ACD BRAIN WORKING GROUP

INTERIM REPORT

Meeting of the ACD – September 16, 2013

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CHALLENGE FROM THE PRESIDENT

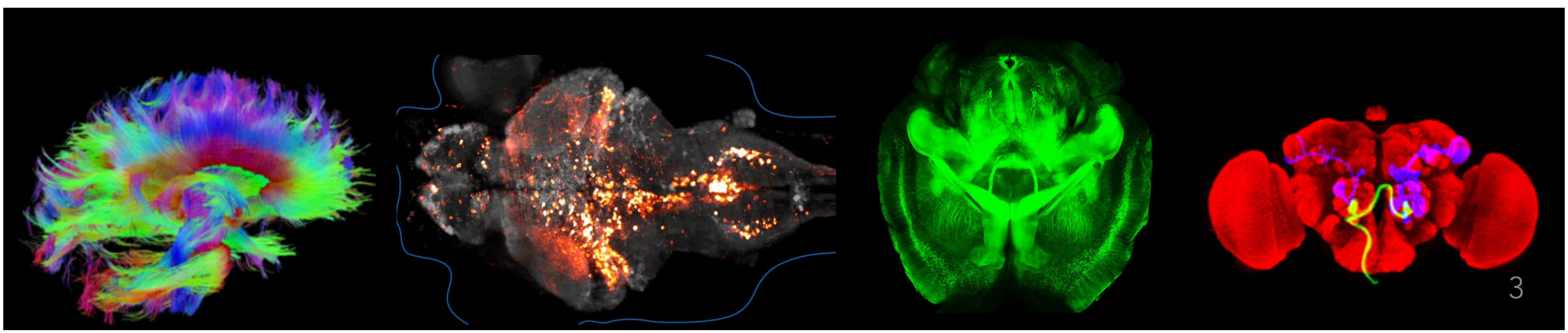
"There is this enormous mystery waiting to be unlocked, ***and the BRAIN Initiative will change that by giving scientists the tools they need to get a dynamic picture of the brain in action*** and better understand how we think and how we learn and how we remember. And that knowledge could be – will be – transformative."

–President Obama, April 2, 2013

OUR CHARGE

Accelerate the development and application of **innovative technologies** to construct a **dynamic picture** of brain function that **integrates neuronal and circuit activity over time and space.**

Build on neuroscience, genetics, physics, engineering, informatics, nanoscience, chemistry, mathematics, to catalyze an interdisciplinary effort of unprecedented scope.



OUR PLAN

Review neuroscience landscape + **Articulate short-, mid- and long-range scientific goals**

Develop rigorous scientific plan, including

- High-priority research areas
- Principles and appropriate structures
- *Collaboration opportunities (TBD)*
- *Timelines, milestones and cost estimates (TBD)*

Deliver interim report on high-priority areas for NIH FY14 funding in summer 2013, and final report in June 2014

OUR PROCESS

WORKING GROUP IDENTIFIED

15 members + 3 ex officio members;
Selected for visionary leadership, broad expertise

FOUR WORKSHOPS

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

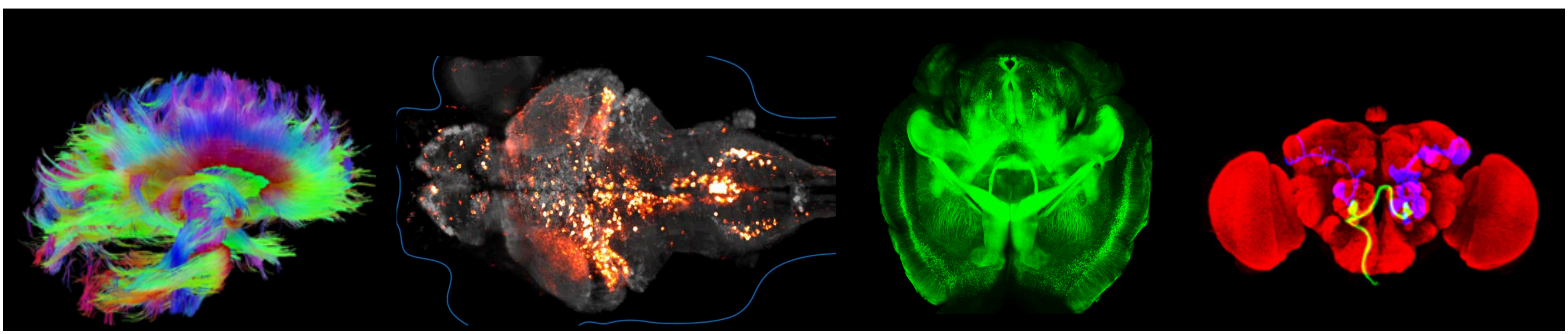
48 outside experts
+
opportunities for public commentary

THREE ADDITIONAL MEETINGS

April 16, May 5, September 8

OVERARCHING GOAL FOR THE BRAIN INITIATIVE

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.



OUR FOCUS ON CIRCUITS

WHY CIRCUITS?

The working group identified the analysis of circuits of interacting neurons as being particularly rich in opportunity, with potential for revolutionary advances.

WHAT WILL IT TAKE TO TRULY UNDERSTAND CIRCUITS?

- Identifying and characterizing the circuit's component cells
- Defining cells' synaptic connections with one another
- Observing dynamic patterns of cellular activity *in vivo* during behavior
- Perturbing these patterns to test their significance
- Defining information processing algorithms *within* a circuit
- Understanding the interaction *between* circuits in the brain as a whole

WHAT WILL WE GAIN?

We expect to see an acceleration of brain research, a deeper understanding of the relationships between brain activity and behavior, and improved scientific foundations for diagnosis and treatment of brain disorders.

APPROACH

Make a broad impact on neuroscience research

- NIH spends approximately $5.5B on neuroscience research
- In 2014, BRAIN will be $40M, or <1%

Target technology development that will yield wide-ranging benefits

- Focus is not on technology per se, but on the development and use of tools for acquiring fundamental insight about how the nervous system functions in health and disease.
- Tool development must emphasize innovation, validation, application, iteration, and dissemination

Pose the problems; don't dictate the solutions

- Allow the most original and compelling ideas to flourish
- Promote collaboration across labs and organizations

PRINCIPLES

1. Use appropriate experimental system and models
2. Cross boundaries in interdisciplinary collaborations
3. Integrate spatial and temporal scales
4. Establish platforms for sharing data
5. Validate and disseminate technology
6. Consider ethical implications of neuroscience research

1) Generate a census of cell types

It is within reach to characterize all cell types in the nervous system, and to develop tools to record, mark, and manipulate these precisely defined neurons *in vivo*.

We envision an integrated, systematic census of neuronal and glial cell types, and new genetic and non-genetic tools to deliver genes, proteins, and chemicals to cells of interest.

Priority should be given to methods that can be applied to many animal species and even to humans.

2) Create structural maps of the brain

It is increasingly possible to map connected neurons in local circuits and distributed brain systems, enabling an understanding of the relationship between neuronal structure and function.

We envision improved technologies – faster, less expensive, scalable – for anatomic reconstruction of neural circuits at all scales, such as molecular markers for synapses, trans-synaptic tracers for identifying circuit inputs and outputs, and electron microscopy for detailed reconstruction.

The effort would begin in animal models, but some mapping techniques may be applied to the human brain, providing for the first time cellular-level information complementary to the Human Connectome Project.

3) Develop new large-scale recording capabilities

We should seize the challenge of recording dynamic neuronal activity from complete neural networks, over long periods, in all areas of the brain.

There are promising opportunities both for improving existing technologies and for developing entirely new technologies for neuronal recording, including methods based on electrodes, optics, molecular genetics, and nanoscience, and encompassing different facets of brain activity, in animals and in some cases in humans.

4) Develop a suite of tools for circuit manipulation

By directly activating and inhibiting populations of neurons, neuroscience is progressing from observation to causation, and much more is possible to enable the immense potential of circuit manipulation.

A new generation of tools for optogenetics, pharmacogenetics, and biochemical and electromagnetic modulation should be developed for use in animals and eventually in human patients. Emphasis should be placed on achieving modulation of circuits in patterns that mimic natural activity.

5) Link neuronal activity to behavior

The clever use of virtual reality, machine learning, and miniaturized recording devices has the potential to dramatically increase our understanding of how neuronal activity underlies cognition and behavior.

This path can be enabled by developing technologies to quantify and interpret animal behavior, at high temporal and spatial resolution, reliably, objectively, over long periods of time, under a broad set of conditions, and in combination with concurrent measurement and manipulation of neuronal activity.

6) Integrate theory, modeling, statistics, and computation with experimentation

Rigorous theory, modeling and statistics are advancing our understanding of complex, nonlinear brain functions where human intuition fails. New kinds of data are accruing at increasing rates, mandating new methods of data analysis and interpretation.

To enable progress in theory and data analysis, we must foster collaborations between experimentalists and scientists from statistics, physics, mathematics, engineering and computer science.

7) Delineate mechanisms underlying human imaging technologies

We must improve spatial resolution and/or temporal sampling of human brain imaging techniques, and develop a better understanding of cellular mechanisms underlying commonly measured human brain signals (fMRI, Diffusion Weighted Imaging (DWI), EEG, MEG, PET)—for example, by linking fMRI signals to cellular-resolution population activity of neurons and glia contained within the imaged voxel, or by linking DWI connectivity information to axonal anatomy.

Understanding these links will permit more effective use of clinical tools for diagnosis and treatment of brain disorders.

8) Create mechanisms to enable collection of human data

Humans who are undergoing diagnostic brain monitoring or receiving neurotechnology for clinical applications provide an extraordinary opportunity for scientific research on healthy human brain function, mechanisms of human brain disorders, and effects of therapies.

Meeting this opportunity requires closely integrated research teams of clinicians, engineers, and scientists, all performing according to the highest ethical standards of clinical care and research. New mechanisms are needed to maximize the collection of this priceless information and ensure that it benefits people with brain disorders.

9) Disseminate knowledge and training

Progress would be dramatically accelerated by the rapid dissemination of skills across the scientific and medical communities.

To enable the broadest possible impact of newly developed methods, and their rigorous application, support should be provided for training—for example, in summer courses and course modules in imaging, electrophysiology, optogenetics, computational neuroscience, statistics—and for educating non-neuroscientists in neuroscience.

HIGH PRIORITY RESEARCH AREAS: SUMMARY

1) Generate a census of cell types
2) Create structural maps of the brain
3) Develop new large-scale network recording capabilities
4) Develop a suite of tools for circuit manipulation
5) Link neuronal activity to behavior
6) Integrate theory, modeling, statistics, and computation with experimentation
7) Delineate mechanisms underlying human imaging technologies
8) Create mechanisms to enable collection of human data
9) Disseminate knowledge and training

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