What the BRAIN Initiative Means for Psychiatry

Psychiatry faces the most difficult problem in medicine, because its organ of interest, the brain, is by orders of magnitude the most complex of the body. The human brain is composed of an intricate network of perhaps 200 billion cells (neurons and glia) and 30 trillion synaptic connections (1). Moreover, brain cells are diverse and vary markedly both within and between brain regions; the anatomical complexity of other organs, such as the kidney, liver, or lung, pales in comparison (1). Diversity of structure is accompanied by diversity of function; the myriad functions of the brain are associated with specialized anatomical structures and circuits that are each composed of many different cell types (1). The functions of the brain that underpin behavior, including cognition, perception, emotion, thought, and creativity, are the most highly evolved abilities of the human species. Consequently, it is not surprising that these functions have proved elusive to our scientific grasp, and it is disturbances in these mental functions that are the province of psychiatry.

For these reasons, the announcement by President Obama on April 2, 2013, of the BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies) (http://www.whitehouse.gov/blog/2013/04/02/brain-initiative-challenges-researchers-unlock-mysteries-human-mind) was especially welcome to the fields of psychiatry and mental health care. The acquisition of human knowledge has always depended on the availability of technology and instrumentation: Pasteur could not have discovered that microorganisms cause disease without a microscope. We could not map the human genome until the enabling sequencing technologies and computing capacity were developed. Our ability to deconstruct and understand the brain has been limited by our scientific instrumentation and technological capability. To make further progress in our understanding of the brain, and particularly its integrative higher-order functions, we need more powerful tools and technologies. Neuroscience has generated spectacular maps of the visual system, but these maps do not explain the neural processes that allow us to recognize a tennis racquet—let alone those that orchestrate our ability to watch and comprehend a tennis match, recognize the players, interpret their actions and intentions, and feel by turns excited, disappointed, and bored. The BRAIN Initiative (http://www.nih.gov/science/brain/) promises to accelerate the invention of new technologies that will help researchers produce real-time pictures of complex neural circuits and visualize the rapid-fire interactions of thousands of cells that occur at the speed of thought.

Although this initiative will advance all medical disciplines that involve the brain, psychiatry is likely to be its biggest beneficiary. This is because mental disorders are "connectopathies" with complex pathologic mechanisms that apply at the level of circuits and their communication, and this level is the intended focus of the BRAIN Initiative (2). Neurological disorders leave their marks on the macroscopic structures of the brain, where we can see physical brain lesions after stroke or devastating shrinking and degeneration of neurons in Alzheimer's disease, Huntington's disease, or Parkinson's disease. By contrast, mental illness does not leave pathological footprints that clinicians and scientists can easily detect. There may be changes in brain structure in the progression of mental illness, but the pathogeneses of mental disorders are insidious and developmental, and their pathology subtle, distributed, and complex.

Mental disorders are, fundamentally, disorders of the brain in action, and only by observing the brain in action will we find their signatures and unravel their secrets. However, while current methods for observing human brain activity, such as functional magnetic resonance imaging (fMRI) can monitor the entire brain, they have low temporal and spatial resolution—a satellite view (3). Other modern methods can track the activity of individual nerve cells. But the neurobiological basis of a thought, emotion, or memory is not a single neuron, or an fMRI "voxel," but rather a network of many nerve cells that interact with each other, locally and throughout the brain. The BRAIN Initiative's goal is to develop and apply technologies to observe, understand, and modify these complex, distributed patterns of activity. We must do more than simply observe activity; we must know which cells are active, how they are connected to each other, which activity patterns are causal to behavior, and the quantitative logic of neural systems.

There are many questions to answer in mental illness: What cell types are functionally altered? Are common circuits altered in the same way by different genetic and environmental risk factors for psychiatric disorders? Can we relate these circuit changes to the circuits that communicate by neurotransmitters, such as serotonin, glutamate, norepinephrine, and dopamine, that are targeted by most psychotropic drugs? In psychiatric disorders that wax and wane, or cycle like bipolar illness, what patterns of brain activity mark the different stages of the illness? Can we develop signatures of those states? Can states of disturbed mental activity be stabilized with cognitive therapy, medications, or neuromodulatory or electroceutical interventions such as transcranial magnetic stimulation and deep brain stimulation? In what way do psychotherapies, such as cognitive-behavioral therapy, alter activity patterns and/or plasticity in the brain?

The neurobiological basis of a thought, emotion, or memory is not a single neuron, or an fMRI "voxel."

The BRAIN Initiative includes multiple collaborating federal agencies and private research foundations. Francis Collins, Director of the National Institutes of Health, appointed an advisory committee, co-chaired by Dr. Bargmann and William Newsome of Stanford University, of 15 neuroscientists from around the country with expertise in molecular, cellular, and systems neuroscience but also with expertise in physics, chemistry, and engineering. Among its members are scientists at the frontiers of human brain imaging, human intraoperative brain research, brain-computer interfaces, and (of course) a psychiatrist, Karl Deisseroth. Deisseroth is a psychiatrist and biomedical engineer at Stanford University, who has developed innovative optical technologies to characterize brain structure, synapse and circuit formation, and its applications to the study of neuropsychiatric illnesses.

To jumpstart the initiative, NIH Director Collins requested an interim report from the committee, to guide the allocation of the $4.5 billion in new federal funding that was requested over 10 years, beginning in fiscal year 2016, to support the initiative. Of the areas identified as key priorities for the BRAIN Initiative (http://www.nih.gov/science/brain/2025/index.htm), some entail research primarily in animal models, but the final two are specifically targeted to research in human beings, including persons who have mental illnesses:

> **Advancing human neuroscience: Develop innovative technologies to understand the human brain and treat its disorders; create and support integrated human brain research networks.** Consenting 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.
>
> **From BRAIN Initiative to the brain: Integrate new technological and conceptual approaches to discover how dynamic patterns of neural activity are transformed into cognition, emotion, perception, and action in health and disease.** The most important outcome of the BRAIN Initiative will be a comprehensive, mechanistic understanding of mental function that emerges from synergistic application of the new technologies and conceptual structures developed under the BRAIN Initiative.

The goals of the BRAIN Initiative are to measure the fluctuating patterns of electrical and chemical activity flowing within the cells and circuits of the brain over time and space and to understand how their interplay creates our unique mental and behavioral activities. Dramatic advances in molecular genetics, optogenetics, optical physics, engineering, and computing over the past decade have put these goals within our sights if not our reach, but all of these technologies must become much more powerful to achieve these goals. The BRAIN Initiative has a technology bent, but its purpose is not technology per se, but rather the development of technologies for their application to study important problems in basic and translational neuroscience that will ultimately enhance our understanding of, and ability to treat, human disease. This emphasis on more powerful instruments and technology may mean more to psychiatrists, and ultimately persons with mental illness, than any other medical discipline.

References

1. Lichtman JW, Denk W: The big and the small: challenges of imaging the brain's circuits. Science 2011; 334:618–623
2. Morgan JL, Lichtman JW: Why not connectomics? Nat Methods 2013; 10:494–500
3. Lichtman JW, Sanes JR: Ome sweet ome: what can the genome tell us about the connectome? Curr Opin Neurobiol 2008; 18:346–353

CORNELIA I. BARGMANN, PH.D.
JEFFREY A. LIEBERMAN, M.D.

From the Lulu and Anthony Wang Laboratory of Neural Circuits and Behavior, Rockefeller University, New York; the Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York; the Department of Psychiatry, New York Presbyterian Hospital–Columbia University Medical Center, New York; and the New York State Psychiatric Institute, New York. Dr. Bargmann is co-chairperson of the BRAIN Initiative advisory committee; Dr. Lieberman is immediate past President of APA. Address correspondence to Dr. Lieberman (jlieberman@columbia.edu). *Commentary accepted for publication August 2014 (doi: 10.1176/appi.ajp.2014.14081029).*

Dr. Bargmann reports no financial relationships with commercial interests. Dr. Lieberman serves on the Advisory Board of EnVivo and Intracellular Therapies and does not receive direct financial compensation or salary support for his participation; receives grant support from Biomarin, EnVivo, Genentech, Novartis, Psychogenics, and Sunovion; is a member of the Advisory Board of Pear Therapeutics and holds a financial interest; and holds a patent from Repligen. Dr. Freedman has reviewed this commentary and found no evidence of influence from these relationships.