The Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative and Neurology

On April 2, 2013, President Obama announced the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative, a partnership between the National Institutes of Health (NIH), the National Science Foundation, the Defense Advanced Research Projects Agency, private foundations, and researchers. The charge of the BRAIN Initiative, as summarized by NIH Director Francis Collins, MD, PhD, is “to 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.” This is an exciting goal with an ambitious scope.

The NIH’s contribution to the BRAIN Initiative will be $40 million in the first year. Although meaningful, this represents less than 1% of the NIH’s $5.5 billion annual investment in neuroscience research, providing both opportunities and constraints. With this in mind, Dr Collins convened a working group of scientists to ask what could best be done with these resources to crack the big problems of neural circuits, coding, and dynamics. Taking the N for “Neurotechnologies” seriously, the working group included expertise in engineering, physics, and chemistry as well as biology and also included physicians and scientists who have made innovative advances in human brain imaging, recording, and brain-computer interfaces. Improvements in technology benefit all scientists, so a technology emphasis will increase the value and impact of the BRAIN Initiative for a large research community. However, technology develops best when it is pointed to the most important problems; therefore, the working group has also identified compelling scientific questions that should be pursued with these technologies.

The scientific question at the heart of the BRAIN Initiative is how rapidly fluctuating chemical and electrical activity flows through stable anatomical circuits to generate cognition and behavior. Beginning with Paul Broca in the 19th century, studies of clinical cases have shown that different brain areas are specialized for different tasks. Around the turn of the 20th century, Santiago Ramón y Cajal and his successors began to describe the anatomical pathways that link different areas of the brain into functional networks. Subsequently, single-neuron recordings and molecular biology have shown us that neurons within these networks have characteristic physiological properties and molecular components associated with their functions. More recently, functional brain imaging has provided views of regional brain activity associated with a wide range of cognitive functions in humans.

Missing, however, has been an understanding of how the many millions of neurons associated with a perception, thought, decision, or movement are dynamically linked within circuits and networks. Even the simplest perceptual task involves the activity of millions of neurons distributed across many brain regions. How simple percepts arise from patterned neural activity and how the resulting percepts are linked to emotion, motivation, and action are deeply mysterious. In the past, answers to these questions seemed out of reach.

Why do we believe that a BRAIN Initiative can solve circuits now? Recent technological advances are changing the landscape of the possible—likely the leading edge of a revolution in experimental neuroscience. The first advance is the development of new recording capabilities. In contrast to the traditional one-neuron-at-a-time approach, multielectrode arrays enable recording from hundreds of neurons at once in any anatomically targeted brain region. Genetically encoded indicators of neuronal activity, combined with new microscopes and endoscopes, are making high-density recordings possible from nearly all neurons within a particular brain region or from select populations based on cell type or anatomical projection targets. These new population recordings allow us to observe patterns of neural activity during behavior in ways that have not been possible heretofore.

A second remarkable advance is the development of new tools to perturb the activity of neurons in precise ways. Optogenetics, for example, uses genetic tools to target specific neurons for activation or inactivation with light, through the expression of light-sensitive channels from single-celled bacteria and protozoa. With these methods, it becomes possible not just to observe the neurons that are active at a particular time but also to ask whether they are necessary for a behavioral outcome or sufficient to drive it.

A third advance uses the conceptual tools of computational neuroscience to identify signals that are distributed across large neural populations. This intellectual advance, along with technological advances in computing power, makes it possible to analyze the patterns of activity from many thousands or millions of neurons that collectively represent information and perform computations.

Inspired by these examples, a first view of a BRAIN Initiative to solve brain circuits and networks was outlined in an interim report released by the working group in September 2013, with a final report due in June 2014. The BRAIN Initiative should identify all cell types in the brain, define their connections both locally and across...
regions, develop methods for even larger-scale recordings of neuronal activity during behavior, develop more powerful perturbation methods that can be performed noninvasively, and advance computational methods for understanding the meaning of patterned neuronal activity. These approaches will be most powerful when deployed in combination with each other: we should record and perturb neuronal activity in defined sets of neurons with defined connections during a variety of behaviors. This is a frankly ambitious agenda that would have been considered impossible only a few years ago, but many of the necessary technologies are now within our grasp or on the horizon.

Importantly, the ultimate goal of the BRAIN Initiative is to understand the human brain, so these goals must all be pursued in humans as well as nonhuman animals from the outset and not sequentially. The Human Connectome Project is attacking both activity and connectivity of the human brain with the best current methods, but we need imaginative new technologies for noninvasive study of humans and for maximizing the value of invasive recordings in human patients that are conducted, for example, in the context of epilepsy surgery.

The circuit-level focus of the BRAIN Initiative receives a clinical justification from the successes of circuit-based interventions in neurology. The development of deep brain stimulation for controlling motor symptoms in Parkinson disease resulted from an understanding of cell types and circuitry of the basal ganglia. That promising step provides a clinical incentive to map the circuits associated with other brain regions as well.

The BRAIN Initiative must not make false promises or raise false hopes, but scientific understanding will shed light on disease processes and in some cases will suggest new therapeutic approaches. The BRAIN Initiative is playing for this long game. For example, patients often come to their physicians with pain, which can result from many underlying pathologies. On its own terms, though, pain arises from circuits in the brain and spinal cord that are only partly mapped. Defining these cells and connections, as well as their normal patterns of activity, could be the first step toward understanding the neural substrates of chronic pain states and planning new interventions for pain management.

One goal of the BRAIN Initiative potentially relevant to neurology is a comprehensive census of cell types in the nervous system. Cell types matter: of the billions of cells in the human brain, the approximately 20,000 neurons in the hypothalamus that express orexin/hypocretin play a central role in controlling sleep and waking states, and their loss leads to narcolepsy with cataplexy. These neurons and their functions were not discovered until the late 1990s—how many similarly important cell types remain to be discovered?

Neurology in particular stands to benefit from the BRAIN Initiative’s mission to be comprehensive. Historically, neuroscience has focused on a few brain regions, especially the cerebral cortex with its unique contributions to human abilities like language. Neurologists, however, know that the whole brain matters. The basal ganglia come into focus in movement disorders; the brainstem is essential for all life functions. These areas lack the simple columnar organization of the cortex, and their circuits are only beginning to be described. New tools for characterizing and manipulating circuits will increase knowledge of many relatively neglected brain areas.

The BRAIN Initiative focuses on basic science, but its goals are to provide a foundation for translational neuroscience as well. It will benefit from the participation of neurologists, and it should provide benefits to neurology in the form of knowledge, technology, and infrastructure. Like any scientific approach, it will lead in directions that we do not expect. Even we who are not neurologists can anticipate advances relevant for neurology; the readers of this journal will anticipate many more.

**ARTICLE INFORMATION**

Published Online: April 7, 2014. doi:10.1001/jamaneurol.2014.411.

Conflict of Interest Disclosures: Drs Bargmann and Newsome are neuroscientists and cochairs of the working group of the advisory committee to the NIH director charged with planning the scientific program of the BRAIN Initiative. No other disclosures were reported.

Additional Contributions: Robert H. Brown Jr, MD, PhD, University of Massachusetts Worcester, Timothy Pedley, MD, Columbia University College of Physicians and Surgeons, Stanley Prusiner, MD, University of California, San Francisco, Bruce Rosen, MD, PhD, Harvard Medical School and Massachusetts General Hospital, and others provided guidance and insight. No compensation was received for these contributions.

**REFERENCES**

