

**Brain Research through Advancing
Innovative Neurotechnologies (BRAIN) Working Group**

INTERIM REPORT – EXECUTIVE SUMMARY

On April 2, 2013, President Obama launched the BRAIN Initiative to “accelerate the development and application of new technologies that will enable researchers to produce dynamic pictures of the brain that show how individual brain cells and complex neural circuits interact at the speed of thought.” In response to this Grand Challenge, NIH convened a working group of the Advisory Committee to the Director, NIH, to develop a rigorous plan for achieving this scientific vision. To ensure a swift start, the NIH Director asked the group to deliver an interim report identifying high priority research areas that should be considered for the BRAIN Initiative NIH funding in Fiscal Year 2014. These areas of priority are reflected in this report and, ultimately, will be incorporated into the working group’s broader scientific plan detailing a larger vision, timelines and milestones.

The goals voiced in the charge from the President and from the NIH Director are bold and ambitious. The working group agreed that in its initial stages, the best way to enable these goals is to accelerate technology development, as reflected in the name of the BRAIN Initiative: “Brain Research through Advancing Innovative Neurotechnologies.” The 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. In addition, since this initiative is only one part of the NIH’s substantial investment in basic and translational neuroscience, these technologies were evaluated for their potential to accelerate and advance other areas of neuroscience as well.

In analyzing these goals and the current state of neuroscience, the working group identified the analysis of circuits of interacting neurons as being particularly rich in opportunity, with potential for revolutionary advances. Truly understanding a circuit requires identifying and characterizing the component cells, defining their synaptic connections with one another, observing their dynamic patterns of activity *in vivo* during behavior, and perturbing these patterns to test their significance. It also requires an understanding of the algorithms that govern information processing within a circuit, and between interacting circuits in the brain as a whole. With these considerations in mind, the working group consulted extensively with the scientific community to evaluate challenges and opportunities in the field. Over the past four months, the working group met seven times and held workshops with invited experts to discuss technologies in chemistry and molecular biology; electrophysiology and optics; structural neurobiology; computation, theory, and data analysis; and human neuroscience (a full list of speakers and topics can be found in Appendix A). Workshop discussions addressed the value of

appropriate experimental systems, animal and human models, and behavioral analysis. Each workshop included opportunity for public comments, which were valuable for considering the perspectives of patient advocacy groups, physicians, and members of the lay public.

Although we emphasize that this is an interim report, which will develop with much additional advice before June 2014, certain themes have already emerged that should become core principles for the NIH BRAIN Initiative.

1. *Use appropriate experimental system and models.* The goal is to understand the human brain, but many methods and ideas will be developed first in animal models. Experiments should take advantage of the unique strengths of diverse animal systems.
2. *Cross boundaries in interdisciplinary collaborations.* No single researcher or discovery will crack the brain's code. The most exciting approaches will bridge fields, linking experiment to theory, biology to engineering, tool development to experimental application, human neuroscience to non-human models, and more, in innovative ways.
3. *Integrate spatial and temporal scales.* A unified view of the brain will cross spatial and temporal levels, recognizing that the nervous system consists of interacting molecules, cells, and circuits across the entire body, and important functions can occur in milliseconds, minutes, or take a lifetime.
4. *Establish platforms for sharing data.* Public, integrated repositories for datasets and data analysis tools, with an emphasis on user accessibility and central maintenance, would have immense value.
5. *Validate and disseminate technology.* New methods should be critically tested through iterative interaction between tool-makers and experimentalists. After validation, mechanisms must be developed to make new tools available to all.
6. *Consider ethical implications of neuroscience research.* BRAIN Initiative research may raise important issues about neural enhancement, data privacy, and appropriate use of brain data in law, education and business. Involvement of the President's Bioethics Commission and neuroethics scholars will be invaluable in promoting serious and sustained consideration of these important issues. BRAIN Initiative research should hew to the highest ethical and legal standards for research with human subjects and with non-human animals under applicable federal and local laws.

The following research areas are identified as high-priority research areas in FY 2014.

#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 Network 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 MRI (DW MRI), 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 DW MRI connectivity information to axonal anatomy. Understanding these links will permit more effective use of clinical tools for manipulating circuit activity, such as deep brain stimulation and transcranial magnetic stimulation.

#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. This setting enables research on human brain function, the mechanisms of human brain disorders, the effect of therapy, and the value of diagnostics. Meeting this opportunity requires closely integrated research teams including 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 community. To enable the broadest possible impact of newly developed methods, and their rigorous application, support should be provided for training—for example, summer courses and course modules in computational neuroscience, statistics, imaging, electrophysiology, and optogenetics—and for educating non-neuroscientists in neuroscience.

Although these FY 2014 research priorities are presented as nine individual recommendations, the overarching vision is to combine these approaches into a single, integrated science of cells, circuits, brain and behavior. For example, there is immense added value if recordings from neuronal populations are conducted in identified cell types whose anatomical connections are established in the same study. Such an experiment is currently an exceptional tour de force; with new technology, it could become routine. In another example, neuronal populations recorded during complex behavior might be immediately retested with circuit manipulation techniques to determine their causal role in generating the behavior. Theory and modeling could be woven into successive stages of ongoing experiments, enabling effective bridges to be built from single cells to connectivity maps, population dynamics, and behavior. Facilitating this vision of integrated, seamless inquiry across levels is the initial goal of the BRAIN Initiative, to be explored and refined before the final report in June 2014.

INTERIM REPORT, APPENDIX A – EXPERT CONSULTATIONS

MAY 29, 2013 – MOLECULAR APPROACHES

Edward Callaway, PhD, Audrey Geisel Chair and Professor, Salk Institute for Biological Studies

Nathaniel Heintz, PhD, James and Marilyn Simons Professor, Rockefeller University

Ehud Isacoff, PhD, Professor and Head of Neurobiology, University of California, Berkeley

Loren Looger, PhD, Group Leader, Janelia Farm Research Campus

Liqun Luo, PhD, Professor of Biology, Stanford University

Clay Reid, PhD, Senior Investigator, Allen Institute for Brain Science

Gerald Rubin, PhD, Vice President and Executive Director, Janelia Farm Research Campus

Michael Stryker, PhD, WF Ganong Professor of Physiology, University of California, San Francisco

Alice Ting, PhD, Ellen Swallow Richards Associate Professor of Chemistry, Massachusetts Institute of Technology

Hongkui Zeng, PhD, Senior Director, Allen Institute for Brain Science

Feng Zhang, PhD, Core Member, Broad Institute; Investigator, McGovern Institute for Brain Research; and Assistant Professor of Neuroscience, Massachusetts Institute of Technology

JUNE 26, 2013 – LARGE-SCALE RECORDING TECHNOLOGIES AND STRUCTURAL NEUROBIOLOGY

Edward Boyden, PhD, Benesse Chair, New York Stem Cell Foundation-Robertson Investigator, and Paul Allen Distinguished Investigator, Massachusetts Institute of Technology; Associate Professor, MIT Media Lab and McGovern Institute

György Buzsáki, MD, PhD, FAAAS, Biggs Professor of Neural Sciences, New York University

Winfried Denk, PhD, Director, Max Planck Institute for Medical Research

Florian Engert, PhD, Professor of Molecular and Cellular Biology, Harvard University

Michale Fee, PhD, Professor, McGovern Institute, Massachusetts Institute of Technology

Jeff Lichtman, MD, PhD, Professor of Molecular and Cellular Biology, Harvard University

Markus Meister, PhD, Professor of Biology, California Institute of Technology

Pavel Osten, MD, PhD, Associate Professor, Cold Spring Harbor Laboratory

Hongkun Park, PhD, Professor of Chemistry and Physics, Harvard University

Kristin Scott, PhD, Associate Professor, University of California, Berkeley

Karel Svoboda, PhD, Group Leader, Janelia Farm Research Campus

Rafael Yuste, MD, PhD, Professor, Columbia University

JULY 29, 2013 – COMPUTATION, THEORY, AND BIG DATA

Kwabena Boahen, PhD, Professor of Bioengineering, Stanford University

Kristin Branson, PhD, Lab Head, Janelia Farm Research Campus

Jennifer Chayes, PhD, Distinguished Scientist and Managing Director, Microsoft Research

Todd Coleman, PhD, Associate Professor of Bioengineering, University of California, San Diego

Uri Eden, PhD, Associate Professor of Statistics, Boston University

Jack Gallant, PhD, Professor of Psychology, University of California, Berkeley

Surya Ganguli, PhD, Assistant Professor of Applied Physics, Stanford University

Stephanie Jones, PhD, Assistant Professor of Neuroscience, Brown University

Nancy Kopell, PhD, William Fairfield Warren Distinguished Professor and Co-Director of the Center for Computational Neuroscience and Neural Technology, Boston University

Maryann Martone, PhD, Professor-in-Residence, University of California, San Diego

Bruno Olshausen, PhD, Director of the Redwood Center for Theoretical Neuroscience and Professor, University of California, Berkeley

Patrick Purdon, PhD, Instructor of Anaesthesia, Harvard University, and Assistant in Bioengineering, Massachusetts General Hospital

Sebastian Seung, PhD, Professor of Computational Neuroscience, Massachusetts Institute of Technology

AUGUST 29, 2013 – HUMAN NEUROSCIENCE

Krystof Bankiewicz, MD, PhD, Professor of Neurosurgery and Neurology and Kinetics Foundation Chair in Translation Research, University of California, San Francisco

Sydney Cash, MD, PhD, Associate Professor of Neurology, Harvard University

Timothy Denison, PhD, Director of Core Technology and Technical Fellow, Medtronic Neuromodulation

Rainer Goebel, PhD, Professor of Cognitive Science, Maastricht University

Brian Litt, MD, Professor of Neurology, University of Pennsylvania

Helen Mayberg, MD, Professor of Psychiatry, Neurology, and Radiology, and Dorothy C Fuqua Chair of Psychiatry Neuroimaging and Therapeutics, Emory University

Alvaro Pascual-Leone, MD, PhD, Professor of Neurology and Director of the Berenson-Allen Center for Noninvasive Brain Stimulation, Harvard University

Bruce Rosen, MD, PhD, Professor in Radiology, Harvard Medical School, and Director of the Athinoula A Martinos Center for Biomedical Imaging, Massachusetts General Hospital

Nicholas Schiff, MD, Director of the Laboratory of Cognitive Neuromodulation, Cornell University

Stephen Smith, PhD, Associate Director of the Centre for Functional MRI of the Brain and Professor of Biomedical Engineering, University of Oxford

Doris Tsao, PhD, Assistant Professor of Biology and Computation and Neural Systems, California Institute of Technology

David Van Essen, PhD, Professor of Anatomy and Neurobiology, Washington University