The NIH BRAIN Initiative:

Accelerating Discovery Toward Cures

John Ngai, PhD

Director, NIH BRAIN Initiative

NIH Advisory Committee to the Director

June 13, 2024

National Institutes of Health
The BRAIN Initiative®

10 Years of BRAIN
A Decade of Innovation

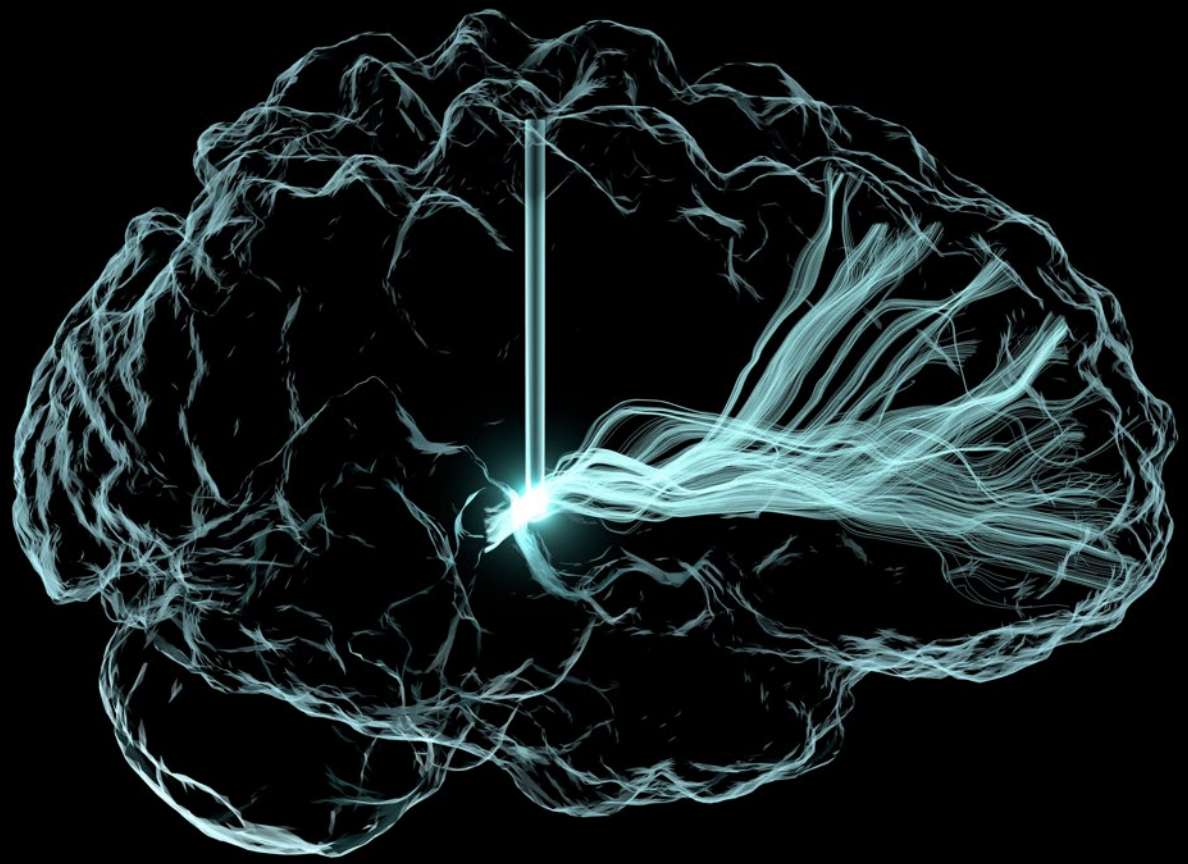


Image Courtesy of Andrew Janson, University of Utah Scientific Computing and Imaging Institute

The U.S. BRAIN Initiative

The *Brain Research Through Advancing Innovative Neurotechnologies*® (BRAIN) Initiative

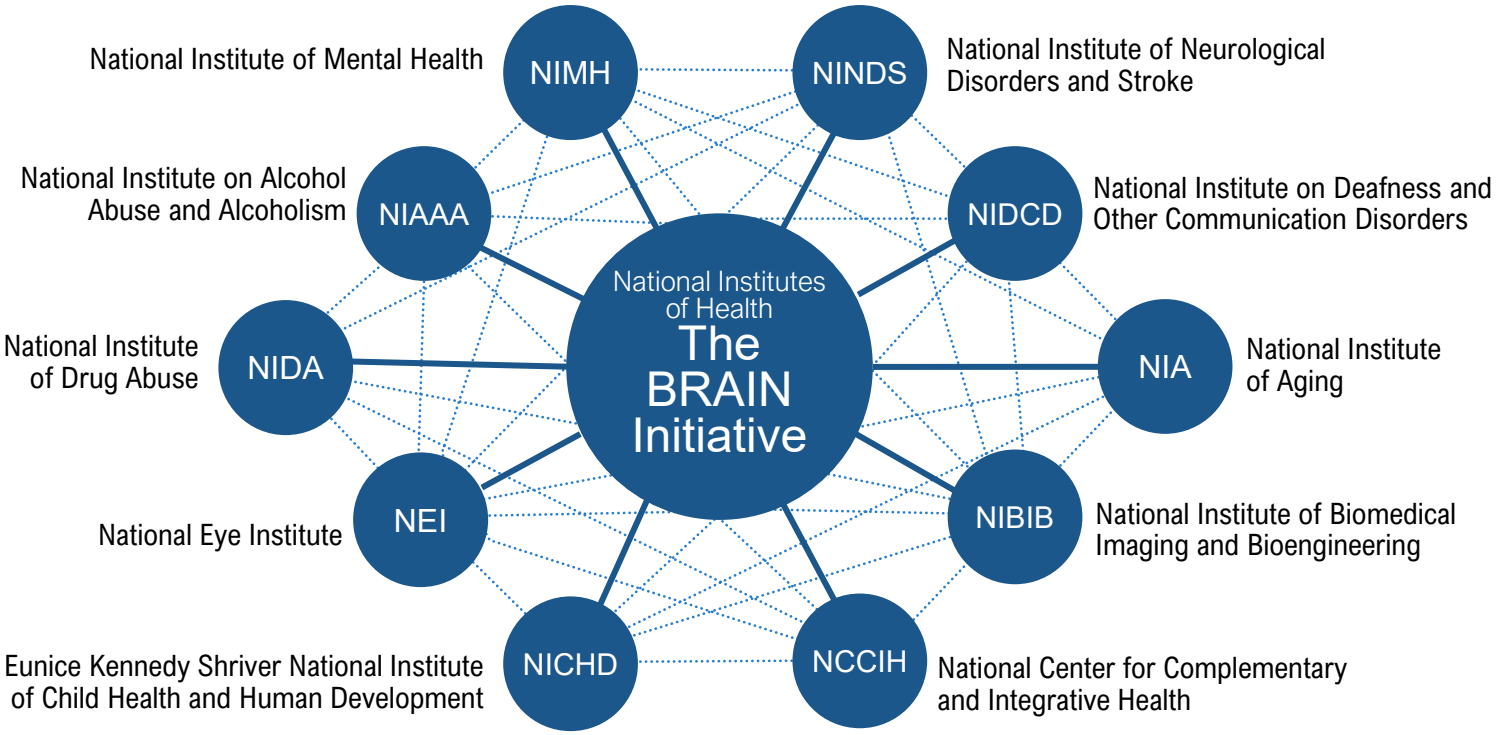
Mission: To revolutionize our understanding of the human brain by accelerating the development and application of innovative technologies

- 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*)

NIH National Institutes of Health · NSF · DARPA · IARPA BE THE FUTURE · FDA · THE KAVLI FOUNDATION · ALLEN INSTITUTE · IEEE brain · SIMONS FOUNDATION · BRAIN INITIATIVE BRAIN Initiative Alliance

The NIH BRAIN Initiative

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



10 Years of BRAIN

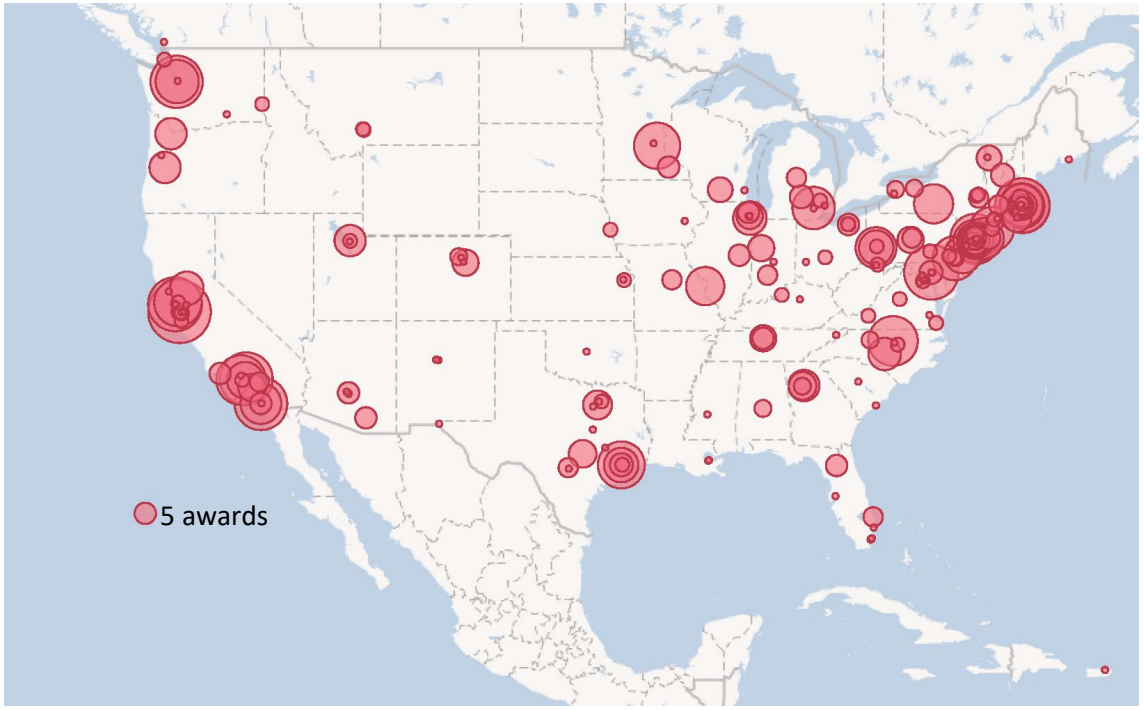
A Decade of INNOVATION

- 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

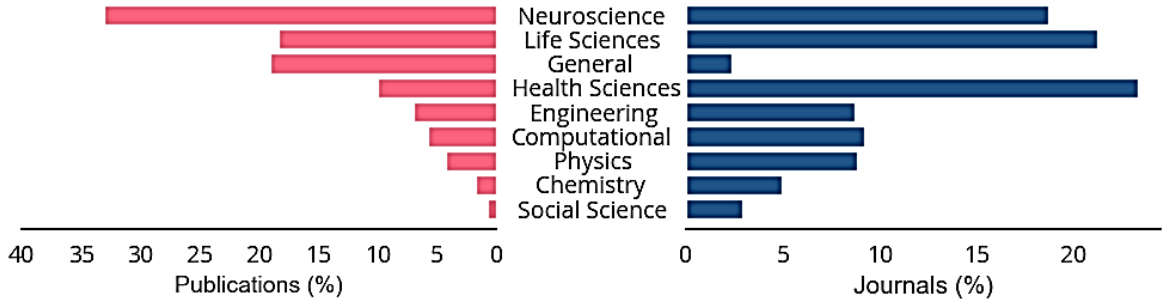
National Institutes of Health
The BRAIN Initiative

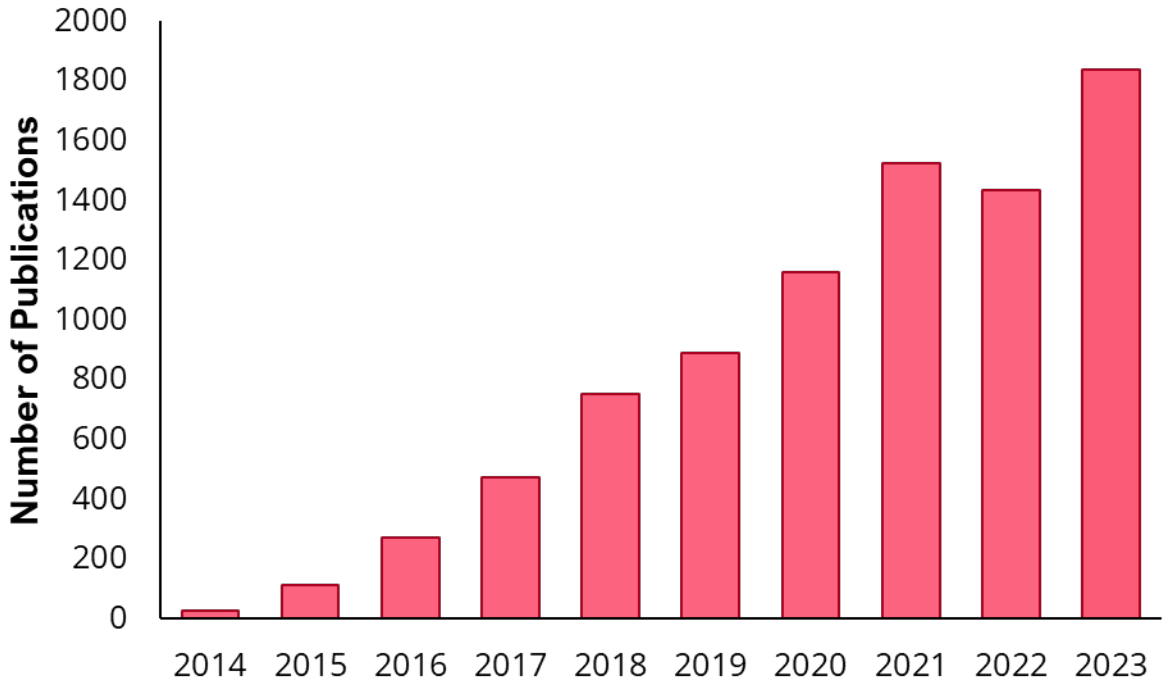
BRAIN Publications: 2014–2023

1,575 Awards
supporting **1,705** PIs
across **265** Institutions



8,478 Publications in **1,035** Journals





BRAIN Research Areas Overview

- Brain Cell & Circuit Technologies
- Neural Recording & Modulation
- Neuroimaging Technologies Across Scales
- Systems Neuroscience
- Human Neuroscience
- Data Science & Informatics
- Training, Inclusion, and Equity
- Neuroethics
- Dissemination & Commercialization

Three Key Takeaways

1. BRAIN–funded advancements in tools and technology are making their way into the clinic – with big potential to see positive impacts on human health

2. BRAIN–funded teams are developing new resources and technologies that are laying down a foundation for future cures

3. BRAIN is creating a new paradigm for doing science that is accelerating the pace of discovery

Impacting human health with new recording and stimulation technologies

nature medicine — BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-020-01175-8
Check for updates

State-dependent responses to intracranial brain stimulation in a patient with depression

NATURE MEDICINE | VOL 27 | FEBRUARY 2021 | 229–231 |

nature medicine

Article
https://doi.org/10.1038/s41591-023-02638-4

Thalamic deep brain stimulation in traumatic brain injury: a phase 1, randomized feasibility study

Nature Medicine | Volume 29 | December 2023 | 3162–3174

ARTICLES
https://doi.org/10.1038/s41591-021-01550-z
nature medicine
Check for updates

Long-term ecological assessment of intracranial electrophysiology synchronized to behavioral markers in obsessive-compulsive disorder

NATURE MEDICINE | VOL 27 | DECEMBER 2021 | 2154–2164 | www.nature.com/naturemedicine

nature

Article

Cingulate dynamics track depression recovery with deep brain stimulation

130 | Nature | Vol 622 | 5 October 2023

nature medicine

Article
https://doi.org/10.1038/s41591-022-02202-6

Epidural stimulation of the cervical spinal cord for post-stroke upper-limb paresis

Nature Medicine | Volume 29 | March 2023 | 689–699

Neuron
CellPress
OPEN ACCESS

Case Study

Responsive deep brain stimulation guided by ventral striatal electrophysiology of obsession durably ameliorates compulsion

Neuron *112*, 73–83, January 3, 2024 © 2023 The Authors. Published by Elsevier Inc.

Biological Psychiatry — Techniques and Methods

Deep Brain Stimulation for Depression Informed by Intracranial Recordings

Biological Psychiatry August 1, 2022; 92:246–251 www.sobp.org/journal

nature medicine

Article
https://doi.org/10.1038/s41591-023-02507-0

Cerebellar deep brain stimulation for chronic post-stroke motor rehabilitation: a phase I trial

Nature Medicine | Volume 29 | September 2023 | 2366–2374

nature medicine — BRIEF COMMUNICATION
https://doi.org/10.1038/s41591-022-01941-w
Check for updates

OPEN

Pilot study of responsive nucleus accumbens deep brain stimulation for loss-of-control eating

NATURE MEDICINE | VOL 28 | SEPTEMBER 2022 | 1791–1796 | www.nature.com/naturemedicine

nature communications

Article
https://doi.org/10.1038/s41467-023-38712-1

A pilot study of closed-loop neuromodulation for treatment-resistant post-traumatic stress disorder

Nature Communications | (2023)14:2997

nature neuroscience

Article
https://doi.org/10.1038/s41593-023-01338-z

First-in-human prediction of chronic pain state using intracranial neural biomarkers

Nature Neuroscience | Volume 26 | June 2023 | 1090–1099

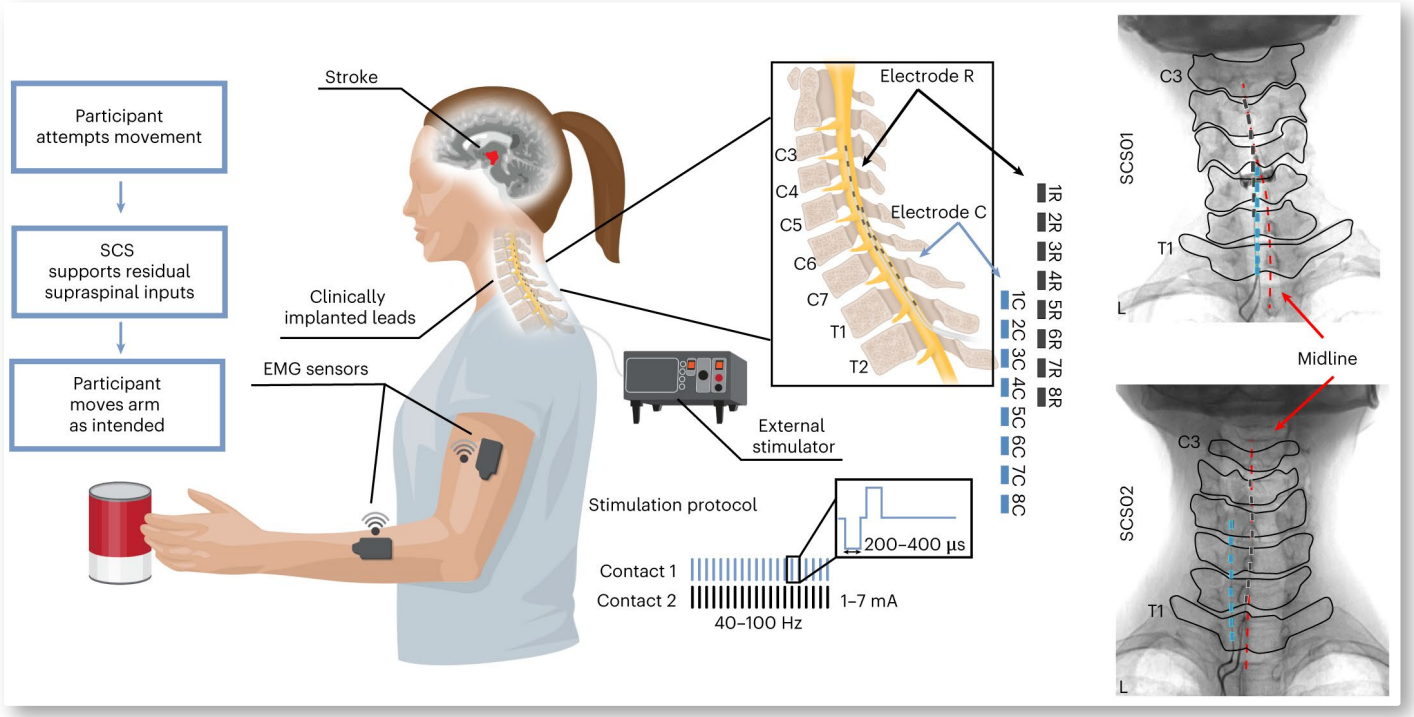
ARTICLES
https://doi.org/10.1038/s41587-021-00897-5
nature biotechnology
Check for updates

Long-term wireless streaming of neural recordings for circuit discovery and adaptive stimulation in individuals with Parkinson's disease

NATURE BIOTECHNOLOGY | VOL 39 | SEPTEMBER 2021 | 1078–1085 | www.nature.com/naturebiotechnology

Spinal Cord Stimulation Aids Stroke Recovery

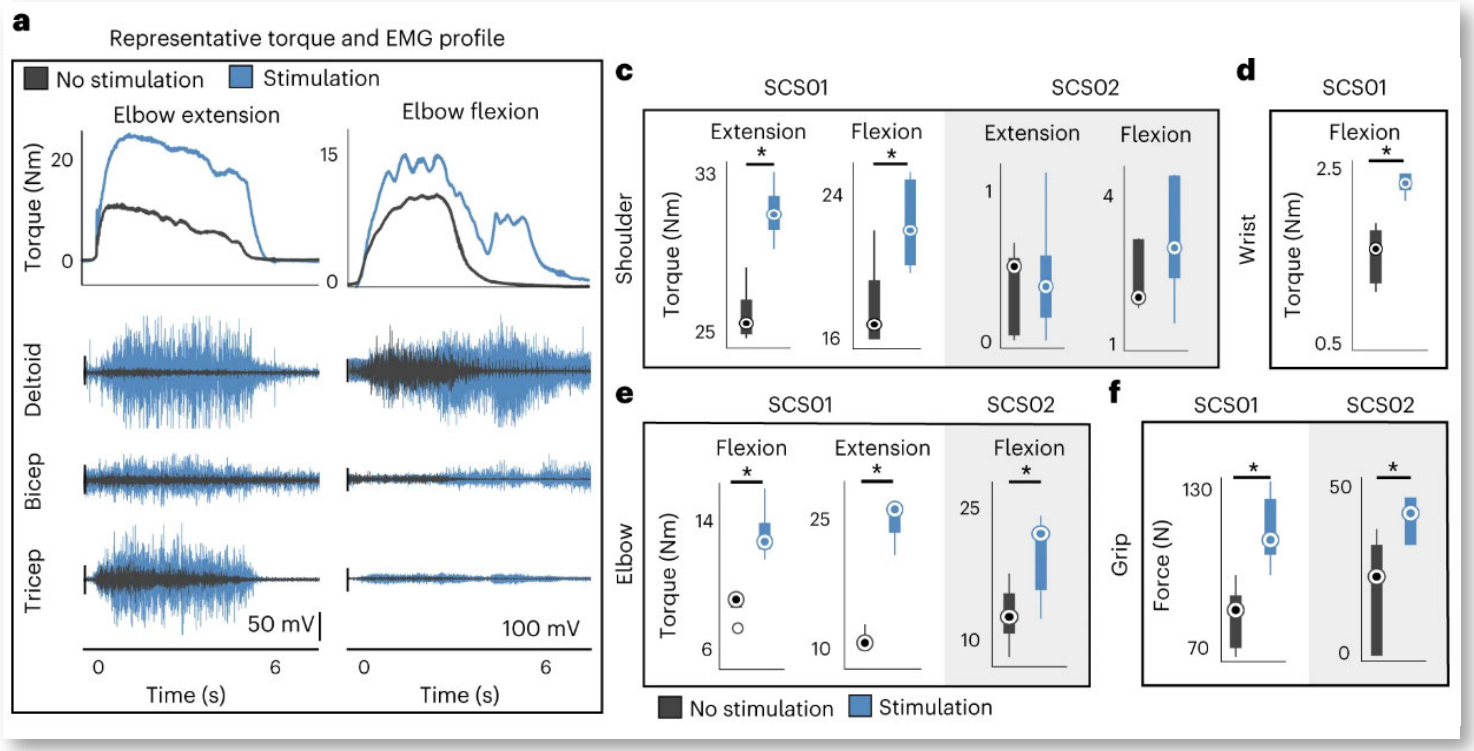
Two stroke patients with chronic upper limb paresis were implanted with clinical Spinal Cord Stimulation (SCS) leads for 4 weeks



[Powell et al, Nat Med, 2023]

Spinal Cord Stimulation Aids Stroke Recovery

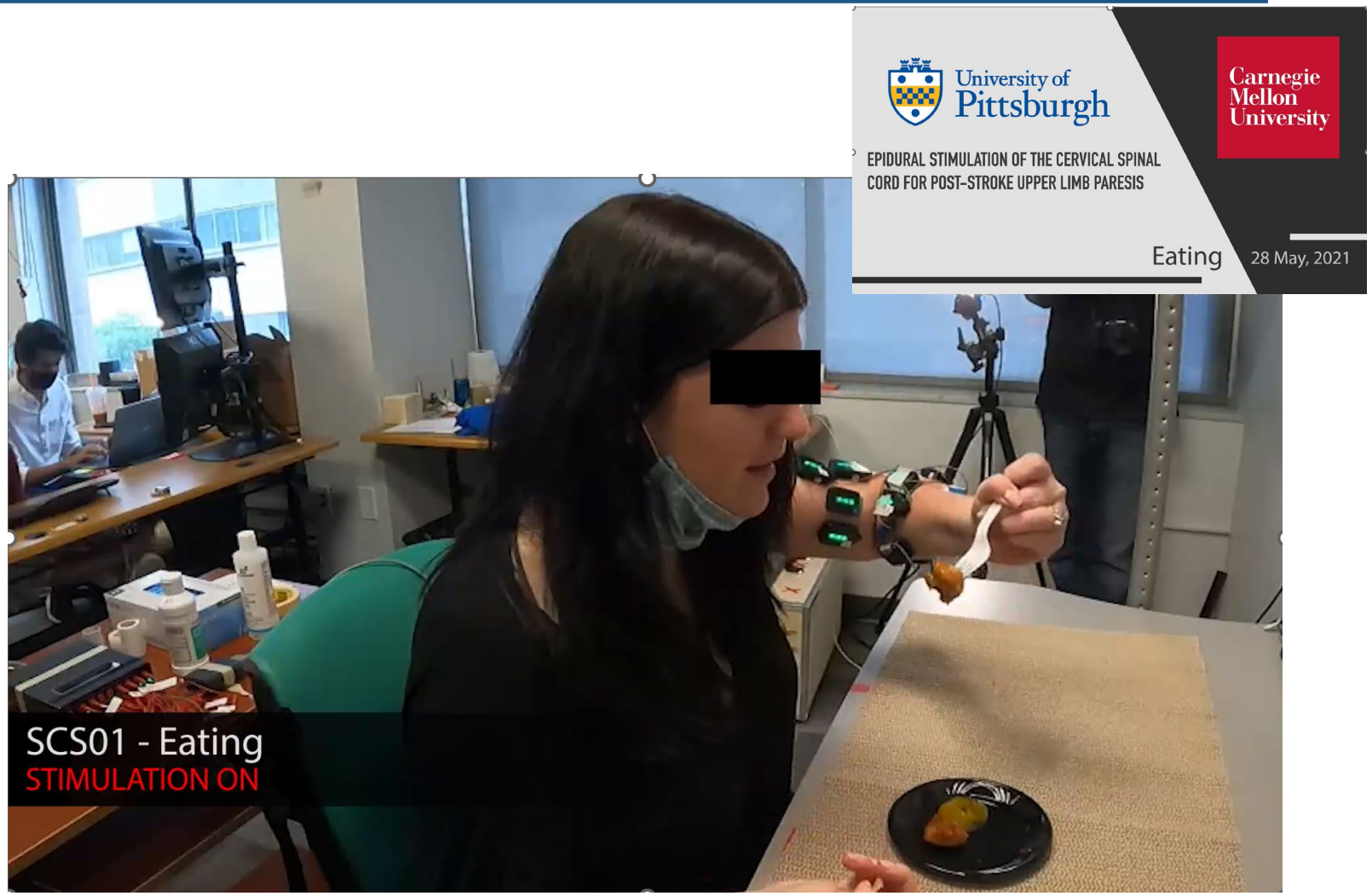
Stimulation protocols were optimized to each individual and led to significant increases in muscle activation



Powell et al, Nat Med, 2023

Spinal Cord Stimulation Aids Stroke Recovery
continued

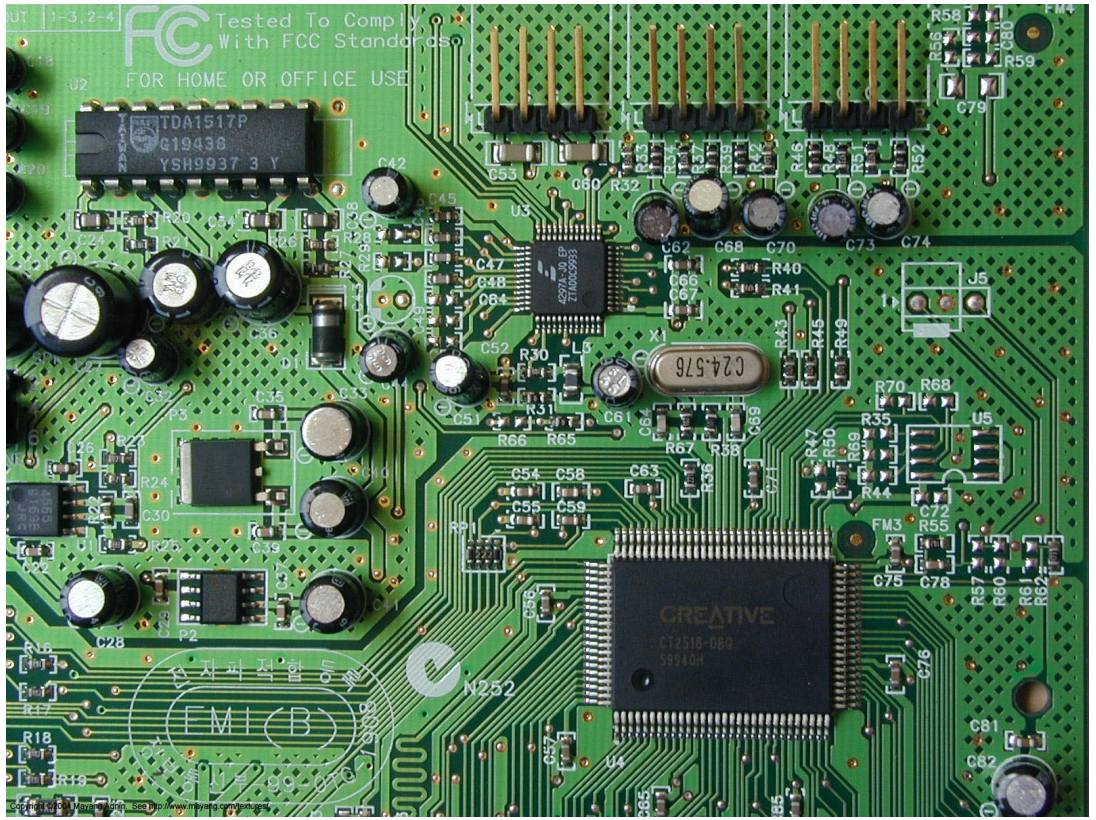
SCS resulted in immediate and lasting (up to 4 wks) functional recovery of limb coordination including ability to self-feed



Powell et al, Nat Med, 2023

Developing Foundational Resources to Accelerate Neuroscience Research

We need a “parts list” and “wiring diagram” for the brain…



…and a way to *interrogate* and *modulate* brain circuits and behavioral processes

CellPress

Neuron
Perspective

The BRAIN Initiative Cell Census Consortium: Lessons Learned toward Generating a Comprehensive Brain Cell Atlas

Joseph R. Ecker,[1] Daniel H. Geschwind,[2] Arnold R. Kriegstein,[3] John Ngai,[4,*] Pavel Osten,[5] Damon Polioudakis,[2] Aviv Regev,[6] Nenad Sestan,[7] Ian R. Wickersham,[8] and Hongkui Zeng[9]
*Correspondence: jngai@berkeley.edu
https://doi.org/10.1016/j.neuron.2017.10.007

A crucible for developing, validating, and scaling up emerging genomic and anatomical mapping technologies for creating a complete inventory of neuronal cell types and their connections in multiple species and during development

"The BICCN [BRAIN Initiative Cell Census Network] aspires to revolutionize the ability to classify brain cell types based on an integrated analysis of their molecular, anatomical, and physiological properties…"

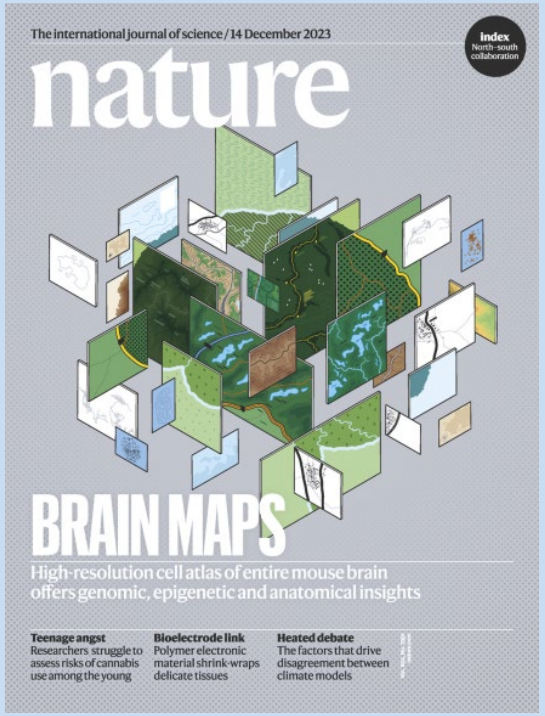
BICCC Pilot Phase: 2014-2017

BICCN: 2017-2022

BRAIN Initiative Cell Atlas Network (BICAN): 2022-2027

BRAIN Initiative Cell Census Network (BICCN)

Primary Motor Cortex
October 2021
17 articles + 10 articles in Nature sister journals



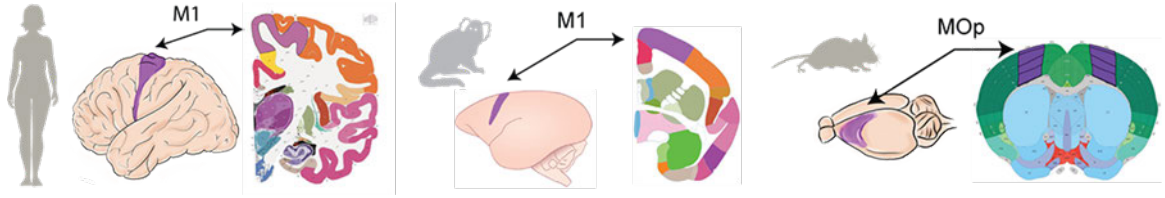
Whole Mouse Atlas
December 2023
10 articles

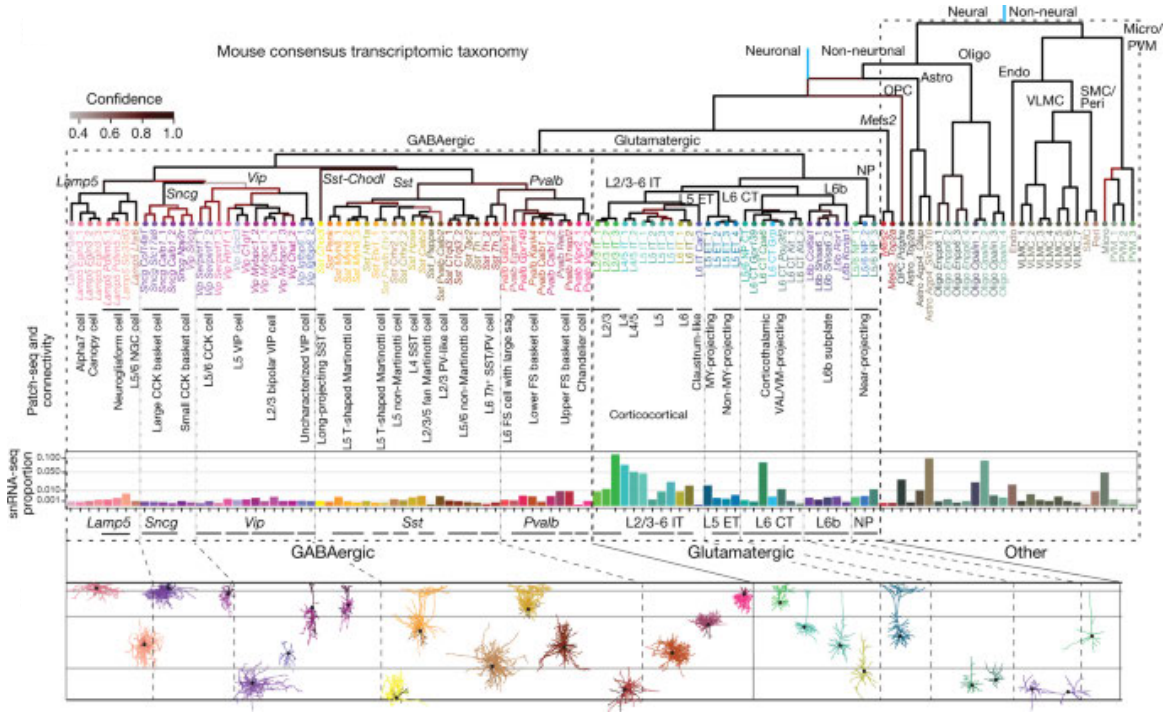
Draft Human & Non-Human Primate Atlas
October 2023
21 articles

The BRAIN Initiative Cell Census Network:
Scaling Science, Technology and Collaboration

Primary Motor Cortex
October 2021

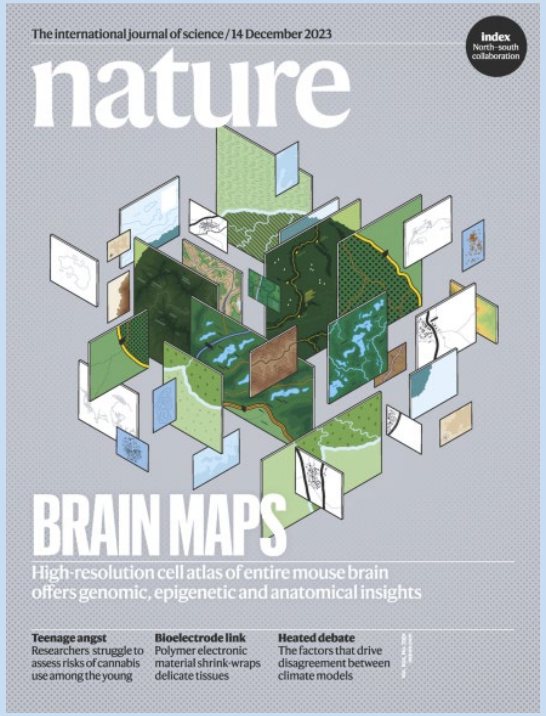
- A multimodal census and atlas of the **primary motor cortex** in multiple mammalian species
- Triumph of team science:
  - 250⁺ researchers
  - 89 affiliations
  - 45⁺ institutions
  - 3 continents
- Set the stage for larger and more comprehensive atlases





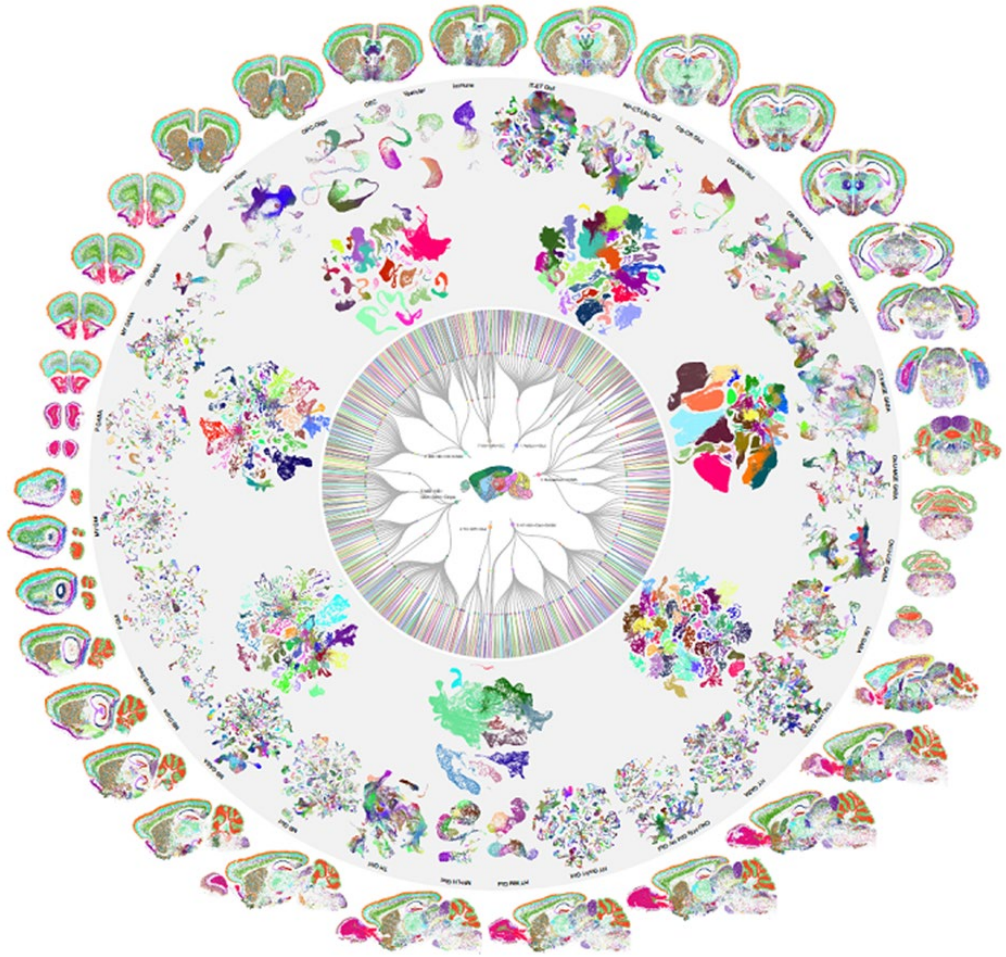
[BICCN, Nature 2021]

The BRAIN Initiative Cell Census Network:
A Comprehensive Atlas of the Entire Mouse Brain

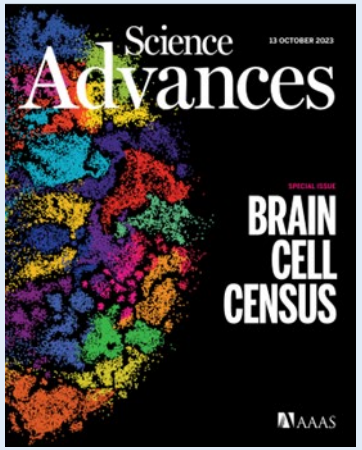


Whole Mouse Atlas
December 2023

- **32⁺ million cells** across the adult mouse brain were profiled using a combination high-resolution, single-cell techniques
- **5,300⁺ neuronal and non-neuronal cell types** identified
- Reveals the **organizational principles** underlying the diversification of brain cell types



The BRAIN Initiative Cell Census Network:
Charting the Course for a Human Brain Cell Atlas

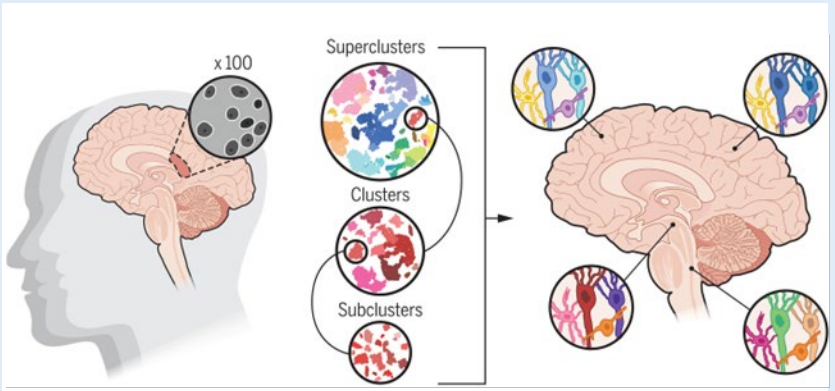


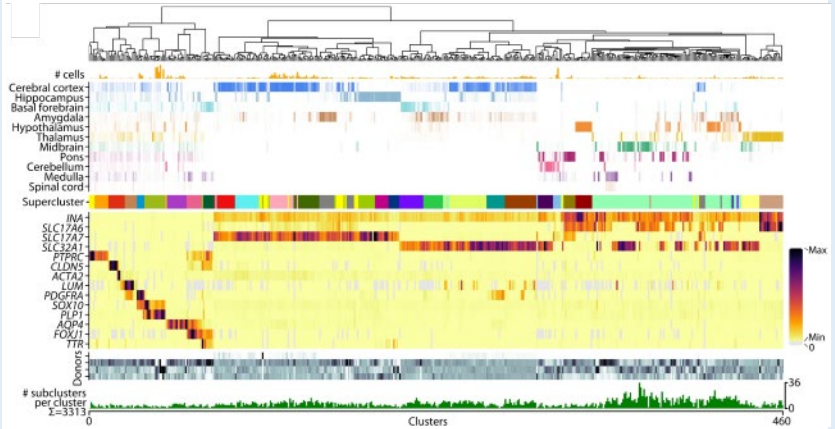
Draft Human/NHP Atlas
October 2023

- **21** joint publications across **3** *Science* family journals
- Mapping unprecedented complexities across **space**, **species**, and **time**
- Paving the road toward a **greater understanding** of the human brain at the cellular level in **health** and **disease**

Ushering in a New Era of Human Brain Research…

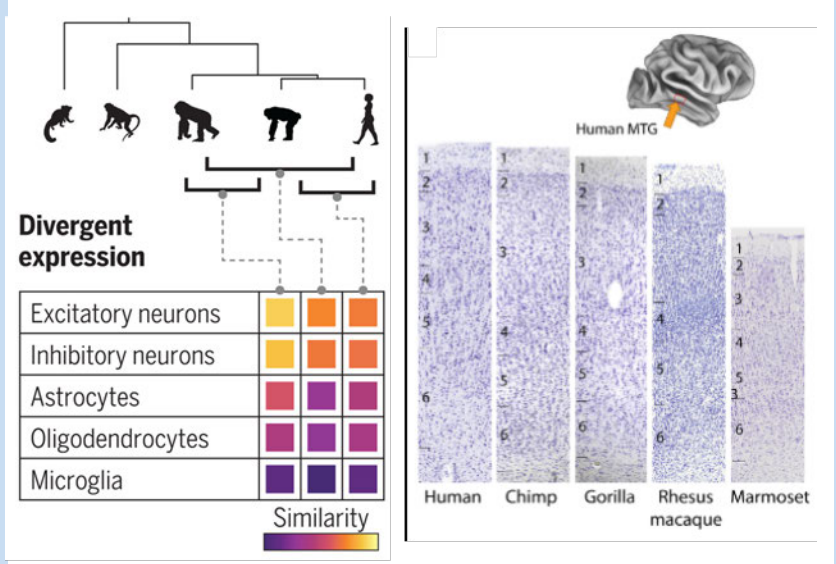
across **space**…

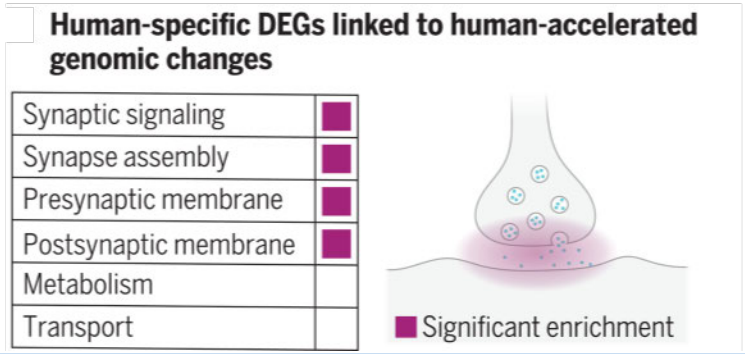




Siletti et al 2023; Yang et al 2023; Tian et al 2023; Jorstad et al 2023; Johansen et al 2023; Costantini et al 2023

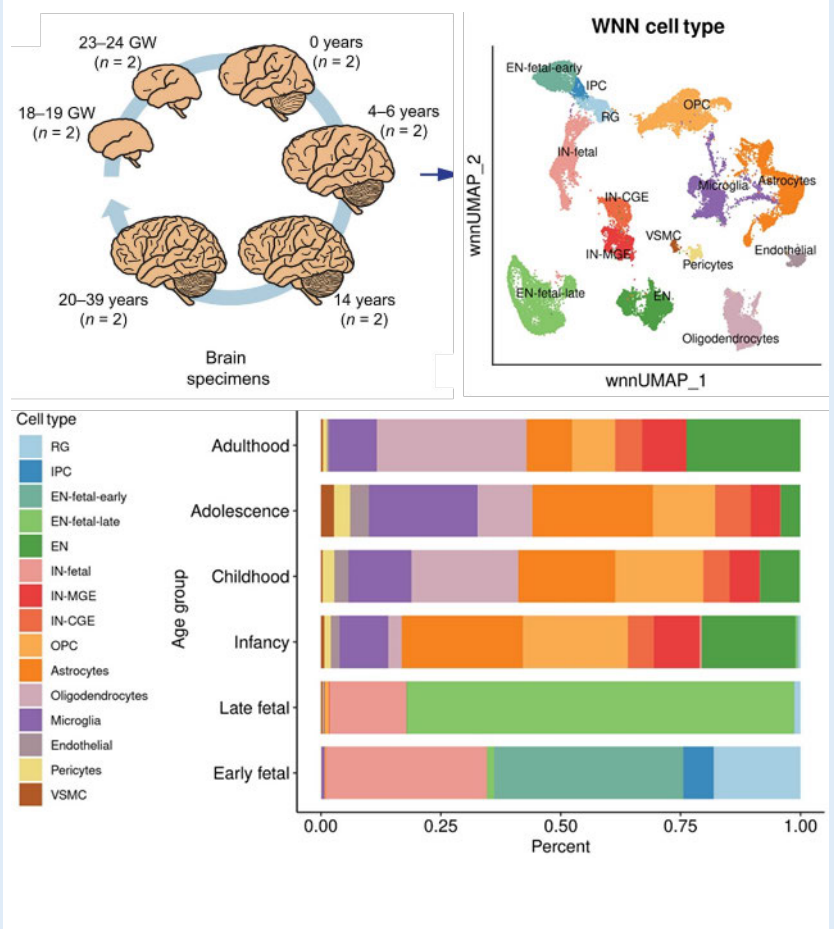
across **species**…





Jorstad et al Science 2023

across **time**…



Zhu et al 2023; Ament et al 2023; Braun et al 2023; Kim et al 2023; Herb et al 2023; Velmeshev et al 2023; Micali et al 20233;

BRAIN Initiative Transformative Projects

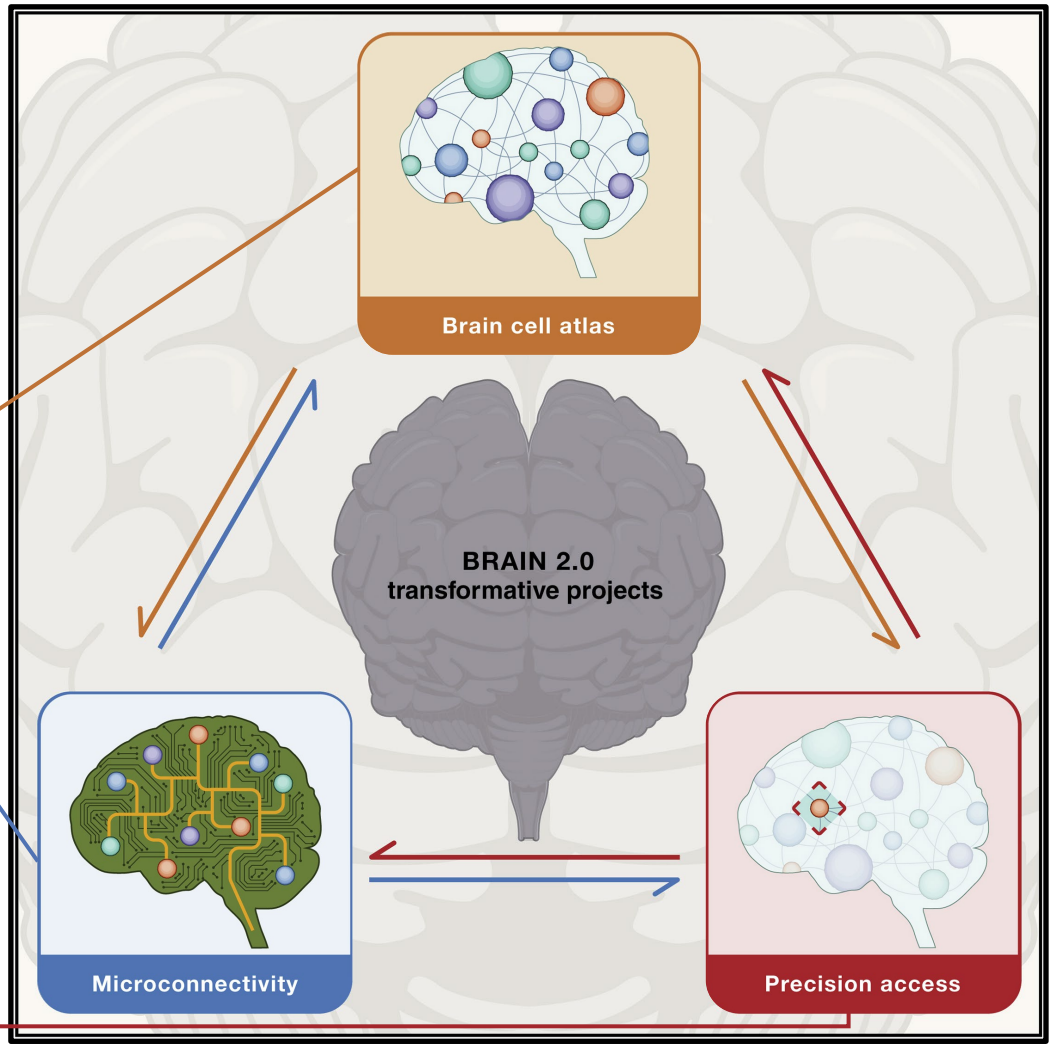
CellPress
Cell
Leading Edge

Commentary

BRAIN 2.0: Transforming neuroscience

John Ngai[1,*]
[1]NIH BRAIN Initiative, National Institutes of Health, Bethesda, MD, USA
*Correspondence: john.ngai@nih.gov
https://doi.org/10.1016/j.cell.2021.11.037

- The **BRAIN Initiative Cell Atlas Network (BICAN)** will map brain cells and circuits across multiple species, with an emphasis on humans
- **BRAIN Initiative Connectivity Across Scales (BRAIN CONNECTS) Network** will provide a wiring diagram by mapping all the connections in the brain
- The **Armamentarium for Precision Brain Cell Access** leverages new brain cell census data to build a toolkit to access brain cells based on their molecular identity



Ngai, Cell 2022

BRAIN Initiative Transformative Projects: BICAN

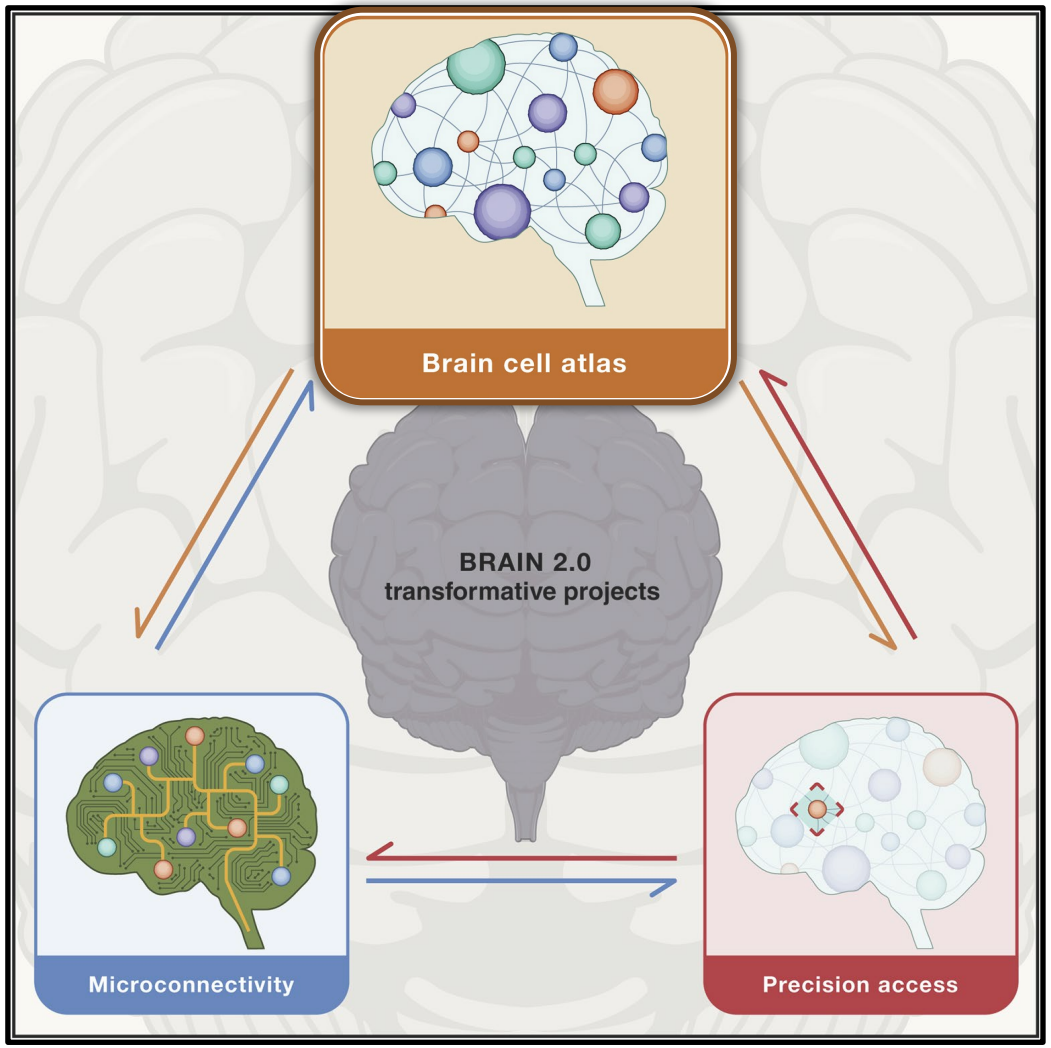
CellPress
Cell
Leading Edge

Commentary

BRAIN 2.0: Transforming neuroscience

John Ngai[1,*]
[1]NIH BRAIN Initiative, National Institutes of Health, Bethesda, MD, USA
*Correspondence: john.ngai@nih.gov
https://doi.org/10.1016/j.cell.2021.11.037

- The **BRAIN Initiative Cell Atlas Network (BICAN)** will map brain cells and circuits across multiple species, with an emphasis on humans
- **BRAIN Initiative Connectivity Across Scales (BRAIN CONNECTS) Network** will provide a wiring diagram by mapping all the connections in the brain
- The **Armamentarium for Precision Brain Cell Access** leverages new brain cell census data to build a toolkit to access brain cells based on their molecular identity

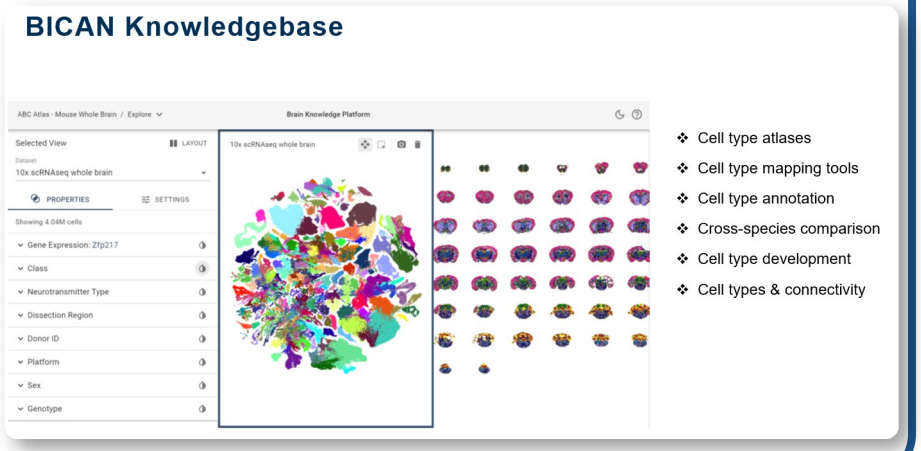


Ngai, Cell 2022

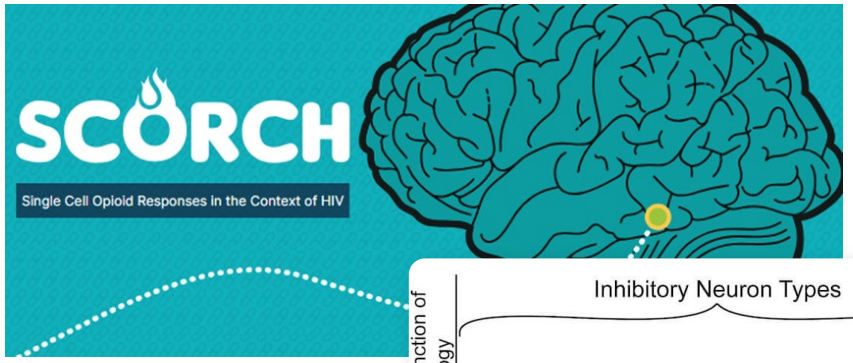
From BICCN to BICAN

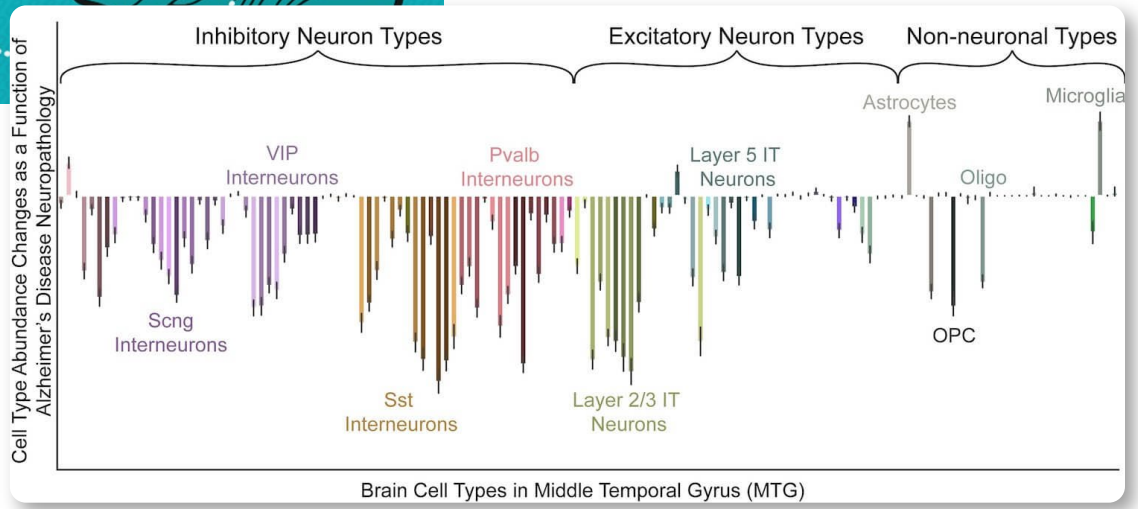
BRAIN Initiative Cell Atlas Network (BICAN)

Moving beyond data to develop **new knowledge** for neuroscience



Leveraging new biological insights to understand **brain health** & **dysfunction**





Seattle Alzheimer's Disease Brain Cell Atlas

BRAIN Initiative Transformative Projects: BRAIN CONNECTS

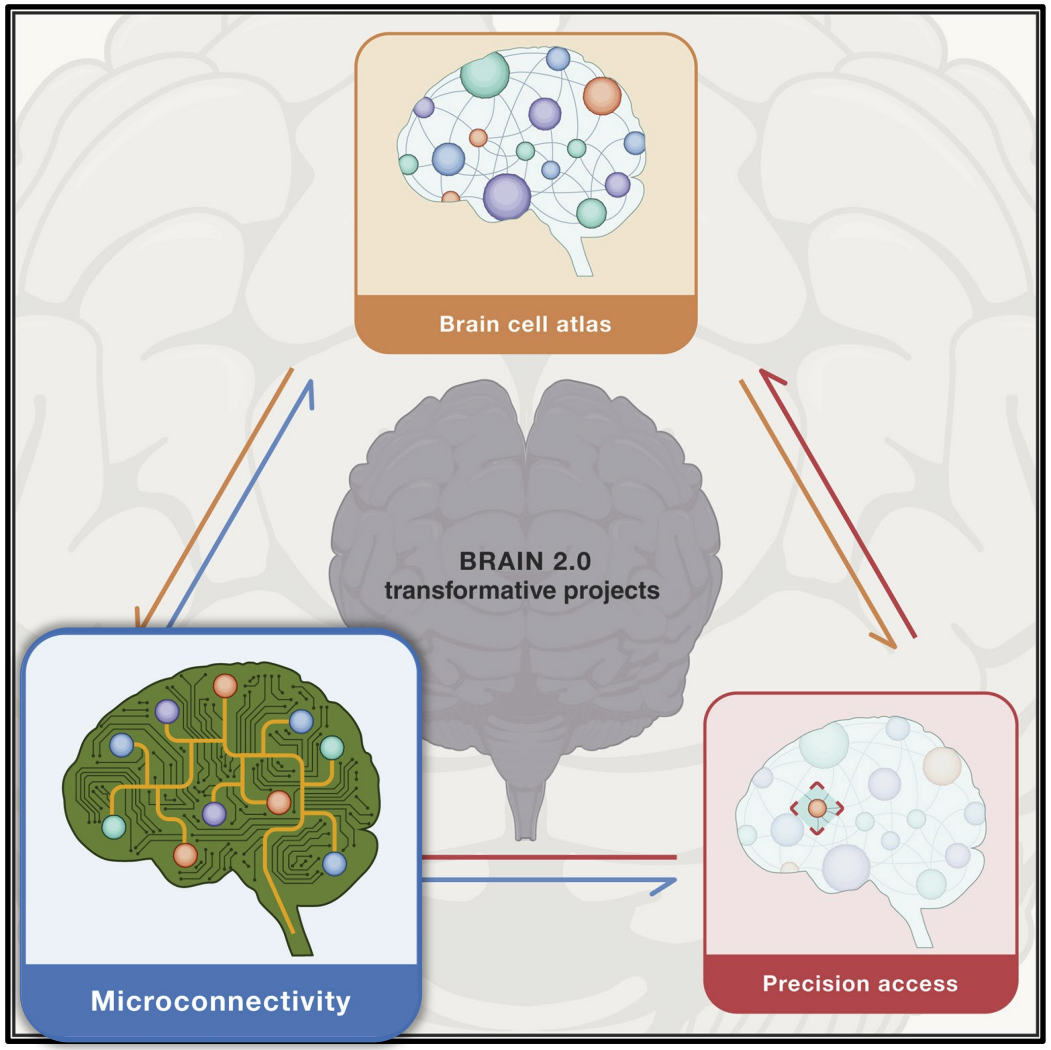
CellPress
Cell
Leading Edge

Commentary

BRAIN 2.0: Transforming neuroscience

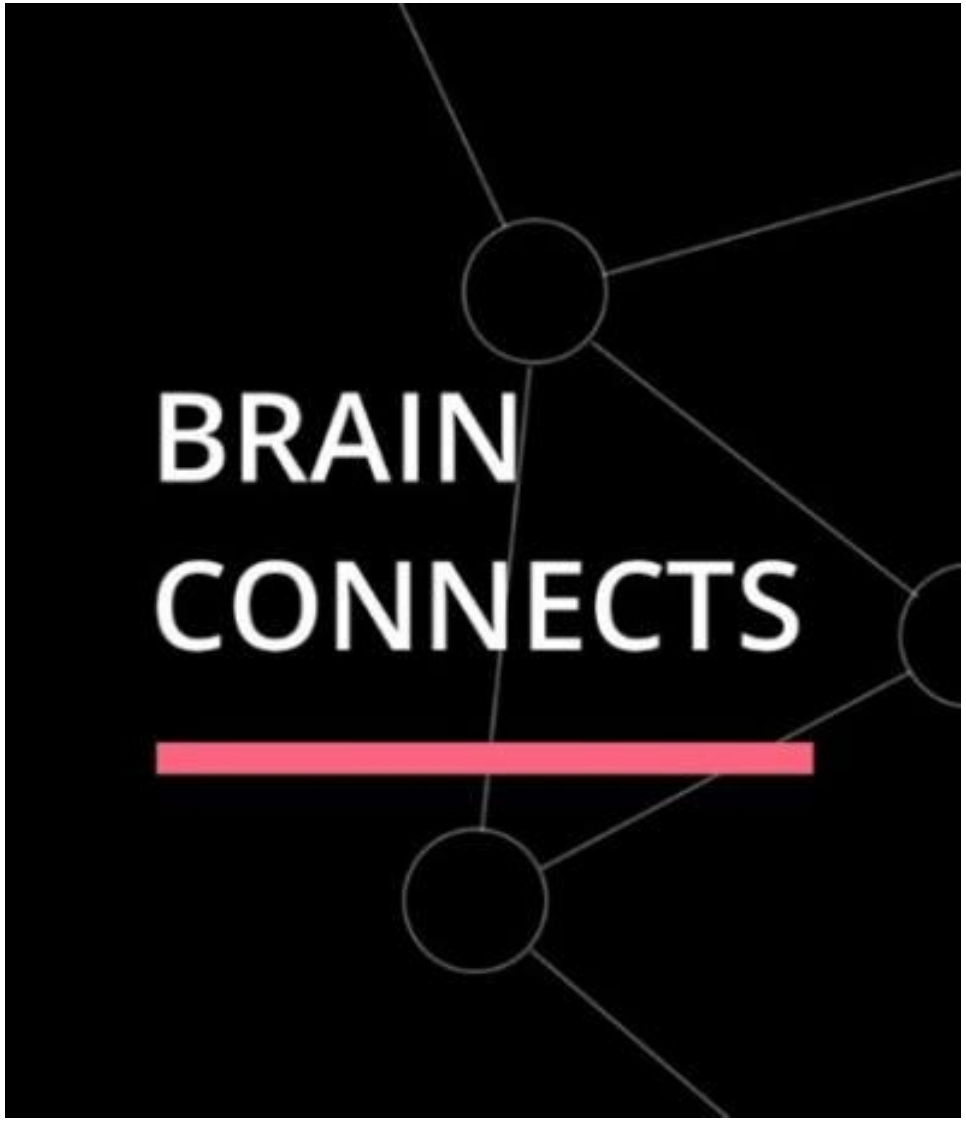
John Ngai[1,*]
[1]NIH BRAIN Initiative, National Institutes of Health, Bethesda, MD, USA
*Correspondence: john.ngai@nih.gov
https://doi.org/10.1016/j.cell.2021.11.037

- The **BRAIN Initiative Cell Atlas Network (BICAN)** will map brain cells and circuits across multiple species, with an emphasis on humans
- **BRAIN Initiative Connectivity Across Scales (BRAIN CONNECTS) Network** will provide a wiring diagram by mapping all the connections in the brain
- The **Armamentarium for Precision Brain Cell Access** leverages new brain cell census data to build a toolkit to access brain cells based on their molecular identity



Ngai, Cell 2022

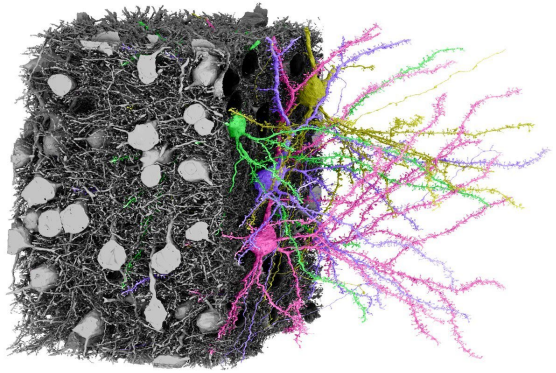
- The CONNECTS program launched in Fall 2023 with **11 grants** supporting research teams and their collaborators across **40 universities and research institutions**
- Over **the next five years**, researchers will leverage cutting edge technology to image and analyze brain connectivity with unparalleled speed and resolution



Innovative Technologies to Map the Brain Across Scales, part 2

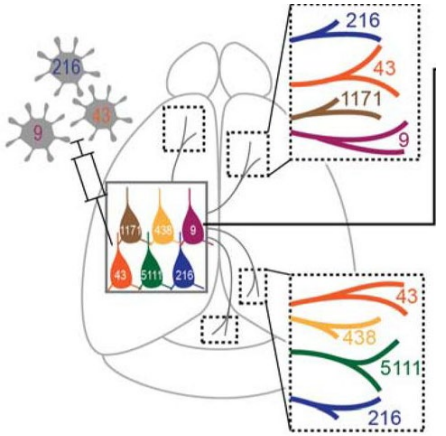
The projects will develop complementary brain mapping methods, covering **three core technologies**

Electron Microscopy Pipelines



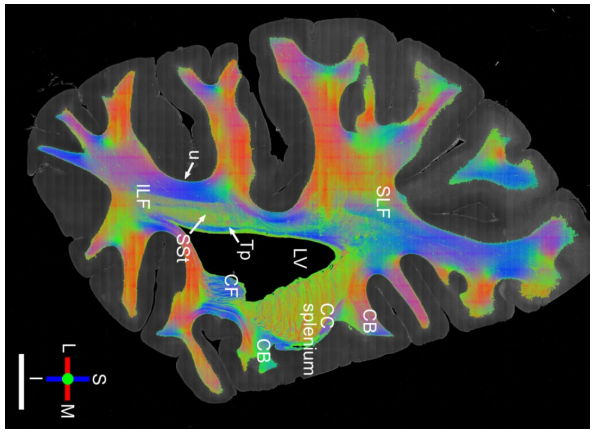
MICrONS-Explorer.org

Sequencing Tools

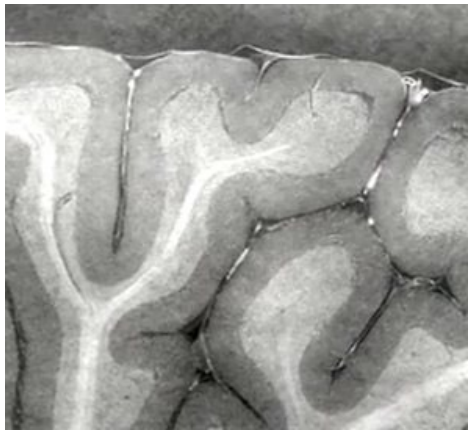


Sun et al bioRxiv 2023

Novel Tools in Humans and Non-Human Primates



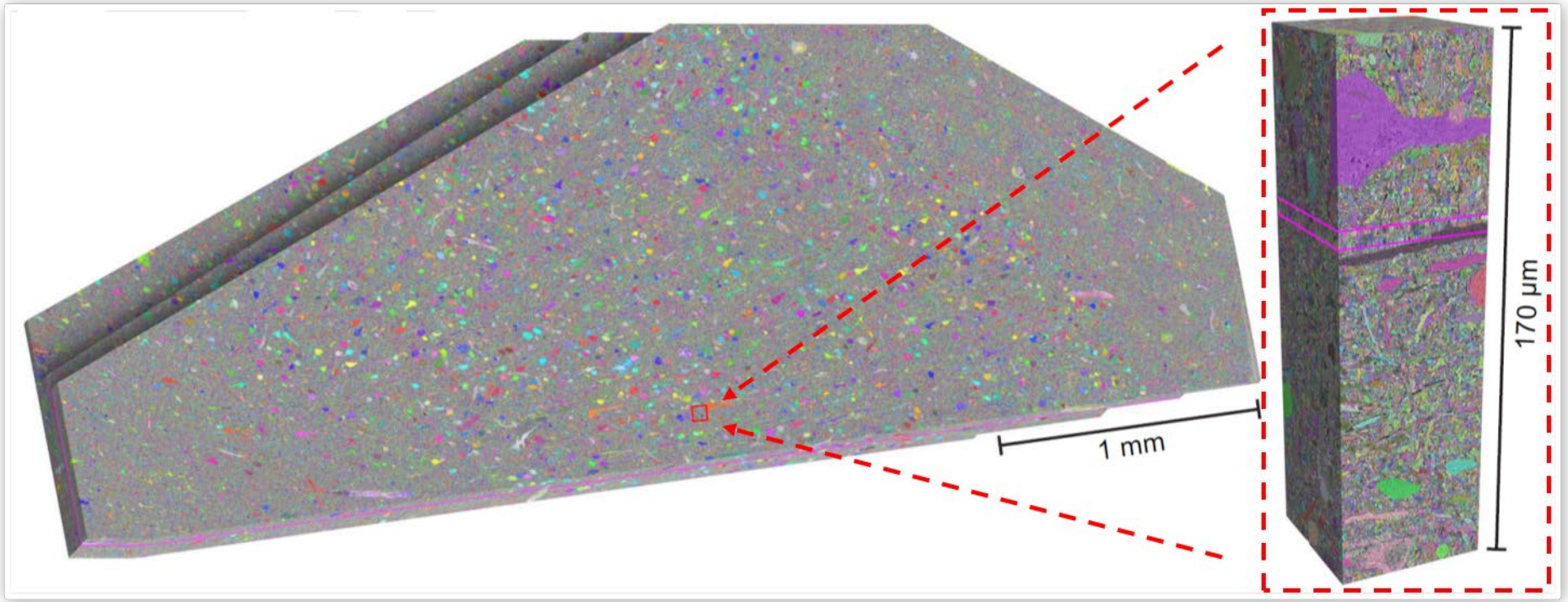
Liu et al bioRxiv 2023



Walsh et al Nat Methods 2021

A petavoxel fragment of human cerebral cortex reconstructed at nanoscale resolution 1 of 2

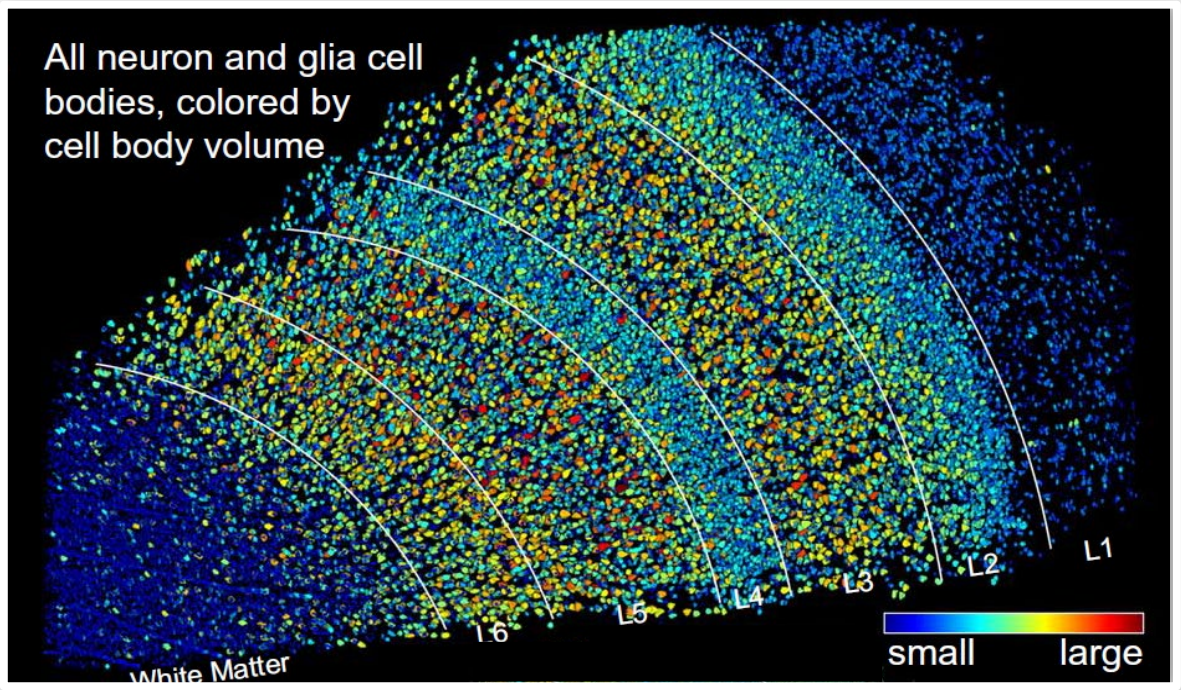
Ultrastructural reconstruction of a cubic millimeter of human temporal cortex spanning all cortical layers, yielding 1.4 petabytes of data

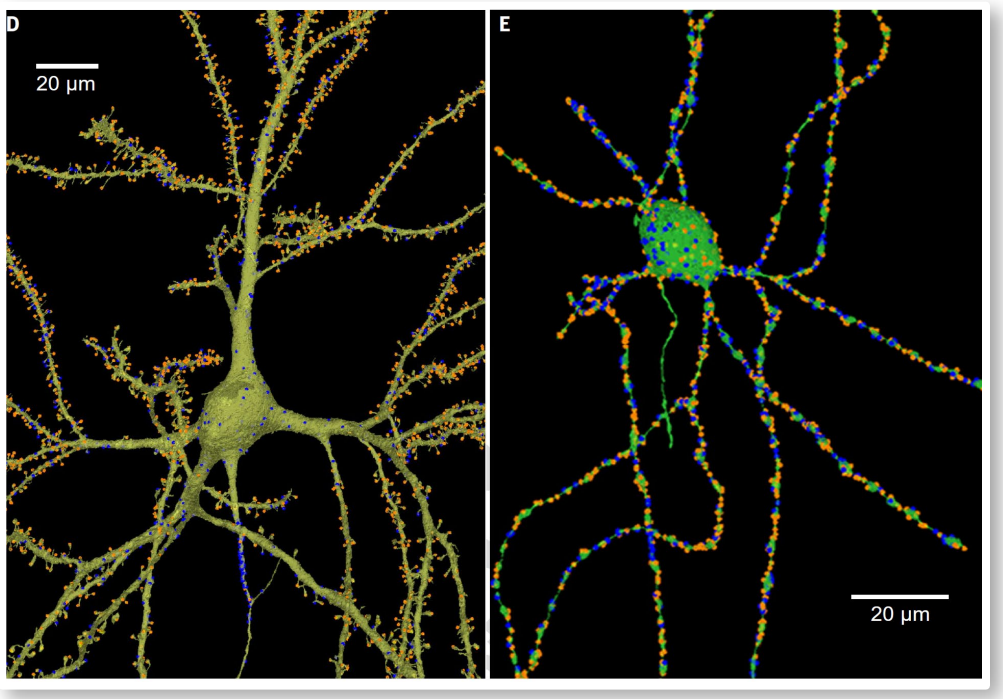


Shapson-Coe A, Januszewski M, Berger DR et al, Science 2024

A petavoxel fragment of human cerebral cortex reconstructed at nanoscale resolution 2 of 2

- Reconstruction of 57,000 cells, 230 millimeters of blood vessels, and 150 million synapses
- Images, reconstructions, annotations, and analysis tools all available online for further exploration.





Shapson-Coe A, Januszewski M, Berger DR et al, Science 2024

BRAIN Initiative Transformative Projects:
Armamentarium for Precision Brain Cell Access

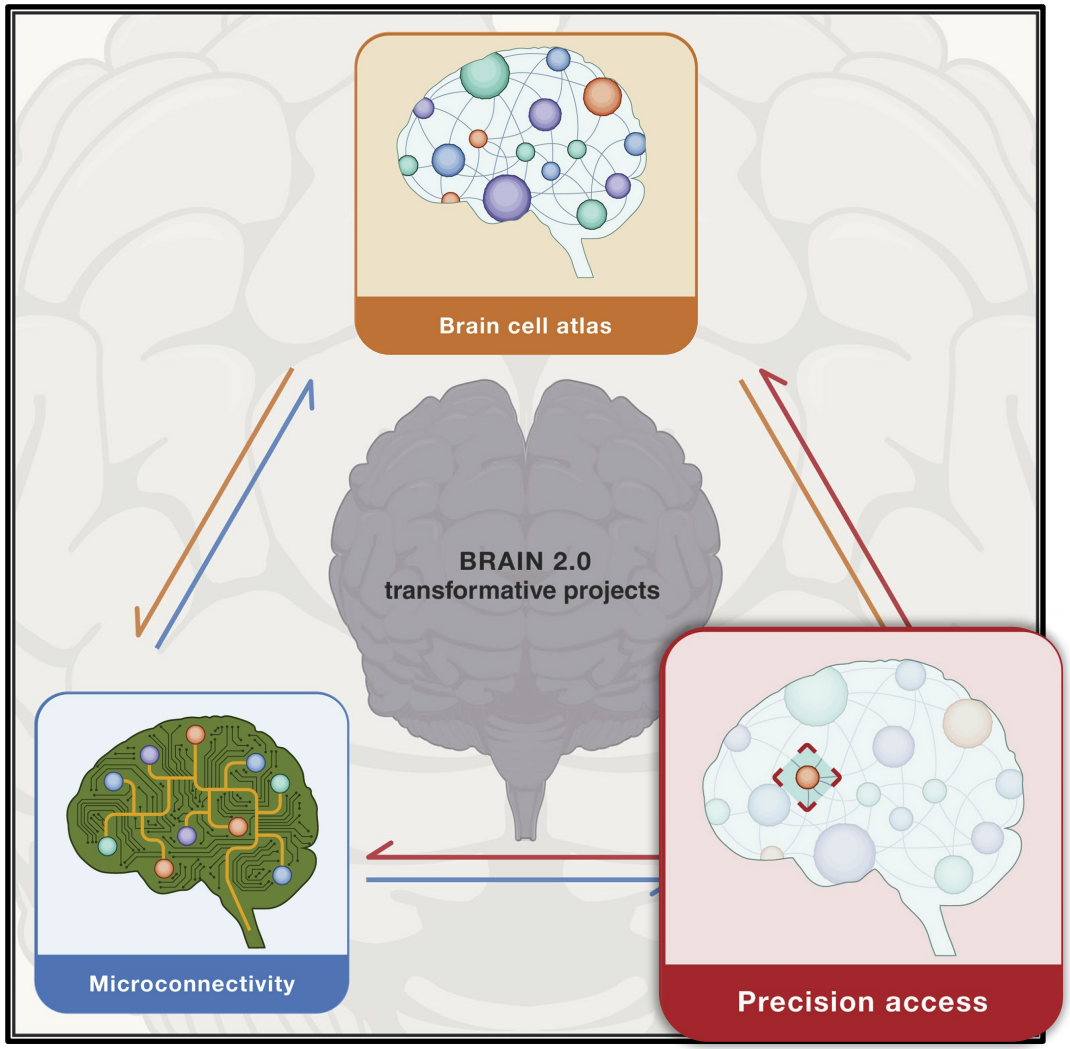
CellPress
Cell
Leading Edge

Commentary

BRAIN 2.0: Transforming neuroscience

John Ngai[1,*]
[1]NIH BRAIN Initiative, National Institutes of Health, Bethesda, MD, USA
*Correspondence: john.ngai@nih.gov
https://doi.org/10.1016/j.cell.2021.11.037

- The **BRAIN Initiative Cell Atlas Network (BICAN)** will map brain cells and circuits across multiple species, with an emphasis on humans
- **BRAIN Initiative Connectivity Across Scales (BRAIN CONNECTS) Network** will provide a wiring diagram by mapping all the connections in the brain
- The **Armamentarium for Precision Brain Cell Access** leverages new brain cell census data to build a toolkit to access brain cells based on their molecular identity



Ngai, Cell 2022

Armamentarium for Precision Brain Cell Access

BRAIN 2.0 Transformative Project

"...generate and implement methods to specifically access, manipulate, and model a few hundred clinically-relevant cell types across multiple species..." BRAIN 2.0 report

Access Tools

(U01) Pilot resources for brain cell type-specific access and manipulation (RFA-MH-20-556

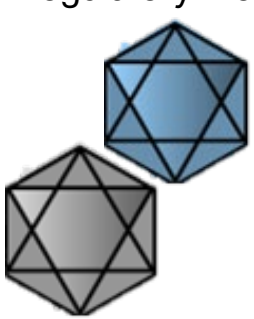
Dissemination

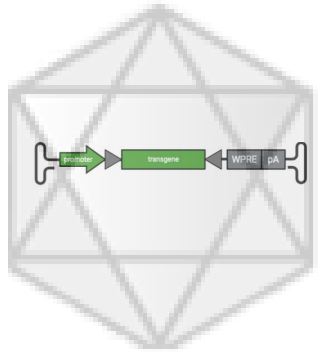
(U24) Reagent resources for brain cell type-specific access and manipulation to broaden distribution of enabling technologies for neuroscience (RFA-MH- 21-180)

Molecular Payloads

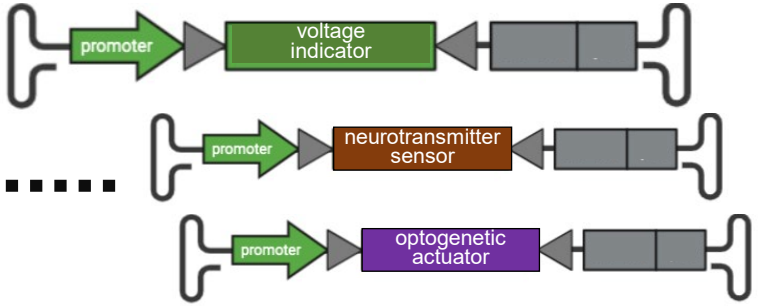
(UM1) Engineering and optimization of molecular technologies for functional dissection of neural circuits (RFA-MH-22-245

Delivery Vectors,
Gene Regulatory Elements





Molecular Payloads

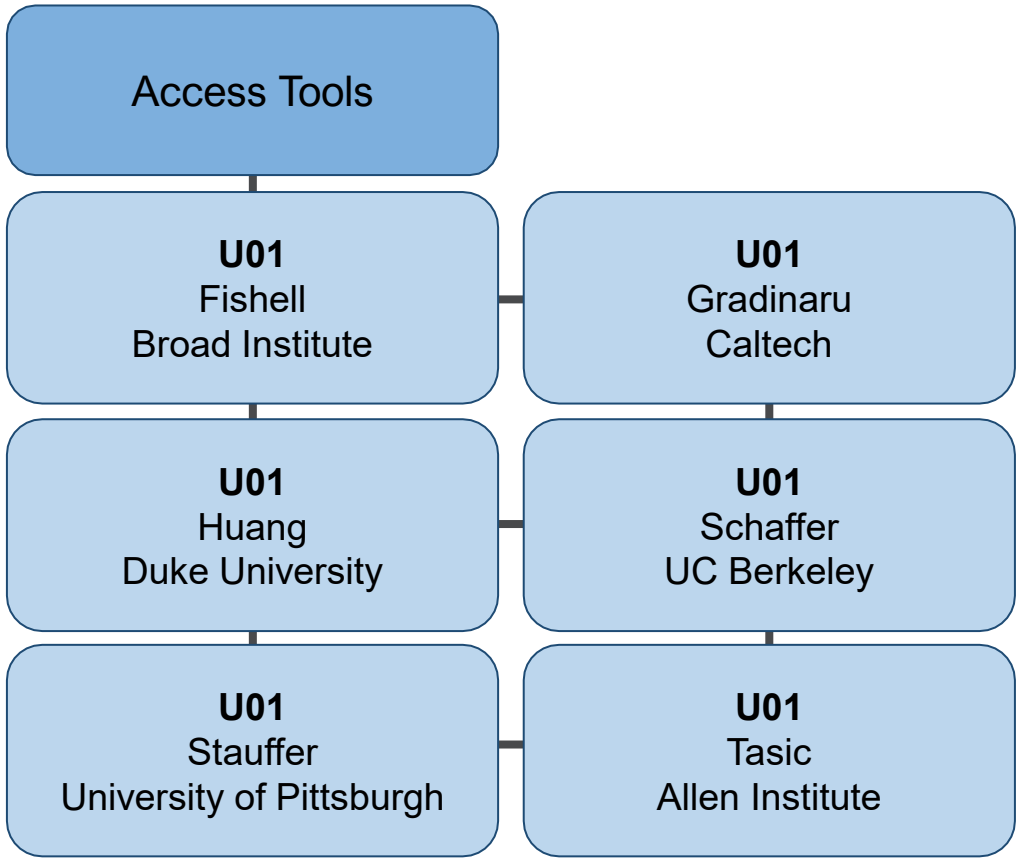


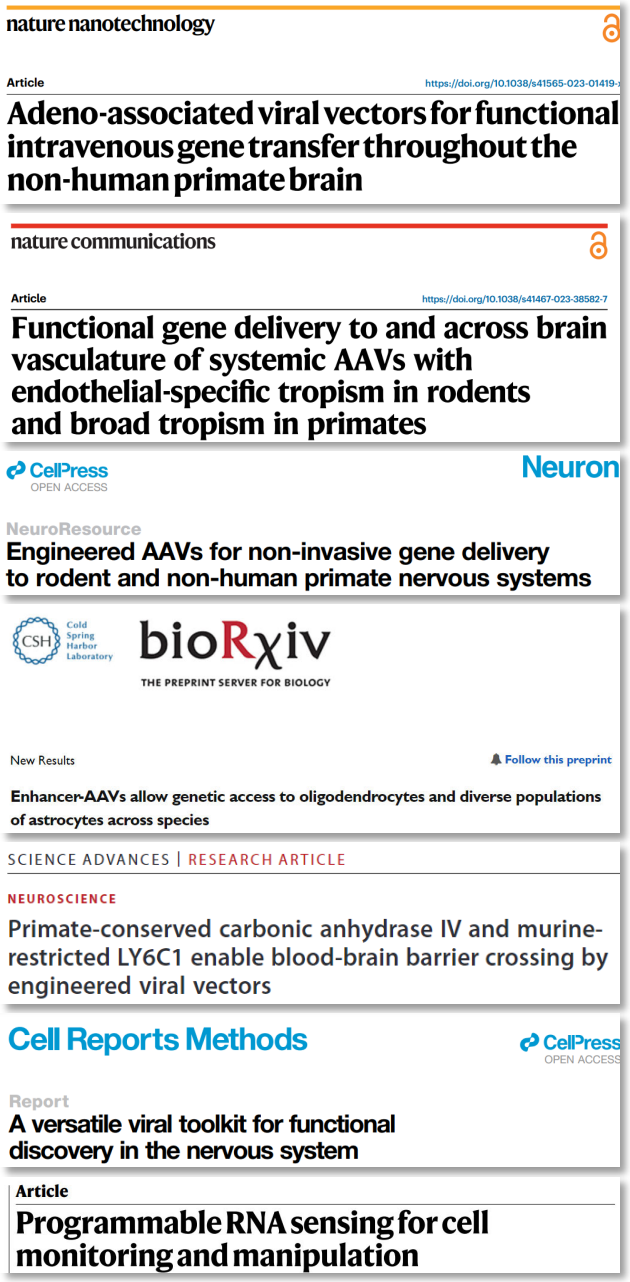
Armamentarium: pilot phase

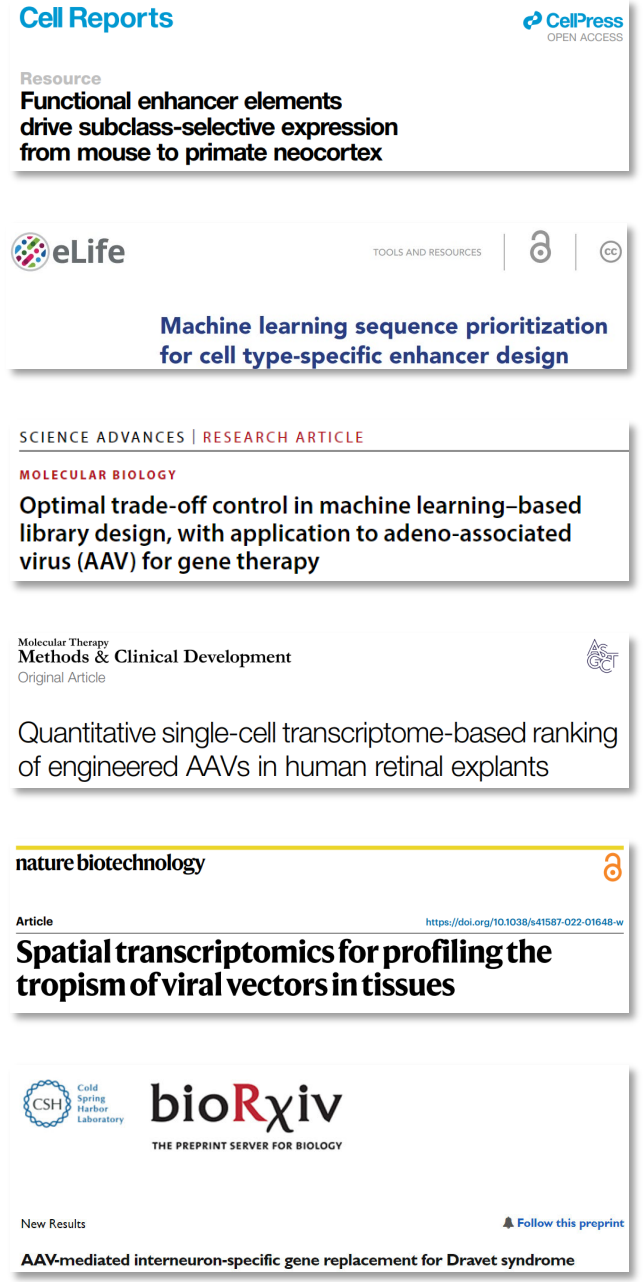
Armamentarium Consortium

Coordination to start building a comprehensive toolkit

FY21-present



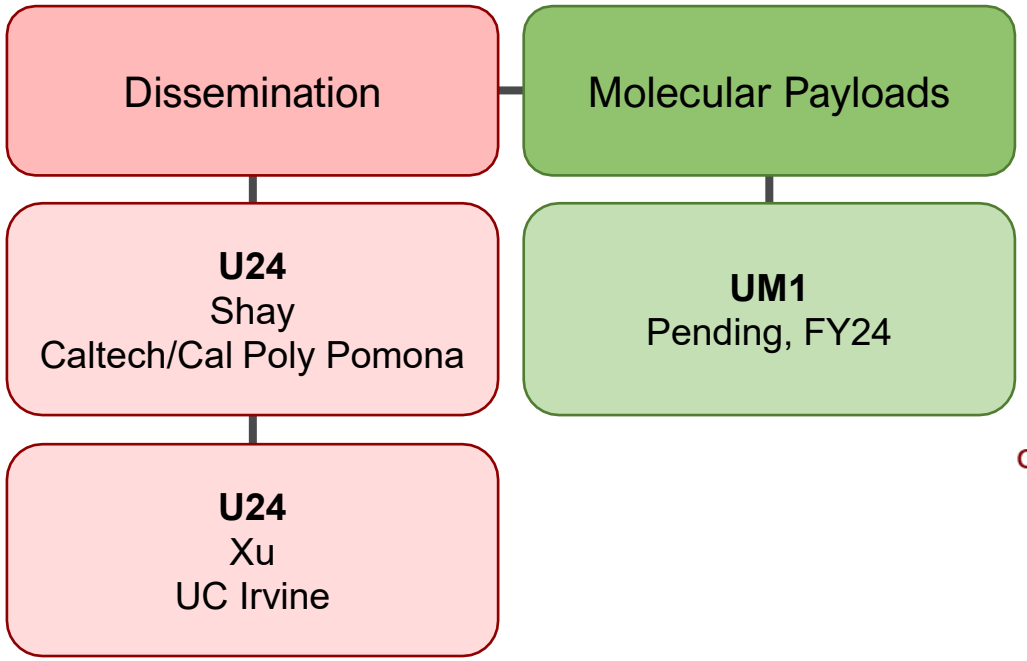




Armamentarium Consortium

Coordination to start building a comprehensive toolkit

FY21-present



Project	U24 Minority-Serving Institution	U01 Armamentarium Partner	Council
U24MH131054	Cal Poly Pomona (PI Shay)	Caltech (PI Gradinaru)	5/2022
U24MH133236	UC Irvine (PI Xu)	Broad Institute (PI Fishell)	1/2023

BRAIN Initiative Transformative Projects

Creating a New Paradigm for Doing Science

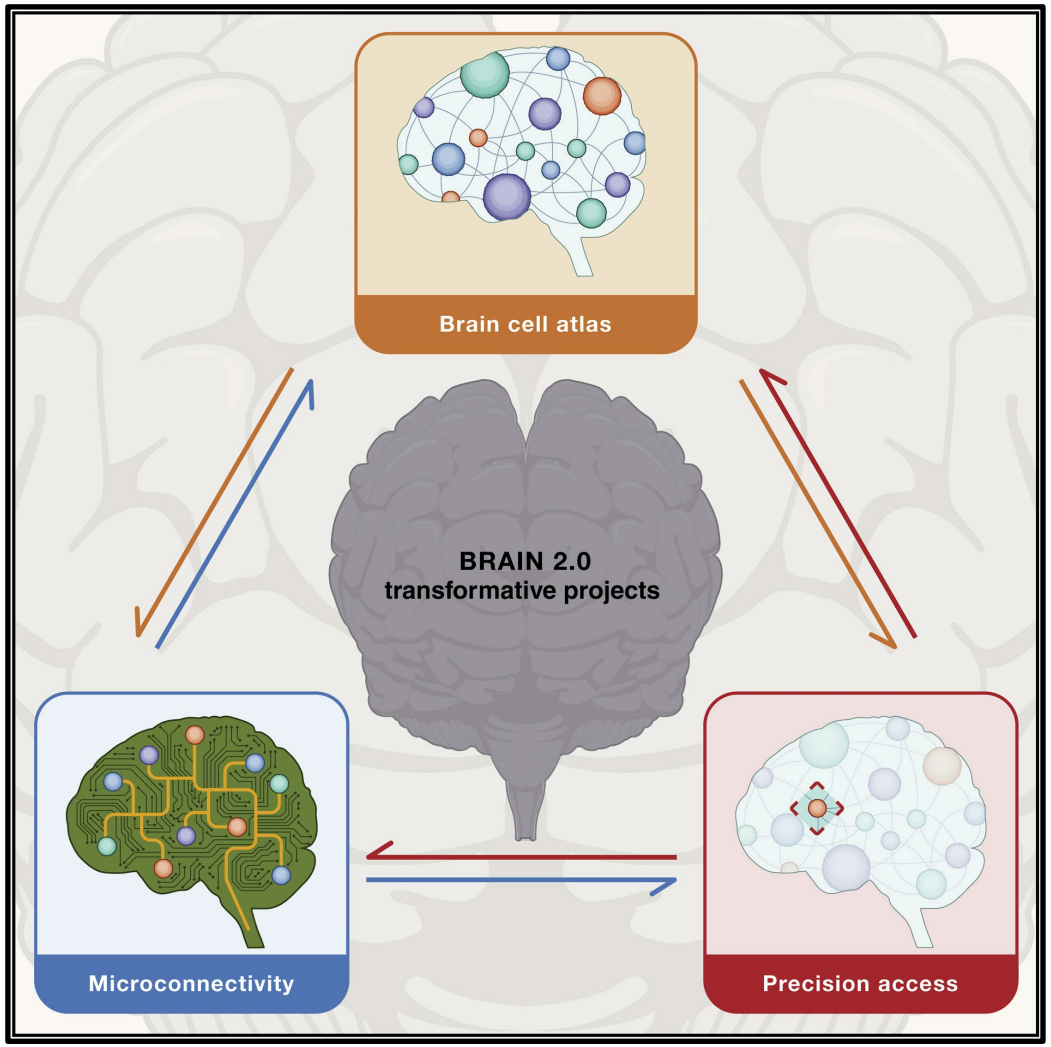
CellPress
Cell
Leading Edge

Commentary

BRAIN 2.0: Transforming neuroscience

John Ngai[1,*]
[1]NIH BRAIN Initiative, National Institutes of Health, Bethesda, MD, USA
*Correspondence: john.ngai@nih.gov
https://doi.org/10.1016/j.cell.2021.11.037

- The **BRAIN Initiative Cell Atlas Network (BICAN)** will map brain cells and circuits across multiple species, with an emphasis on humans
- **BRAIN Initiative Connectivity Across Scales (BRAIN CONNECTS) Network** will provide a wiring diagram by mapping all the connections in the brain
- The **Armamentarium for Precision Brain Cell Access** leverages new brain cell census data to build a toolkit to access brain cells based on their molecular identity

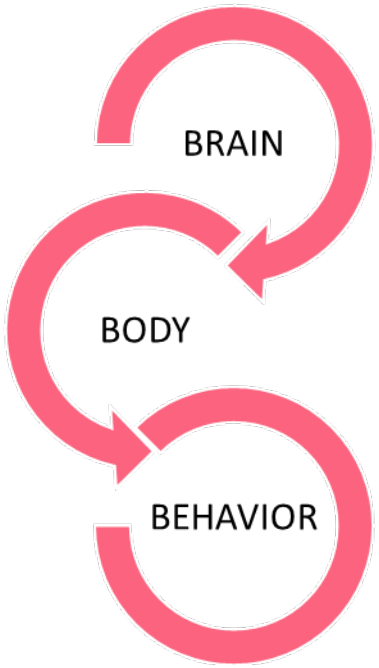


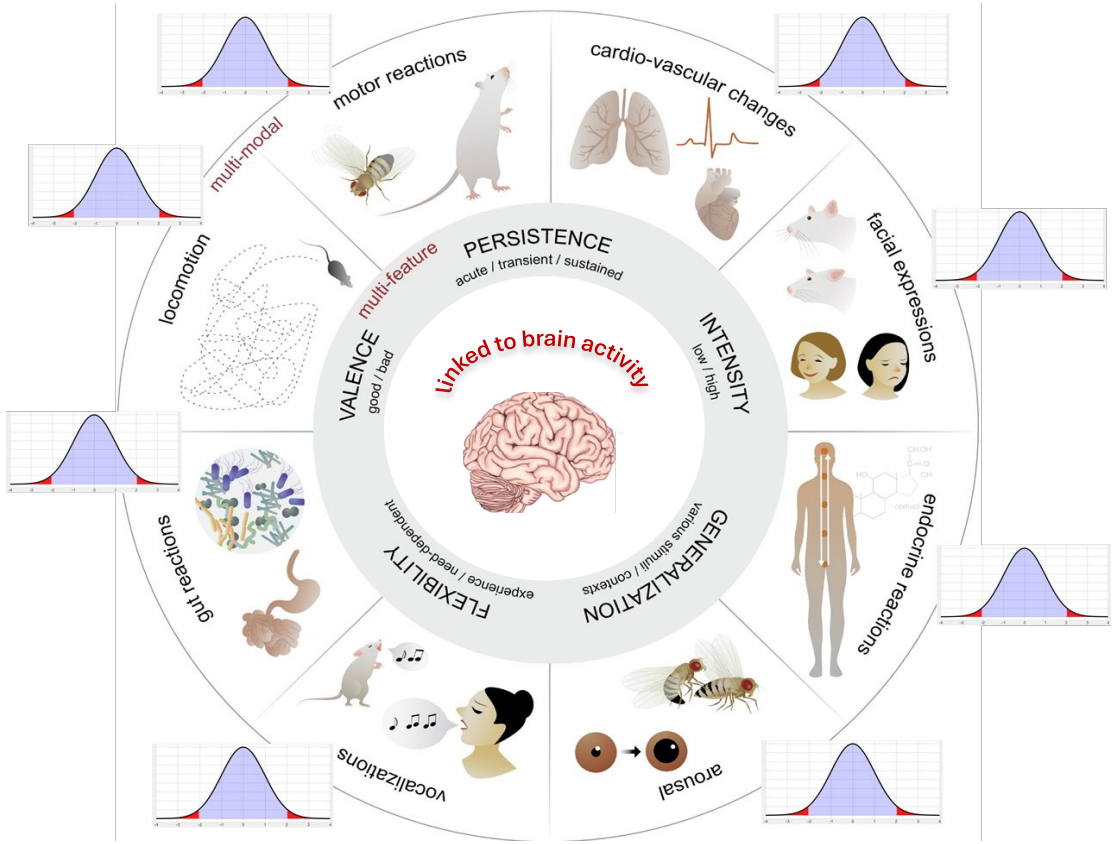
Ngai, Cell 2022

The Brain Behavior Quantification and Synchronization (BBQS) Program

Goal: to develop and validate next-gen tools, methods, and analytic approaches to precisely quantify complex behaviors and combine them with simultaneous recordings of brain activity

- Animal models
- Human models
- Sensor development
- Data coordination
- Theory, computational models & AI approaches





Zych & Gogolla, 2021

National Institutes of Health
The BRAIN Initiative®

Creating new opportunities to study the human brain…

An awake patient moves her fingers during surgery to remove a brain tumor.

WINDOW OF OPPORTUNITY

When surgery to treat neurological conditions lets researchers peer into the brain, ethical questions abound

JANUARY 2022 • VOL 375 ISSUE 6578

science.org SCIENCE

Neuroethics

The study of ethical issues raised by our evolving understanding of the brain and our ability to monitor and influence it

The NIH BRAIN Initiative neuroethics strategy emphasizes ***proactive***, ***ongoing assessment*** of the ***neuroethical implications*** of the development and application of BRAIN-funded tools and neurotechnologies.

Integrating *neuroethics* into the science:

- ✓ Neuroethics Working Group
- ✓ Neuroethics Guiding Principles
- ✓ Topical workshops
- ✓ NIH team of program directors
- ✓ Funded neuroethics research

Data Science & Informatics

Mission

To promote the data science advances and data sharing & informatics infrastructure needed to leverage BRAIN-supported research data to understand the brain and enable biomedical discoveries to enhance brain health

Strategy

- BRAIN Data Archives
- Data Management & Sharing Policy
- Funding Opportunities:
  - Integration & Analysis of BRAIN Data (R01)
  - Theories, Models, and Methods (R01)
  - Data Coordination & AI Center (U24)

Data Archive	Data Domain	Dataset Totals
BIL (Brain Image Library)	light microscopy	5,757 datasets 473 anatomical structures 12 modalities
NeMO (Neuroscience Multi-omic Archive)	multi-omics	409.9 TB 473,901 samples 5 modalities
DANDI (Distributed Archives for Neurophysiology Data Integration)	neurophysiology behavior	501 TB 318 dandisets 934 users
OpenNeuro (integrated with NEMAR, OpenNeuroPET)	human neuroimaging	847 datasets 32,977 participants
DABI (Data Archive BRAIN Initiative)	human invasive neurophysiology	49 studies 895 subjects
BossDB (Brain Observatory Storage Service & Database)	electron microscopy X-ray microtomography	42 projects 9 modalities 6 species

Building a Stronger Workforce

NeuroView

Advancing scientific excellence through inclusivity in the NIH BRAIN Initiative

Ryan R. Richardson,[1] Devon C. Crawford,[1] John Ngai,[1,*] and Andrea C. Beckel-Mitchener[1,*]
[1]NIH BRAIN Initiative, National Institutes of Health, Bethesda, MD, USA
*Correspondence: john.ngai@nih.gov (J.N.), amitchen@mail.nih.gov (A.C.B.-M.)
https://doi.org/10.1016/j.neuron.2021.10.021

Plan for Enhancing Diverse Perspectives

A PEDP, or "Plan for Enhancing **Diverse Perspectives**," is a summary of **actionable strategies** to advance the scientific and technical merit of the proposed project through enhanced inclusivity.

Diverse Perspectives

- The *people* **WHO DO** the research
- The *people* **WHO PARTICIPATE** in the research as part of the study population
- The *places* **WHERE** research is done

&

Actionable Strategies

- Personnel recruitment, mentoring, training, etc.
- Research participant recruitment, community engagement, advisory boards, etc.
- Outreach, partnership, dissemination, etc.

Three Key Takeaways

1. BRAIN-funded advancements in tools and technology are making their way into the clinic—with big potential to see positive impacts on human health
2. BRAIN-funded teams are developing new resources and technologies that are laying down a foundation for future cures
3. BRAIN is creating a new paradigm for doing science that is accelerating the pace of discovery

~~Three~~ Four Key Takeaways

1. BRAIN-funded advancements in tools and technology are making their way into the clinic—with big potential to see positive impacts on human health
2. BRAIN-funded teams are developing new resources and technologies that are laying down a foundation for future cures
3. BRAIN is creating a new paradigm for doing science that is accelerating the pace of discovery
4. ***Continue building momentum*** to bring cures for devastating human brain disorders in our lifetime

NIH National Institutes of Health
The BRAIN Initiative®

Upcoming Event

10th Annual BRAIN Initiative

Conference

Celebrating a decade of innovation

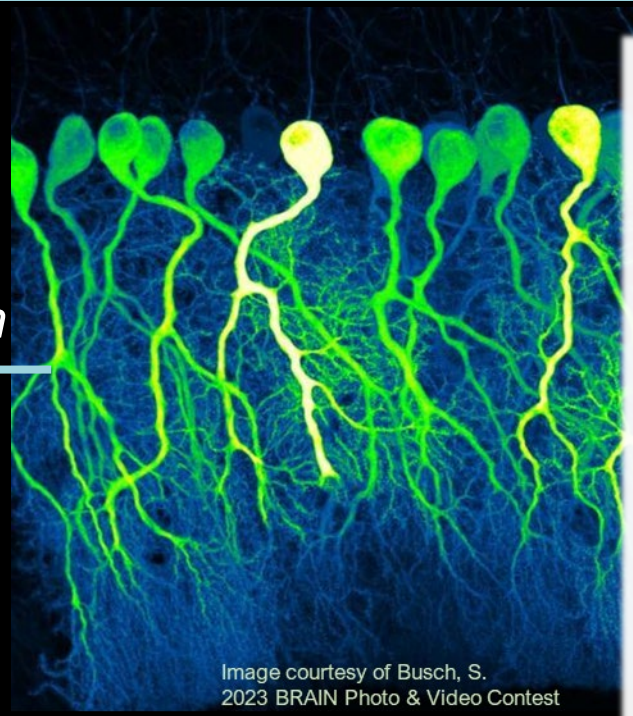


Image courtesy of Busch, S.
2023 BRAIN Photo & Video Contest

Join Us!

June 16, 2024
Early career event

JUNE 17-JUNE 18, 2024
Plenary talks, symposia sessions, and more

Hybrid Conference
Bethesda North Marriott
Rockville, MD

Plenary Sessions

Deconstructing the Serotonin System in the Mouse Brain
- *Liqun Luo, PhD*

Building on a Decade of Innovation
- *Cori Bargmann, PhD*
- *Edward Chang, MD*
- *Francis Collins, MD, PhD*
- *Caroline Montojo, PhD*
- *William Newsome, PhD*

Blood–Brain Barrier: Friend and Foe
- *Viviana Gradinaru, PhD*

https://brainmeeting.swoogo.com/2024/home

NIH National Institutes of Health
The BRAIN Initiative®

BRAIN.gov

https://www.braininitiative.nih.gov

National Institutes of Health
The BRAIN Initiative®