DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

The Frontiers of Human Brain Research

Testimony before the

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Committee on Science, Space, and Technology

Subcommittee on Research

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Mr. Chairman and Members of the Committee:

I am pleased to testify today about advances in neuroscience, the role of the National Institutes of Health (NIH), and opportunities to accelerate progress through the *Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative*, which the President announced as part of his Fiscal Year (FY) 2014 Budget.

THE IMPORTANCE OF NEUROSCIENCE RESEARCH

Diseases of the brain and nervous system impose an enormous burden on individuals, families, and society. The Institute for Health Metrics and Evaluation, an independent research center, estimates that brain disorders (neurologic, substance abuse, and mental and behavioral disorders) are the number one source of disability globally from all medical causes in those aged 15 to 49 years.[1] The costs of dementia alone—by one recent estimate at $159 billion to $215 billion in the United States for 2012—already rival those of cancer and heart disease, and could rise dramatically in coming decades with a growing elderly population.[2]

Although the burden of nervous system diseases is daunting, the complementary efforts of the NIH and the private sector are making real progress. For example, the age adjusted death rate for stroke fell by 70 percent over the last 50 years, and by approximately 37 percent just from 1999 to 2009.[3] NIH research contributed to this progress by identifying risk factors, determining through many clinical trials which preventive measures are most effective for people with specific risk profiles, and developing the only effective emergency treatment for stroke. New treatments are also available or in testing for many other brain diseases, including Alzheimer's disease, Parkinson's disease, and epilepsy. For example, 20 years ago there were no effective drugs for multiple sclerosis, and now there are nine that slow progression of the disease.

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[1] Global Burden of Disease Compare, http://www.healthmetricsandevaluation.org/gbd/visualizations/country.
[2] New England Journal of Medicine 368:1326, 2013
[3] Circulation 134:e6-245, 2013.

ADVANCES AND OPPORTUNIES IN NEUROSCIENCE

NIH supports neuroscience research to reduce the burden of brain disorders, from basic research to understand how the brain and nervous system work and what goes wrong as a result of disease, through translational and clinical research to develop and test candidate therapies in the laboratory and in human trials. Many NIH Institutes and Centers support neuroscience research, as appropriate to their missions. Basic neuroscience research, which is my focus today, is an especially critical aspect of the NIH mission because the outcomes and applications of basic research are often too far upstream and high-risk to attract substantial private investment. Basic studies lay the foundation for the development of better diagnosis, treatment, and prevention of neurological and mental health disorders by uncovering disease mechanisms and identifying potential targets for intervention. This research is inherently interdisciplinary and spans multiple levels of analysis, from the intact human brain to single cells, genes, and molecules.

Until recently, the living human brain was largely inaccessible to direct study. Neuroscientists inferred how the human brain works from animal studies and from indirect observations of the human brain, including behavioral experiments, electrical recordings of brain activity from outside the skull, and the consequences of disease and injury to particular parts of the brain. Over the last two decades, advances in brain imaging, which build on developments in physics, engineering, mathematics and other disciplines, have revolutionized both clinical care and neuroscience research. Dr. Marcus Raichle, a pioneer in brain imaging, will testify at this hearing about how brain imaging allows increasingly detailed studies of structure, function, connectivity, and even biochemistry in the living human brain.

Basic neuroscience research focused on molecules, genes, and single cells has also made remarkable progress. Studies at the resolution of single atoms reveal how ion channels control the flow of electrical currents in nerve cells and how receptor molecules on cells sense chemical signals. Just last year, a Nobel Prize recognized the importance of research on a broad class of receptors, called G-protein coupled receptors. Many drugs now in use target these receptors and ion channels, and understanding their structures informs better drug design. The discovery of hundreds of gene defects that cause disease has led to faster diagnoses for families confronting rare neurological disorders. Findings from genetics also lead to better understanding of mechanisms of disease and to rational strategies for the development of therapies by NIH and the private sector. In one dramatic example that may be a harbinger of the future, researchers using "next generation" sequencing methods, which rely on advances in computational analysis, decoded the entire genome of twins with a rare form of dystonia, a movement disorder characterized by abnormally sustained muscle contractions. With insight from this analysis, the research team quickly discovered that a known drug dramatically improved the twins' lives.

Understanding how brain circuits function resides in a middle ground between research on the living human brain and studies of molecules and single cells, and is at the core of some of neuroscience's greatest challenges and opportunities. A unique aspect of the brain, compared to other organs, is the importance of precise connections between brain cells that influence one another's functional output. By one estimate, the human brain has more than 80 billion neurons, each of which may form thousands of synapses (functional connections), with other cells.[4] We perceive, think, and act through the computations performed by these networks of cells, and all but the simplest reflex behaviors in mammals require the concerted activity of many thousands of neurons. Our understanding of how synapses between pairs of nerve cells transmit information has advanced greatly, but research on brain circuits has faced challenges because of the difficulty of monitoring activity in many cells at once. The complete wiring diagram of

[4] Ann. Rev. Neurosci.1988. 11 :423-53

neuronal connections has been mapped in one organism, a nematode worm with 302 neurons, but anatomical mapping in mammalian brains has been limited to specific pathways and small parts of circuits. It is as if neuroscientists studying circuits have been trying to watch an HDTV show by observing a few pixels at a time rather than seeing the entire picture at once.

In the last few years, however, new techniques for studying brains in laboratory animals have made mapping the structure and function of brain circuits one of the most exciting and promising areas of neuroscience. Historically, neuroscience has applied advances from multiple disciplines, so it is not surprising that these transformative advances arise from a convergence of neurobiology, genetics, optics, computer science, chemistry, engineering, and other fields and are the products of long term investments by the NIH, the National Science Foundation (NSF), and others. Breakthrough microscopy methods, together with fluorescent indicators that sense specific ions or detect voltages, can simultaneously monitor the activity of thousands of individually resolved cells deep in the brains of living experimental animals. In some experiments, researchers have monitored activity in the same cells for weeks at a time as animals explore their environment and learn. A complementary technique, optogenetics, has dramatically improved researchers' ability to control the activity of specific types of neurons in experimental animals. This method uses genetic engineering to install light-sensitive switches into identified nerve cells, enabling researchers to turn cells' electrical activity on or off with precisely timed light pulses and has quickly become an important tool for neuroscientists exploring neural circuits. For example, a decade ago scientists discovered that adult brains, even in 60 year old people, generate new nerve cells. This year optogenetics revealed that these new cells readily adjust the strength of their synapses and lay down new memories in mice. Optogenetics has also advanced understanding of brain circuits in animal models of Parkinson's disease, post-stroke epilepsy, and the generalization of fearful memories, a process relevant to post-traumatic stress disorder.

New techniques for tracing connections between neurons are also providing unprecedented anatomical maps of the brain's architecture. "Brainbow," for example, labels individual nerve cells and fibers with approximately 100 different colors so that researchers can follow the paths of intertwined nerve fibers through the brain. Another technique called CLARITY[5] renders brain tissue completely transparent, allowing scientists to observe complete trajectories of labeled cells and fiber pathways in the intact brain.

BRAIN INITIATIVE

Although these tools represent remarkable advances, they are not yet adequate to capture the behavior of complete brain circuits functioning in real time in the living human brain. To improve our knowledge and understanding of brain functioning, the President announced the BRAIN Initiative as part of his FY 2014 Budget. Through this initiative, researchers will build on emerging insights from multiple disciplines to develop, disseminate, and apply new tools and technologies that will allow scientists to generate a dynamic, real time picture of entire functioning brain circuits. The BRAIN Initiative will involve the coordinated activities of the NIH, NSF, the Defense Advanced Research Projects Agency (DARPA), the Office of Science and Technology Policy (OSTP), and private organizations, including the Howard Hughes Medical Institute, the Allen Institute for Brain Science, the Salk Institute for Biological Studies, and the Kavli Foundation. Coordination across NIH will be facilitated by the NIH Blueprint for Neuroscience, which brings together sixteen institutes and centers, and across Federal agencies

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[5] According to the developer's paper (http://www.nature.com/nature/journal/v497/n7449/full/nature12107.html), "the term was an acronym to describe the Clear Lipid-exchanged Acrylamide-hybridized Rigid Imaging/Immunostaining/*In situ* hybridization-compatible Tissue-hYdrogel." However, due to the length of the actual phrase and because the method actually goes beyond the original acronym, we did not provide the phrase in the text above.

through the Interagency Working Group recently formed under the auspices of OSTP. In addition, the President also directed his Commission for the Study of Bioethical Issues to engage with the scientific community and other stakeholders to identify proactively a set of core ethical standards both to guide neuroscience research and to address potential ethical dilemmas raised by the application of neuroscience research findings. The President formally charged the Commission with this task on July 1, 2013, and the Commission will begin to deliberate the request at its public meeting on August 20, 2013.

The BRAIN Initiative can take many lessons from the success of the Human Genome Project, including the importance of computational sciences and sharing data widely, with appropriate privacy protections. High-resolution activity recordings and large-scale anatomical circuit reconstruction produce vast quantities of data, and making sense of multidimensional datasets generated through the BRAIN Initiative will be an enormous challenge. By one estimate, the human brain can produce in 30 seconds as much data as the Hubble Space Telescope has produced in its lifetime.[6] A joint NIH-NSF initiative on "Big Data Science" is underway, which will be important in addressing these data challenges. Furthermore, we do not understand the "neural code" through which the rate, timing, and patterns of activity in populations of brain cells represent and transform information. NIH and NSF have collaborated for almost a decade in computational neuroscience, which is essential to take on this challenge. Human brain imaging, including information from the ongoing NIH Human Connectome Project, will also complement the goals of the BRAIN Initiative.

To develop a blueprint for NIH's role in the BRAIN Initiative, NIH has established a group of 18 highly qualified external advisors, including 3 *ex officio* members from the Federal partner agencies. They have wide ranging expertise, including contributing to the development of

[6] Nature 499:274, 2013.

several of the transformative new techniques described today. This working group of the Advisory Committee to the NIH Director is expected to present interim recommendations to the Director late this summer and final recommendations are anticipated in the summer of 2014. The group is already interacting extensively with the NIH research community to develop a more complete scientific plan, anticipated next summer, that will: 1) identify high priority investments (*e.g.*, improving current tools, identifying new directions); 2) develop principles for achieving the goals (*e.g.*, the balance between small groups and large consortia); 3) suggest collaborations with foundations, industry, other agencies, and international programs; and 4) deliver timelines and milestones.

In basic neuroscience, as in other areas of research, NIH emphasizes investigator-initiated research, which engages the wisdom and ingenuity of the research community. Tool development empowers the research community by providing better, cheaper technologies and open-access databases. We are confident that the BRAIN Initiative will have a catalytic effect on neuroscience research in the coming years. In addition to the BRAIN Initiative, NIH will also continue to support research across the full range of basic and applied neuroscience.

There are excellent reasons for our confidence in the importance of the BRAIN Initiative as a critical aspect of research addressing brain disorders. Foremost, many diseases of the brain, including autism, dystonia, epilepsy, and schizophrenia, are fundamentally disorders of brain circuitry; and others, such as Parkinson's disease and Alzheimer's disease, cause symptoms by disrupting the performance of circuits as brain cells degenerate. Even with our limited understanding of brain circuits and the relatively imprecise technologies for interventions, therapies that compensate for malfunctioning brain circuits already produce remarkable results for some people. Deep brain stimulation, which uses chronically implanted electrodes, has proven to have long term benefit in clinical trials for Parkinson's disease and dystonia, and has shown promise for Tourette's syndrome, depression, epilepsy, obsessive compulsive disorder, chronic pain, and several other disorders. Cochlear implants send coded auditory signals that brain circuits can interpret to restore useful hearing to thousands of people, visual prostheses have restored rudimentary sight in pilot studies, and brain computer interfaces that monitor signals from the movement control circuits of the brain have enabled people with paralysis to move a robotic arm, using only their thoughts. Decades of pioneering NIH interdisciplinary research and, more recently, extensive cooperation with DARPA, have been critical to these advances in neural prostheses, some of which you will hear more about today. These advances provide a glimpse of the future. Better understanding of brain circuits would not only improve the sophistication of stimulation-based interventions and prosthetics, but also inform development of treatments for the full range of brain diseases that affect circuits. Looking more broadly, unanticipated benefits will likely flow from the BRAIN Initiative beyond neuroscience, just as the Human Genome Project had entirely unexpected benefits. History has shown that the most important outcomes of the BRAIN Initiative may well be those we have yet to imagine.