BRAIN 2.0: The Next Phase of the NIH BRAIN Initiative

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Disclosure Information

John Ngai, Ph.D.

- No Disclosures

The U.S. BRAIN Initiative

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

- Mission: to revolutionize our understanding of the human brain by accelerating the development and application of innovative technologies
- Announced by the White House in 2013, first awards in 2014
- Partnership between five U.S. federal agencies & private foundations
- NIH efforts guided by two strategic plans (BRAIN 2025 and BRAIN 2.0 reports)

Goal

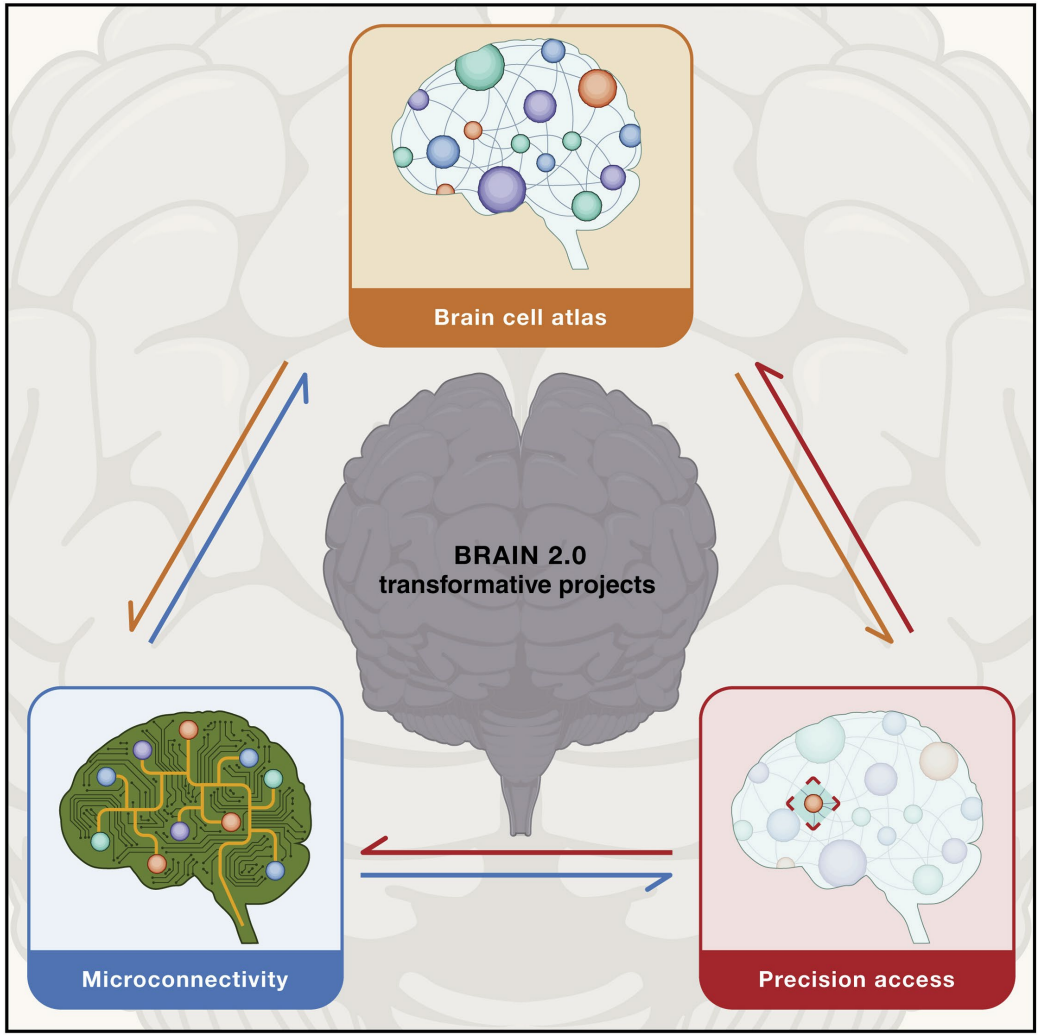
Develop and apply new tools for understanding how neural circuits underlie complex behaviors in health and disease.

- Leverage emerging technologies 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 ***for the benefit of all.***

>1200 BRAIN-Funded Projects Through 2021

- New sensors and actuators of cellular activity
- Powerful imaging modalities to visualize activity within neural circuits and across brain regions
- Electrode technologies that allow simultaneous recording from thousands of cells
- Deeper understanding of neural circuit function, including in humans
- First-in-human trials of novel neurotechnologies
- ML/AI approaches to deconstruct behavior and other complex datasets
- ***Where are the opportunities to transform the field?***

BRAIN 2.0: Transforming Neuroscience



CellPress
Cell
Leading Edge

Commentary

BRAIN 2.0: Transforming neuroscience

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The **NIH BRAIN Initiative** is entering a new phase. Three large new projects — a comprehensive **human brain cell atlas**, a whole mammalian brain **microconnectivity map**, and **tools for precision access** to brain cell types — promise to transform neuroscience research and the treatment of human brain disorders.

Ngai, Cell 2022

BRAIN 2.0 Transformative Projects

- Brain Cell Census Phase III: BRAIN Initiative Cell Atlas Network (BICAN)*
  - Will build on success of BICCN mouse brain cell census; shift emphasis to humans
  - RFA-MH-21-235, 236, 237 (1st awards just issued)

* FY22 Congressionally Directed Funds

BRAIN Initiative Cell Census Network

A Multimodal Cell Census and Atlas of Mammalian Primary Motor Cortex

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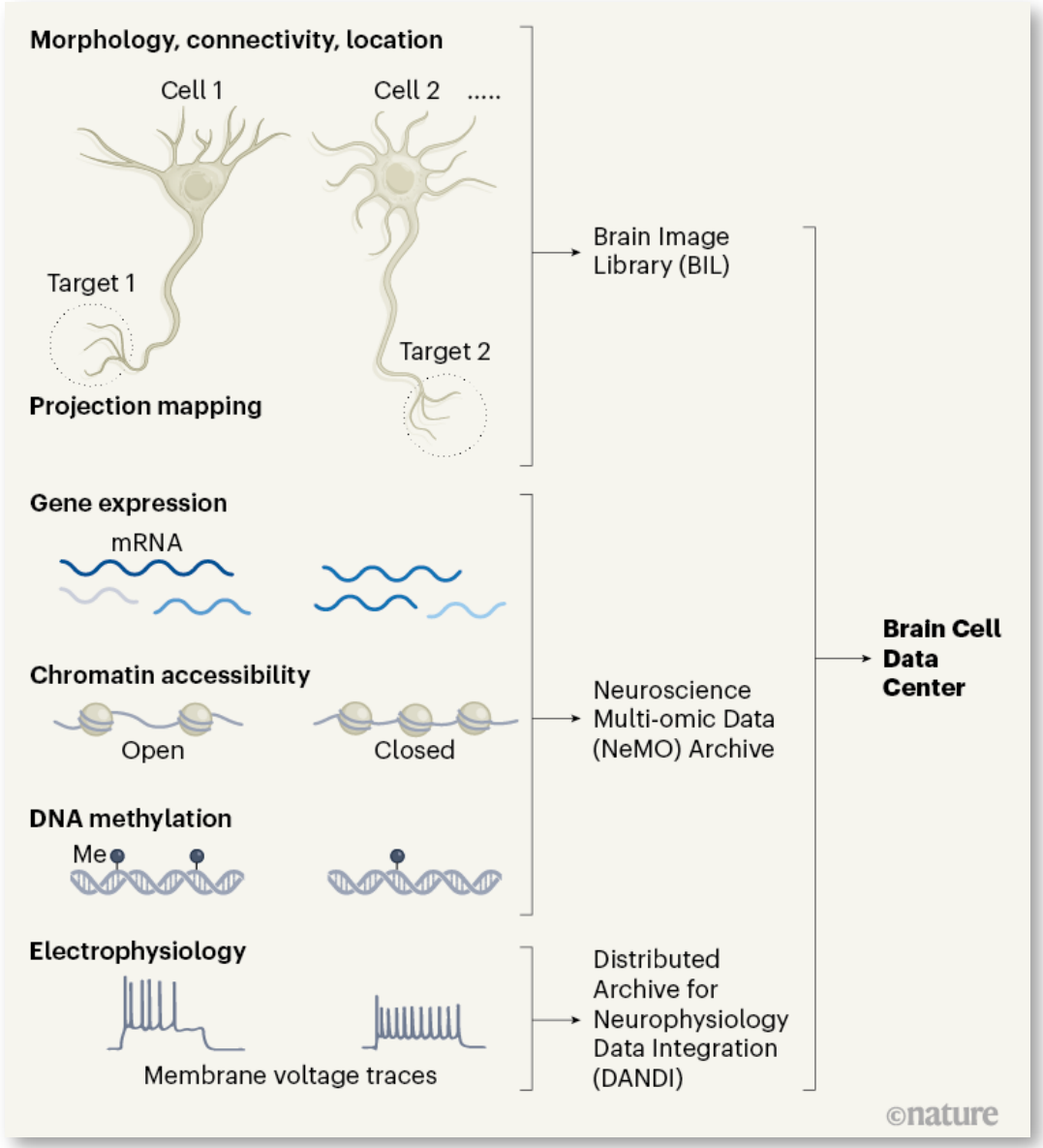
- A multimodal analysis of primary motor cortex in multiple mammalian species integrating molecular characteristics with spatial distribution, morphology, physiology and connectivity.



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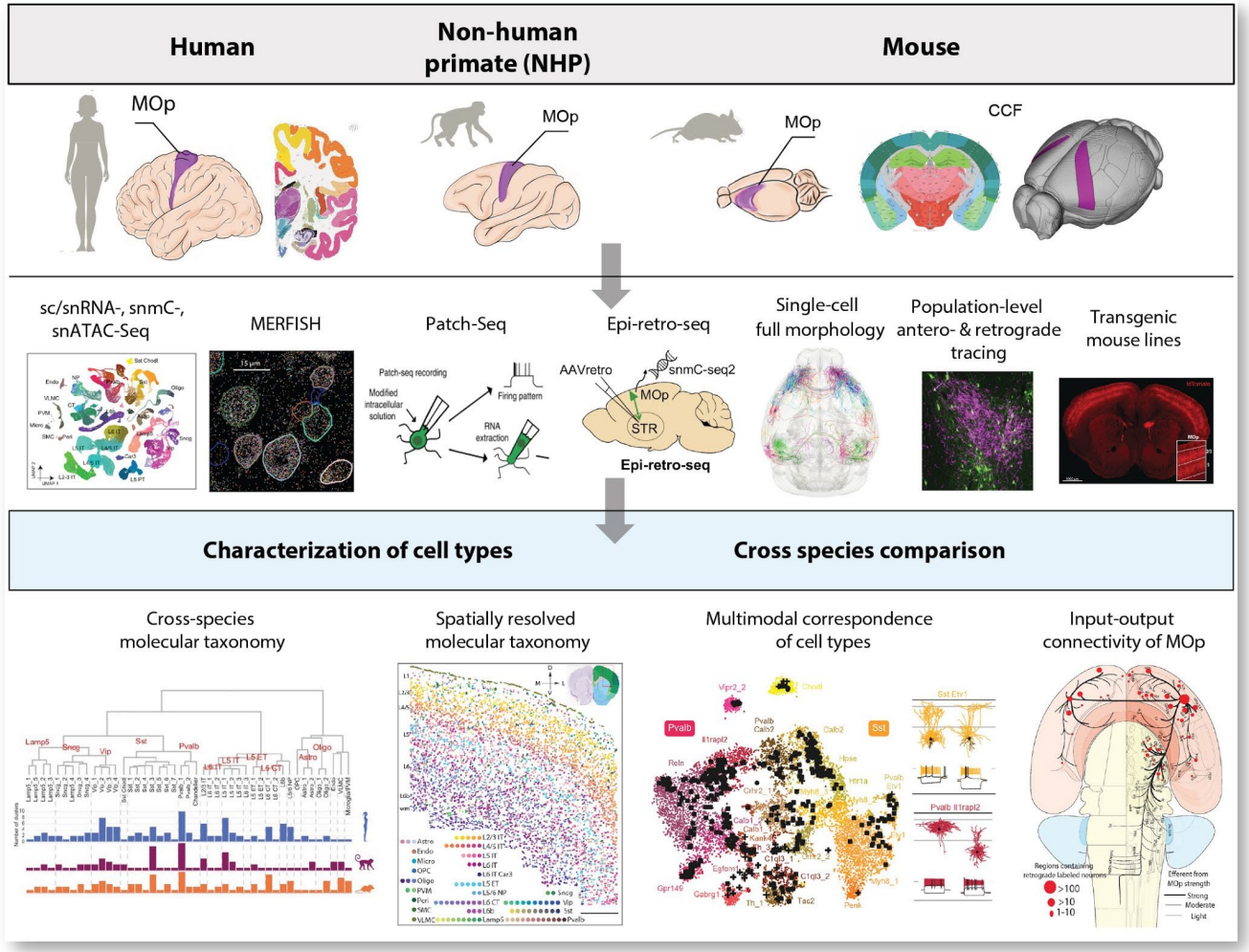
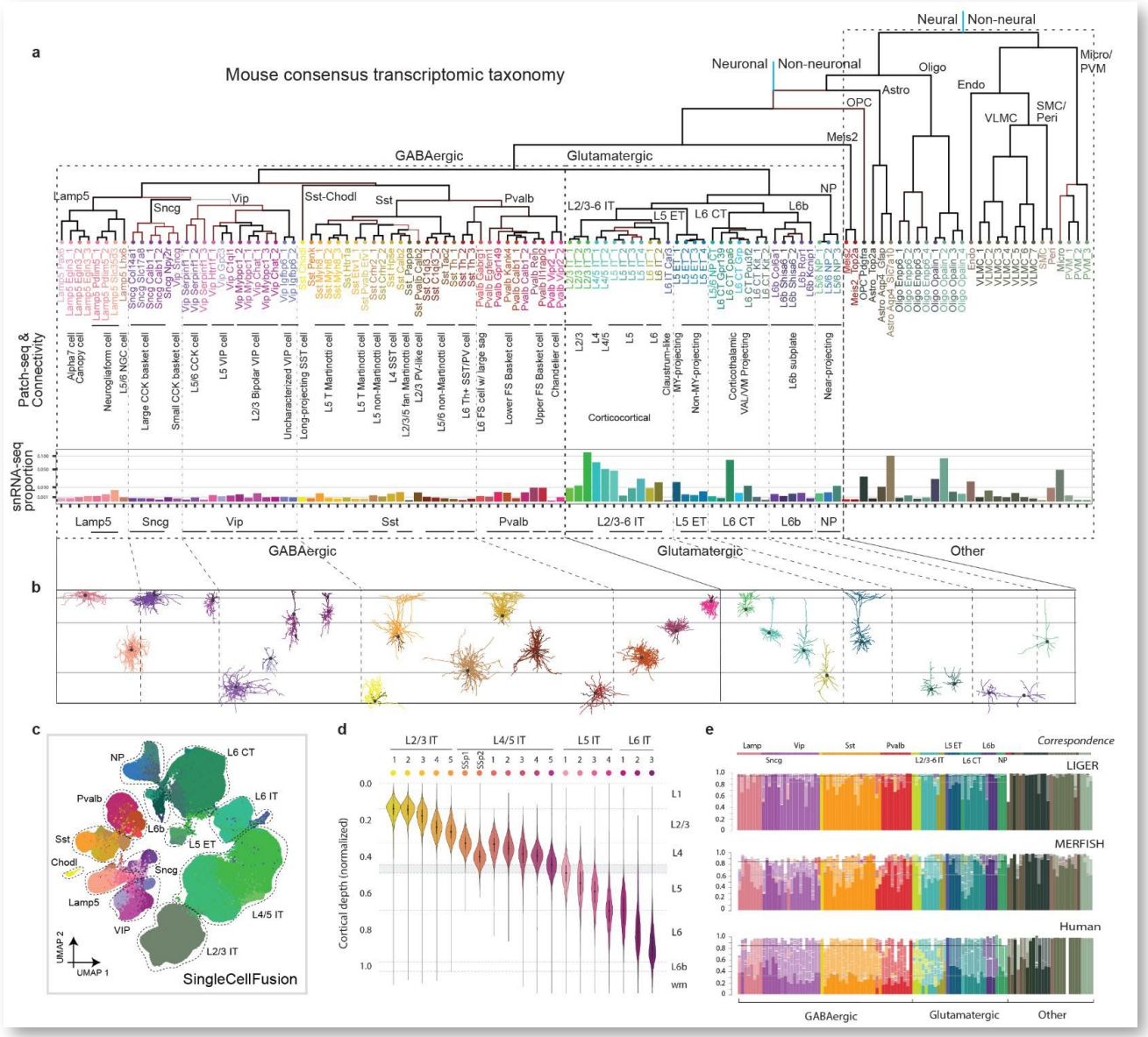
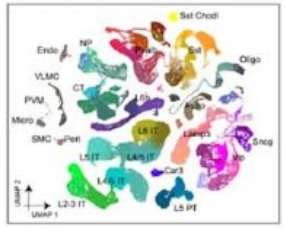




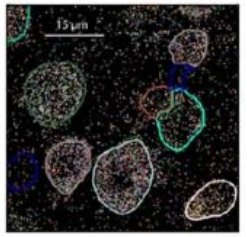
- A multimodal analysis of primary motor cortex in multiple mammalian species integrating molecular characteristics with spatial distribution, morphology, physiology and connectivity
- Organizational principles underlying diversification of brain cell types. Remarkable conservation of cell types between mouse, marmoset and human => sets stage for human brain cell atlas
- The power of team science:
  - > 250 researchers
  - 89 affiliations (> 45 institutions)
  - 3 continents

Toward a Brain Cell Atlas Data Ecosystem

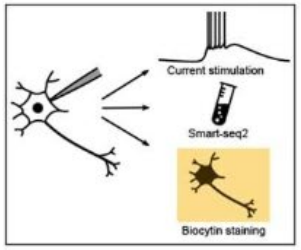
sc/sn RNA-, snmC-, snATAC-seq



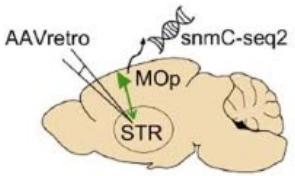
MERFISH



Patch-seq

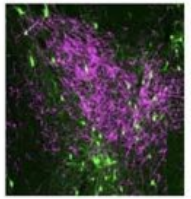


Epi-retro-seq

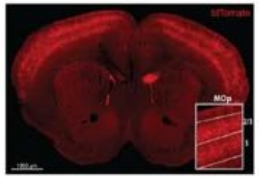


Single-cell morphology

Circuits tracing



Cell type-specific tools



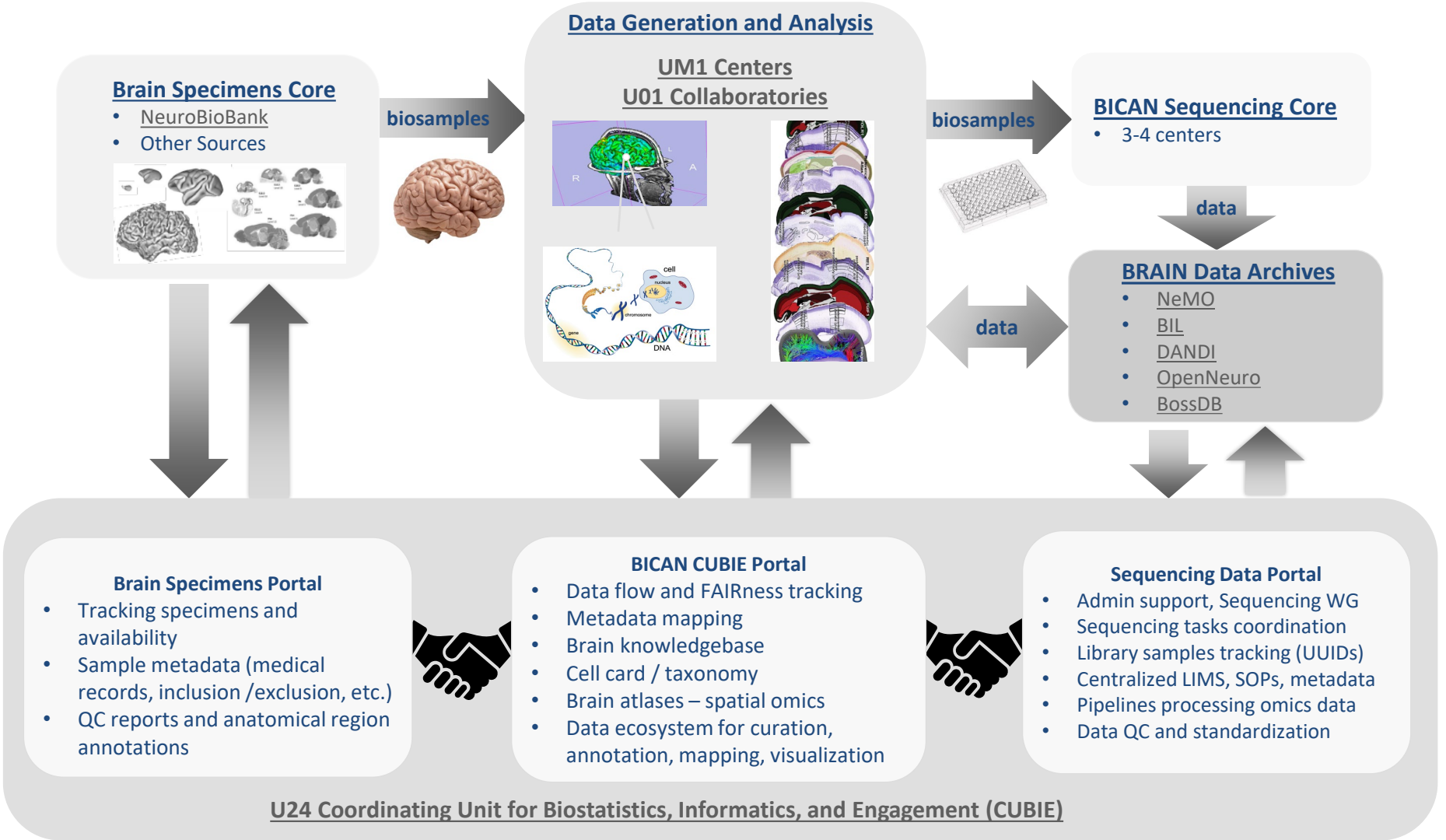
BICCN 2.0 Publications

- Whole Mouse Brain WG
- Morphology and Circuits WG
- Human+NHP WG
- Developing Brain Atlas WG
- Infrastructure WG

Unfindable Lab Data

FAIR Public Data

BRAIN Initiative Cell Atlas Network (BICAN) Coordination



First BICAN awards just issued

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  - RFA-MH-21-235, 236, 237 (1st awards just issued)

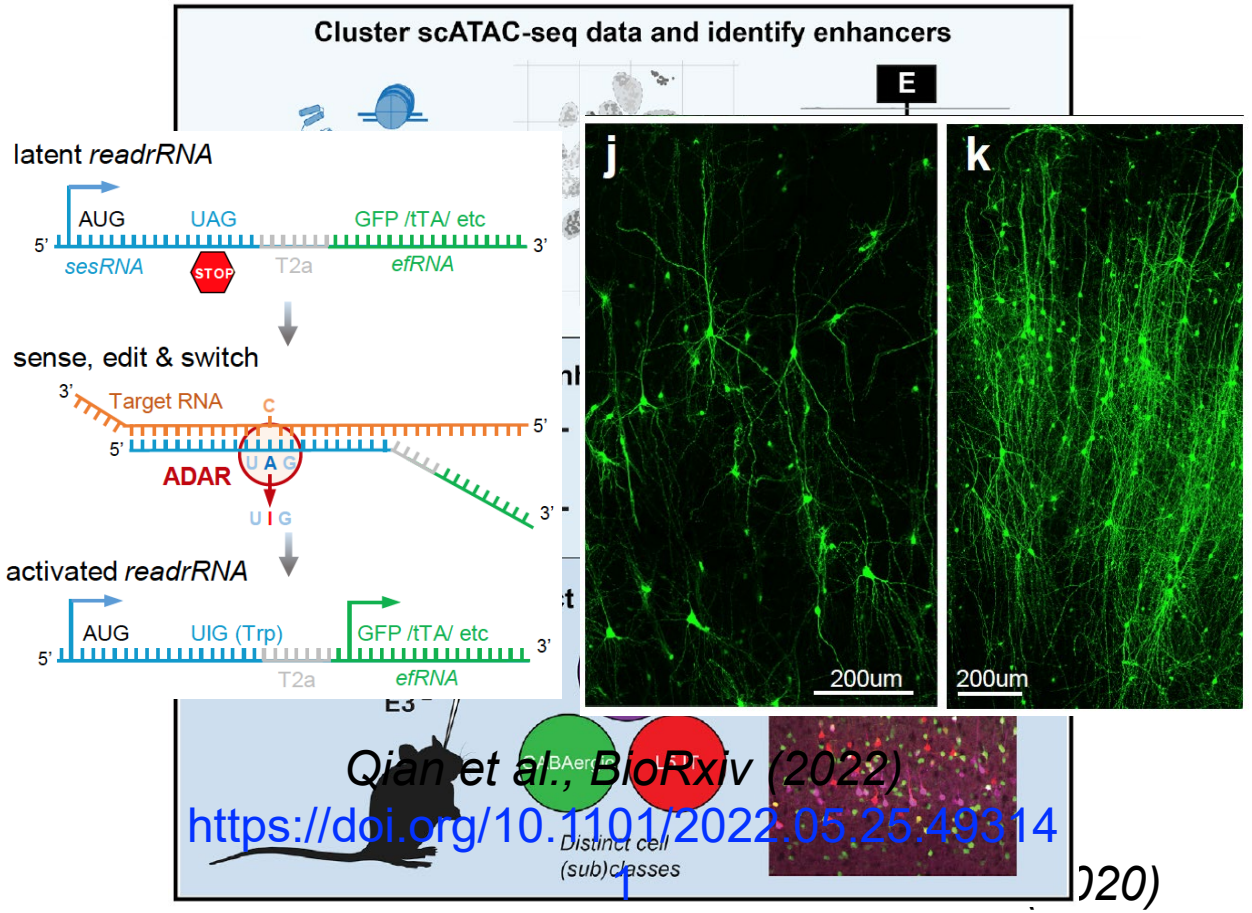
- Organizing Resources for Brain Cell Type Access and Manipulation Across Species (cell type-specific armamentarium)*
  - Develop tools for cell access in rodent and NHP brains, human cells and tissue
  - Long-term goal: new therapeutic strategies for human brain disorders
  - RFA-MH-20-556 (2nd awards just issued); RFA-MH-21-180 (2nd receipt date: July 2022)

* FY22 Congressionally Directed Funds

Armamentarium for Precision Cell Access

First awards issued in 2021

- Gradinaru (Caltech): *Engineered AAV identification, validation, and dissemination pipeline for brain cell type-specific manipulation across species (1UF1MH128336)*
- Tasic (Allen Institute): *Open-access AAV toolbox for basal ganglia cell types and circuits (1UF1MH128339)*
- Huang (Duke): *RNA-programmable cell type targeting and manipulation across vertebrate nervous systems (1UF1MH128337)*



Qian et al., BioRxiv (2022)
https://doi.org/10.1101/2022.05.25.493144

Graybuck et al., Neuron 109, 1449 (2021)

Second round of awards just issued

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- BRAIN Initiative Connectivity across Scales (BRAIN CONNECTS)
  - Develop and leverage technologies to generate comprehensive atlases of brain connectivity, with an emphasis on mouse, non-human primate (NHP), and human.
  - RFA-NS-22-047, 048, 049 (1st receipt date: July 2022)

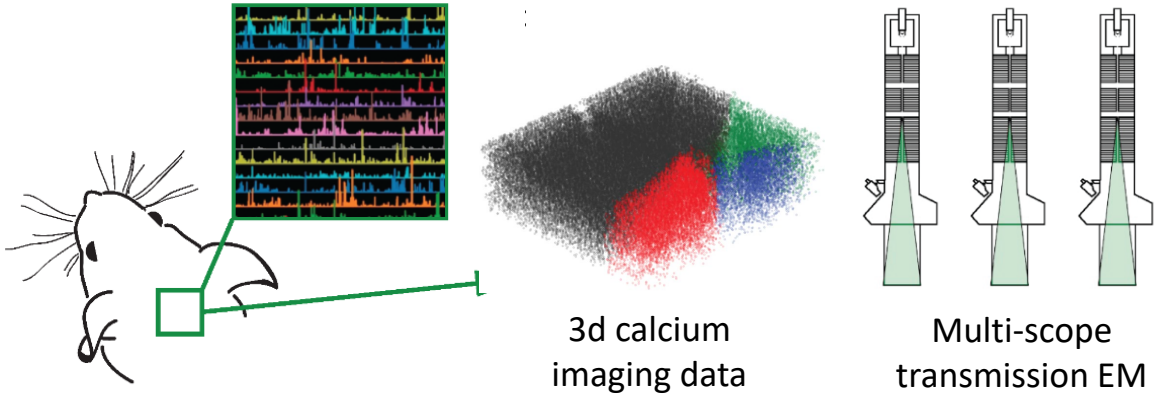
* FY22 Congressionally Directed Funds

Mapping Brain Connectivity

EM Connectomics State of Art

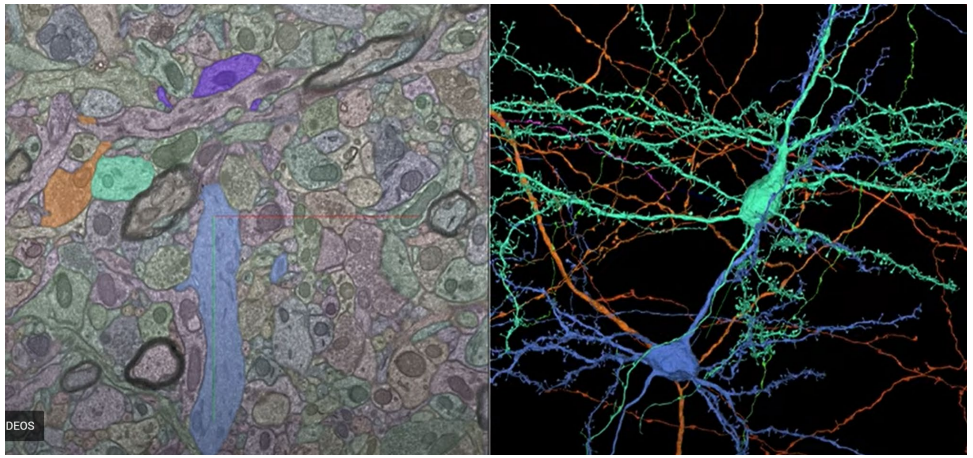
MICrONs Consortium, BioRxiv 2021
Functional connectomics across mouse visual cortex

- 1 mm3 volume spanning mouse V1 and higher visual areas
- Calcium imaging in vivo using 2p microscopy during visual stimuli and locomotion - single-cell functional data from ~75K neurons
- Followed by ex vivo microCT and transmission EM using multiple microscopes in parallel
- Anatomical reconstruction of ~120K neurons and ~80K non-neuronal cells, >500M synapses
- Data and code available online for interactive analysis



3d calcium imaging data

Multi-scope transmission EM



https://doi.org/10.1101/2021.07.28.454025
https://www.microns-explorer.org/

BRAIN CONNECTS

Strategy for Mapping Brain Connectivity Across Scales

Phase I of a 10-year effort

Goals for the first five years:

- Assess different approaches for their ability to achieve the necessary scale-up
- Deliver unique research products with high impact for the neuroscience community
- Evaluate strategic choices for addressing key questions and trade-offs
- Develop a plan for implementing Phase II (scale-up)

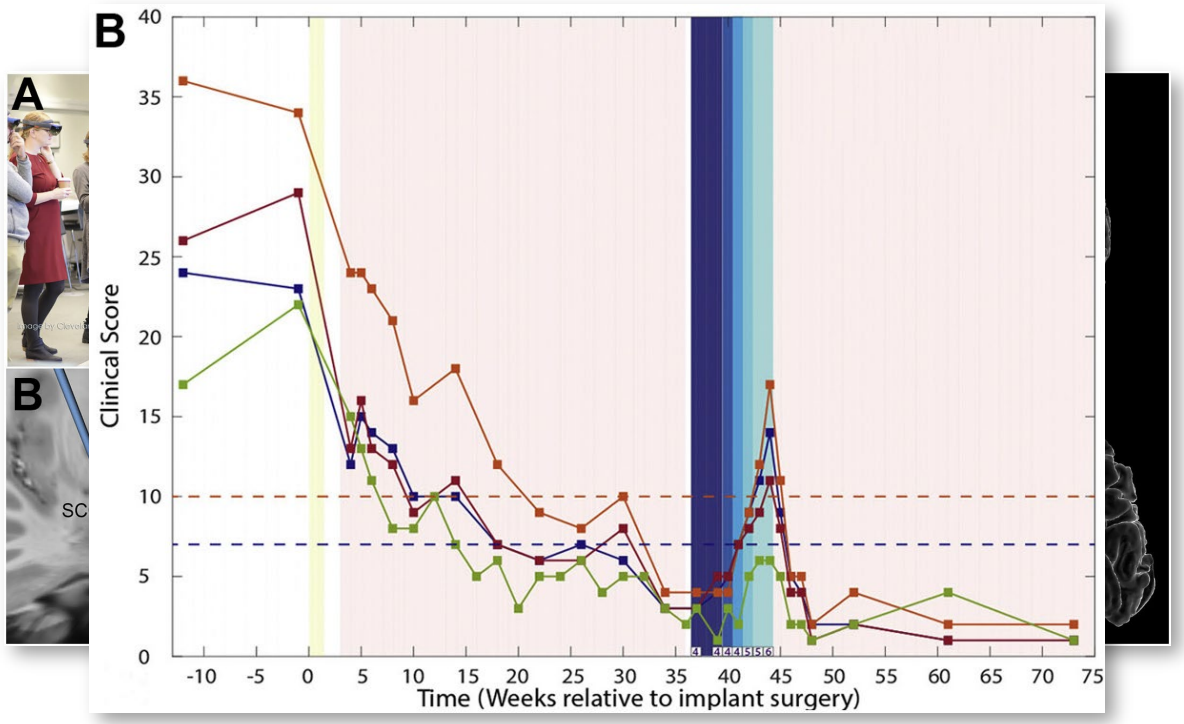
NIH BRAIN funding approach:

- Mix of large integrated projects aimed at achieving all components of the pipeline, and smaller awards targeting specific approaches and testing new methods and technologies
- Managed as a coordinated effort, with pre-publication sharing and concrete go/no-go deliverables

Toward Personalized DBS for Depression

Deep Brain Stimulation for Depression Informed by Intracranial Recordings

- Using surgery planned with holographic augmented reality, a patient with severe treatment resistant major depressive disorder received brain implants with DBS leads and sEEG recording electrodes.
- sEEG recordings monitored alongside DBS enabled optimization of stimulation parameters.
- 18 weeks after start of DBS treatment, patient's severe depression improved, leading to remission. Discontinuation of DBS resulted in worsening mood and anxiety that remitted upon reinstation of DBS.



Sheth et al, *Biol Psychiatry,* 2021

Looking Ahead

Opportunities for discovery and human translation:

- Novel technologies that are advancing our understanding of neural circuit function in models of health and disease
- First-in-human technologies for treating and/or curing devastating brain circuit disorders
- Team science for generating resources at scale

https://www.braininitiative.nih.gov