RESEARCH PRIORITIES

The NIH BRAIN Initiative

The NIH BRAIN Initiative will build on recent successes in neuroscience to create and apply new tools for understanding brain activity.

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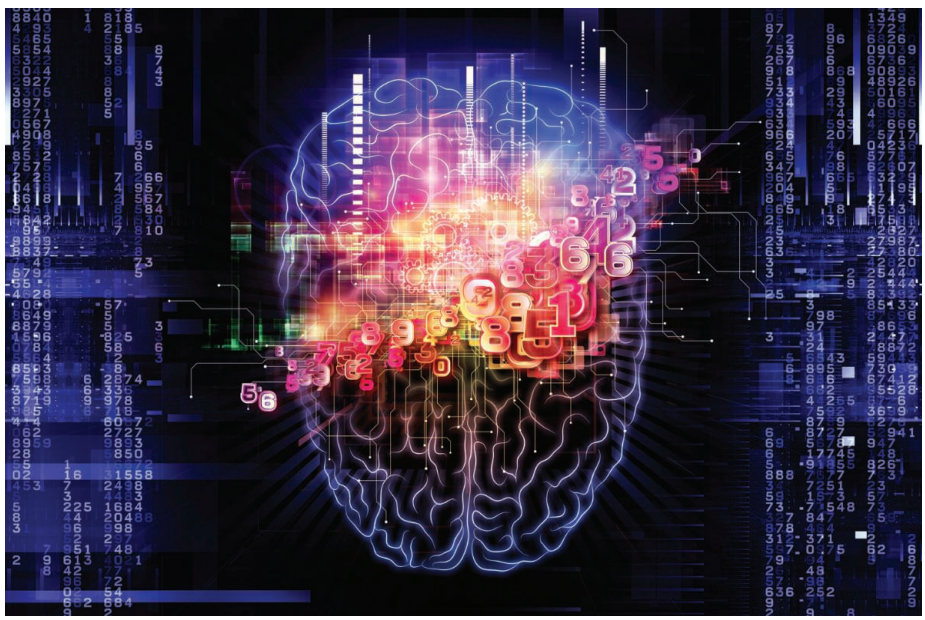

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On 2 April 2013, President Barack Obama announced the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. In front of some 200 scientists in the East Room of the White House, the President declared, "…there is this enormous 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" (*1*).

Many scientists have been skeptical of an ambitious new project when support of existing science is eroding. Others have been confused about how this project will accomplish its goals, because mapping the brain is far more complex and open-ended than mapping the genome. Still others have speculated about whether this is really a new initiative with new funding, or if it simply reflects rebranding of current research. Here, we will try to address these concerns and explain in more detail the NIH vision for the BRAIN Initiative.

The BRAIN Initiative is being launched with a proposal for federal funding of just over $100 million in the next fiscal year and will be led by the National Institutes of Health, the Defense Advanced Research Projects Agency (DARPA), and the National Science Foundation (NSF). Private partners—including the Allen Institute for Brain Science, the Howard Hughes Medical Institute, the Kavli Foundation, and the Salk Institute for Biological Studies—are also committed to ensuring its success. A preliminary vision, called the "Brain Activity Map," was initially developed at a series of meetings sponsored by the Kavli Foundation, the Gatsby Charitable Foundation, and the Allen Institute for Brain Science (*2*, *3*). BRAIN seeks to significantly extend and shape that vision, exposing the research plan to rigorous scientific debate with broad input from the neuroscience community.

Mapping brain structure and function is already an exciting field of science. New anatomic techniques, from Brainbow to CLARITY, provide unprecedented images of neural architecture (*4*, *5*). Breakthrough technologies—such as two-photon imaging, light-sheet microscopy, and miniaturized microendoscopes, together with calcium imaging and voltage imaging—have given us the first dynamic views of how the brain encodes information in modular circuits (*6*–*8*). Optogenetics has enabled precise manipulation of circuit activity with light pulses (*9*).

In addition to these technical innovations exploited in experimental animals, human neuroimaging has advanced considerably in the past decade. The Human Connectome Project has increased gradient strength and improved white matter imaging to provide the first detailed "wiring diagram" with new insights into the three-dimensional organization of fiber tracts in the living human brain (*10*). Improvements in functional magnetic resonance imaging (fMRI) have given us better maps of human brain activity, allowing more precise localization of complex functions such as language, emotion, decision-making, and hallucinations. Even the analysis of fMRI signals from individuals who are not performing a task ("resting state" imaging) has been explored as a powerful marker of individual cognitive traits (*11*).

Do current technological advances render the BRAIN Initiative unnecessary? We argue that this success is precisely the springboard needed for a new revolution. Brain function is a dynamic process with changes on a millisecond scale, but some of our most powerful current mapping techniques are static. Neural circuits involve at least 10^6 cells in a complex, recursive network, but neurophysiology has been based classically on single-cell recordings or, more recently, on small ensembles of cells. Human neuroimaging captures the whole brain in action, but each 1-mm^3 voxel includes at least 80,000 neurons and 4.5 million synapses. An fMRI scan, with 680,000 voxels, is capturing local changes in blood flow and oxygen consumption—but these changes are low-resolution and slow surrogates for neuronal activity. Much of the progress over the past decade has been based on optimization of existing tools like MRI and physiological recording. Now is the time to create the next generation of tools by harnessing advances in diverse disciplines from engineering to computational science.

Of course, there are many questions about how to focus this new effort. Should we concentrate on tools for mapping the activity of the 302 neurons in *Caenorhabditis elegans* to yield a comprehensive dynamic picture of nervous system activity associated with behavior and, thereby, establish basic principles of circuit function? How would these technologies or these principles scale from 10^2

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neurons to 10^6 neurons in simple vertebrates or 10^{11} neurons in humans? Should we create a noninvasive version of optogenetics for use in the human brain, allowing functional dissection of neural circuits and enabling more precise diagnostics and therapeutics for brain disorders? What would substitute for light pulses to make this noninvasive, and how would the pulse be directed in the absence of a light-sensitive transgene? Should we create nanoscience tools to record from as many neurons as possible, scaling up modern neurophysiology by several orders of magnitude?

These kinds of questions deserve a thoughtful discussion. That is why we have invited a group of 15 external advisers, cochaired by Cornelia Bargmann from The Rockefeller University and William Newsome from Stanford University, to lead such a discussion over the next several months (*12*). The charge to this group is to develop a scientific plan that will (i) identify areas of high priority (i.e., improving current tools, identifying new directions); (ii) develop some principles for achieving the goals of the BRAIN Initiative (i.e., balance between individual groups and large consortia, balance between problem-solving and technology-driven science); (iii) suggest opportunities for collaboration with foundations, industry, and other agencies; and (iv) deliver specific recommendations for timelines, milestones, and cost estimates. These 15 neuroscientists will be reaching out to a broad community of scientists. We realize that the seeds for the next generation of neurotechnologies may already be sitting in laboratories far removed from neuroscience. Optical physics, nanotechnology, organic chemistry, materials science, molecular biology, computational science, and many other areas will be vital to this effort. Our hope is that the core group of external advisers will serve as a hub to build spokes to other areas of science, creating a national interdisciplinary effort, not just a neuroscience effort.

What will the BRAIN Initiative cost? We are now spending more than $5 billion on neuroscience at NIH. President Obama has asked for roughly $100 million to launch the first year of this project and noted that a serious, sustained effort would be necessary. The NIH budget for 2014 will be determined by Congress and may not be final for several months. Nevertheless, NIH's intention is to commit at least $40 million for new projects within BRAIN next year and to ramp up this commitment in subsequent years. We have asked the Bargmann-Newsome team to provide initial recommendations by the fall of 2013, to give us time to issue requests for applications to jumpstart NIH BRAIN in 2014.

In the first year, much of the funding will come from sources set aside for special projects. One of the largest contributions ($10 million) will be from the NIH Neuroscience Blueprint, a consortium of 15 institutes and centers at NIH developed to support cross-cutting initiatives like technology development and neuroscience training. The NIH Director's Office will be another major contributor ($10 million). The balance will be contributed by individual institutes, including National Institute of Biomedical Imaging and Bioengineering, National Institute on Drug Abuse, National Institute of Mental Health, and National Institute of Neurological Disorders and Stroke. Will this new commitment reduce support for investigator-initiated R01 grants in these institutes? This will represent less than 1% of NIH's support for neuroscience research, any impact on the payline in these institutes should be quite modest. Indeed, experience from the Human Genome Project, which was met initially with some anxiety and skepticism from NIH R01 grantees, predicts that tool development efforts empower individual labs by providing better, cheaper discovery technologies and open-access databases.

Where will NIH BRAIN live? The BRAIN advisory group will report to the Advisory Committee to the Director, chaired by the NIH director. Rather than embedding NIH BRAIN in a single institute or center, we want this project to involve many parts of NIH. That explains the important role of the NIH Neuroscience Blueprint. NIH BRAIN will also need to synergize with DARPA and NSF and their plans, as well as projects outside of government, industry programs, and some spectacular new efforts outside of the United States, such as the European Human Brain Project (www.humanbrainproject.eu/). Bridges to all of these efforts will be developed to avoid redundancy and expedite progress.

The goal of NIH's contribution to the BRAIN Initiative is to produce insights into brain disorders that will lead to better diagnosis, prevention, and treatment. The Institute for Health Metrics and Evaluation estimates that brain disorders (neurologic, substance abuse, and mental and behavioral disorders) are the number-one source of disability globally, accounting for 22% of disability adjusted life years (DALYs) from all medical causes in the 15- to 49-years age bracket (*13*). The World Economic Forum predicts that these same disorders will have the largest costs of chronic, noncommunicable diseases globally over the next 20 years (*14*). Recent estimates of the cost of Alzheimer's disease alone demonstrate the profound increase we can expect over the next few decades if we do not find a way to preempt, delay, or treat dementia (*15*). Building a foundation of understanding of the emergent properties of the brain will provide an opportunity for deeper insights into Alzheimer's disease, Parkinson's disease, schizophrenia, bipolar illness, autism, epilepsy, attention deficit hyperactivity disorder, traumatic brain injury, and a long list of other brain disorders. Those clinical benefits will be the ultimate payoff of this initiative for human health—but we must be careful not to overpromise the immediacy of such outcomes.

President Obama ended his announcement of the BRAIN Initiative by saying, "I don't want our children or grandchildren to look back on this day and wish we had done more to keep America at the cutting edge. I want them to look back and be proud that we took some risks, that we seized this opportunity." The combination of public health need and scientific opportunity is really why the BRAIN Initiative is "the next great American project." As with the Human Genome Project in 1988, the starting gate is a careful, inclusive, deliberate planning process. Mapping the brain is not as simple as mapping the genome—there will be no linear sequence to decode and no obvious end point. But the lessons learned from this earlier effort—lessons about tool development, ethical implications, and partnerships—can be helpful as we launch a new, even more daunting adventure. Just as the Human Genome Project transformed biology, we predict that the BRAIN Initiative will not only transform neuroscience but will yield the intellectual and technological framework for better diagnostics and therapeutics for the millions worldwide who suffer from brain disorders.

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