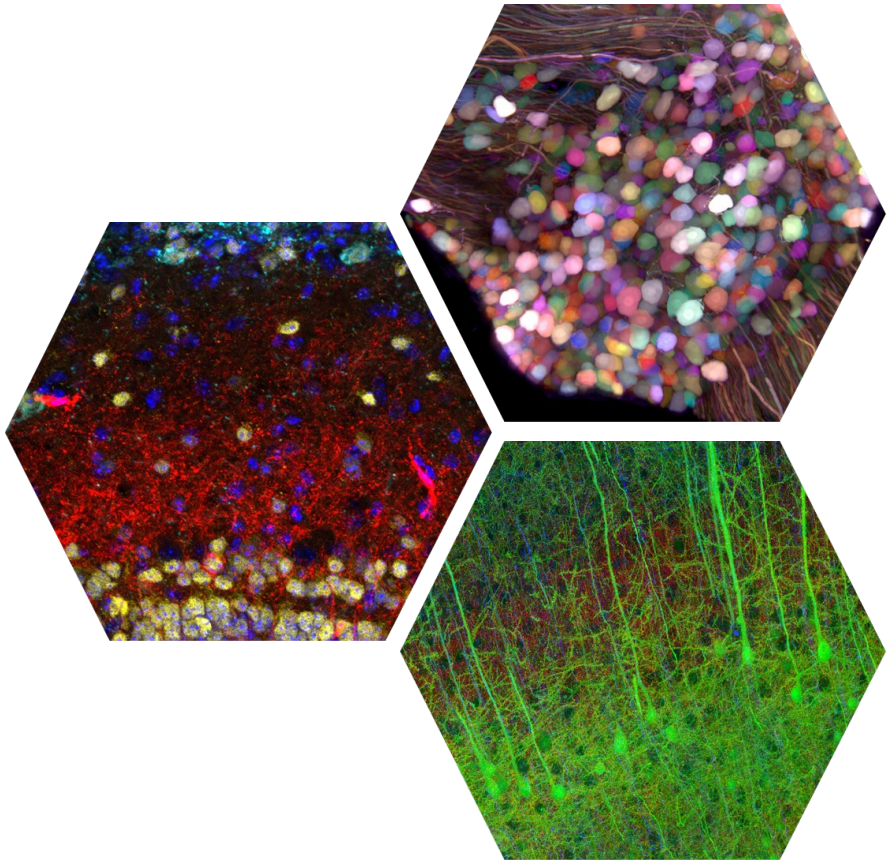
Interim Update to the Advisory Committee to the NIH Director



NIH The BRAIN Initiative®

From Cells to Circuits, Toward Cures

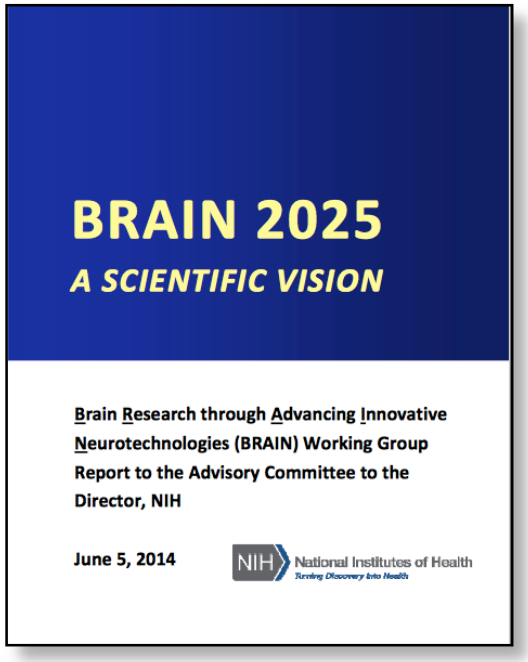
Catherine Dulac, Ph.D.

John Maunsell, Ph.D.

Co-Chairs

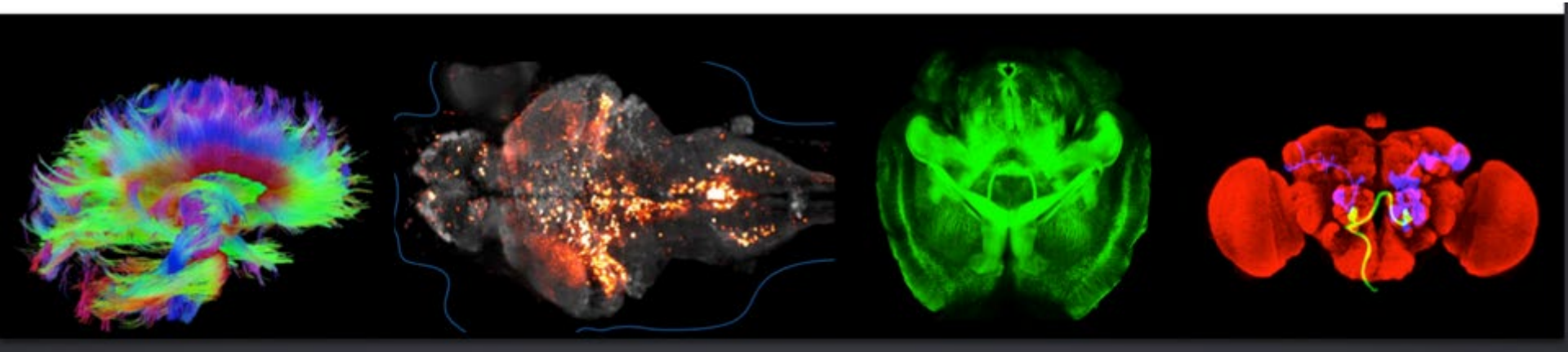
December 14, 2018

A focus on circuits and networks



"The challenge is to map the circuits of the brain, measure the fluctuating patterns of electrical and chemical activity flowing within those circuits, and understand how their interplay creates our unique cognitive and behavioral capabilities."

BRAIN 2025
(June 2014)



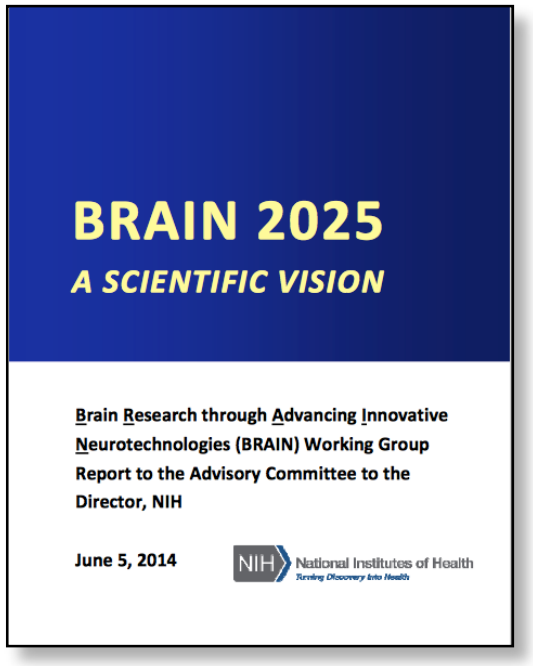
Presentation Outline

- Charge and Process
- Assessment by Priority Area
- Summary

Presentation Outline

Charge and Process

Charge to Working Group 2.0



- **Review** BRAIN Initiative activities and progress
- Suggest **tune-ups** to specific goals based on the evolving scientific landscape
- Identify **new opportunities** for research and technology development as well as large **transformative projects**
- Consider opportunities to **train, empower** and **diversify** a broader neuroscience research community

Working Group Roster

- Catherine Dulac (Co-Chair), Harvard
- John Maunsell (Co-Chair), U Chicago
- David Anderson, Caltech
- Polina Anikeeva, MIT
- Paola Arlotta, Harvard
- Anne Churchland, CSHL
- Karl Deisseroth, Stanford
- Tim Denison, Medtronic/Oxford
- Kafui Dzirasa, Duke U
- Adrienne Fairhall, U Washington
- Elizabeth Hillman, Columbia
- Lisa Monteggia, Vanderbilt
- Bruce Rosen, MGH
- Krishna Shenoy, Stanford
- Doris Tsao, Caltech
- Huda Zoghbi, Baylor

Ex Officio:

- James Deshler, NSF
- Alfred Emondi, DARPA
- Christine Grady, Bioethics, NIH
- Lyric Jorgenson, NIH
- David Markowitz, IARPA
- Carlos Peña, FDA

Executive Secretary
Samantha White, NINDS

Science Committee Specialist
Nina Hsu, NINDS

Science Writer
Alison Davis

BRAIN Neuroethics Subgroup

*Goal - Develop a **Neuroethics Roadmap** for the NIH BRAIN Initiative*

- **James Eberwine (Co-Chair), University of Pennsylvania[+]**
- **Jeffrey Kahn (Co-Chair), Johns Hopkins University**
- **Adrienne Fairhall, University of Washington***
- **Christine Grady, NIH*[+]**
- **Elizabeth Hillman, Columbia University***
- **Insoo Hyun, Case Western University**
- **Andre Machado, Cleveland Clinic**
- **Laura Roberts, Stanford University**
- **Karen Rommelfanger, Emory University[+]**
- **Francis Shen, University of Minnesota**

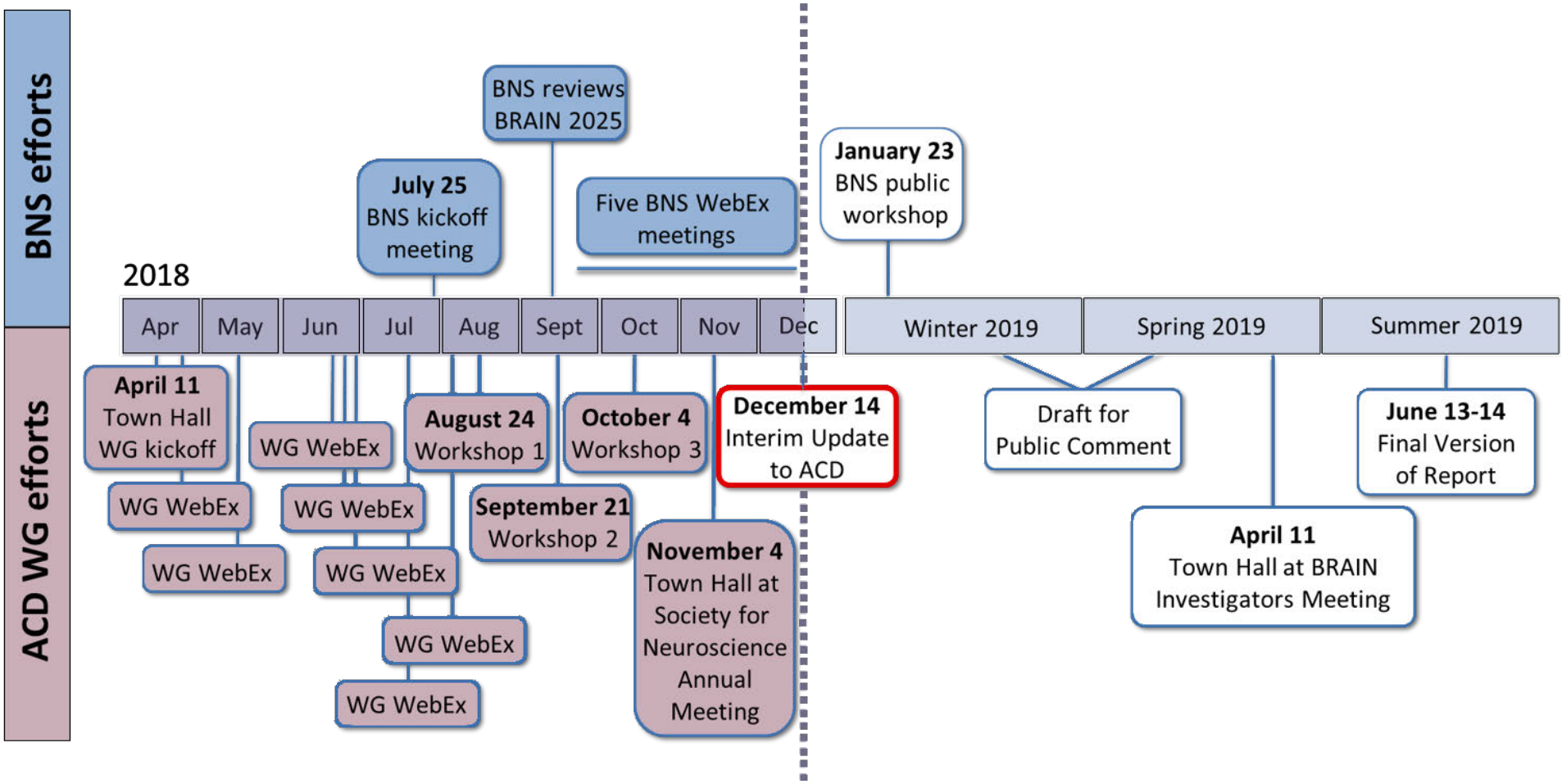
* ACD BRAIN WG 2.0 member

[+] BRAIN Multi-Council Working Group Neuroethics Working Group

Executive Secretary: Ellen Gadbois (NIH Office of Science Policy)

BRAIN 2025 2.0: Timeline

Timeline for NIH ACD BRAIN Initiative WG:



BRAIN Neuroethics Subgroup

To date:

- July 25 BRAIN Initiative overview WebEx; five subsequent phone/WebEx meetings
- Reviewed Brain 2025 Report from neuroethics perspective
- Updates from ACD BRAIN 2.0 Working Group members
- Members attend the ACD Site Workshops/Discussion
- Interviewed 2 outside experts
- Developed case studies to help focus discussion
- Have developed framework for writing the report that is being reviewed by the BNS

Future:

- Phone meetings for continuing deliberations including discussion of case studies
- Consider responses to BRAIN Initiative RFI question on neuroethics
- January 23, 2019, workshop at NIH (public session a.m.)

Final Product:

- Anticipate neuroethics considerations to be presented in two formats
  - Integrated throughout the ACD BRAIN 2.0 Working Group Report
  - A stand-alone summary document focused on neuroethics issues

WG 2.0 Data-Gathering Phase

- **8 WebEx Working Group Meetings**
  - Reviewed BRAIN 1.0 progress
  - Identified topics and speakers for workshops
- **Scientific and Public Input**
  - 3 Public Workshops (followed by closed sessions)
    - Boston (Aug 24) *"Human Neuroscience"*
    - Chicago (Sep 21) *"Looking Ahead: Emerging Opportunities"*
    - Houston (Oct 4) *"From Experiments to Theory and Back"*
  - SfN Town Hall, San Diego (Nov 4)
  - Request for Information

Public Workshops

Workshop 1: Human Neuroscience

- Recording and Stimulation
- Functional Imaging
- Brain Connectivity
- Translation from Mouse to Human

Workshop 2: Emerging Opportunities

- Developing and Disseminating New Technologies
- Sensitive Molecular and Cellular Methods to Circuit Analysis
- Revolutionizing Circuit-to-Behavior Analyses

Workshop 3: From Experiments to Theory and Back

- Theory: Building understanding of brain function
- Data tools and management
- Big (Team) versus Individual Lab Science

Request for Information

- 69 submissions received from July to November
- Diverse requests and recommendations
  - Advancing Human Neuroscience was addressed most often
  - Extension of cell census to non-neuronal cells
  - Data sharing, support for tool development and dissemination, theory, training

We will continue to collect responses through March 2019

We thank NINDS OSPP for coding and analyzing responses

Presentation Outline

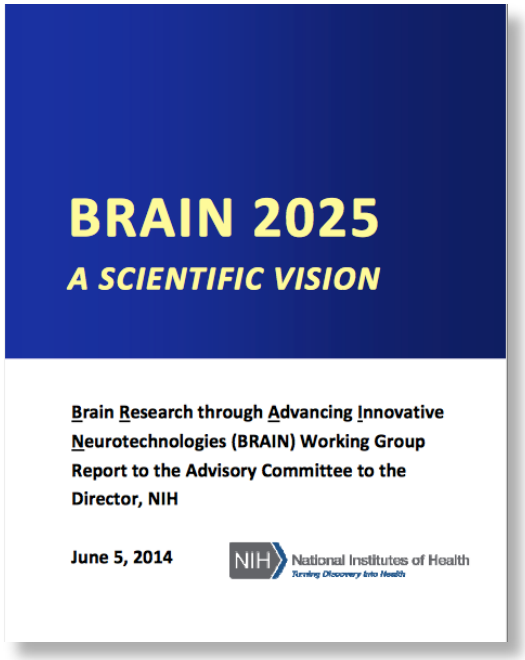
Assessment by Priority Area

Interim Update: Overview

The roll-out of the BRAIN Initiative 2014-2018

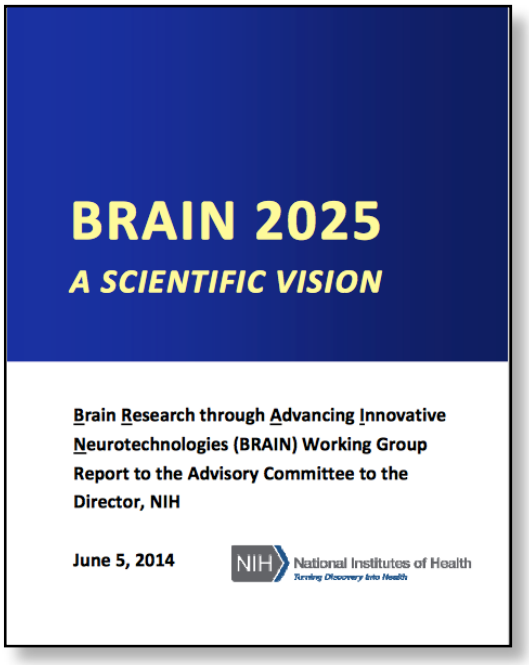
- Faithful to BRAIN 2025
- Well-crafted execution
- Thoughtful strategic efforts from NIH Program Staff
- Largely fulfilling, sometimes surpassing, the initial vision
- Opportunities for refinements & enhancement

BRAIN 2025 Vision and 7 Priorities



1. Discovering diversity (cell types)
2. Maps at multiple scales (circuit analyses)
3. The brain in action (monitoring neural activity)
4. Demonstrating causality (precise interventional tools)
5. Identifying fundamental principles (theory and data-analysis tools)
6. Advancing human neuroscience
7. From BRAIN Initiative to the brain (integrative approaches)

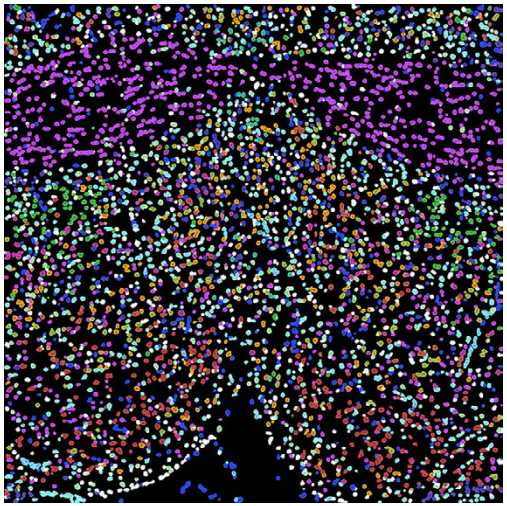
BRAIN 2025 Vision and 7 Priorities



1. **Discovering diversity (cell types)**

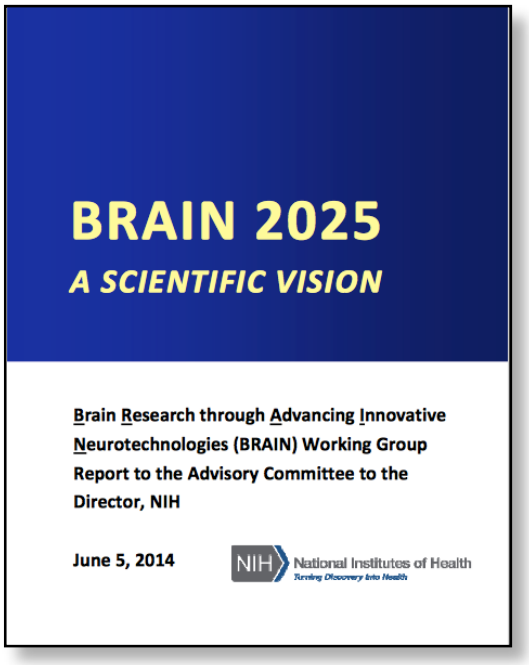
1. Discovering Diversity

- Overall progress: ***Flagship accomplishment***
- Notable BRAIN 1.0 advances
  - Cell census of many brain regions
  - Spatially aware transcriptomics
  - Single cell epigenomics
- BRAIN 2.0 Opportunities
  - Expand on human brain and cross-species comparison
  - Generate and exploit protein-based tools
  - Multi-modal assessment of, access to, and modeling of, cell types as units of brain function and physiopathology



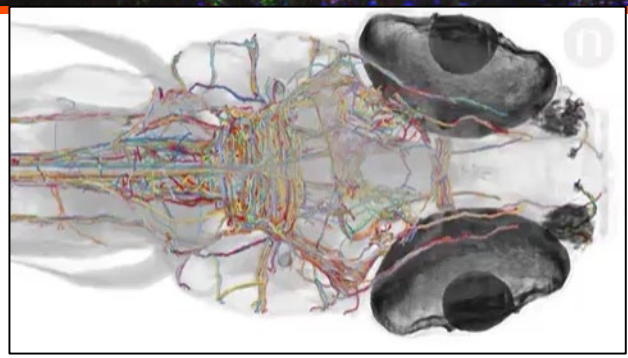
Moffitt et al., *Science,* 2018

BRAIN 2025 Vision and 7 Priorities



2. **Maps at multiple scales (circuit analyses)**

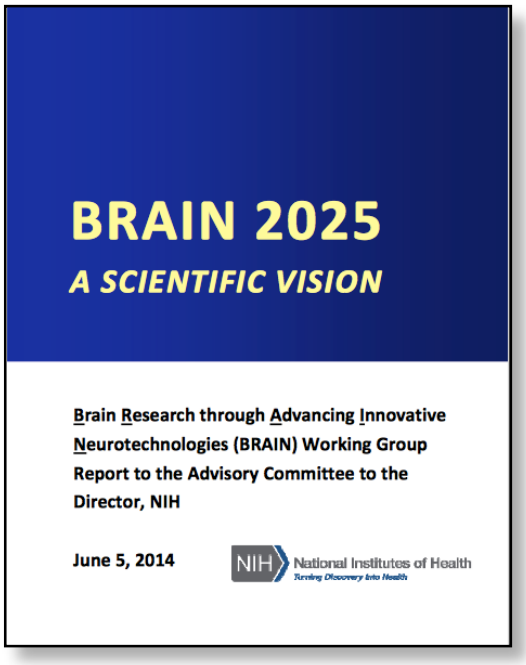
2. Maps at Multiple Scales



Hildebrand et al., *Nature,* 2017

- Overall progress: *Good*
- Notable BRAIN 1.0 advances
  - Brain-clearing techniques, serial EM, X-ray tomography, automated segmentation
  - Machine-learning tools applied to large-scale analyses
  - Large-scale reconstructions of single cell connectivity
- BRAIN 2.0 Opportunities
  - Mesoscale mapping: anterograde trans-synaptic tools
  - Non-MRI imaging methods
  - Link human structural and functional connectivity
  - Bridge different scales and integrate with theory

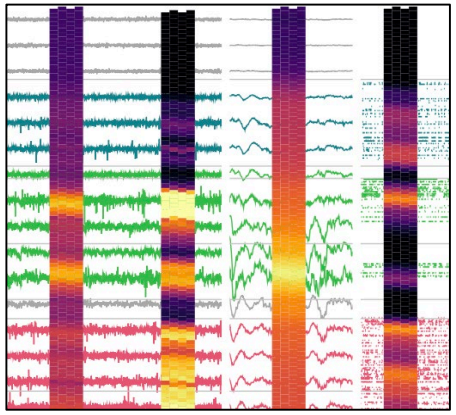
BRAIN 2025 Vision and 7 Priorities



3. **The brain in action (monitoring neural activity)**

3. Brain in Action

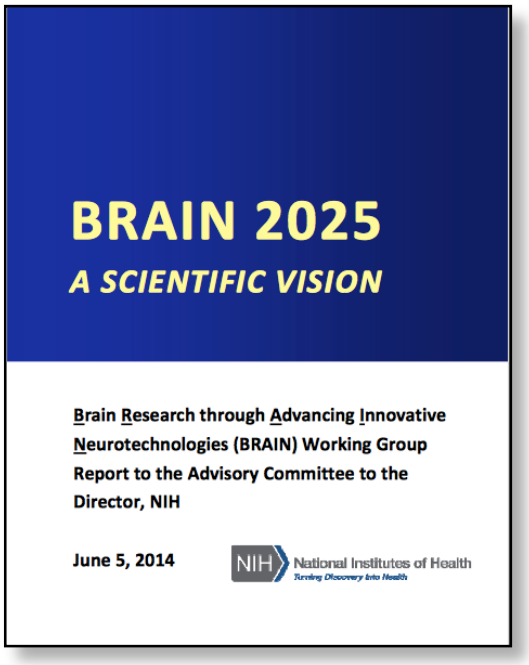
- Overall Progress: *Moderate – Good*
- Notable BRAIN 1.0 advances
  - Improved electrical and optical techniques (Neuropixels, eCOG, optical indicators, wide-field imaging, microendoscopy)
  - Great improvements in human neuroimaging (fMRI spatial resolution, functional near-infrared spectroscopy)



Jun et al., *Nature,* 2017

- BRAIN 2.0 Opportunities
  - Multi-modal tools and integrated technology/analysis/theory
  - Establish a functional chemical connectome
  - Deep-brain imaging of multiple brain areas in behaving animals
  - Tools for long term studies (years rather than weeks)
  - More natural, complex behaviors, improve monitoring and theory
  - New and integrated approaches to human and primate neuroimaging

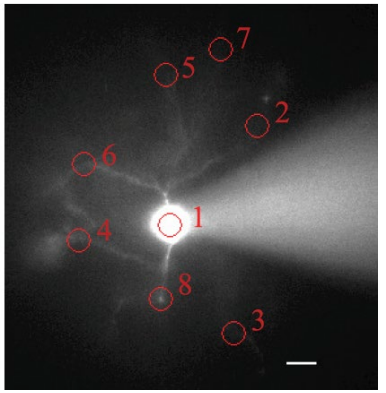
BRAIN 2025 Vision and 7 Priorities



4. **Demonstrating causality (precise interventional tools)**

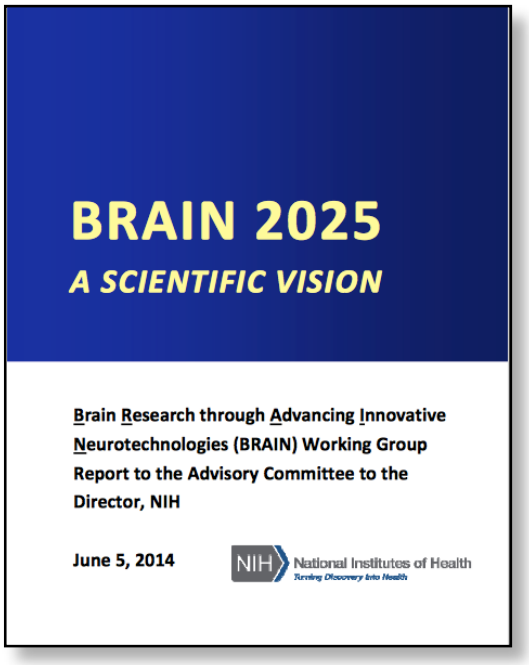
4. Demonstrating Causality

- Overall Progress: *Very Good*
- Notable BRAIN 1.0 advances
  - Fast single-cell optogenetic control of ~100 neurons
  - Increase in spatial and temporal precision
  - Compatibility with activity recording
- BRAIN 2.0 Opportunities
  - Precise closed-loop real-time perturbations of single to many cells
  - Nanoparticle-based non-invasive activation
  - Overcoming challenges in genetically encoded tools in primates



Chaigneau et al., *Front Cell Neuro,* 2016

BRAIN 2025 Vision and 7 Priorities

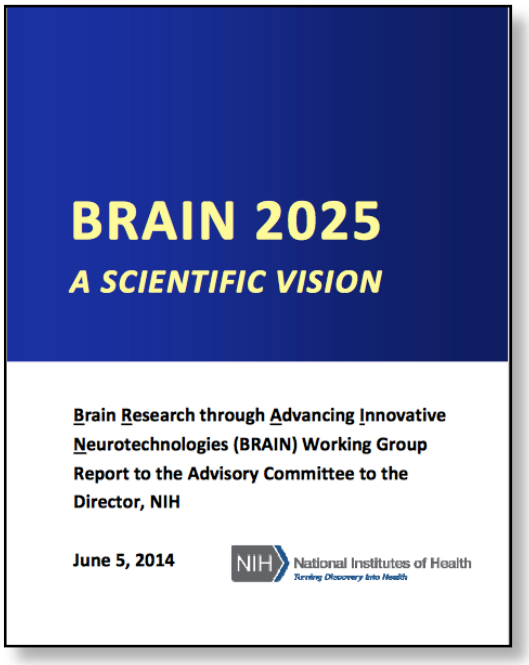


5. **Identifying fundamental principles (theory and data-analysis tools)**

5. Identifying Fundamental Principles

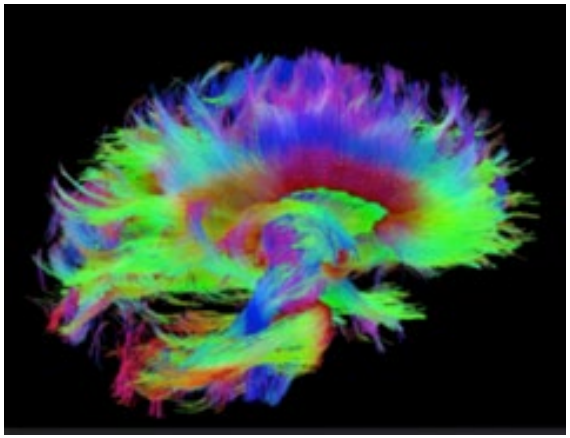
- Overall Progress: *Moderate to Good progress, far to go*
- Notable BRAIN 1.0 advances
  - Trainable artificial neural networks
  - Progress in perceptual decision-making
  - Data processing, dimensionality reduction
- BRAIN 2.0 Opportunities
  - Definitive theories of brain functions
  - Bridging micro (biophysical/molecular) and macro- scales
  - Statistical and analytic circuit models based on connectivity maps
  - A fuller understanding of circuit/plasticity mechanisms supporting different forms of learning

BRAIN 2025 Vision and 7 Priorities



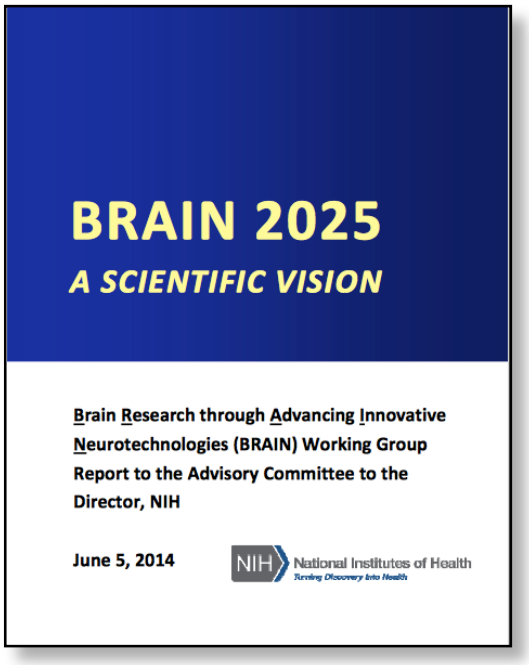
6. Advancing human neuroscience

6. Advancing Human Neuroscience



- Overall Progress: *Good*
- Notable BRAIN 1.0 advances
  - Good advances in MRI, non-invasive mapping and stimulation methods
  - Closed-loop deep-brain stimulation (novel Public-Private Partnership)
- BRAIN 2.0 Opportunities
  - Continued work on:
    - Non-invasive tools to interrogate and modulate brain activity
    - Human brain cell types, connectivity, chemical connectome, viral tools
    - Neuroethics integration with experimentation
    - Improved access to human brain tissue
  - Organoids: technology to watch and accelerating rapidly

BRAIN 2025 Vision and 7 Priorities



7. **From BRAIN Initiative to the brain (integrative approaches)**

7. Integrative Approaches

- **Sociology of Brain Science**
  - Overall Progress: *Moderate*
  - Advance brain science by encouraging early career investigators in:
    - Theory and modeling
    - Physical and chemical sciences and engineering
    - Data science
  - Increase diversity
  - Challenges:
    - Barriers to recruiting and retention from other fields
    - Support for career development
    - Embracing new models of collaboration

7. Integrative Approaches

- **Data sharing and standards**
  - Overall Progress: *Moderate*
  - Establish core principles and practices for data standards, management and sharing
  - Promote standardized data architectures across BRAIN and neuroscience
- **Technology Training and Dissemination**
  - Overall Progress: *Good*
  - Dissemination of new technologies is challenging:
    - costs, market size, and urgency
  - Seeking ways to accelerate and support broad dissemination of BRAIN-funded technology

7. Integrative Approaches

- **Public Outreach**
  - Opportunities to engage public interest
    - The Mouse Project
      - Audience: public high school students
      - Potential to brand as a national project/competition
    - Let's Talk Science
      - Engagement with local museums/science centers
      - Exploiting national coalition of science and technology to promote conversations relevant to BRAIN

Transformative projects

Many ideas discussed by the working group, among which:

- Experimental access to, and functional analysis of, important or clinically relevant cell types without genetic modifications
- Comprehensive mapping of the mouse brain from light microscopy to EM level, including molecular information
- Achieving circuit-level understanding of, and interventions for, a vulnerable circuit as a move toward protecting or correcting a major human neuropsychiatric disease symptom
- Centralized organization to optimize, standardize, and disseminate methods, data analysis, and data sharing

Presentation Outline

Summary

Interim Update: Highlights

- Flagship success: Cell Census
- Bring cell- and circuit-based scales to human neuroscience
- Keep momentum of technology development
- Bridge scales
- Exploit AI revolution and analyses of natural behaviors
- Theory remains a big challenge
- Improve dissemination of new technologies, data sharing
- Improve diversity, recruitment of scientists from related disciplines
- Bring public on board
- Opportunity for transformative projects

Thank You!

Catherine Dulac, Ph.D.
Investigator, HHMI
Higgins Professor of Molecular and Cellular Biology
Harvard University
Co-Chair, ACD BRAIN Working Group 2.0

John Maunsell, Ph.D.
Albert D. Lasker Professor of Neurobiology
University of Chicago
Co-Chair, ACD BRAIN Working Group 2.0