# Update on the ACD BRAIN Initiative Working Group "2.0"

Walter J. Koroshetz, MD
Director, NINDS
Joshua A. Gordon, MD, PhD
Director, NIMH

NIH Advisory Committee to the Director - June 13, 2018

# Outline

- Establishing The BRAIN Initiative®
  - Original ACD BRAIN Initiative Working Group
  - *BRAIN 2025: A Scientific Vision*
- BRAIN at NIH: 2013-today
  - Budget and Awards
  - Scientific Advancements
- Integrating Neuroethics in BRAIN
  - Defining Neuroethics
  - Neuroethics at NIH and Beyond
- Looking Ahead through 2026
  - New ACD BRAIN Initiative Working Group “2.0”
  - Timeline and Deliverables

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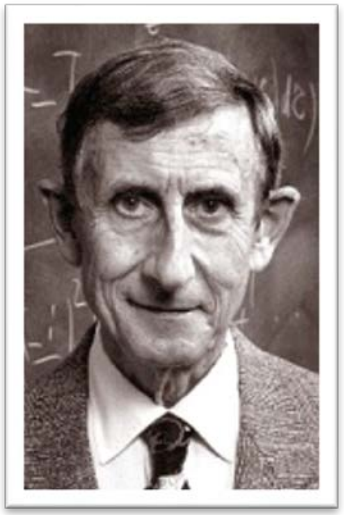
# Where Does Scientific Progress Come From?

"**New directions in science are launched by new tools much more often than by new concepts.** The effect of a concept-driven revolution is to explain old things in new ways. The effect of a tool-driven revolution is to discover new things that have to be explained."

**Freeman Dyson (1997) *Imagined Worlds***
**Harvard University Press, Cambridge, MA**



**The BRAIN Initiative** builds on recent progress to create tools that will accelerate discovery and build the foundation we need to reduce the burden of brain disorders

Science
AAAS
POLICYFORUM
May 10, 2013

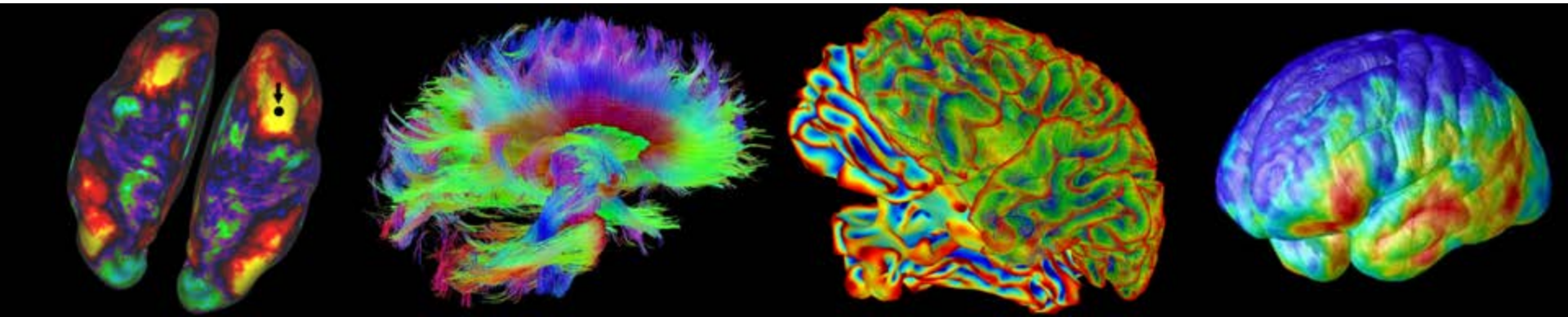
# The NIH BRAIN Initiative

Thomas R. Insel, * Story C. Landis, * Francis S. Collins*

The NIH BRAIN Initiative will build on recent successes in neuroscience to create and apply new tools for understanding brain activity.

- Accelerate development, application of innovative technologies to construct dynamic picture of brain function that integrates neuronal and circuit activity over time and space

- Build on growing scientific foundation – neuroscience, genetics, physics, engineering, informatics, nanoscience, chemistry, mathematics, etc. – to catalyze interdisciplinary effort of unprecedented scope



THE BRAIN INITIATIVE®

# NIH ACD BRAIN Working Group: *Original Members*

**Cornelia Bargmann,** Rockefeller *(co-chair)*

**William Newsome,** Stanford *(co-chair)*

**David Anderson,** Caltech

**Emery Brown,** MIT

**Karl Deisseroth,** Stanford

**John Donoghue,** Brown

**Peter MacLeish,** Morehouse

**Eve Marder,** Brandeis

**Richard Normann,** Utah

**Joshua Sanes,** Harvard

**Mark Schnitzer,** Stanford

**Terrence Sejnowski,** Salk

**David Tank,** Princeton

**Roger Tsien,** UCSD

**Kamil Ugurbil,** Minnesota

## *EX OFFICIO MEMBERS*

**Kathy Hudson,** NIH

**Geoffrey Ling,** DARPA

**Carlos Pena,** FDA

**John Wingfield,** NSF

## *EXECUTIVE SECRETARY*

**Lyric Jorgenson,** NIH

**Participation Across NIH:**

- Blueprint
- NCCIH
- NEI
- NIA
- NIAAA
- NIBIB
- NICHD
- NIDA
- NIDCD
- NIMH
- NINDS
- OBSSR
- OD
- ORWH

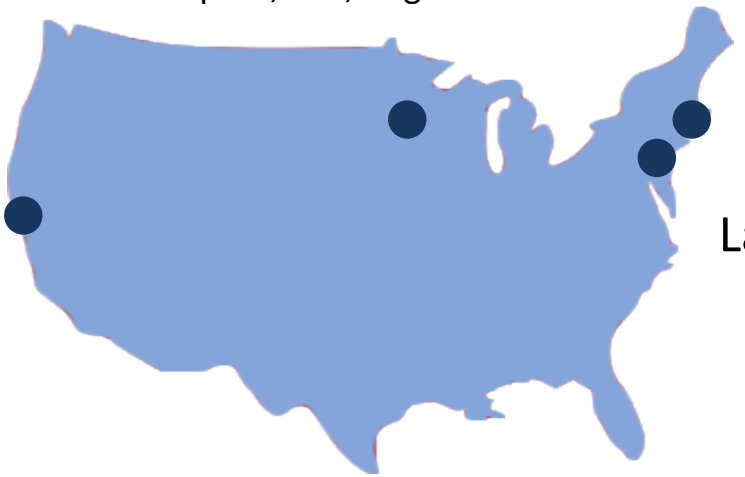
# NIH ACD BRAIN Working Group: *Process to Draft Strategic Plan*

## FOUR WORKSHOPS (SPRING/SUMMER 2013)

- 48 outside experts
- Opportunities for public commentary

Human neuroscience
Minneapolis, MN, August 29-30

Theory, computation and big data
Boston, MA, July 29-30



Molecular approaches
San Francisco, CA, May 29-30

Large-scale recording and structural neurobiology
New York, NY, June 26-27

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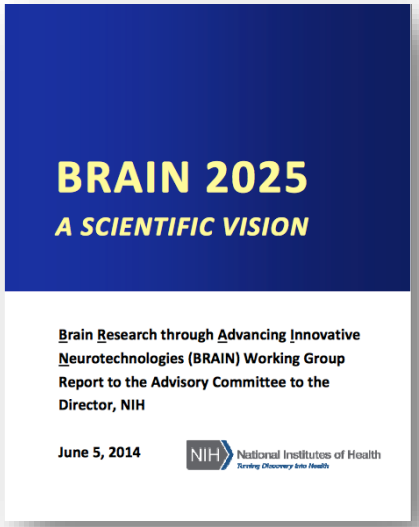
# Vision for the NIH BRAIN Initiative



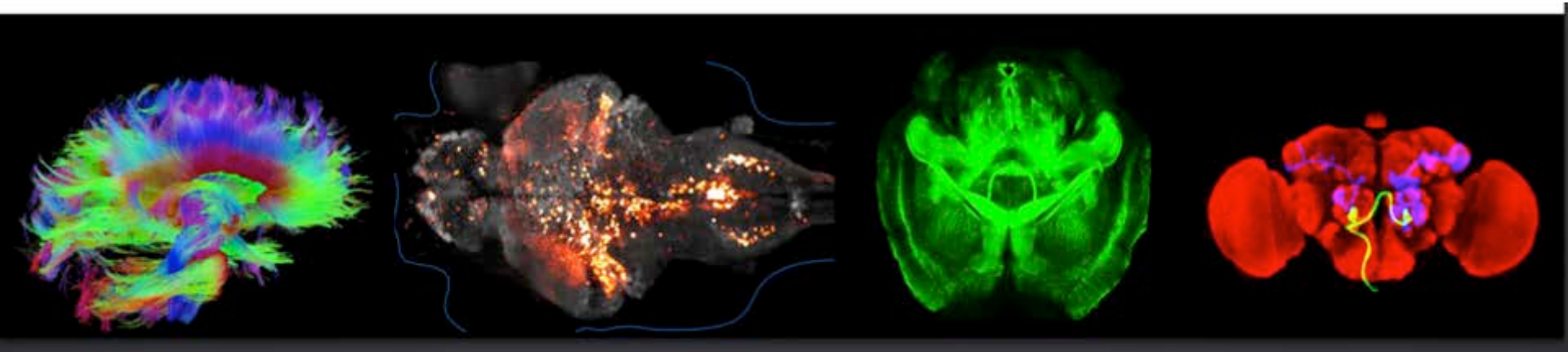

**FIRST FIVE YEARS** → **SECOND FIVE YEARS**

Emphasize technology development

Emphasize discovery driven science

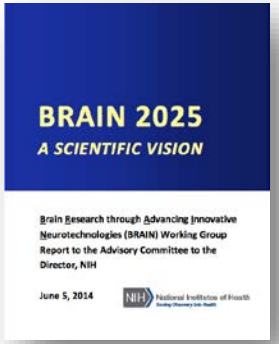
See the circuits in action to understand:

- How the brain controls how we move, plan, execute actions, and remember
- How to monitor/manipulate circuits for improved function
- How disordered brain circuits cause neuro/mental/substance use disorders



# BRAIN Strategic Plan

## Seven High Priority Research Areas




| | |
|---|---|
| Brain Cell Types | 1. Discovering diversity |
| Tools for Circuit Diagrams | 2. Maps at multiple scales |
| Technology to Monitor Neural Activity | 3. The brain in action |
| Precise Interventional Tools | 4. Demonstrating causality |
| Theory and Data Analysis Tools | 5. Identifying fundamental principles |
| Advance Human Neuroscience | 6. Creating human brain research networks |
| Integrate Approaches | 7. From BRAIN Initiative to the brain |

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# BRAIN: *Where Are We?*

**BRAIN Initiative announced**
*April 2013*

**1st meeting of the BRAIN MCWG**
*August 2014*

**1st BRAIN PI Meeting**
*November 2014*

**Neuroethics Division established**
*August 2015*

**BRAIN Initiative Alliance website launches**
*November 2016*

**4th NIH BRAIN awards**
*May, October 2017*

***BRAIN 2025* Report released**
*June 2014*


**1st NIH BRAIN awards**
*September 2014*


**1st BRAIN Initiative Alliance discussion**
*July 2015*

BRAIN INITIATIVE ALLIANCE

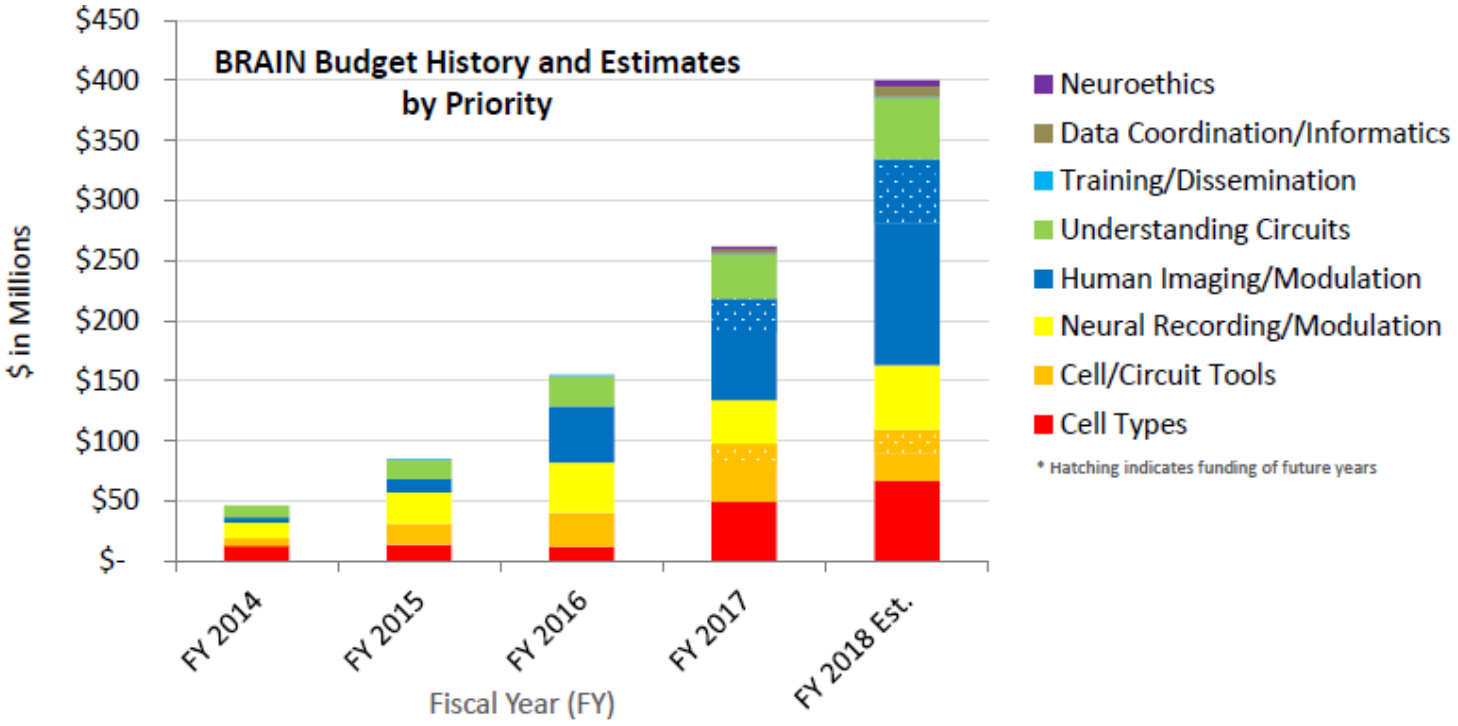
**Public-Private Partnership Program established**
*September 2015*

**21st Century Cures Act signed into law**
*December 2016*


**4th BRAIN PI Meeting**
*April 2018*

NIH National Institutes of Health
*Turning Discovery Into Health*

# BRAIN Investments



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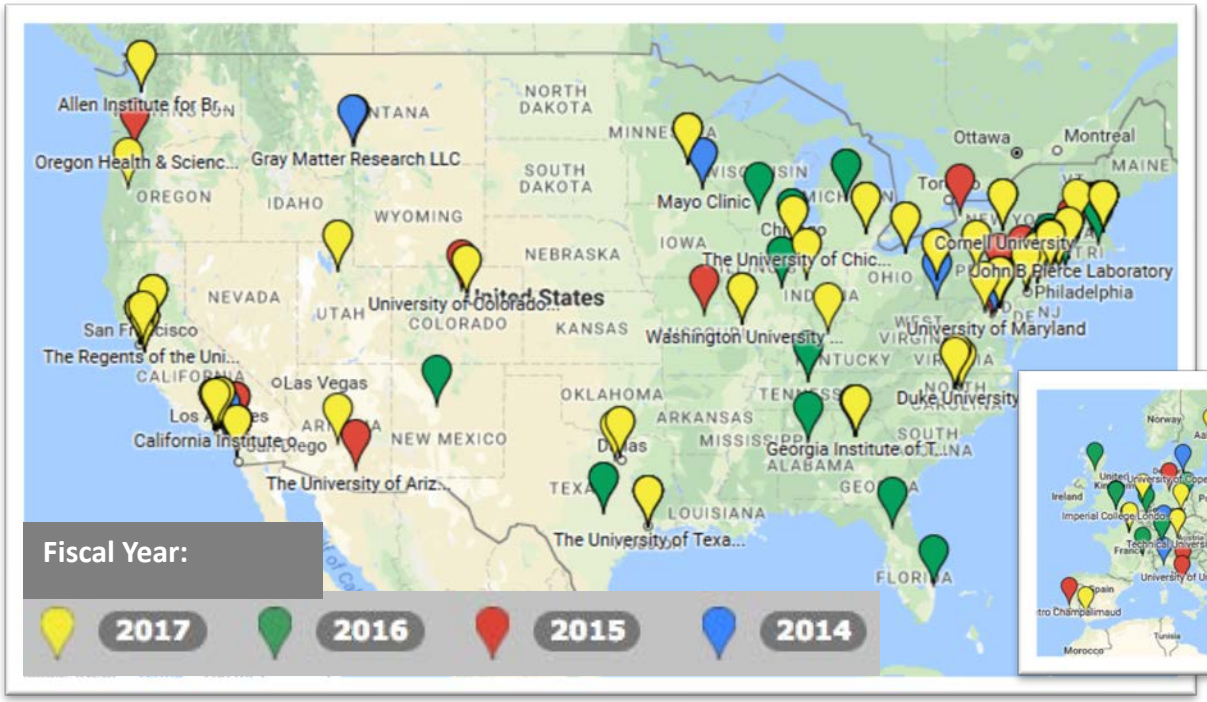
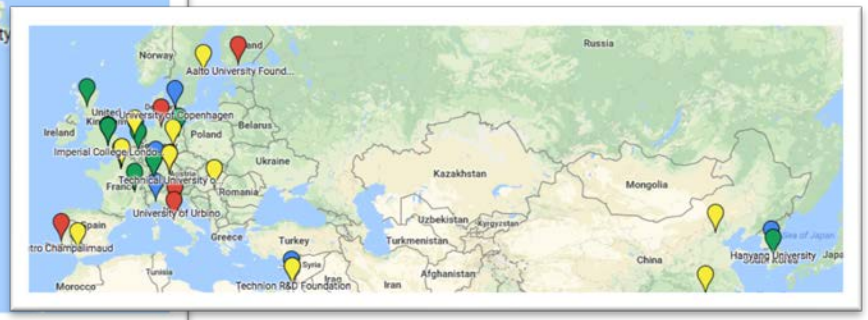
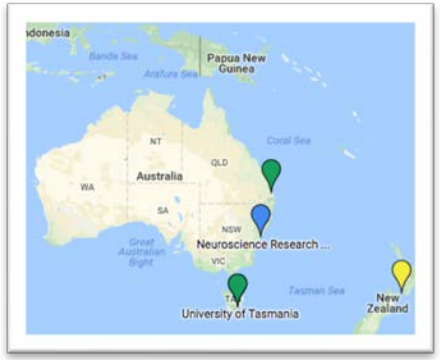
# BRAIN Awards Over the Years




| | New (FY2017) | Since BRAIN Began (FY2014) |
|---|---|---|
| Number awards | 110 | 345 |
| Number investigators | 178 | 504 |
| Investment | $169.6M | $548.3M |

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# NIH-Funded BRAIN Researchers Publish Findings

nature COMMUNICATIONS

History-based action selection bias in posterior parietal cortex

Eun Jung Hwang[1], Jeffrey E. Dahlen[1], Madan Mukundan[1] & Takaki Komiyama[1,2]

Received: 6 July 2017 Accepted: 7 September 2017
Published online: 01 November 2017

International Journal of *Molecular Sciences*

MDPI

*Article*

Transgenic Strategies for Sparse but Strong Expression of Genetically Encoded Voltage and Calcium Indicators

Received: 15 June 2017; Accepted: 4 July 2017; Published: 7 July 2017

Chenchen Song [1], Quyen B. Do [1], Srdjan D. Antic [2] and Thomas Knöpfel [1,3,*]

Research Article | Vol. 25, No. 4 | 20 Feb 2017 | OPTICS EXPRESS 3935

Optics EXPRESS

Imaging moving targets through scattering media

MICHELLE CUA,[1] YANG[1,2,*]

NEUROSCIENCE

Learning-enhanced coupling between ripple oscillations in association cortices and hippocampus

György Buzsáki[1]† 20 October 2017

**Over 450 publications have emerged from NIH BRAIN Initiative to date**

Large-fiel… imaging by multi-pupil adaptive optics

Jung-Hoon Park[1,5,6], Lingjie Kong[1,5,6], Yifeng Zhou[1] & Meng Cui[1–4]

NATURE METHODS | VOL.14 NO.6 | JUNE 2017

Science

ROYAL SOCIETY OF CHEMISTRY

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Cite this: *Chem. Sci.*, 2017, 8, 3080

DNA-barcoded labeling probes for highly multiplexed Exchange-PAINT imaging†

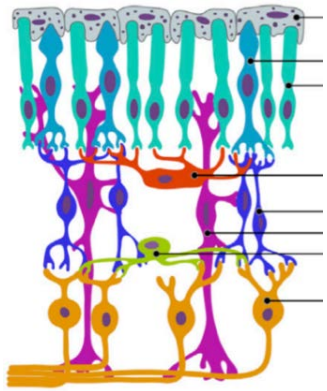
Sarit S. Agasti,‡[abc] Yu Wang,‡[abd] Florian Schueder,[abef] Aishwarya Sukumar,[a] Ralf Jungmann*[abef] and Peng Yin*[ab]

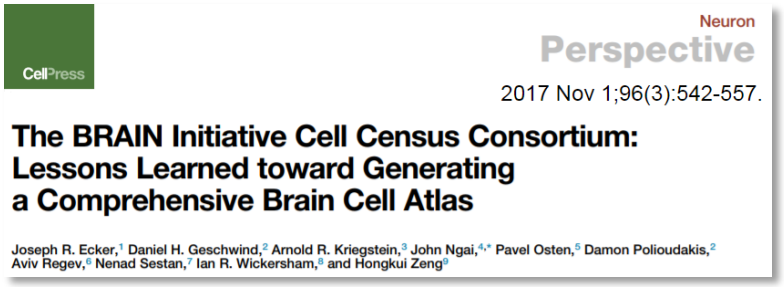
https://www.braininitiative.nih.gov/resources/publication.aspx

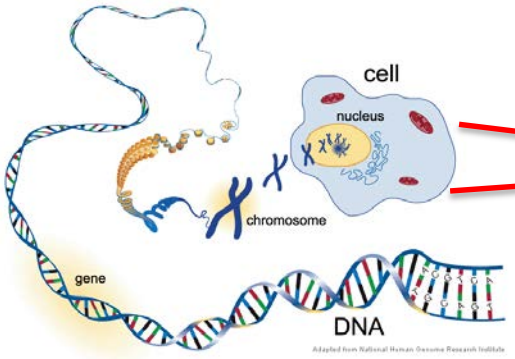
# The BRAIN Initiative Cell Census Network (BICCN)

*Launched FY 2017*

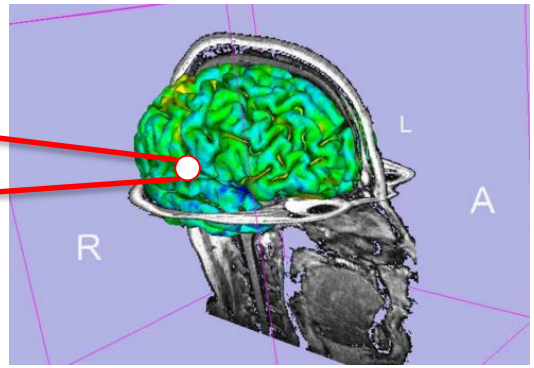
- $250M effort to catalog “parts list” of brain in mouse, monkey, human
- Anticipated outcomes
  - Essential characterization of the diversity of cell types
  - Open-access 3D digital mouse brain cell reference atlas
  - Comprehensive neural circuit diagram in mouse brain
  - Genomic access to specific cell types to monitor, map or modulate their activity





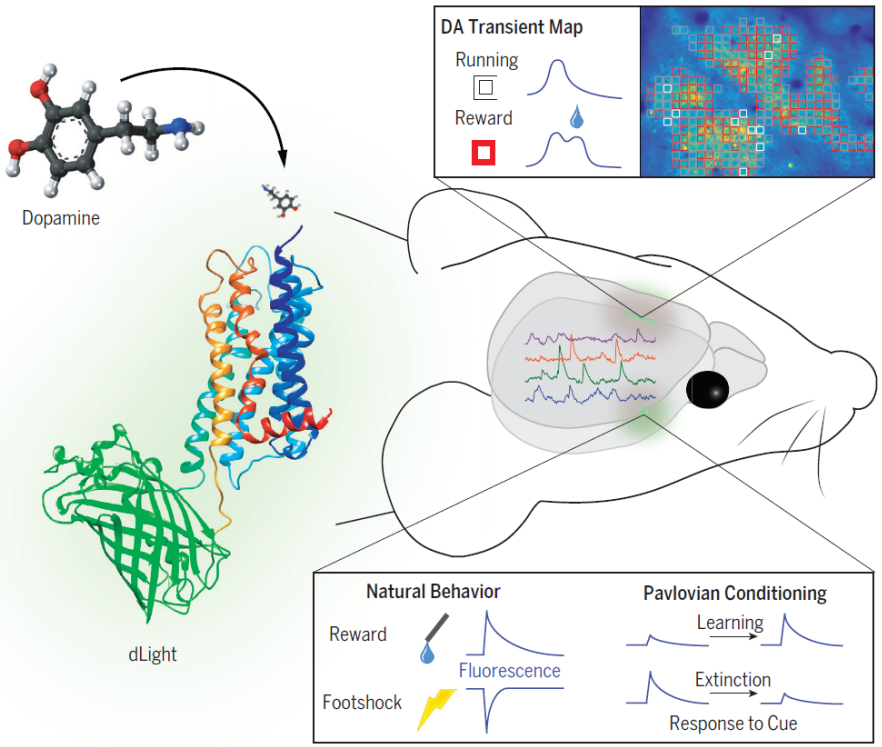




Genome Reference




3D spatial reference – brain GPS

# New Class of Genetically-Encoded Sensors Permit Ultrafast Imaging of Dopamine Activity in the Brain




- New: intensity-based genetically encoded dopamine indicator (dLight1)
- dLight1 allowed dynamic recording of dopamine activity within milliseconds and at the cellular level of live animals during behaviors, like reward learning and running
- Sensor design platform can be used to develop norepinephrine, serotonin, melatonin, and opioid neuropeptide indicators

Patriarchi et al., *Science,* 2018

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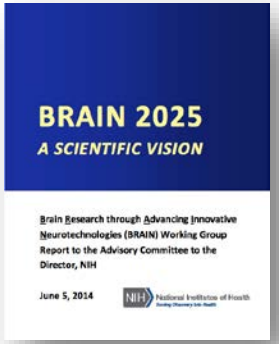
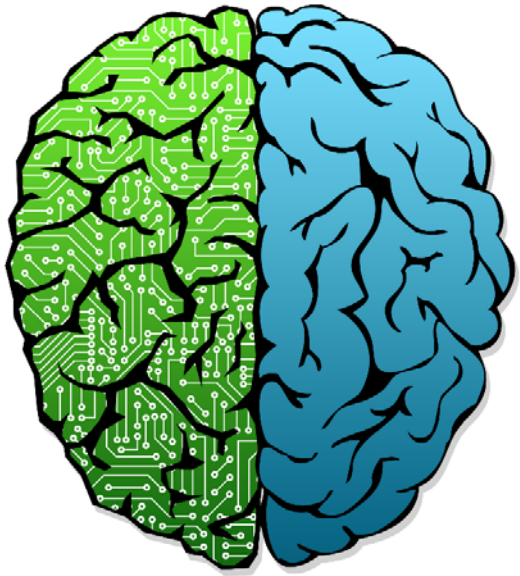
# NIH BRAIN Neuroethics

**From *BRAIN 2025: A Scientific Vision***:

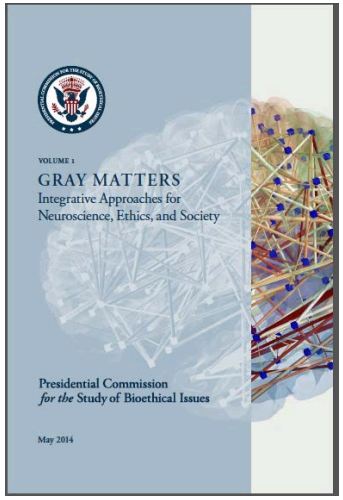


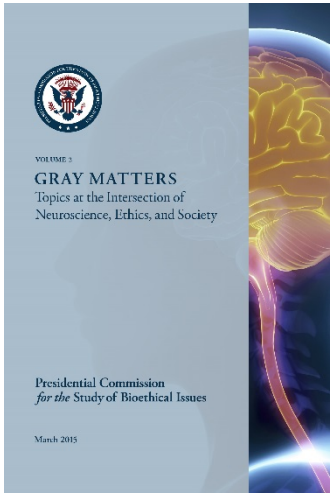

Although brain research entails ethical issues that are common to other areas of biomedical science, it entails special ethical considerations as well. Because the brain gives rise to consciousness, our innermost thoughts and our most basic human needs, mechanistic studies of the brain have already resulted in new social and ethical questions.



# Presidential Commission for the Study of Bioethical Issues

- Charge: Identify proactively a set of core ethical standards to both:
  - Guide neuroscience research, and
  - Address ethical dilemmas raised by application of findings
- Held multiple public meetings
- Issued a two-part report, *Gray Matters,* to respond to rapidly emerging and evolving field




**Key recommendation**: *Integrate neuroethics from the beginning in any neuroscience research program*

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# NIH BRAIN Initiative - Neuroethics

The BRAIN Multi-Council Working Group ensures a coordinated and focused effort to achieve the NIH BRAIN scientific vision

**The Neuroethics Division** of the MCWG provides input on how to address neuroethics questions raised by BRAIN Initiative research

Neuroethics Division holds topical workshops on key issues

- *Ethical Issues in Research with Invasive & Non-Invasive Neural Devices in Humans*
- *Workshop on Research with Human Neural Tissue*

Neuroethics Division is developing *Neuroethics Guiding Principles for NIH BRAIN Initiative*

- Principles will serve as an overarching neuroethics framework
- Will include practical suggestions on how to integrate neuroethics into BRAIN-funded research

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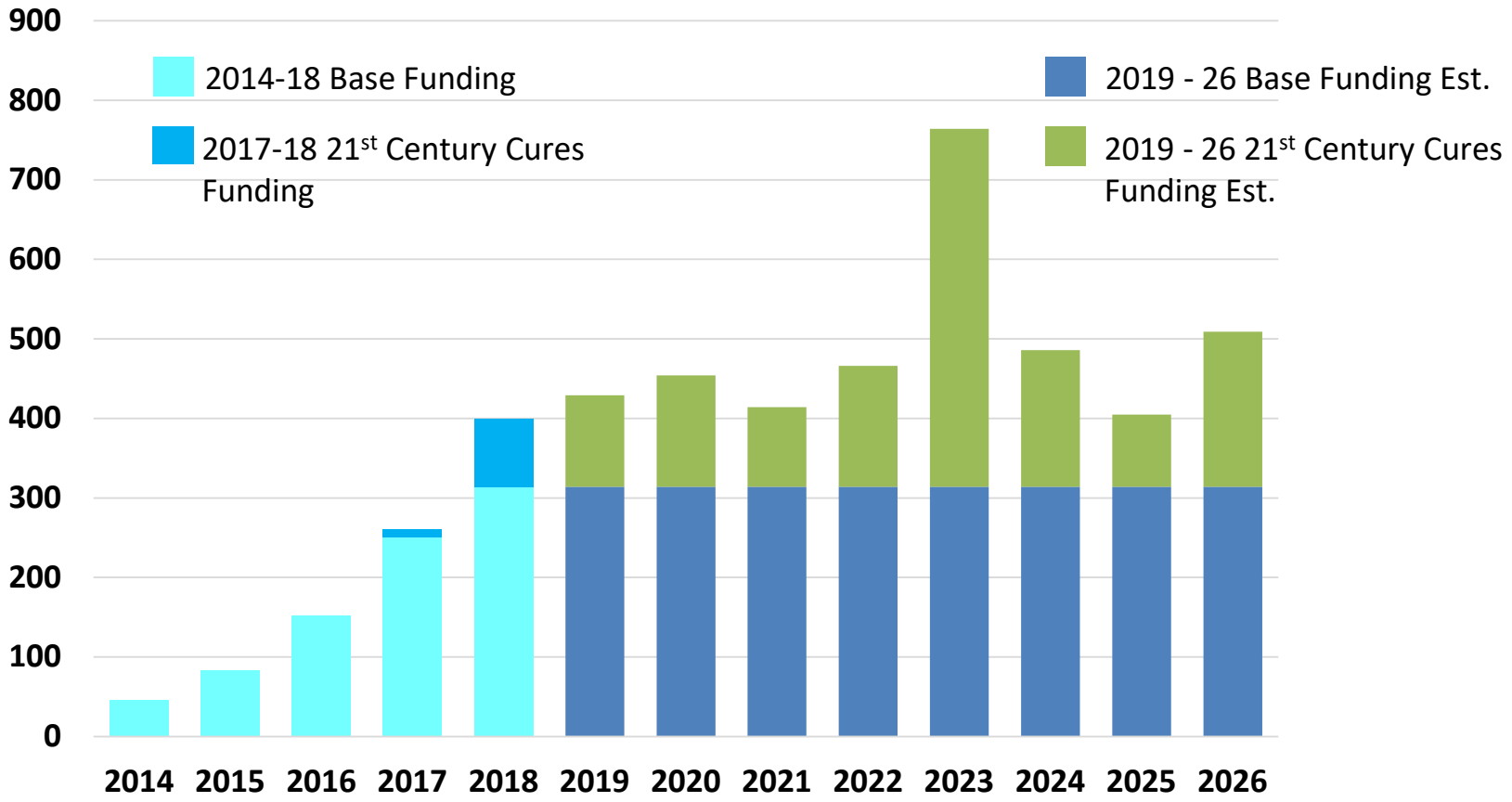
# BRAIN Funding to Ramp Up

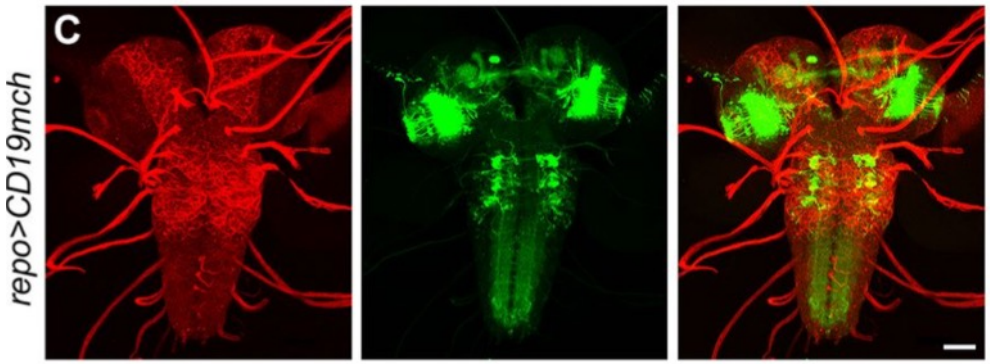

**$4.9 B** **Projected** total for lifetime of BRAIN

**$550 M** BRAIN through 2017: ~11% of the total

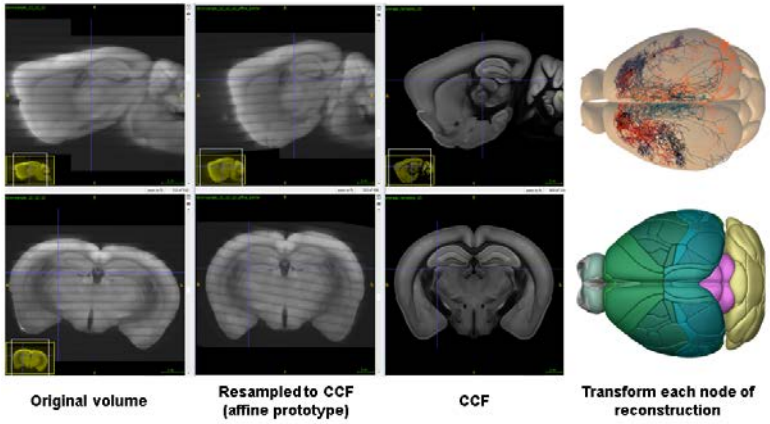


# New ACD BRAIN Initiative Working Group "2.0"

- The Advisory Committee of the NIH Director (ACD) enthusiastically endorsed *BRAIN 2025: A Scientific Vision* as the strategic plan for the NIH BRAIN Initiative in 2014.
- Over the last five years, the NIH BRAIN Initiative has made significant progress toward the priority areas outlined in *BRAIN 2025*




Ting-Hao Huang et al. Development 2016;143:4073-4084




Allen Institute for Brain Science

# Scientific Advancements

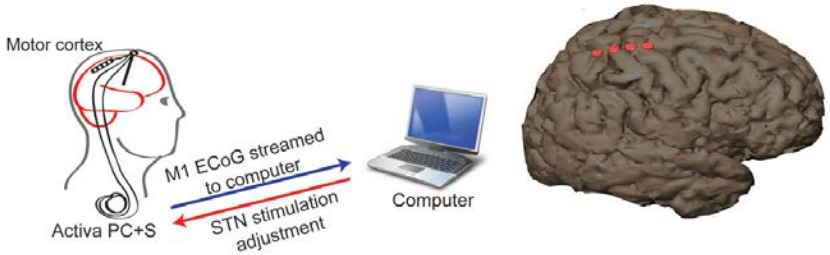
## New, Efficient AAVs Facilitate Multicolor Labeling for Individual Cell Morphology Studies


Chan et al., *Nature Neuroscience,* 2017

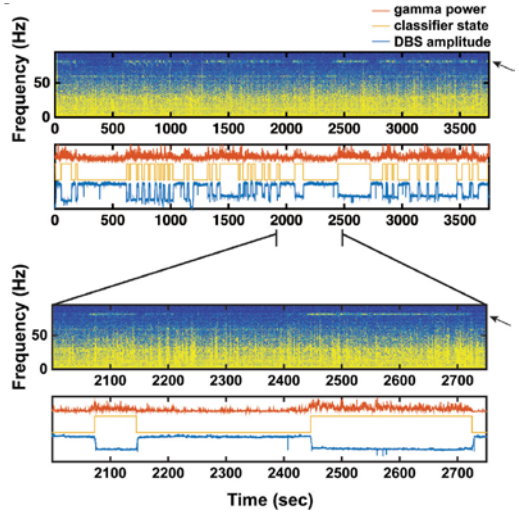
- Allows systemic delivery of viral vectors that were able to cross the blood brain barrier, circumventing the need for transgenic animals in some cases.
- When used with cell type-specific promoters, these AAVs provide targeted gene expression and enable efficient and versatile gene manipulation throughout the nervous system of transgenic and non-transgenic animals.

# Scientific Advancements

## First successful demonstration of adaptive deep brain stimulation in Parkinson's disease using a fully implanted device and neural sensing




*Adaptive DBS setup using activa PC+S*




*aDBS device response during dyskinesia*

- Real-time modification of deep brain stimulation to treat Parkinson's disease
- Fully implanted neural prosthesis senses brain activity and responds by adjusting stimulation
- In two patients, short-term clinical testing showed consistently maintained therapeutic efficacy and substantial energy savings

Swann et al., *J Neural Engineering,* 2018

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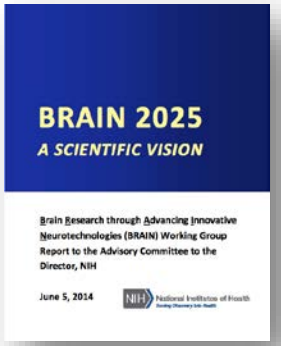
# New ACD BRAIN Initiative Working Group "2.0"

*BRAIN 2025* noted that the Initiative must adapt in response to the evolving scientific landscape. **In light of rapid scientific progress, a new ACD BRAIN Initiative Working Group "2.0" has been formed.**

| FIRST FIVE YEARS | SECOND FIVE YEARS |
|---|---|
| Emphasize technology development | Emphasize discovery driven science |

The scientific expertise of the ACD BRAIN WG 2.0 Members spans all 7 BRAIN priority areas.

Cell Types · Circuits · Monitor Neural Activity · Interventional Tools · Theory/Data Analysis · Human Neurosci · Integrative Approaches




National Institutes of Health
*Turning Discovery Into Health*

# Charge to Working Group

**ACD BRAIN Initiative Working Group 2.0** will provide scientific guidance to ACD on how best to accomplish the ambitious vision for the BRAIN Initiative, considering the current state of neuroscience

- With *BRAIN 2025* as a guide, the ACD-WG will:
  - Review BRAIN Initiative activities and progress
  - Suggest changes to specific goals from the *BRAIN 2025* report in response to the evolving scientific landscape
  - Identify new opportunities for research and technology development, within a solid ethical framework, to ensure the research is of the utmost value to the public it intends to serve
  - Consider unique opportunities for the BRAIN Initiative to train and empower the broader neuroscience research community

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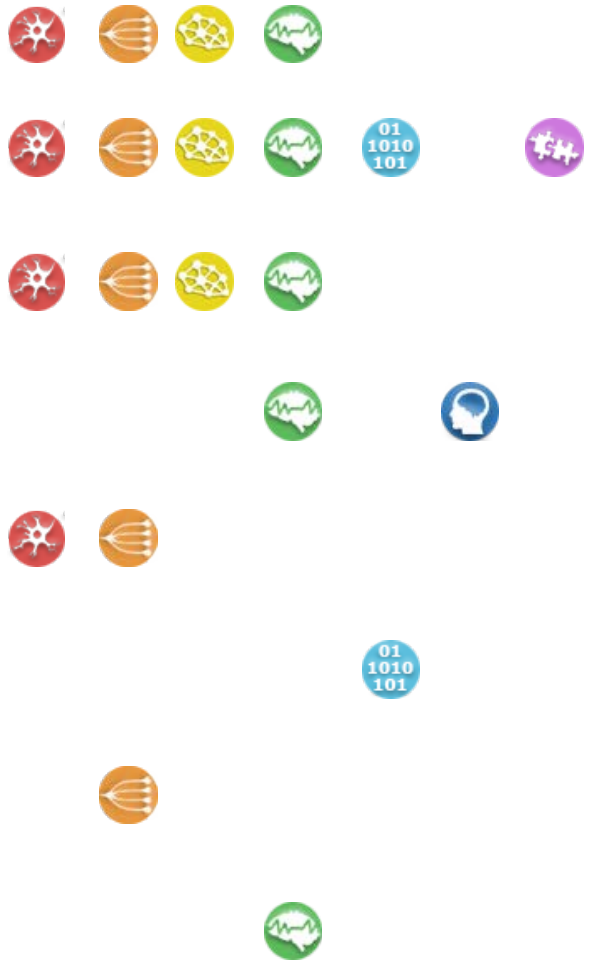
# New ACD BRAIN Initiative Working Group Roster

- Catherine Dulac **(Co-Chair)**
  *Harvard University*
- John Maunsell **(Co-Chair)**
  *University of Chicago*
- David Anderson
  *CalTech*
- Polina Anikeeva
  *MIT*
- Paola Arlotta
  *Harvard University*
- Anne Churchland **(ACD Member)**
  *Cold Spring Harbor Labs*
- Karl Deisseroth
  *Stanford University*
- Tim Denison
  *Medtronic*



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# New ACD BRAIN Initiative Working Group Roster

- Kafui Dzirasa
  *Duke University*
- Adrienne Fairhall
  *University of Washington*
- Elizabeth Hillman
  *Columbia University*
- Lisa Monteggia
  *UT Southwestern*
- Bruce Rosen
  *Massachusetts General Hospital*
- Krishna Shenoy
  *Stanford University*
- Doris Tsao
  *CalTech*
- Huda Zoghbi
  *Baylor College of Medicine*

# New ACD BRAIN Initiative Working Group Roster

## Federal *Ex Officio* Reps

- James Deshler
  *NSF; MCWG ex officio*
- Al Emondi
  *DARPA*
- Christine Grady
  *NIH; Bioethics, MCWG Neuroethics Division co-chair*
- Lyric Jorgenson
  *NIH; Exec Sec of original WG*
- David Markowitz
  *IARPA; MICrONS manager, MCWG ex officio*
- Carlos Peña
  *FDA; MCWG ex officio*

# ACD BRAIN Initiative WG 2.0: Neuroethics Subgroup

## Goal

- Develop a **Neuroethics Roadmap** for the NIH BRAIN Initiative
- Review the priority areas in BRAIN 2025 (incorporating updates from the broader WG 2.0) and characterize the neuroethical implications that may arise
  - as BRAIN Initiative investments produce new tools and neurotechnologies, and/or
  - those tools and neurotechnologies are applied toward advancing the goals of the NIH BRAIN Initiative
- The Subgroup will report back to the ACD WG 2.0 for inclusion in the final report

## Roster

- Members of the ACD WG 2.0, the Neuroethics Division of the MCWG, and external experts

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# ACD WG 2.0 Timeline and Deliverables

## Estimated Timeline for ACD BRAIN WG effort:

# First ACD WG Town Hall

## Community Feedback to ACD WG Solicited

*BRAIN 2025.*
*Town Hall*
**with**
Walter Koroshetz and Joshua Gordon
Bill Newsome Catherine Dulac and John Maunsell

Full footage of Town Hall available on NIH Videocast Website

www.videocast.nih.gov/PastEvents

# Seeking Broad Input


- RFI will remain open through the fall
- Feedback from RFI will be regularly provided to the WG to support their work

- This summer, NIH will release Request for Information (RFI) soliciting feedback from scientific community, patient advocates, and the general public

**RFI will be made available on NIH websites and at ACD WG workshops and town halls**

# Work Is On-Going

- Co-Chairs Drs. Dulac and Maunsell are running a sequence of conference calls with the ACD WG to review NIH BRAIN Initiative success to date
  - Calls cover scientific priority areas and goals of *BRAIN 2025*
  - Completed Discussions: April 30th, May 11th
  - Upcoming Discussions: June 20th-22nd

- NIH Staff providing portfolio analyses to support WG

# Questions? Comments?

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