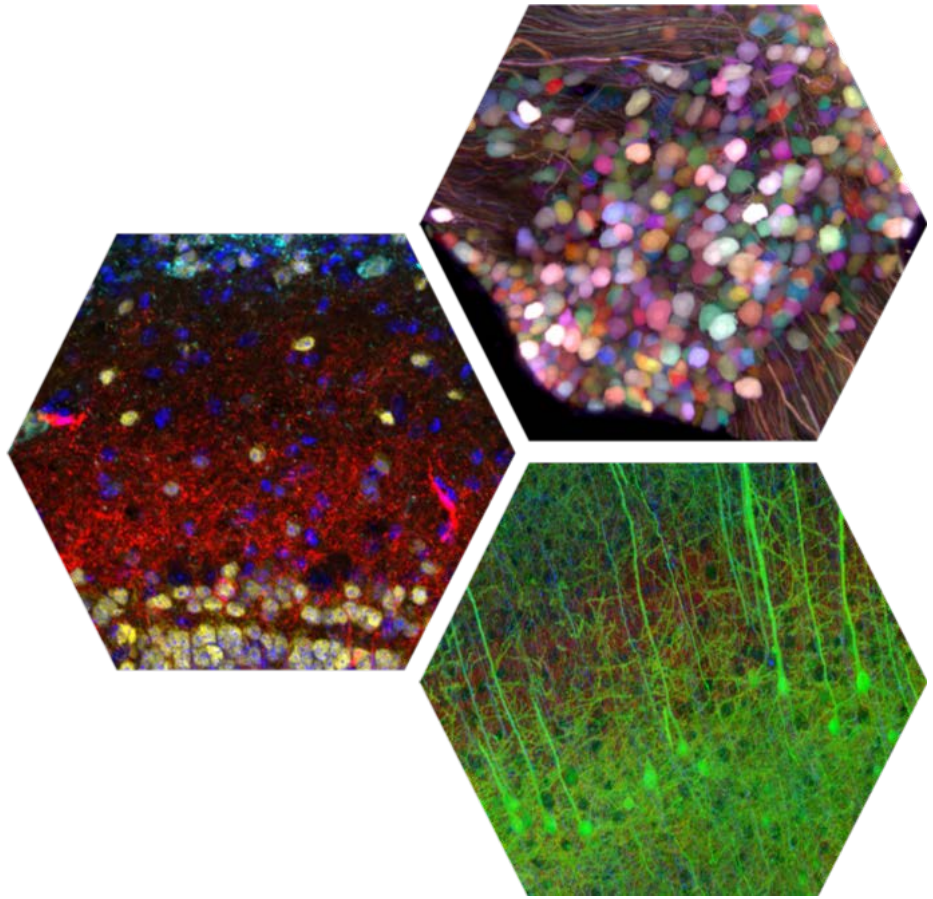


NIH The BRAIN Initiative®

The BRAIN Initiative Cell Census Network: Applications Toward Understanding Sex Differences

John Ngai, Ph.D.
Director, NIH BRAIN Initiative

NAS Forum on Neuroscience and Nervous System Disorders
September 23, 2020

Goal: to develop and apply new tools for understanding how neural circuits underlie complex behaviors in health and disease

- Leverage technological innovations to enable new discoveries about neural circuit function
- Use these discoveries as a foundation for new therapeutic strategies for human brain disorders
- Disseminate and democratize technologies for basic discovery and clinical applications

BRAIN 2.0 Transformative Projects

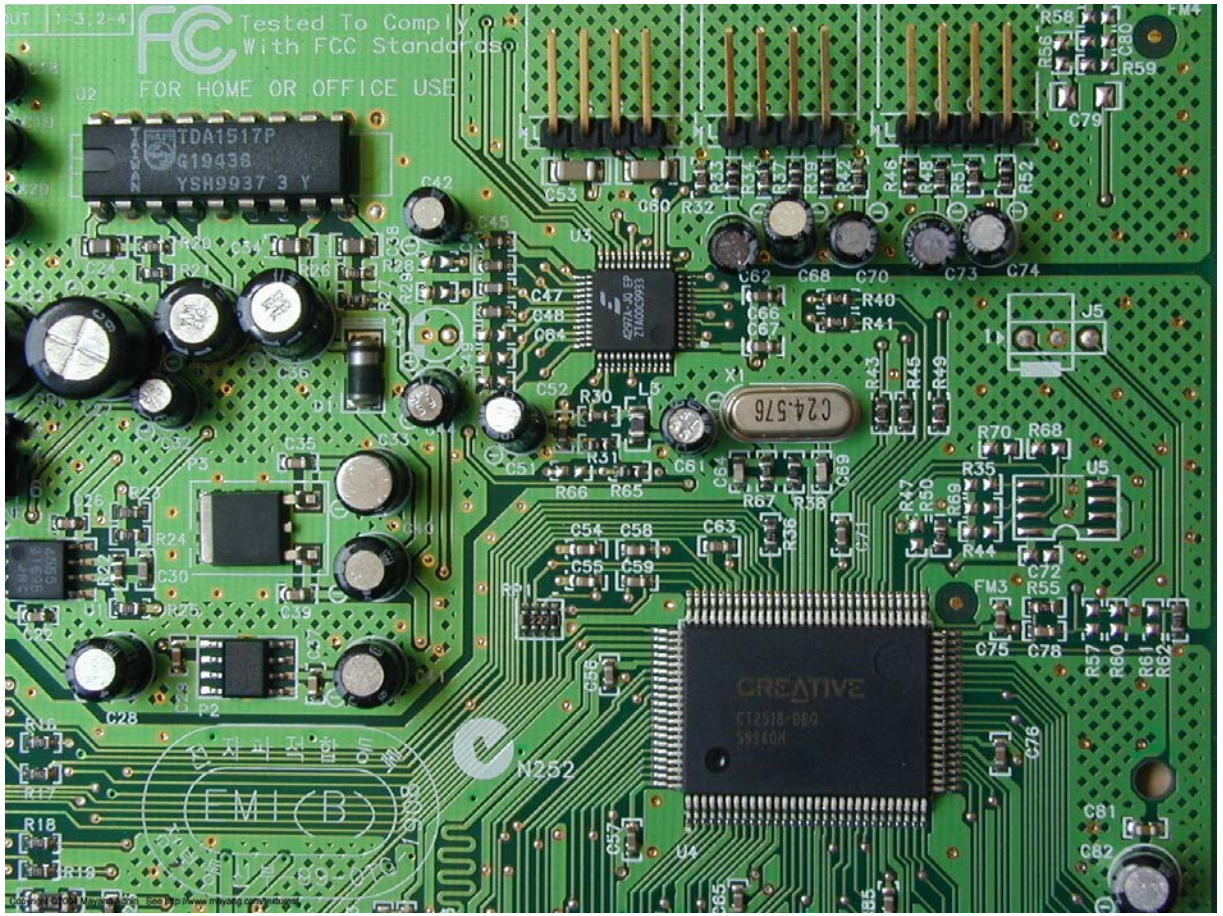
- **Phase III Brain Cell Census**
  - Shift emphasis to construct a human brain cell atlas
  - Will build on success of BICCN mouse cell census

- **Next-Generation Technologies for Brain Microconnectivity Analysis**
  - A wiring diagram of the brain at multiple scales and species

- **Organizing Resources for Brain Cell Type Access and Manipulation Across Species (cell type-specific armamentarium)**
  - Develop tools for cell access in rodent and NHP brains, human cells and tissue
  - Long-term goal: new therapeutic strategies for human brain disorders
  - *First RFA (RFA-MH-20-556) just issued!*

Motivation for a brain cell census

We need a “parts list” for the brain

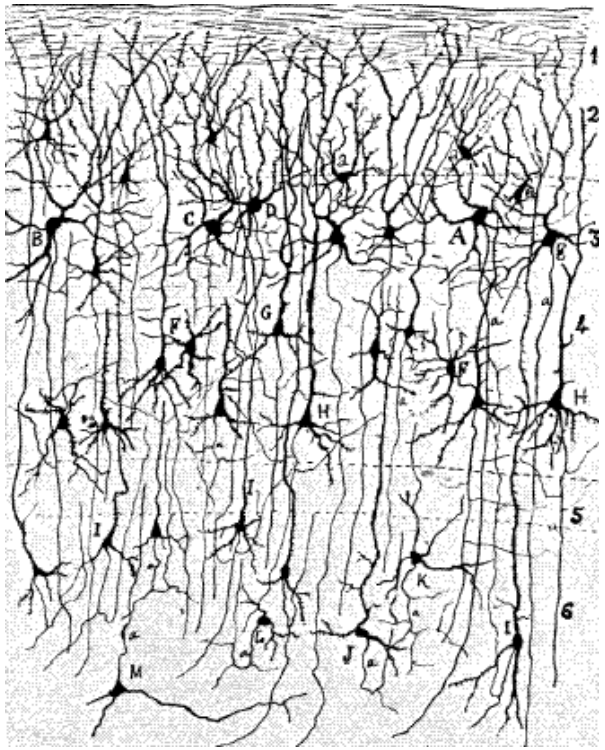


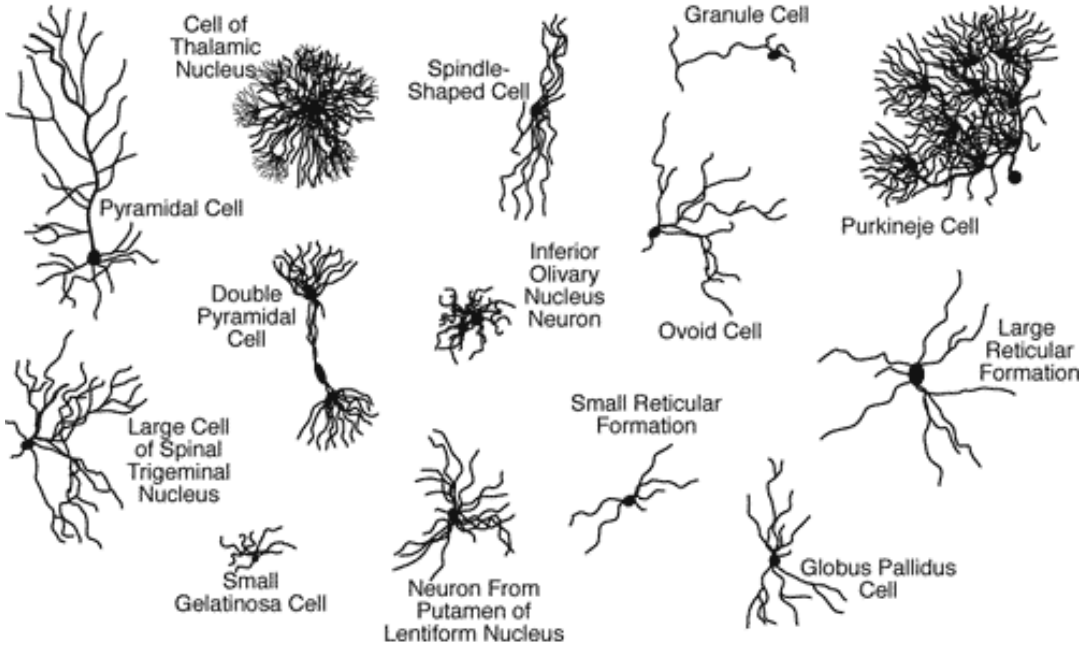
Understanding how a circuit functions requires knowledge about its constituent components

Motivation for a brain cell census

A century-old unsolved problem

Neural circuits in the brain are made up of 100's if not 1000's of different cell types…



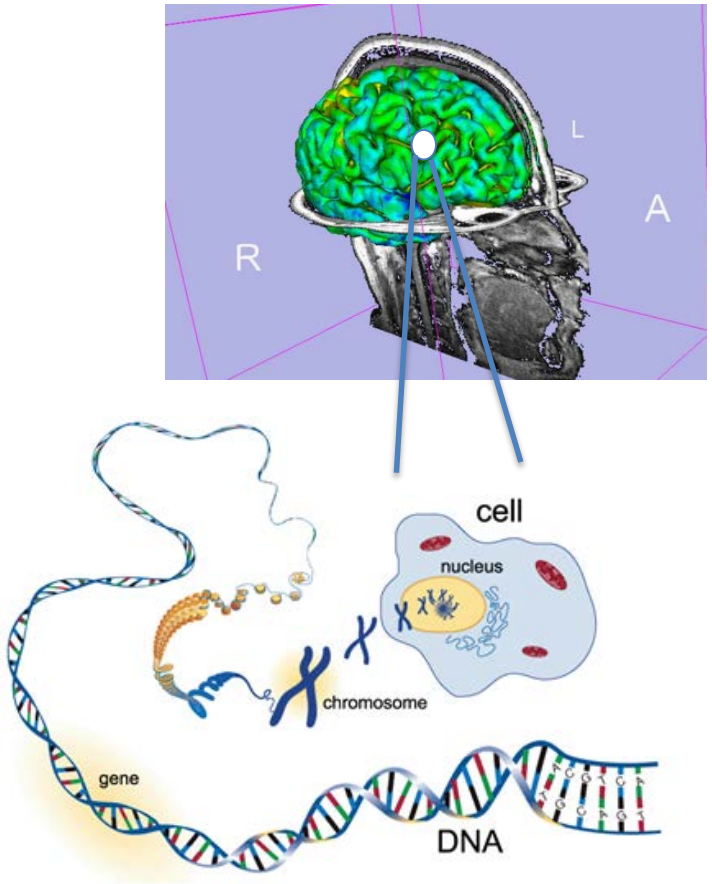


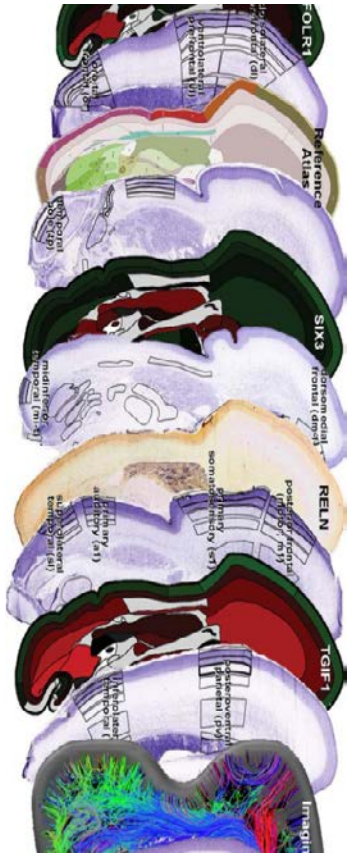
Ramón y Cajal, ca. 1900

…we need a systematic way to identify and classify them

The BRAIN Initiative Cell Census Project

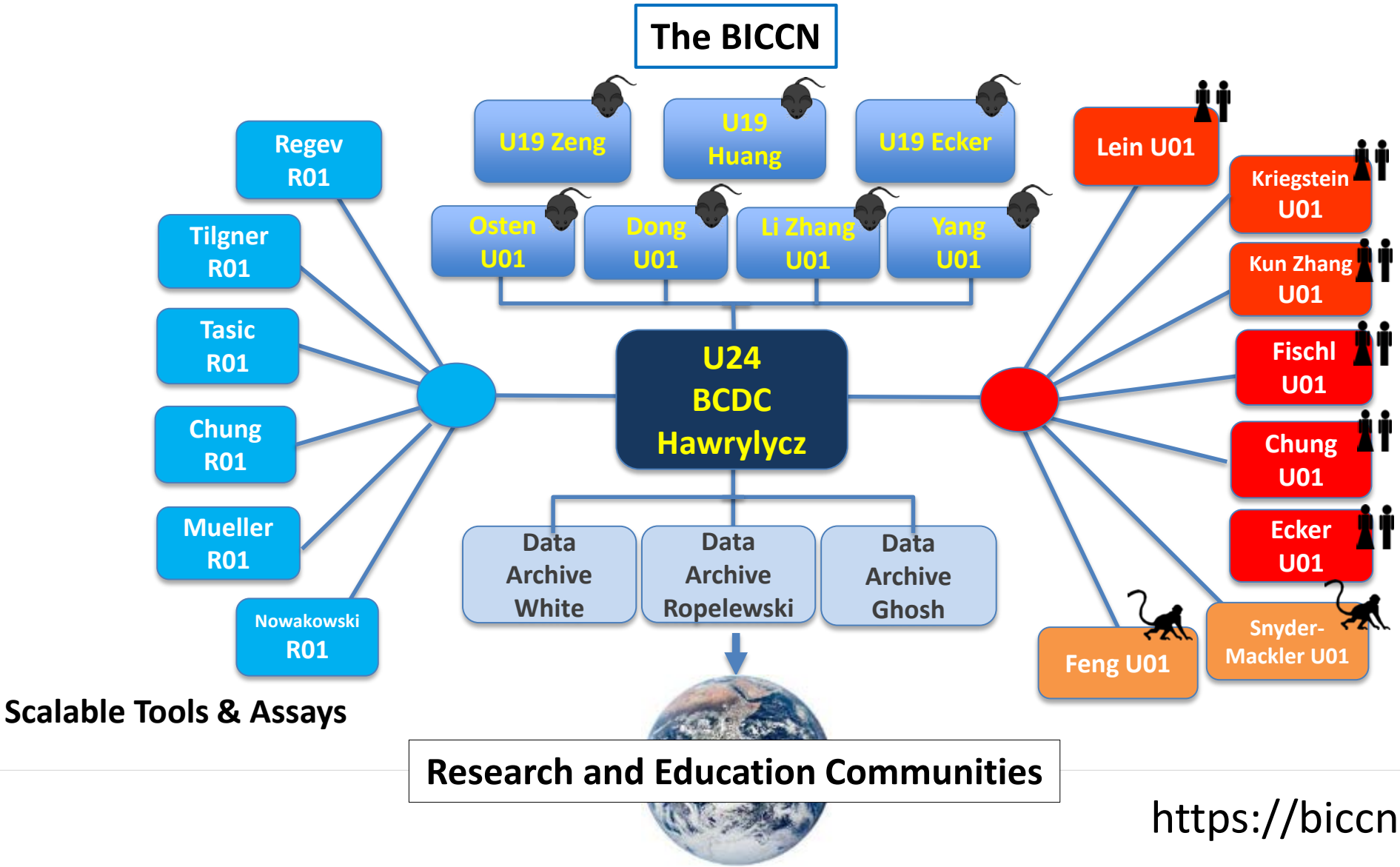
Toward Building Integrated Brain Cell Atlases





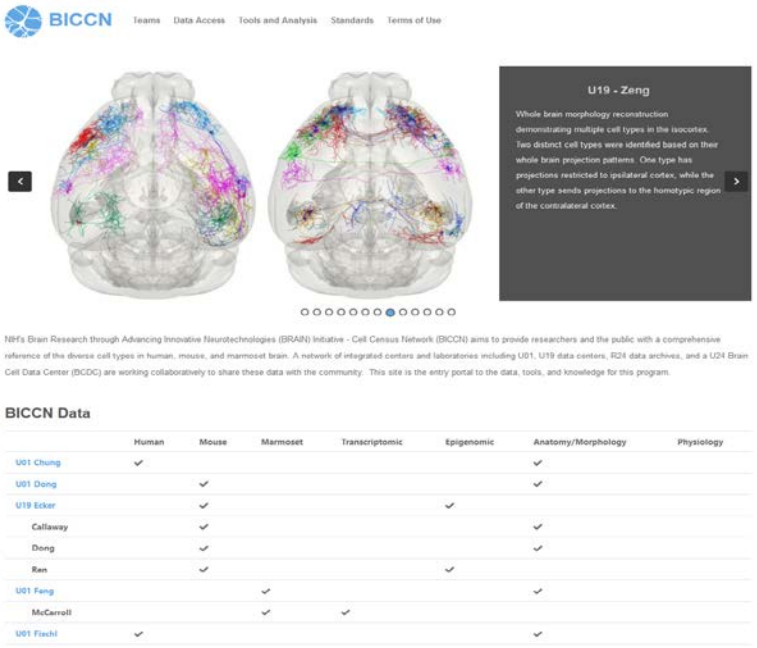
- **Molecular Signatures** (RNA-seq, ATAC-seq, mC-seq, FISH, Immunostaining, etc.)
- **Anatomy** (cell location, size, morphology, synapses, cell type composition and microenvironment, etc.)
- **Neural Circuits** (long distance projections, local circuits, etc.)
- **Functional Measures** (electrophysiology, calcium and voltage imaging, etc.)

The BRAIN Initiative Cell Census Network

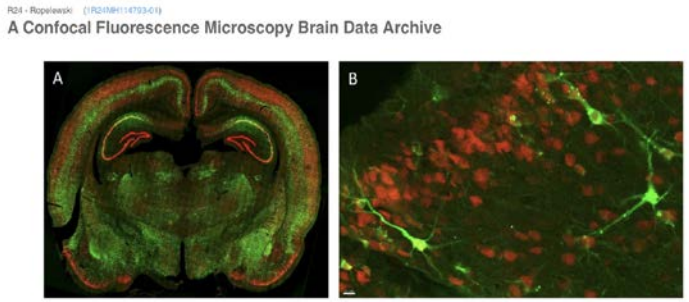


https://biccn.org

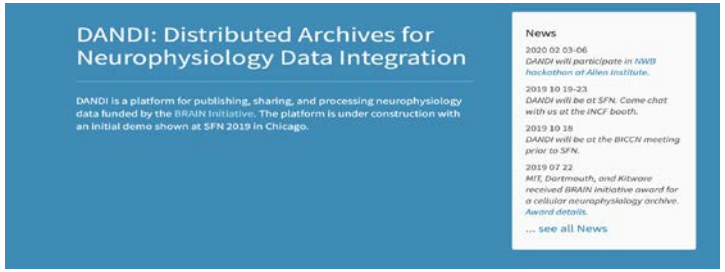
The BRAIN Initiative® BICCN Data Infrastructure Working Group



https://biccn.org

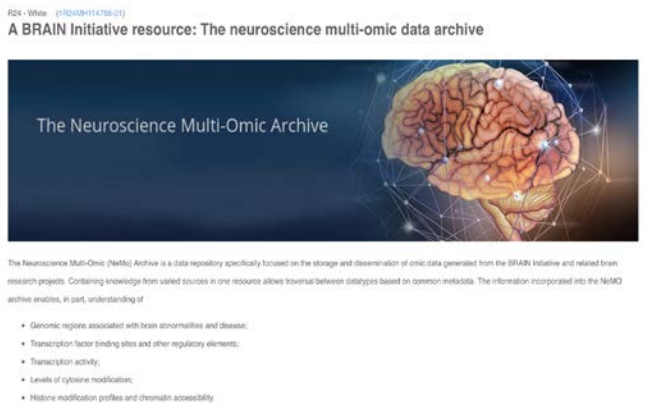


https://www.brainimagelibrary.org



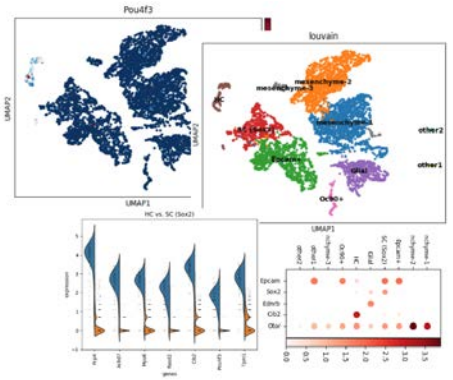
https://gui.dandiarchive.org

Neuroscience Multi-Omic Archive



https://nemoarchive.org

Neuroscience Multi-Omic Analytics



https://nemoanalytics.org

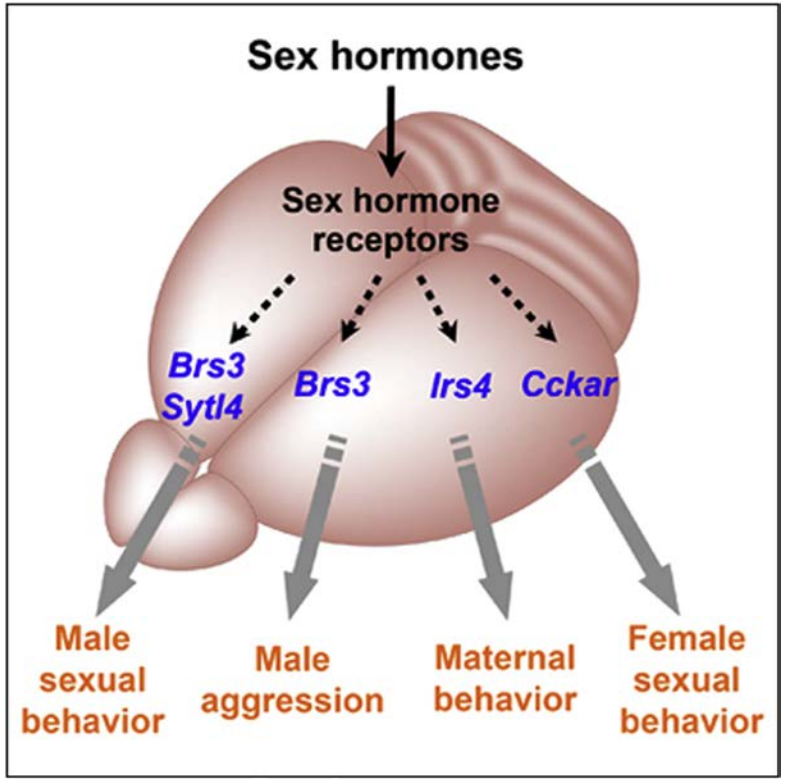
Molecular Analysis of Sexual Dimorphism

Modular Genetic Control of Sexually Dimorphic Behaviors

Xiaohong Xu,[2,4] Jennifer K. Coats,[1,4] Cindy F. Yang,[1] Amy Wang,[2,5] Osama M. Ahmed,[1] Maricruz Alvarado,[2] Tetsuro Izumi,[3] and Nirao M. Shah[1,2,*]

Cell *148*, 596–607, February 3, 2012 ©2012 Elsevier Inc.

- Shah and colleagues used bulk RNA profiling to identify genes showing sexually dimorphic expression in mouse amygdala and hypothalamus
- Mice with targeted deletions in genes identified in this screen exhibited deficits in *specific* sex-specific behaviors
- Strong evidence that sex-specific innate behaviors are governed by discrete genetic programs



Identification of sexually dimorphic genes, neurons and circuits mediating innate behaviors

Molecular Analysis of Sexual Dimorphism

RESEARCH ARTICLE SUMMARY

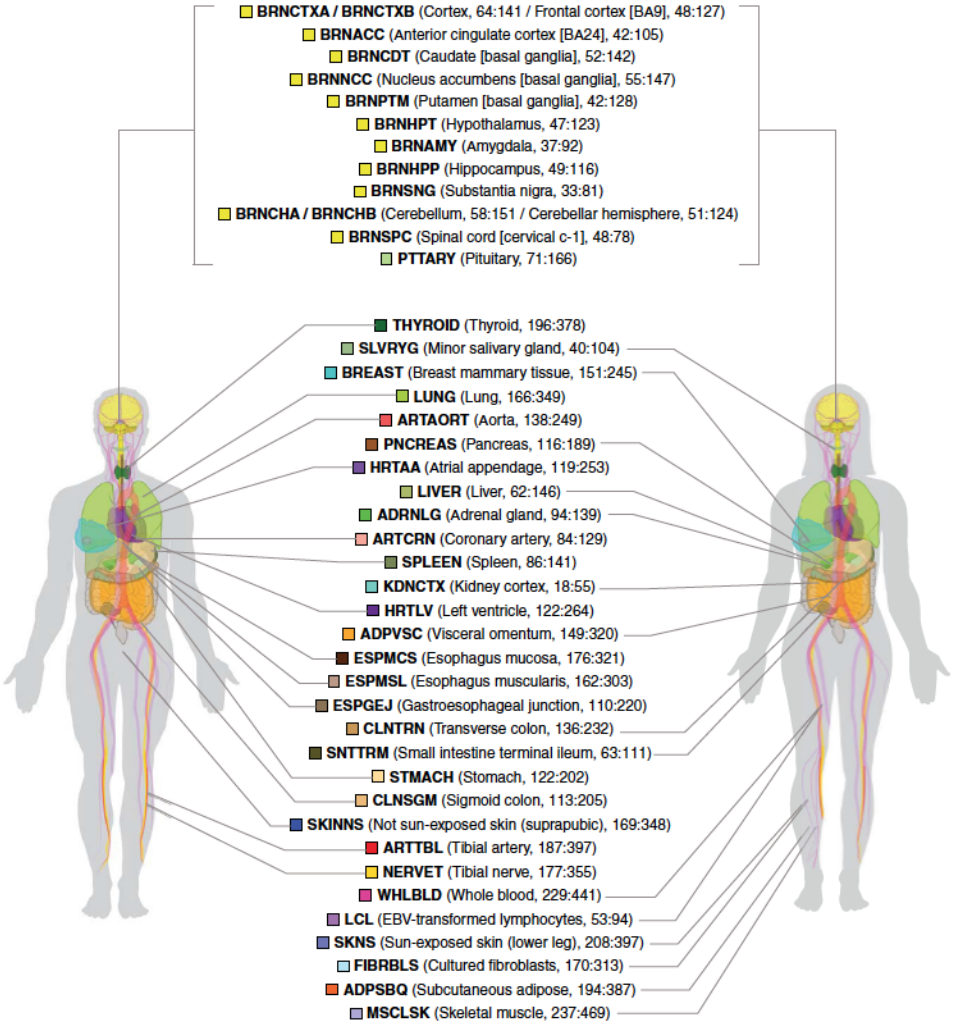
HUMAN GENOMICS

The impact of sex on gene expression across human tissues

Meritxell Oliva*†, Manuel Muñoz-Aguirre†, Sarah Kim-Hellmuth†, Valentin Wucher, Ariel D. H. Gewirtz, Daniel J. Cotter, Princy Parsana, Silva Kasela, Brunilda Balliu, Ana Viñuela, Stephane E. Castel, Pejman Mohammadi, François Aguet, Yuxin Zou, Ekaterina A. Khramtsova, Andrew D. Skol, Diego Garrido-Martín, Ferran Reverter, Andrew Brown, Patrick Evans, Eric R. Gamazon, Anthony Payne, Rodrigo Bonazzola, Alvaro N. Barbeira, Andrew R. Hamel, Angel Martinez-Perez, José Manuel Soria, GTEx Consortium, Brandon L. Pierce, Matthew Stephens, Eleazar Eskin, Emmanouil T. Dermitzakis, Ayellet V. Segrè, Hae Kyung Im, Barbara E. Engelhardt, Kristin G. Ardlie, Stephen B. Montgomery, Alexis J. Battle, Tuuli Lappalainen, Roderic Guigó, Barbara E. Stranger*

Oliva *et al.*, *Science* 369, eaba3066 (2020) 11 September 2020

- 13,294/35,431 genes were found to show sex-specific differences in expression
- Most differences are restricted to 1-2 tissues
- Differences are subtle (average fold-change = 1.04 for autosomal genes)



GTex Project: genetic analysis & bulk RNA profiling of human tissues from 838 individuals (557 male, 281 female)

Single Cell RNA Sequencing:

Unmixing the smoothie to identify and characterize the components

Bulk RNA-seq

VS

Single cell
RNA-seq

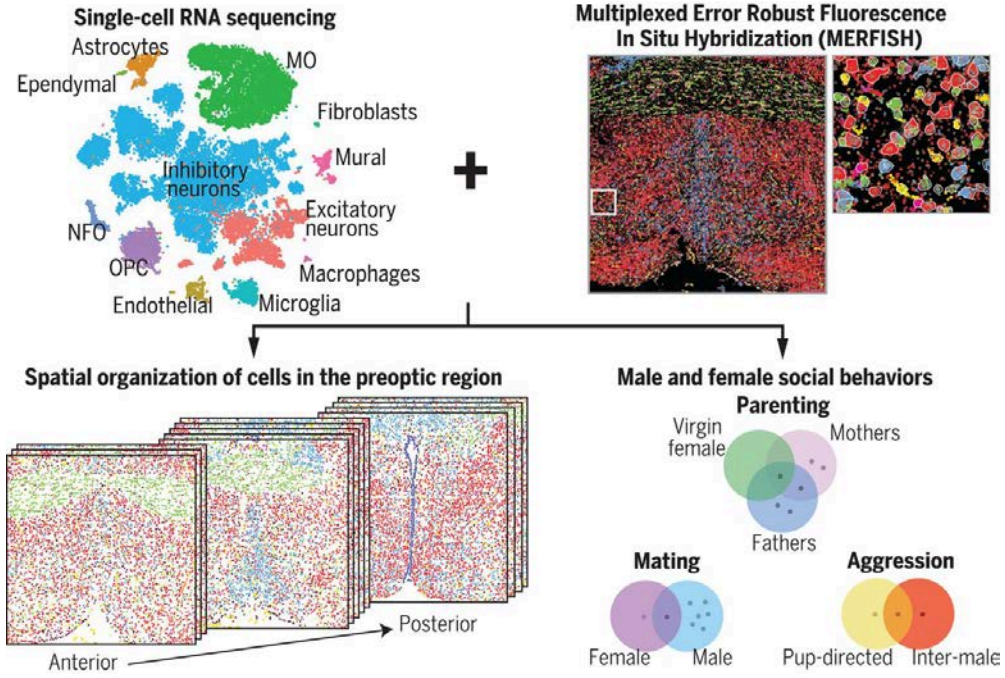
Single cell analysis: a powerful tool for discovery

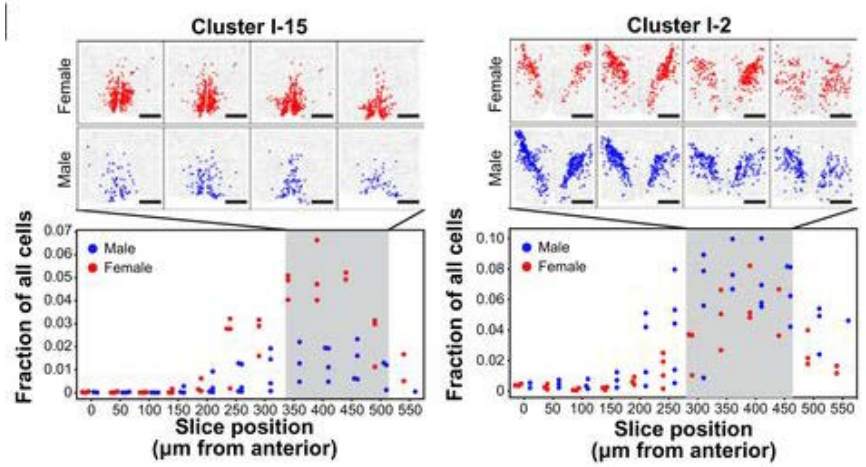
Molecular, spatial, and functional single-cell profiling of the hypothalamic preoptic region

Jeffrey R. Moffitt*, Dhananjay Bambah-Mukku*, Stephen W. Eichhorn†, Eric Vaughn†, Karthik Shekhar, Julio D. Perez, Nimrod D. Rubinstein, Junjie Hao, Aviv Regev, Catherine Dulac‡§, Xiaowei Zhuang‡§

Science **362**, 792 (2018)

Single-cell RNA-seq + spatial RNA profiling





Identification of sexually dimorphic genes, neurons and circuits mediating innate behaviors

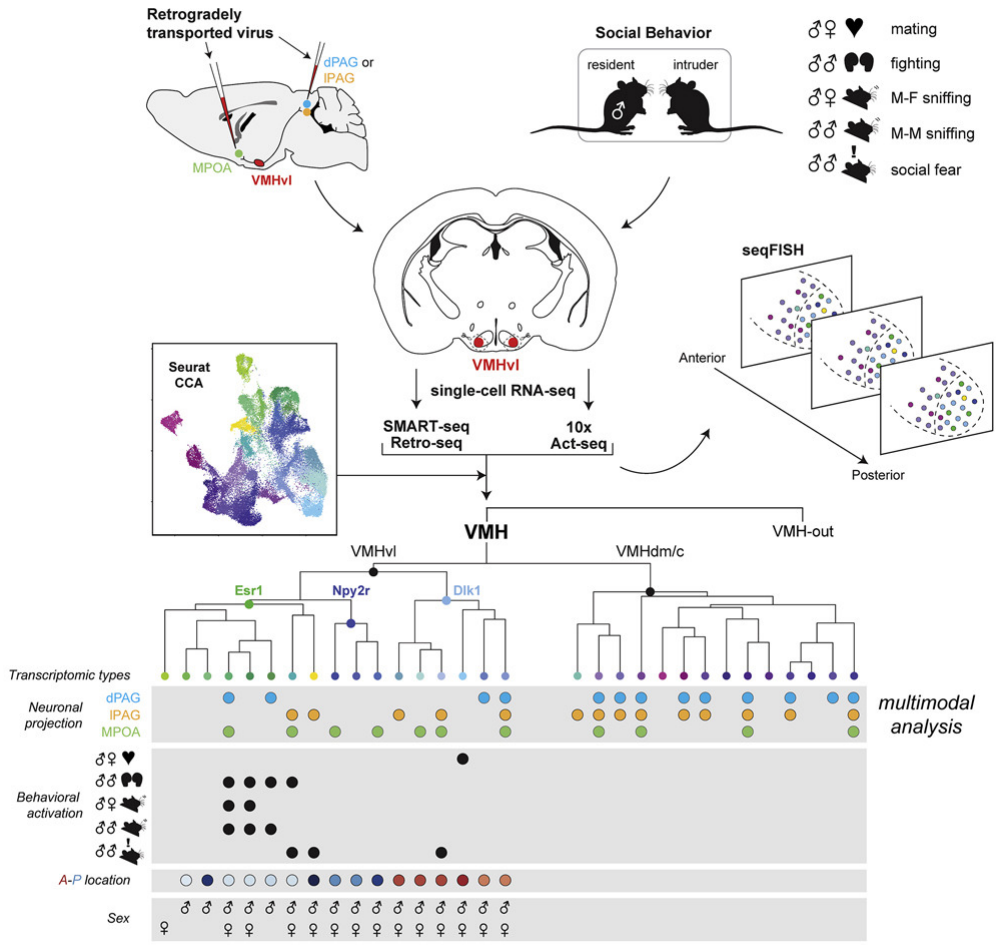
Single cell analysis: a powerful tool for discovery

Multimodal Analysis of Cell Types in a Hypothalamic Node Controlling Social Behavior

Dong-Wook Kim,[1,2,4] Zizhen Yao,[5] Lucas T. Graybuck,[5] Tae Kyung Kim,[5] Thuc Nghi Nguyen,[5] Kimberly A. Smith,[5] Olivia Fong,[5] Lynn Yi,[2] Noushin Koulena,[2] Nico Pierson,[2] Sheel Shah,[2] Liching Lo,[2,3,4] Allan-Hermann Pool,[2] Yuki Oka,[2] Lior Pachter,[2] Long Cai,[2] Bosiljka Tasic,[5] Hongkui Zeng,[5] and David J. Anderson[2,3,4,6,*]

Cell 179, 713–728, October 17, 2019 © 2019 Elsevier Inc.

- Ventrolateral subdivision of the ventral medial hypothalamus (VMHvl) is the locus of innate and sexually dimorphic behaviors
- High depth single cell RNA sequencing allowed identification of 17 transcriptomically distinct cell clusters, including of rare cell types
- Small number of sexually dimorphic cell types
- Mapping of behaviors to specific cell types and projections is the exception rather than the rule



Identification of sexually dimorphic genes, neurons and circuits mediating innate behaviors

Opportunities

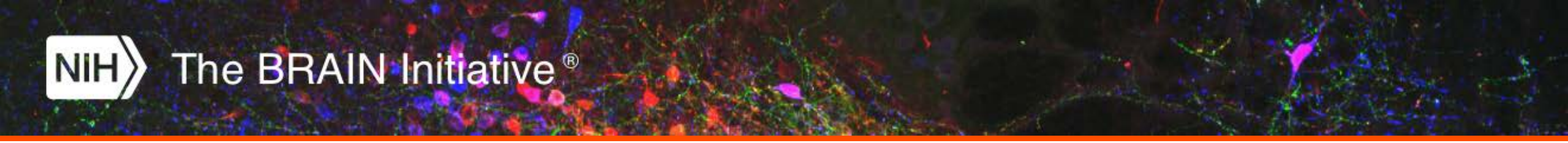
Discoveries supported by BRAIN lay the foundation for understanding sex differences in the nervous system

BRAIN-supported advances are unraveling the circuits and computations underlying innate and learned behaviors

=> Underpinnings of sex-specific behaviors

=> Sex-specific differences in circuits affected in neurologic and neuropsychiatric diseases

=> New therapies…

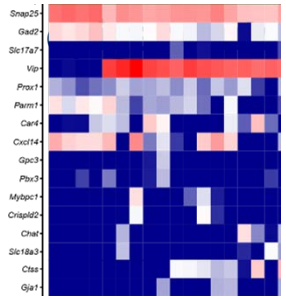


https://www.braininitiative.nih.gov

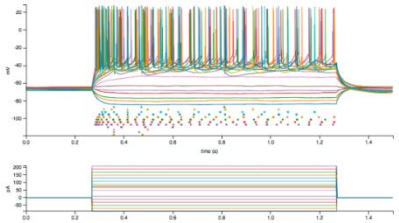
The BICCN: from single cell genomics to cell types, circuits and function

Single-cell Characterizations

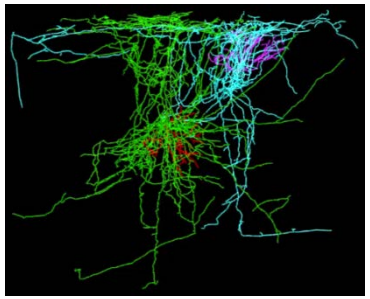
Transcriptomic &



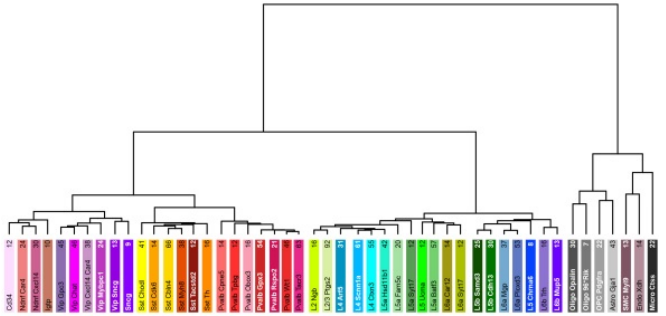
Physiological



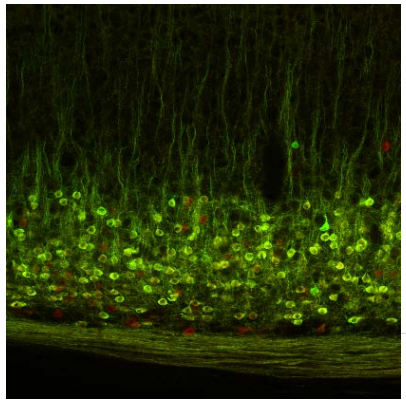
Morphological



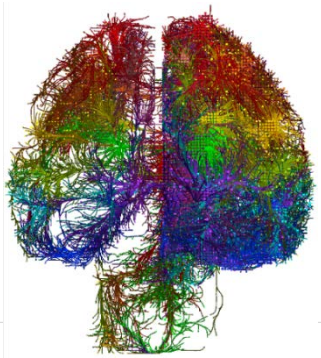
Data-driven Cell Taxonomies

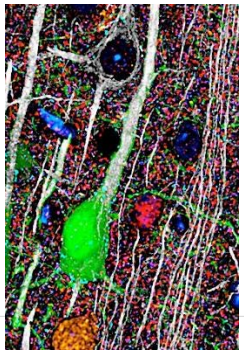


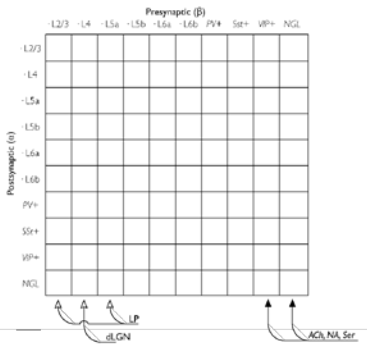
Cell targeting tools



Mapping connectivity of defined cell types

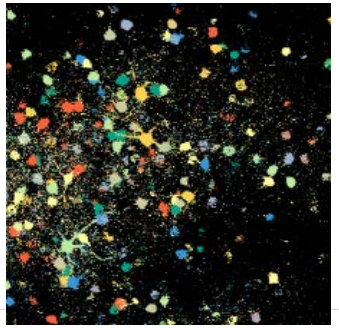


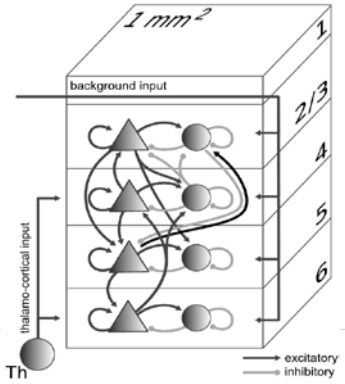




Wiring diagram

Determining the role of cell types in circuit function





Courtesy of M. Hawrylycz

The Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative

- *Mission: to enable and revolutionize our understanding of the human brain by accelerating the development and application of innovative technologies*
- Partnership between five U.S. federal agencies & private foundations
- Announced by the White House in 2013, first awards in 2014
- NIH BRAIN Initiative:
  - US$46M in 2014
  - US$500M (budgeted) in 2020