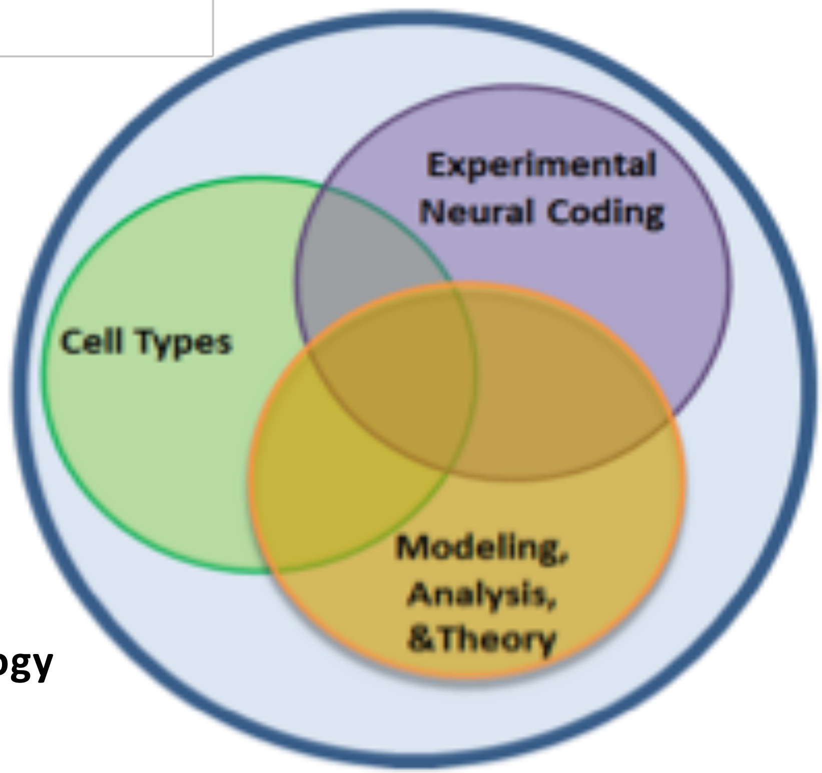
Observe large-scale cellular responses in sleeping, resting and behaving mice while intervening with optogenetic techniques to understand cortical function

Construct large-scale simulator (*iSee*) and use the structural data to model the observed dynamics at the cellular and behavioral levels

Make these and others (software; silicon probes) resources publicly available

MindScope - Organization

Biotech like matrixed organization



Engineering, Program Management, Technology

Understanding Coding

How do the ~2 million nerve cells in the mouse visual cortex represent & transform visual information into behavior? We plan to

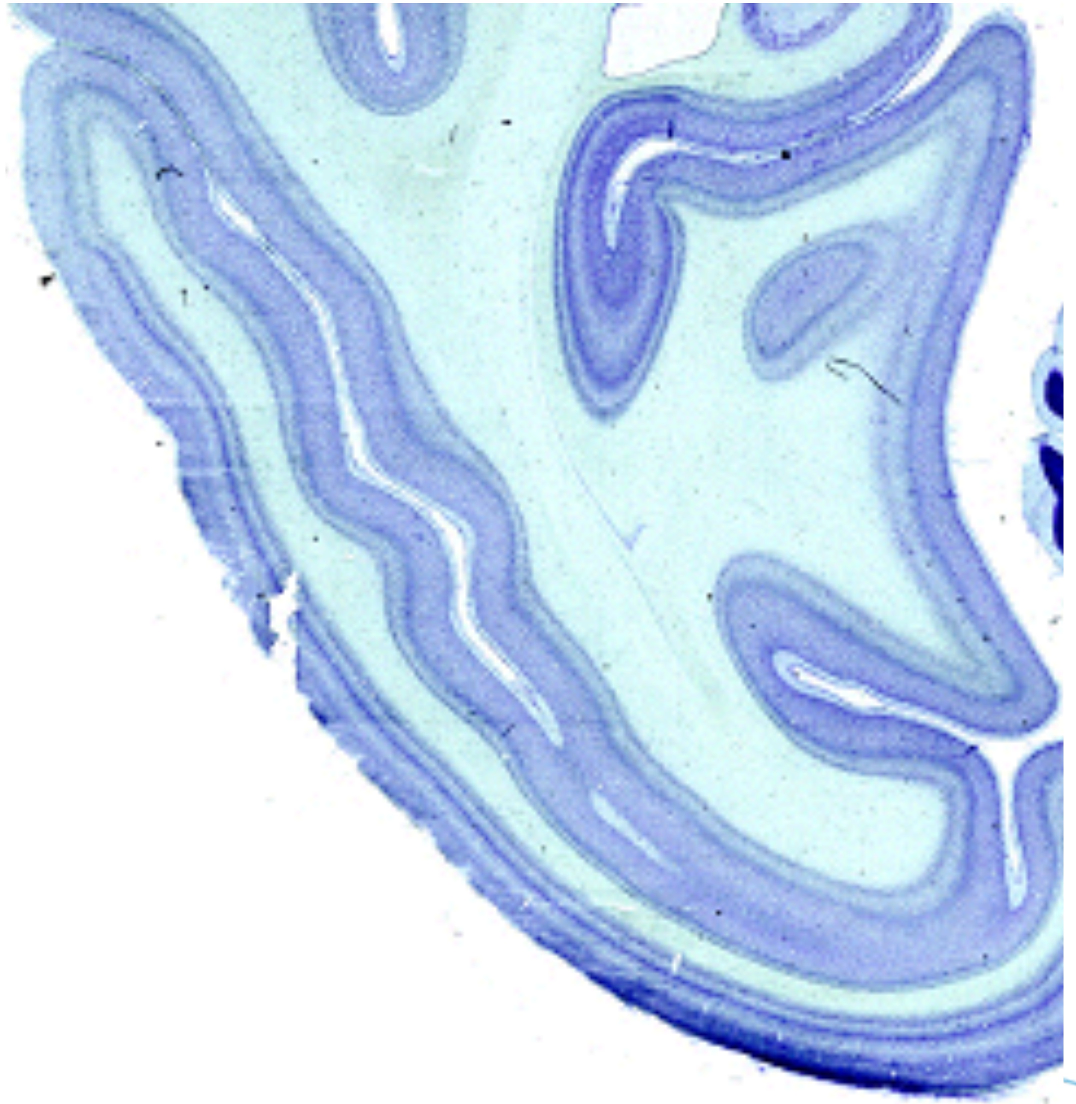
- **Describe -** Characterize genetically identified cell classes and their projections, first under *in vitro* and *in vivo* conditions
- **Count -** Quantify neuroanatomy (cells, cell types, synapses, xyz)
- **Record -** Observe spiking of different cell types under a few canonical behaviors (quiet wakefulness, deep sleep, binary choice behavior)
- **Interfere** - Turn groups of neurons on/off
- **Model** - Describe and predict neuronal dynamics
- **Understand** - Use theories from physics, computer science and mathematics

Why is this difficult?

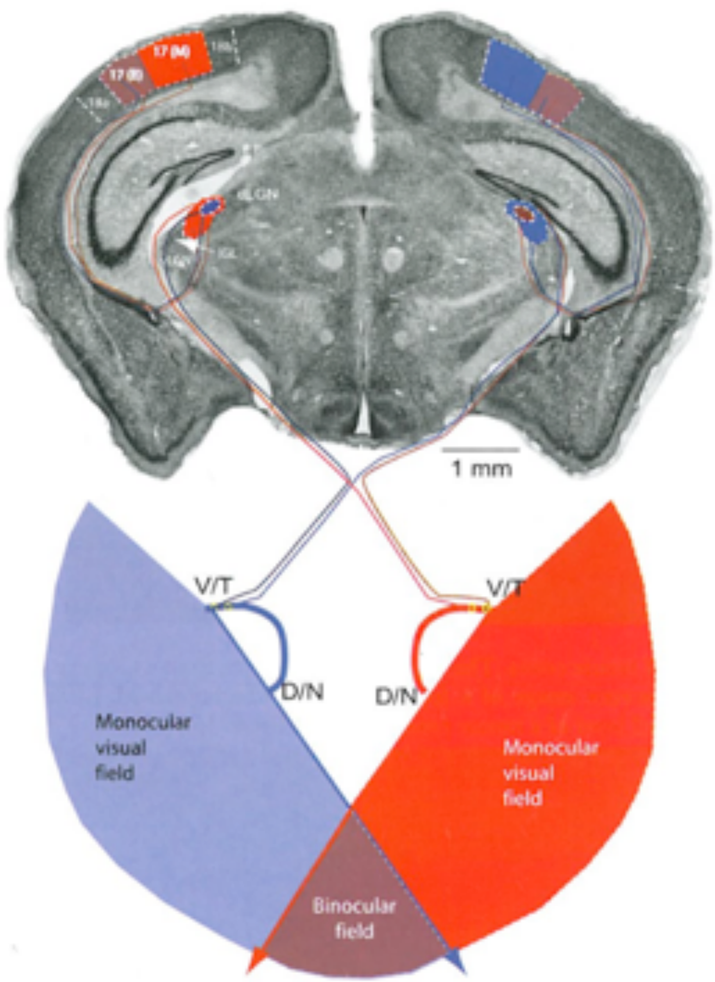
- There are **lots** of neurons
- Difficult to simultaneously record from more than 0.001% of them
- We don't have a list of the cellular components
- No accepted standards for relevant phenomenon - 40 Hz oscillations, synchrony, synfire chain, sharp wave
- No central unifying projects
- O(10,000) laboratories 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

Why Study Neocortex?

- Cortex is a planar computational tissue
- Varies 10^5 in surface areas across mammals
- Relative uniformity
- What is the core, columnar operation performed by cortex that makes natural intelligence so robust and flexible?



Why Study the Mouse?

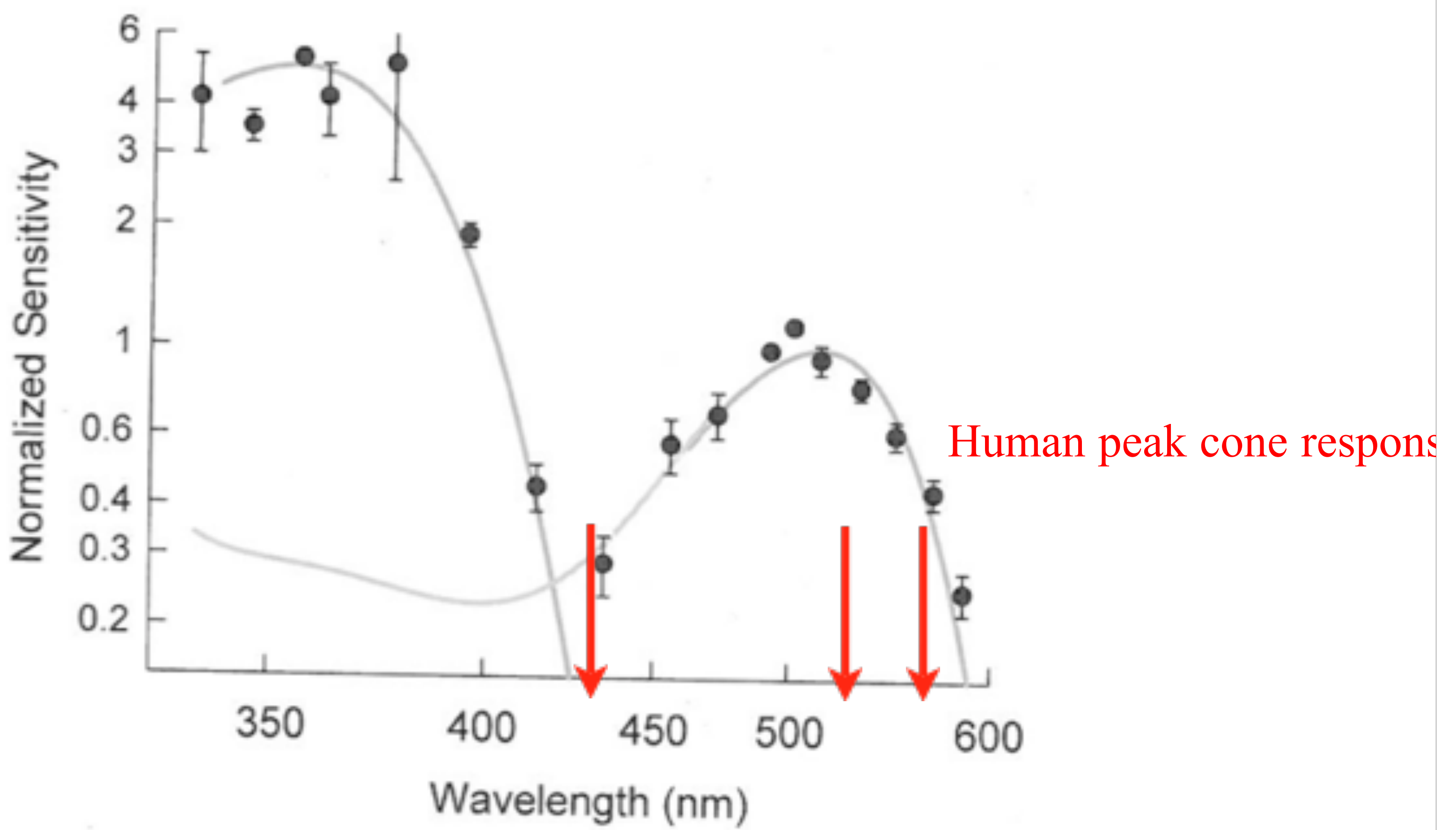


- Lissencephalic animal
- We can intervene at a given point in time, space and in a chosen neuronal population using optogenetics
- Small enough to be feasible to model yet structural similar to human neocortex
- Standardizable, cortex-dependent visuo-motor behaviors
- Can be used to study attention & consciousness

Human - Mouse comparison

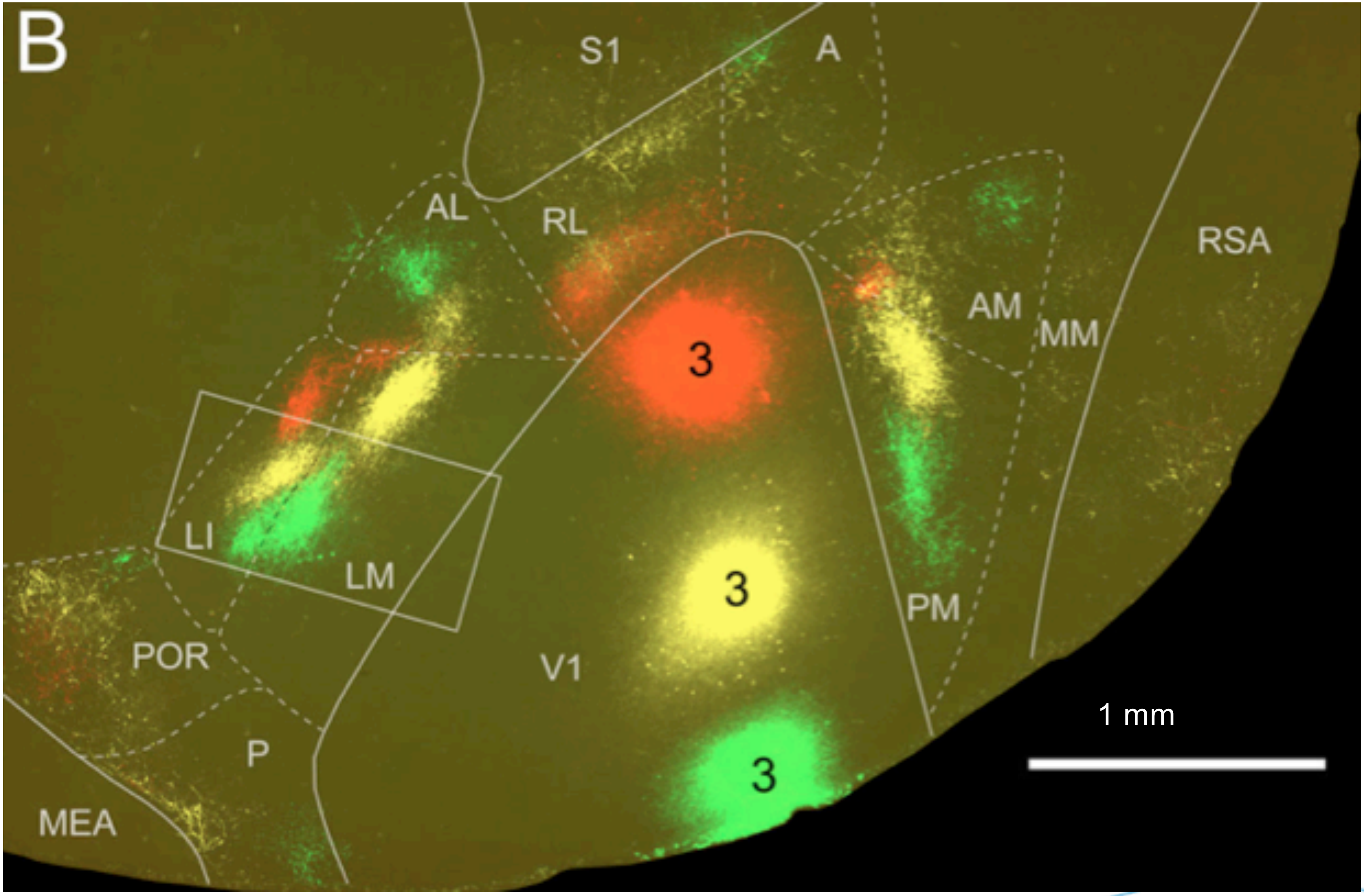
	Human	Mouse
Mass	1500 gr	0.5 gr
Number of neurons	86 billion	71 million
Neurons in cortex	16 billion	14 million
Visual cortex	20% of cortex	10% of cortex
Number of neurons	5 billion	1-2 million
Axons in optic nerve	1 million	44 thousand
Cortical regions	30	10

Cone Vision in the Mouse



Lyubarsky, Nikonov, Daniele & Pugh
(2010)

Mouse Visual Cortex



Wang & Burkhalter (2007)

Connectivity Atlas

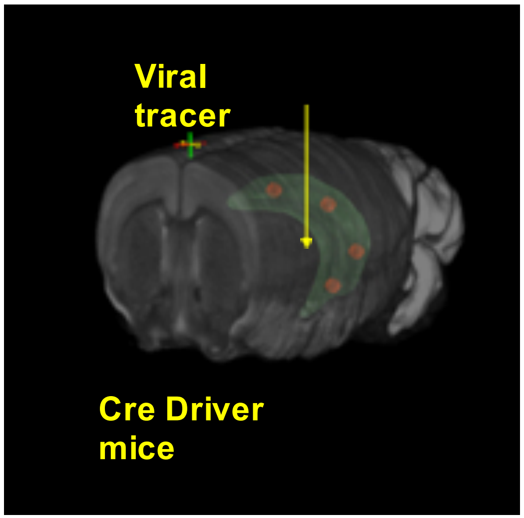
- Anterograde tracing using viral tracer from ~300 brain regions and diverse neuronal populations defined by ~100 Cre drivers lines, and visualized using two-photon tomography
- EGFP-expressing adeno-associated virus vector (rAAV), compared to classical BDA tracer, in adult (P56) C57BL/6J mice
- 300 anatomically defined brain regions and 130 Cre-defined cell types (phase 2)
- Automated (*TissueCyte* 1000) serial two-photon tomography (0.35 µm x-y resolution; z-stacks at 100 µm)
- Reconstruct the brain, via a stack of 140 images at 750 GB total, in 19 hrs
- Free, online database (> 1.2 PB), viewable in 3-D *BrainExplorer*
- 4 year project lead by Hongkui Zeng, with Seung Wook Oh, Julie Harris, Lydia Ng and many others

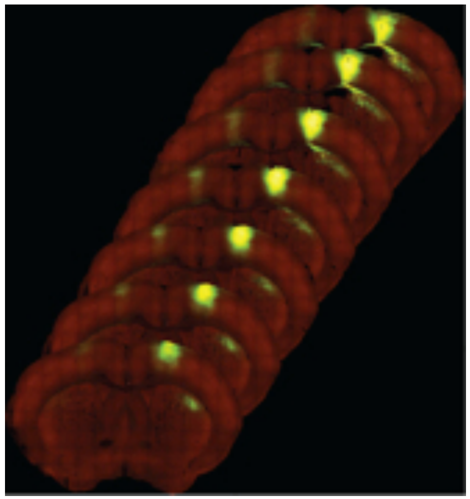
Connectivity Atlas

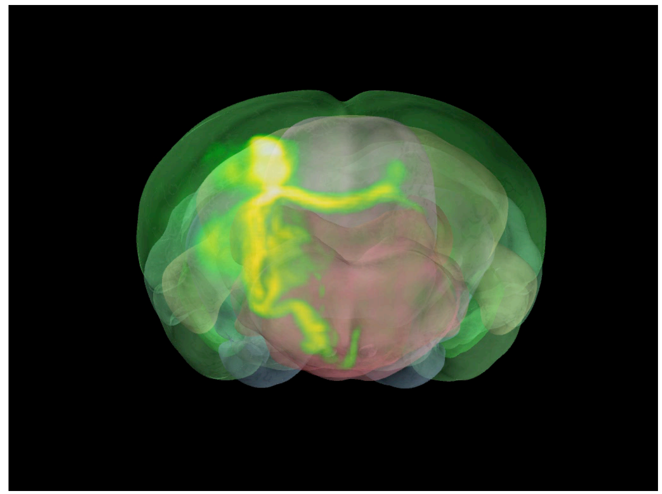
Stereotaxic Injections
(300-500 brain regions, >100 cell-type specific Cre mice)

→ **High-throughput Fluorescence Imaging**

→ **3D Connectivity Map & Model**







Connectivity Atlas Pipeline

Pre-Pipeline Activities

- Viral tracer validation
- Injection site screening
- Cre line characterization

Stereotaxic Injection

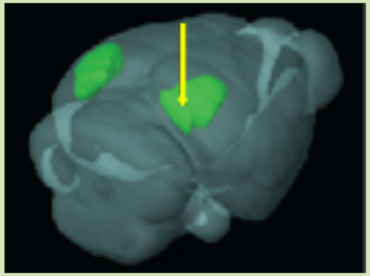
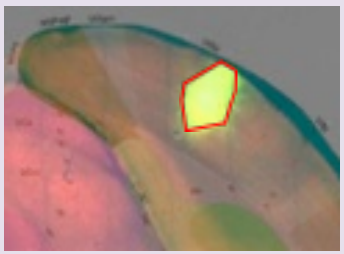
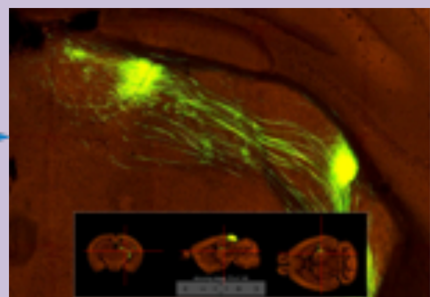


Image Acquisition

Data QC and Injection Site Annotation



Informatics Processing



Online Database

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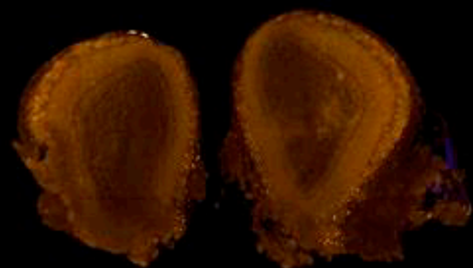
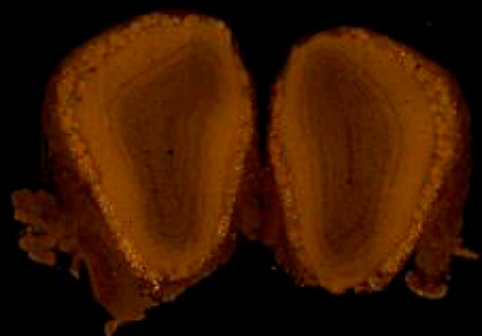
Seung Wook Oh

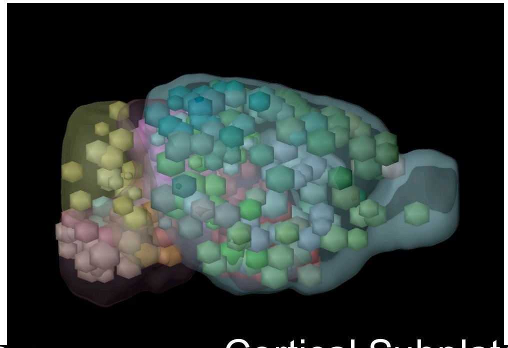
Primary Visual Cortex Injection

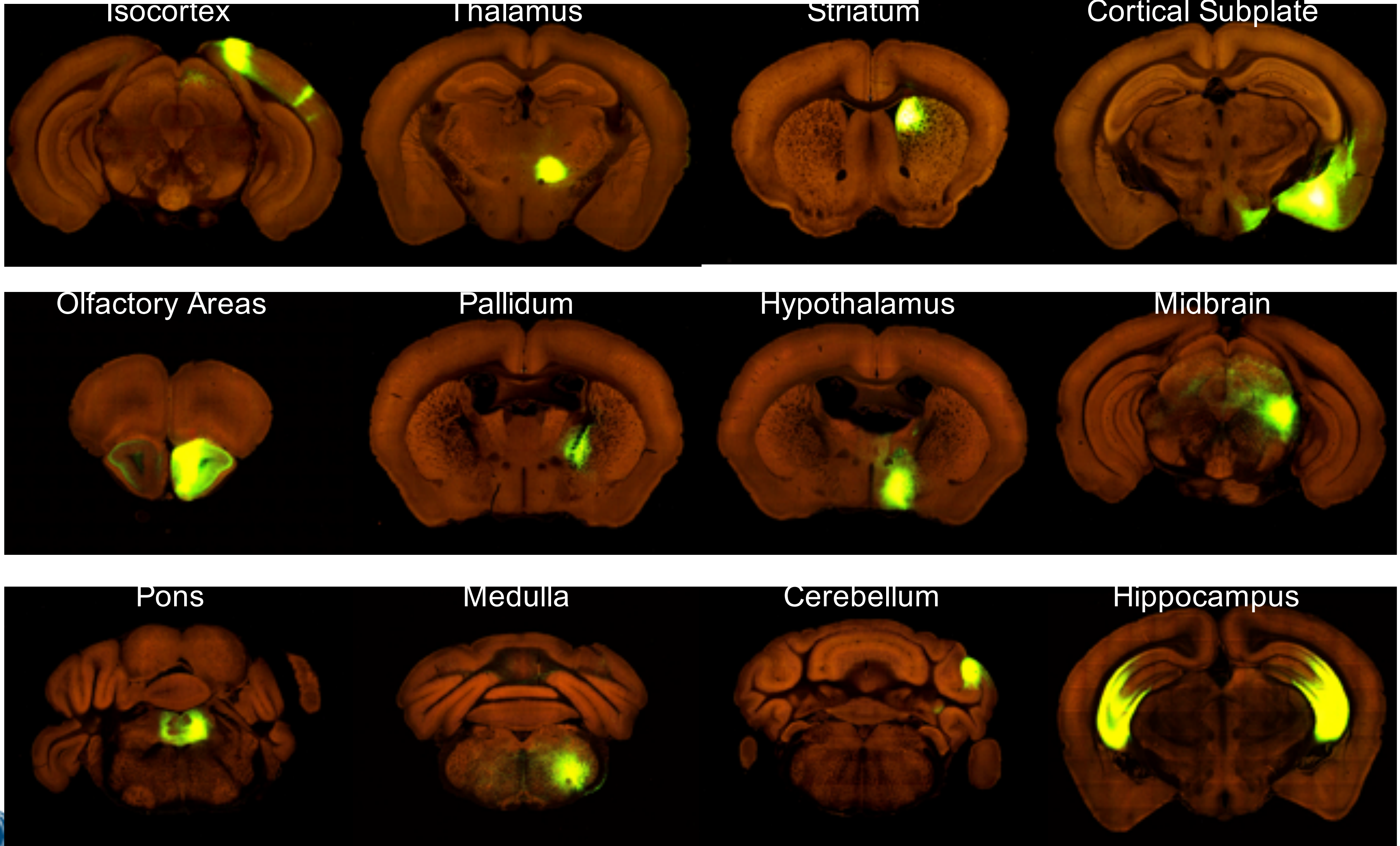


Ventromedial Thalamus



Injection Sites Distributed Throughout Major Brain Structures

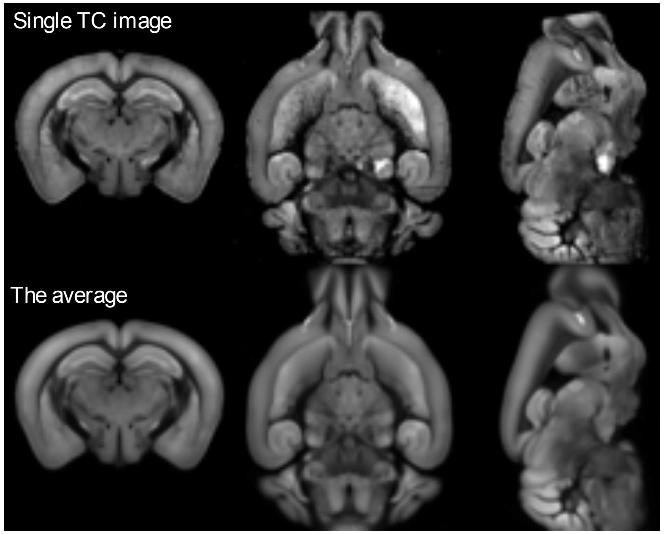




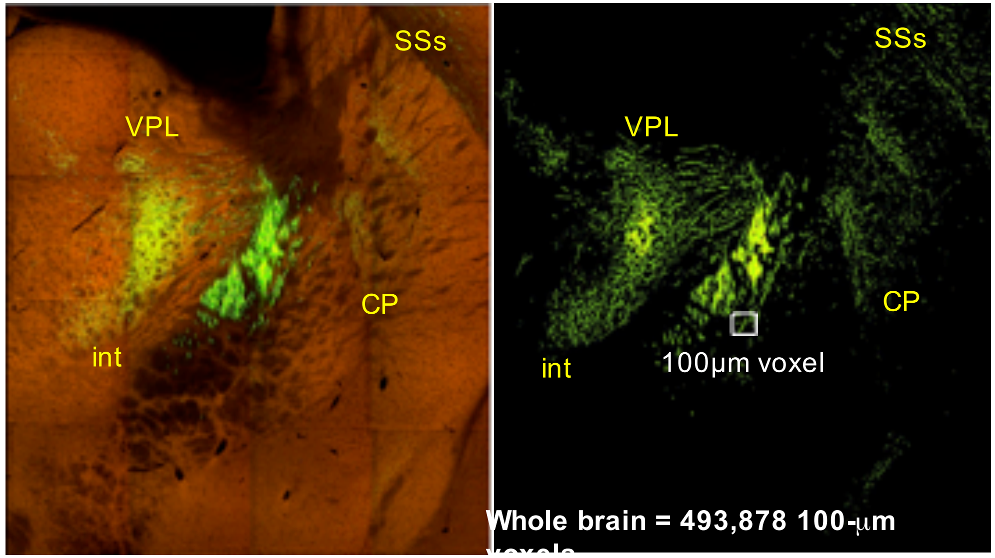
Julie Harris

Informatics Data Processing

Alignment and Registration



Segmentation and Signal Detection



3D Brain Explorer

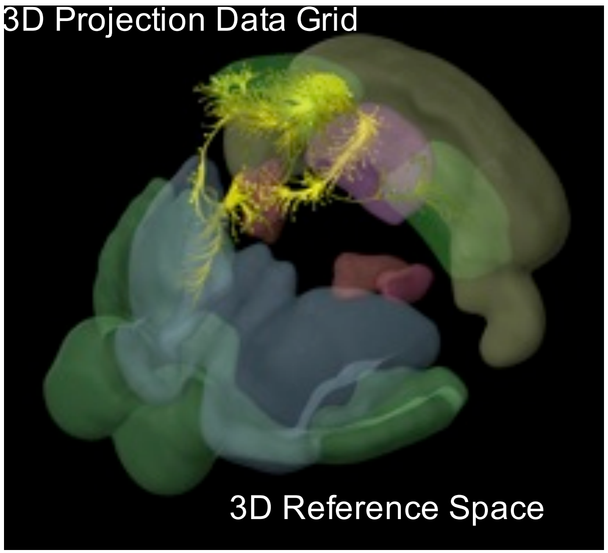
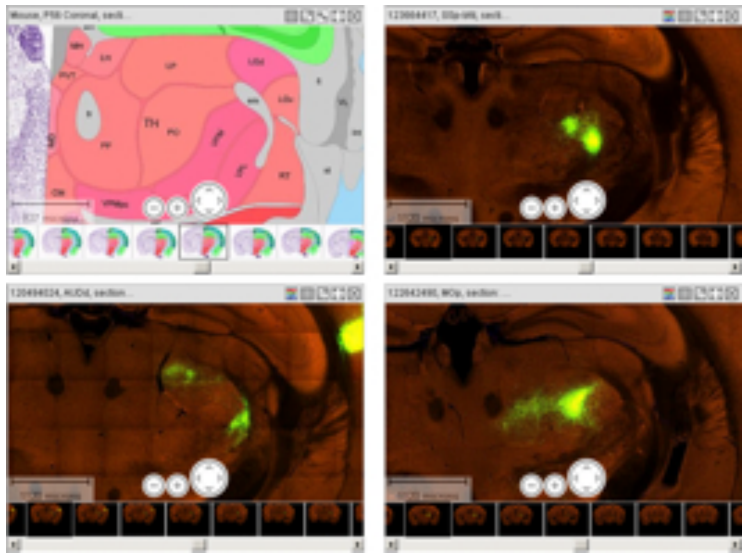


Image "sync" with reference atlas



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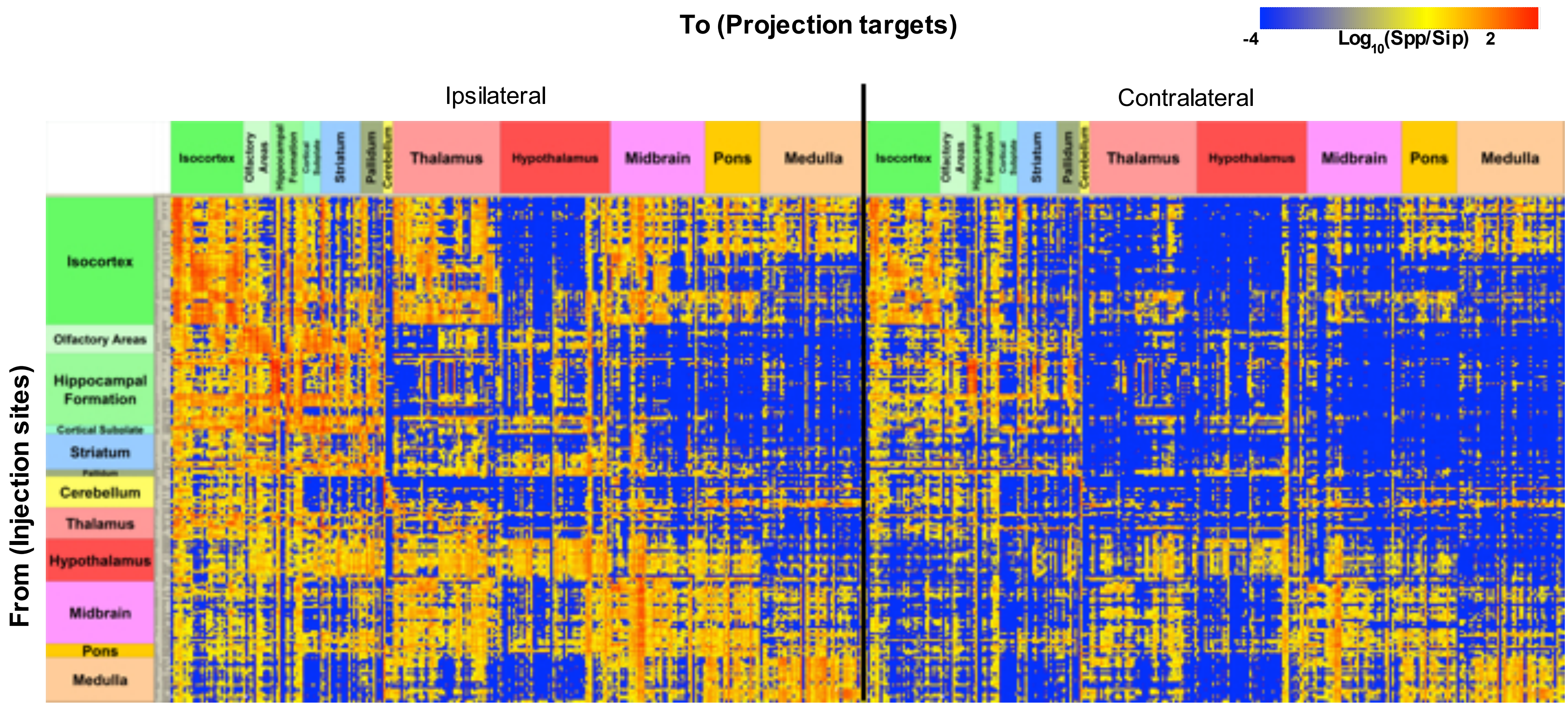
Lydia Ng, Chris Lau, Leonard Kuan, Chinh Dang

Connectivity Matrix for the Entire Mouse Brain



Ng, Lau, Kuan, Dang, Harris, Wook Oh, Zeng ...

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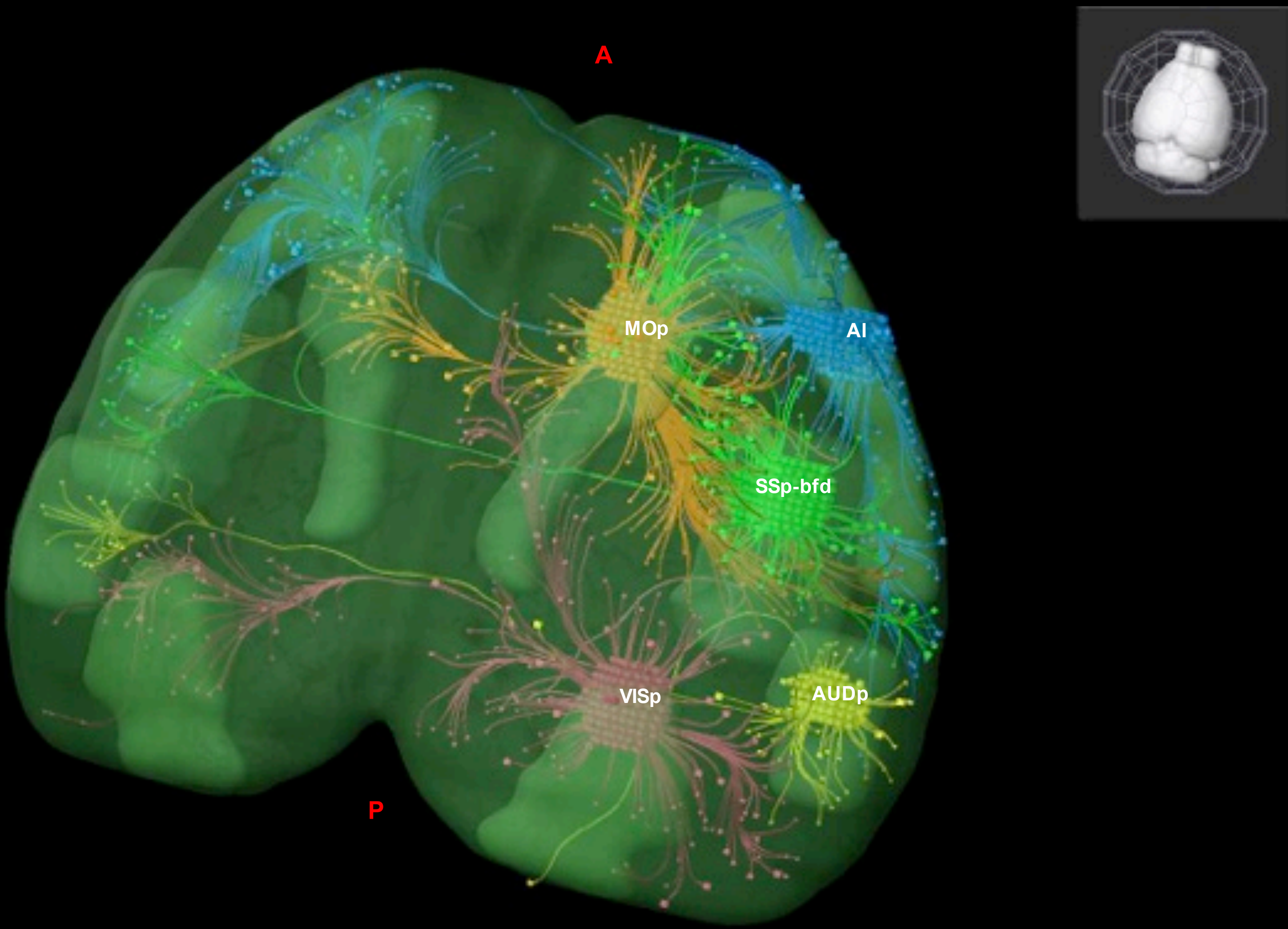
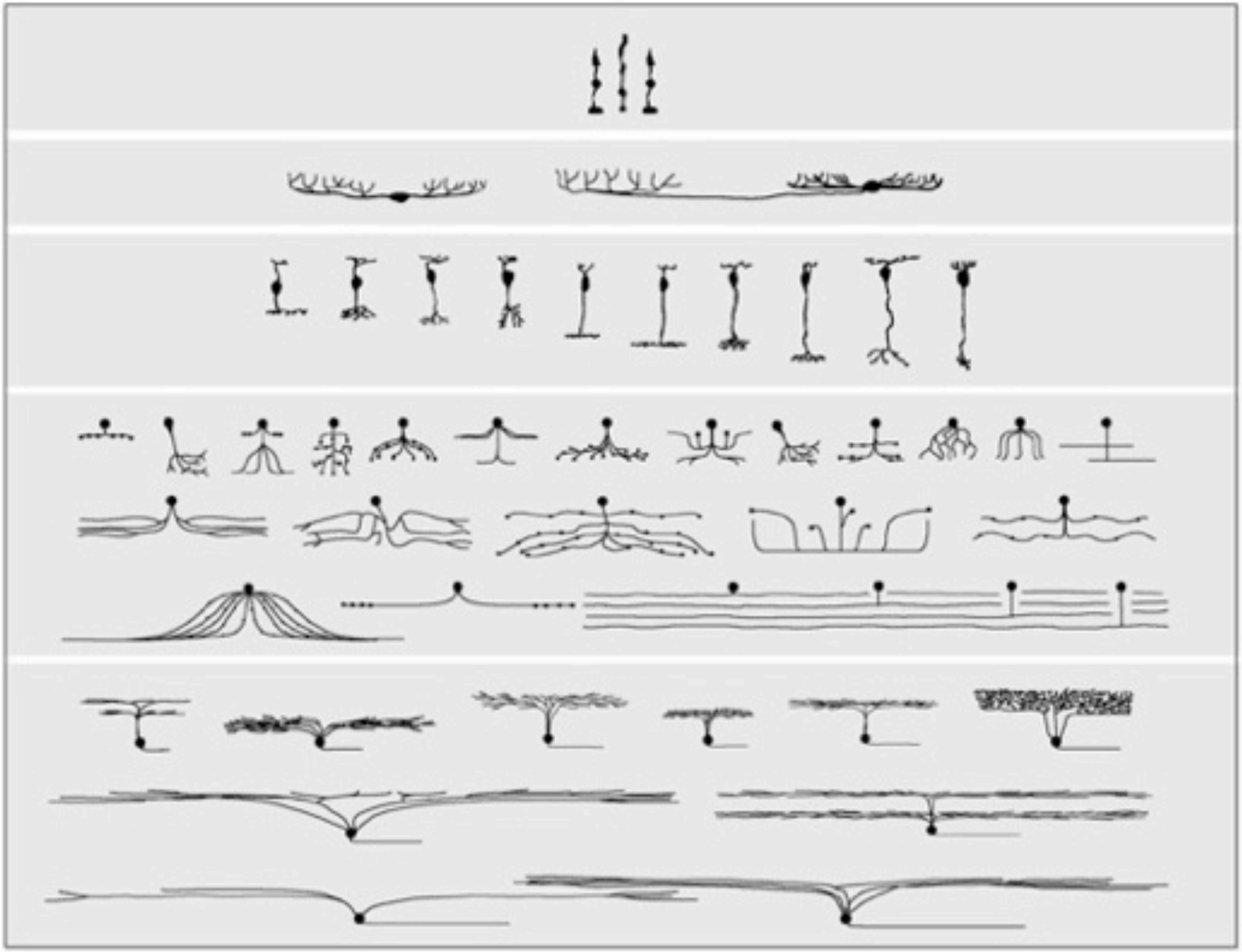
Cortical Projection Map



All data at

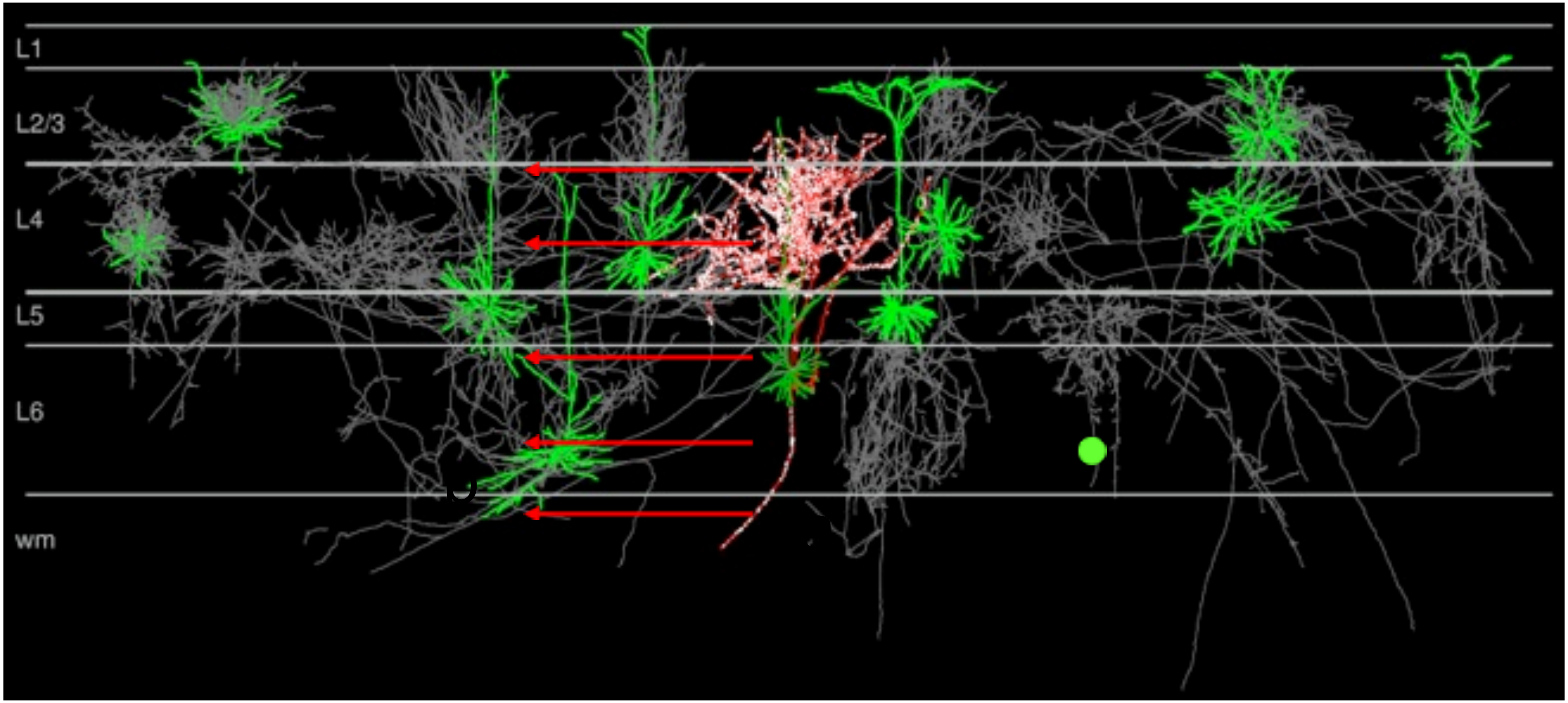
http://connectivity.brain-map.org

Retinal Cell Types



Masland (2001)

Cortical Cell Types and Connectivity



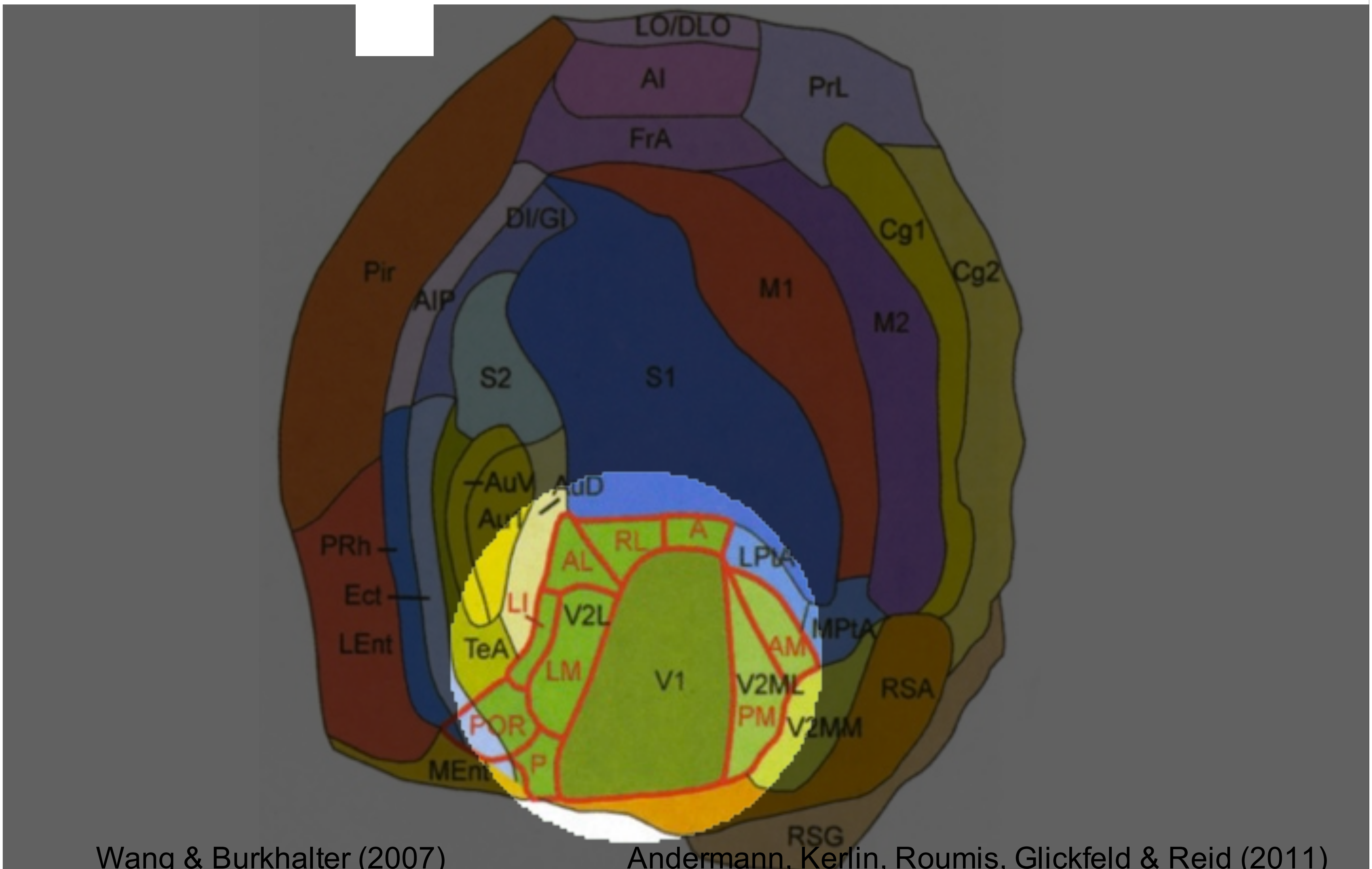
Proportion of synapses of type a formed with type b in layer u	=	Proportion of dendrites of type b in layer u	(Peters' rule)

Binzegger, Douglas & Martin (2004)

Near-Term Goals for Cell Types

- Complete census of all cells (neurons) in mouse cortex
- Establishing technologies and metrics for cell type taxonomy
- 3D reconstruction of full morphology of sparsely labeled neurons representative of each major cell type
- Full-panel characterization of physiological and synaptic properties of visual cortical neurons representative of each major cell type
- Transcriptome profiling of major cell types
- Proof-of-principle studies to link single cell gene expression to morphology and physiology
- Cell Type Connectome ($w_{\alpha\beta}$): Evaluate connectivity between cell types through trans-synaptic, optogenetic and multi-patch recordings, starting with layer 4 neurons
- Developing an online public database for cell types

2-Photon Calcium Imaging in Behaving Animals

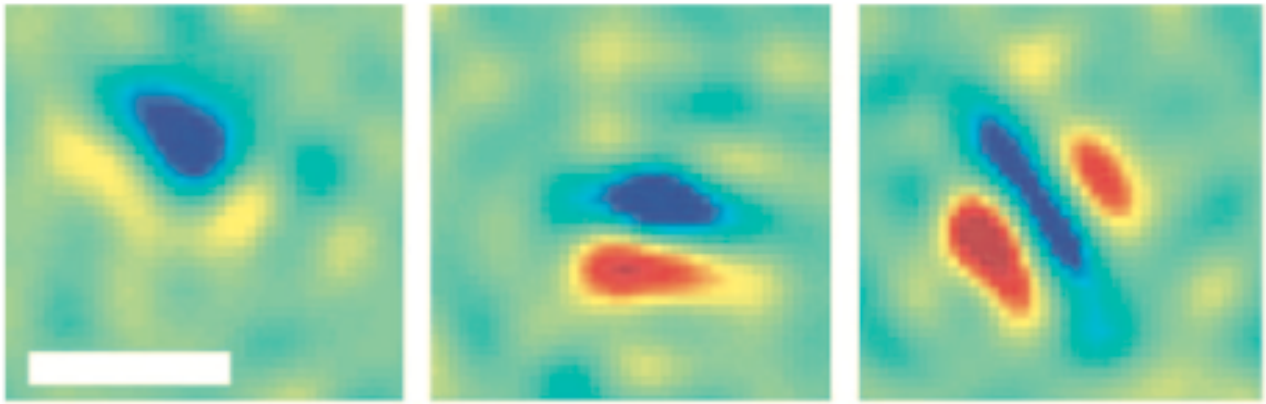


Wang & Burkhalter (2007)

Andermann, Kerlin, Roumis, Glickfeld & Reid (2011)

Mouse Primary Visual Cortex

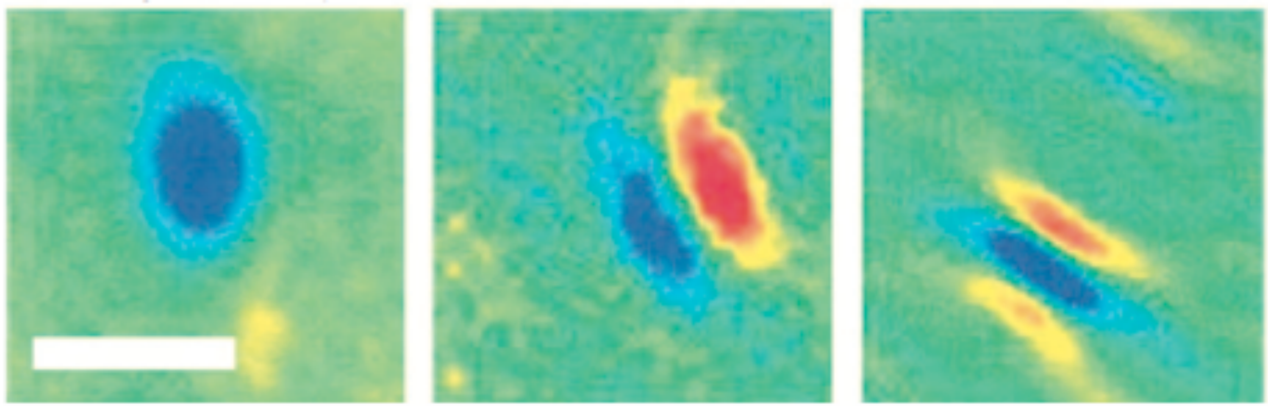
Mouse V1



20^o

Niell & Stryker (2008)

Monkey V1



1^o

Ringach (2002)

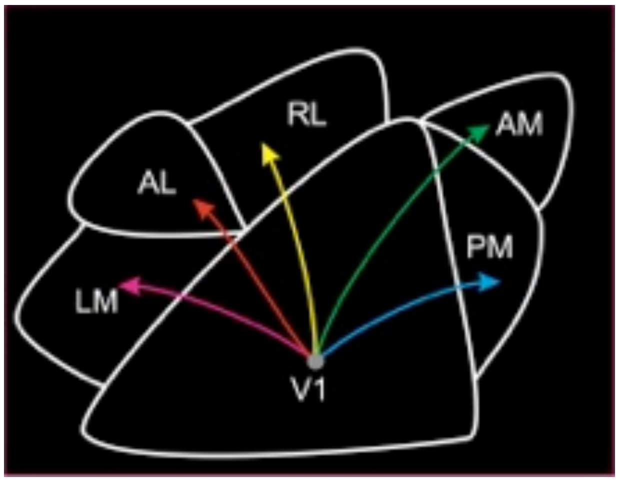
Relationship between cell types, anatomy, and cortical function

Large-scale cortical networks

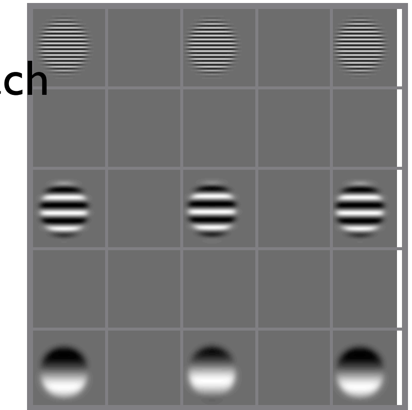
How are physiological responses in each area related to:

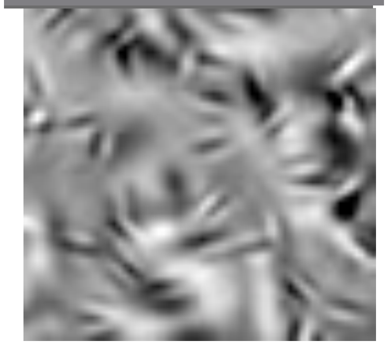
- Visual input and/or behavior
- Cell types
- Physiology of afferents (FF, FB)
- Projection targets

Can we explain a behavior, from retina through action?



Stimuli / Behavior



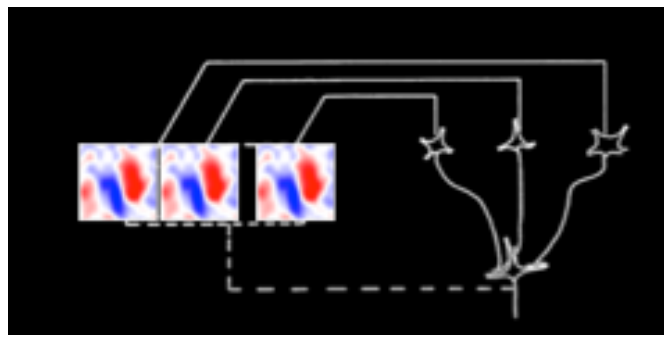


Local cortical networks

Are *local connections* related to:

- Physiology: receptive fields *and* activity during behavior
- Local geometry of neurons
- Cell types (HZ)

With associated anatomy, can we build a mechanistic model of the whole thing, at the single-cell level



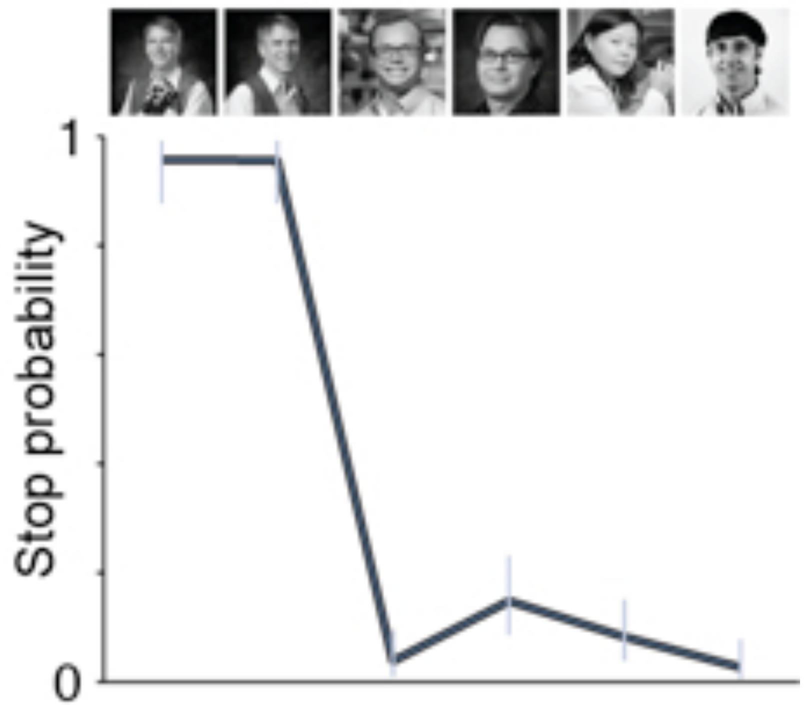
Mitzuseki, Durand, Reid...

Axonal projections from V1 to higher areas are selectively driven by different visual stimuli

	Mean OSI	Mean DSI	Pref. SF (cpd)	Pref. TF (Hz)
V1	0.5	0.26	0.045	0.69
LM	0.55	0.27	0.028	1.8
LI	0.56	0.28	0.04	1.5
AL	0.72	0.35	0.022	1.2
RL	0.69	0.35	0.025	1.3
AM	0.81	0.38	0.033	1.6
PM	0.67	0.29	0.046	0.87

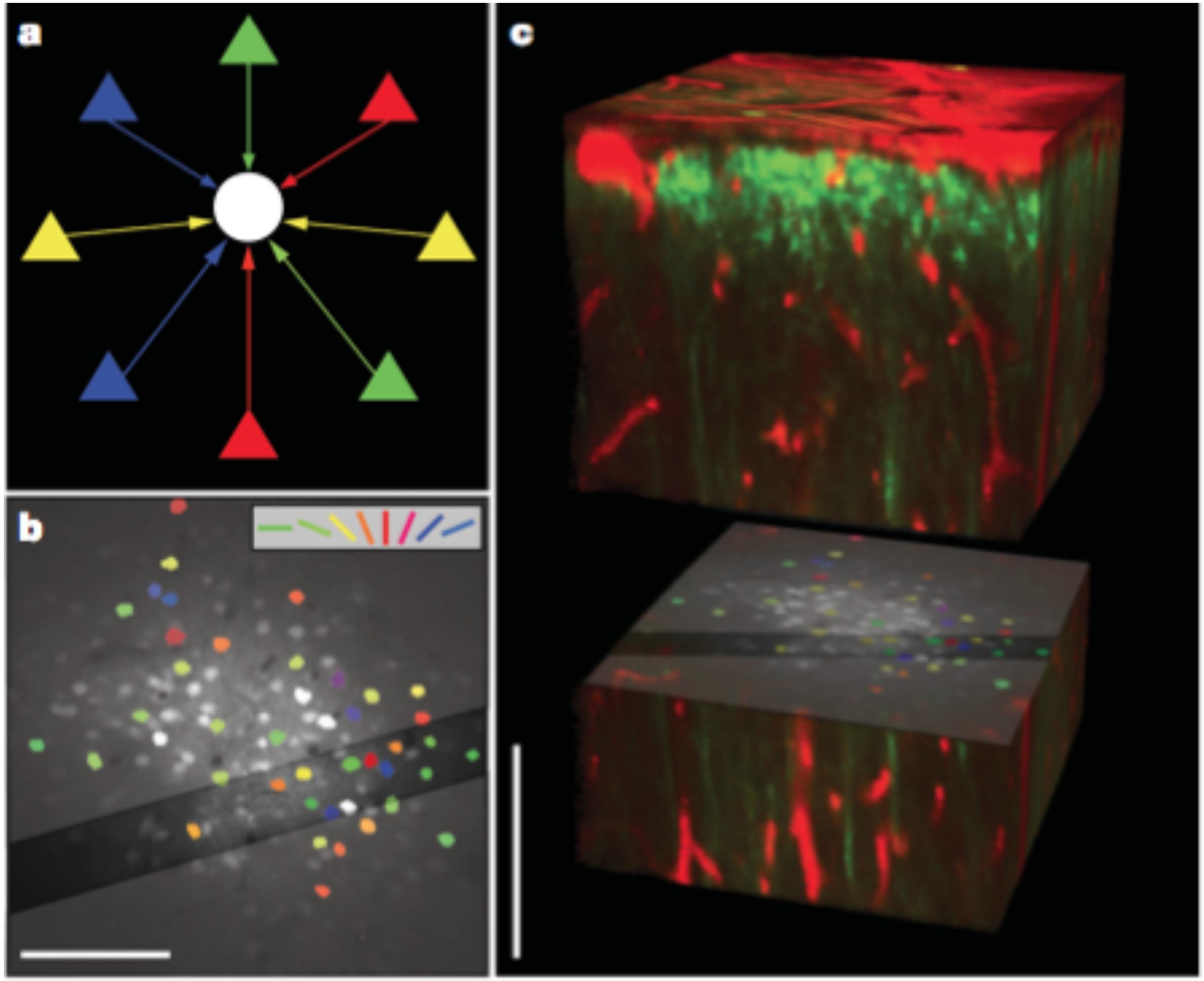
Marshel *et al.* (2011) and Andermann *et al.* (2011)

Foraging for Christof

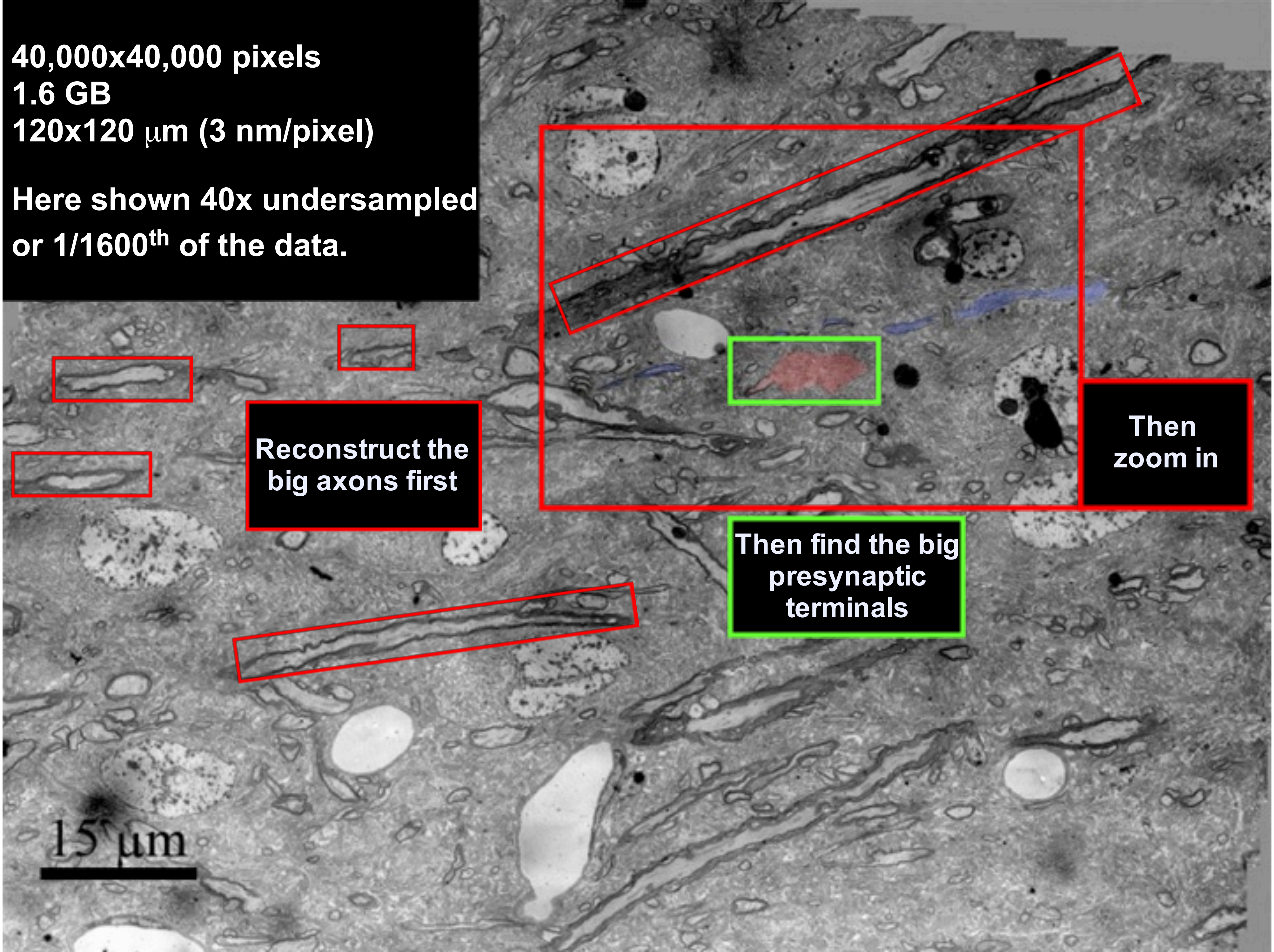


Shawn Olsen, unpublished

Functional Imaging and Electron-Microscopic Reconstruction



Book *et al.* (*Nature* 2011)


40,000x40,000 pixels
1.6 GB
120x120 μm (3 nm/pixel)
Here shown 40x undersampled or 1/1600th of the data.
Reconstruct the big axons first
Then zoom in
Then find the big presynaptic terminals
15 μm

Near-Term Goals for Neural Coding

- Surveys of visual physiology and spontaneous activity of major cell types in V1 and higher visual areas (HVAs) for sleep, alert, and running.
- The Functional Projectome. Perform surveys of visual physiology and spontaneous activity of neurons that project between each visual area (LGN, V1 and HVAs) under different states.
- The V1 Functional Connectome (w_{ij}). Evaluate connectivity between individual cells with known *in vivo* functional properties, through serial-section EM and viral tracing.
- Develop behaviors that can be used to assess the relative importance of different cell types and visual areas in different aspects of vision and decision making, as assessed with optogenetic perturbations.
- Develop multi-electrode recording systems and optogenetic tools to identify cell types with extracellular recordings
- Develop systems for high-throughput, wide field two-photon imaging

From Correlation to Causation

- Use engineered animals and/or viral delivery of ChR2, NpHR, Arch, tdTomato ... to selectively (in)-activate cell class and synaptic connections in a few, canonical behaviors
- Delivered > 3,500 engineered mice, such as Ai32, to labs throughout the world
- Develop suitable sensitive behavioral assay that involve cortex - change detection, selective visual attention, learning
- Inactivate cortico-cortical and cortico-thalamic feedback (*zombie mice*; Crick & Koch; Tononi)

Computational Neuroanatomy

- Convert several TB/day of images into actionable data
- Count cell types, neurons, synaptic boutons, spines
- Extract location of neurons and their targets - for physiology, 2PCI and cell type work - wrt standard atlas (*Waxholm Space*)
- Match cell morphology against database and generate cell models

Hanchuan Peng & Mike Hawrylycz

Modeling, Analysis and Theory - Mike Hawrylycz

Mission:

Construct single neuron and small circuit models based on our *in vitro* physiological studies, combine them with our detailed connectivity and cell type data, to replicate statistics of our *in vivo* physiology and behavior

Strategy:

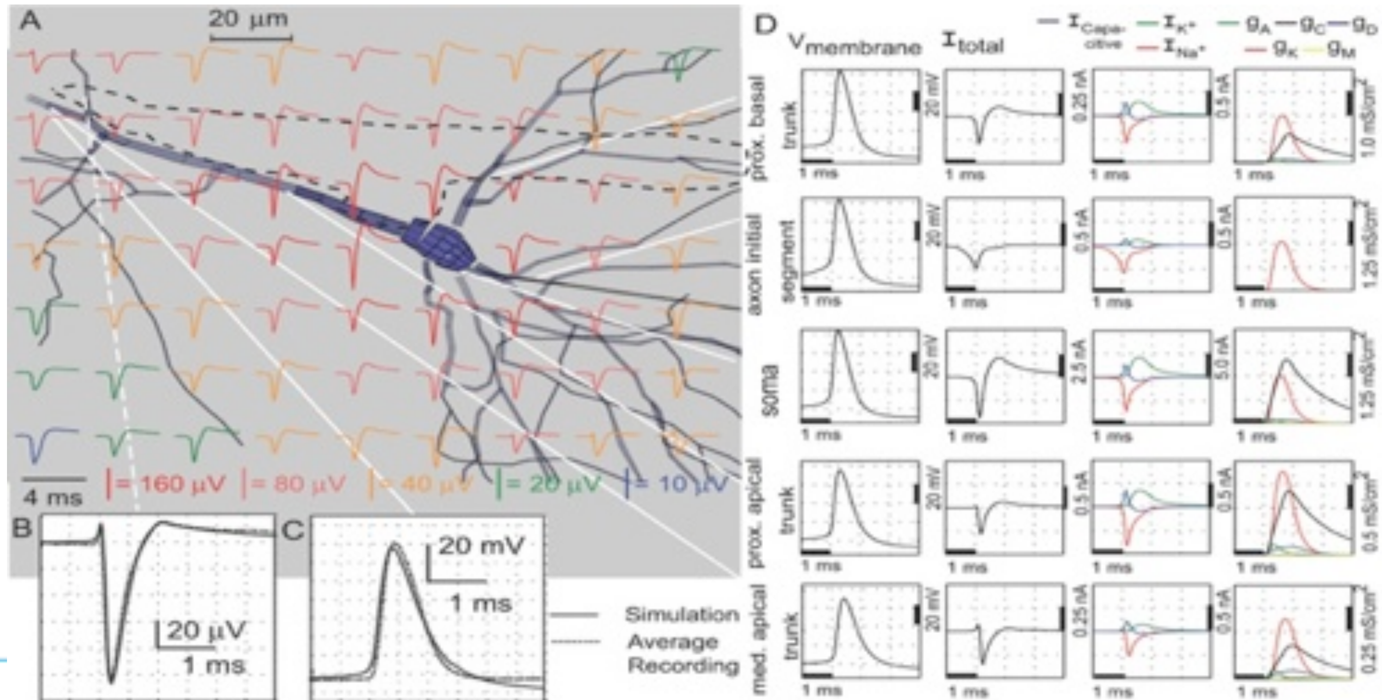
Each model series will start as simple as possible and cellular complexity will be added only if desired behaviors can not be reproduced. The sensitivity of all models to important parameters will be analyzed (*Dakota @ Sandia*)

Coarse-Grained Models

- *iSee,* a coarse-based model that links images & movies to spiking in different cell types with realistic receptive fields in V1
- Link neurons to behavior
- Can simulate state changes (e.g. sleep; Hill & Tononi)
- Retina/LGN module converts images and movies into spikes of distinct RGCs
- Desig, in collaboration with *Google*, a free, open-source, web-based, cross-platform collaboration and simulation environment that efficiently runs integrate-and-fire networks (*Brian;* 1 M units with 1 B synapses) in the Cloud (*BigBrain*)

Biophysical Detailed Modeling

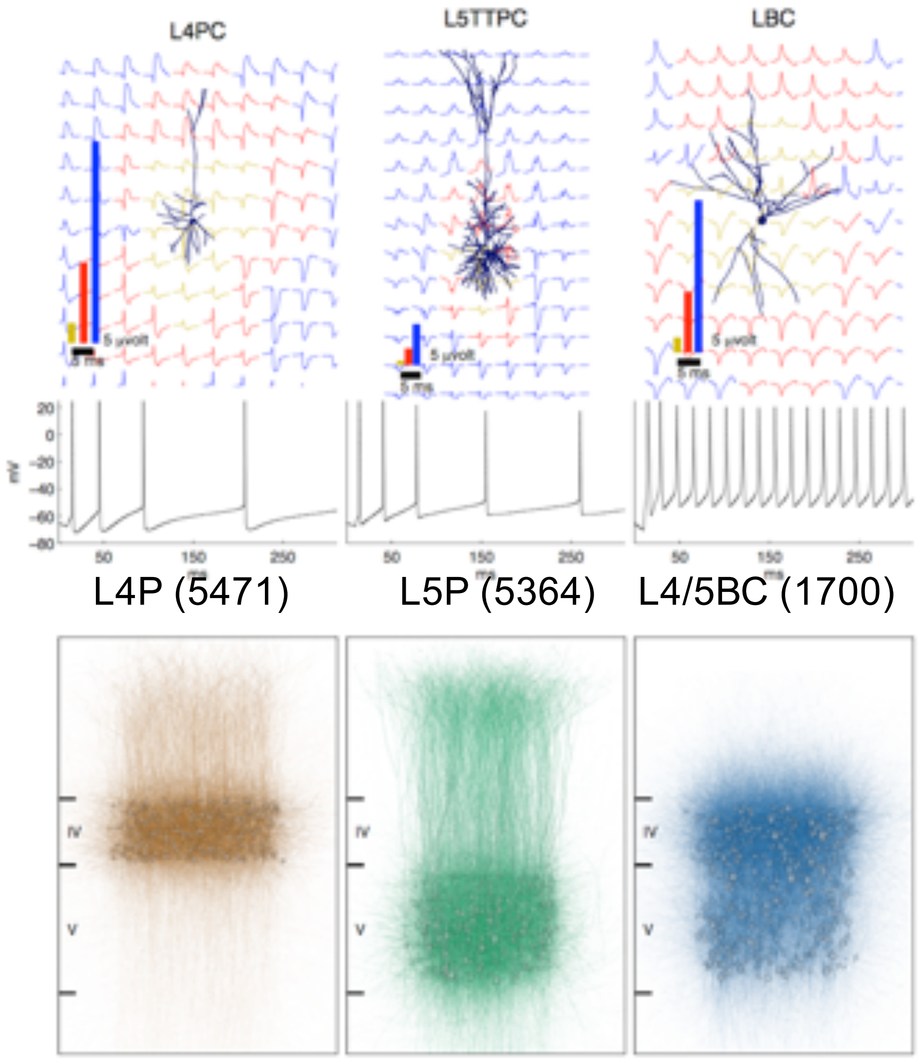
- Model the (bio)physics of excitable tissue using 100s of spatial compartments and conductance based HH-descriptions of synaptic, calcium- and voltage-dependent currents
- Can be made arbitrarily realistic, but expensive to simulate
- Includes calcium dynamics (important to link to 2-PCI) and the electric field (LFP)



Gold,Henze, Koch & Buzsaki (2006)

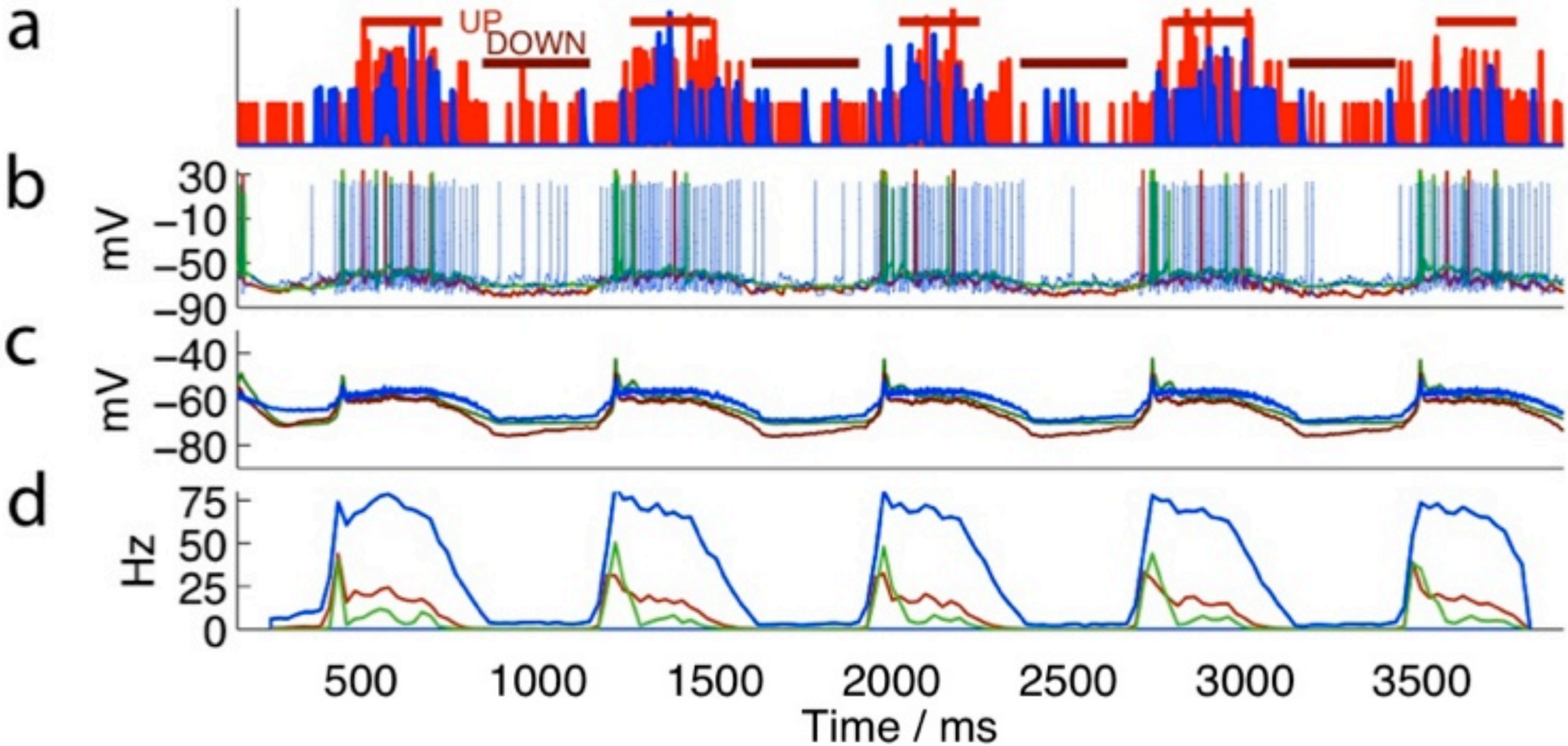
Biophysical Detailed Modeling

- Both high computational cost per neuron and high communication/computation cost *per node* for large networks
- 12,500 neurons, 5 M compartments and 15 M synapses on 4,096 CPUs on *IBM* BlueGene P
- 45 min for 1 sec simulated time
- Collaboration with *BlueBrainProject* at EPFL
- Written in Neuron and C++



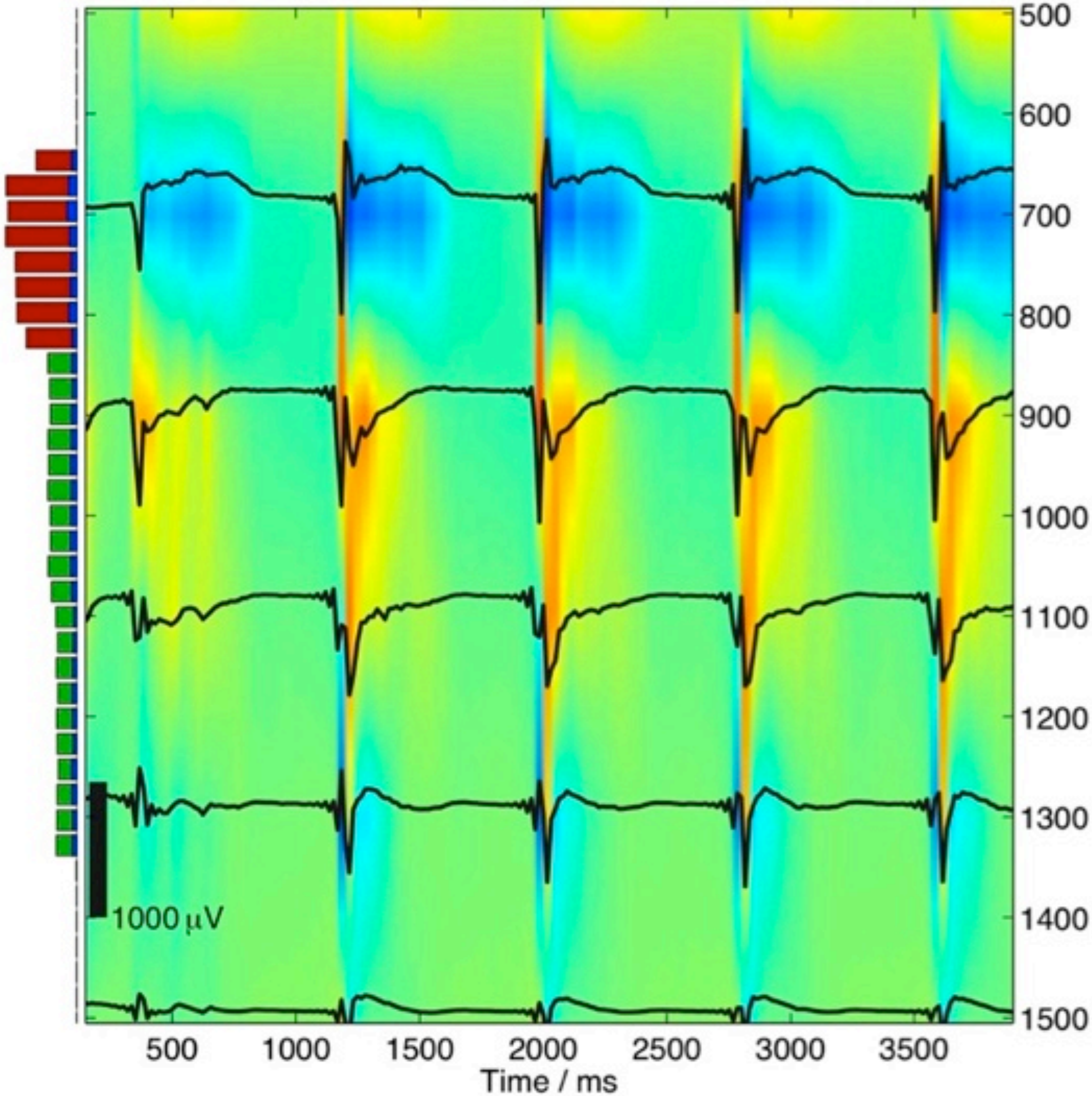
Reismann, Anastassiou, Perin, Hill, Markram & Koch & (2012)

Slow Up/Down Neocortical Activity



Reisman, Anastassiou, Perin, Hill, Markram & Koch & (2012)

Neocortical LFP and CSD



MindScope - Challenges

These are plans for a large scale (250+ scientists, technologists & engineers), high throughput, ten+ years effort that come with unique challenges

- We want to be something different than a world class university neurobiology department
- Build state-of-the-art observatories
- The tight integration of anatomy, distinct physiological methods, modeling and theory ==> virtuous loop
- Harness the creativity and drive of individual investigators while emphasizing the team aspect
- Experiment in the Sociology of Neuroscience