Testimony of
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Oversight Hearing on the Department of Energy's Role in Advancing Biomedical Sciences

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Chairwoman Kaptur, Ranking Member Simpson, and Members of the Subcommittee, thank you for the invitation to appear before you today to discuss the critical role that the U.S. Department of Energy (DOE) plays in developing innovative healthcare technologies and how collaborations between the DOE and the National Institutes of Health (NIH) can:

1. Transform future lifesaving therapies particularly in the area of mental illness
2. Ensure U.S. leadership for decades in not only neuroscience, but in artificial intelligence and energy; and
3. Inspire a new generation of scientists working at the interface of brains, algorithms, and big data.

My name is Bobby Kasthuri and I am an assistant professor in the Department of Neurobiology at the University of Chicago and the only neuroscience researcher at DOE's Argonne National Laboratory. I have these jobs for the same reason I am here today. Almost two decades ago, I started a quest to fundamentally understand and treat mental illness. I began medical school at Washington University in St. Louis ready to tackle the enormous burden of mental illness, which I had witnessed firsthand. However, I quickly found that the neurologists, neuroscientists and psychiatrists I encountered in medical school were brilliant, but our therapies and treatments for the brain lagged far behind our treatments of other organs like the heart or the kidney. The fundamental gap was that we did not really understand the normal brain, and therefore, we could never really cure the pathological brain. So I formed a new goal, to transform how we understood the normal brain in order to transform how we treat the pathological brain. In my testimony, I will explain how the DOE and the unique expertise and capabilities within the DOE National Laboratories is critical to this mission.

The Century of the Brain

Scientists began and ended the great scientific challenge of the 20th century—understanding the genetic basis of life—by creating two maps: one of the atomic structure of DNA in 1953, and another of every nucleotide in a human genome in 2003. That science, enabled by biologist James Watson and physicist Francis Crick and the Human Genome Project, is revolutionizing our understanding of the genetic bases of human health and disease, creating new industries, and inspiring a generation to genetics and bio-informatics. The DOE was critically involved in the earliest days of the Human Genome Project, developing the technology to read out the genetic code and providing the computing for, what was considered astronomical at the time, the resulting gigabytes of data. Considered one of the first and most successful big data and healthcare collaborations ever, this project is an example of how the DOE, and by extension, the DOE National Laboratories, are uniquely suited to play a similar role in the great challenge of the 21st century: understanding the human brain.

A similar revolution awaits us when we understand how human brains acquire knowledge from experience—how we find patterns in our senses and use them to plan and act. When we know exactly how those processes work, we can connect prosthetic limbs to the paralyzed, design rational medical treatments for brain disease, and reverse-engineer human cognition into our supercomputers, with increased energy efficiency.

The medical ramifications alone are tremendous:

- The National Alliance on Mental Illness (NAMI) indicates that approximately 1 in 5 adults in the United States—43.8 million people—experiences mental illness in a given year, resulting in nearly $200 billion in lost earnings annually.

- The Alzheimer's Association reports that an estimated 5.7 million Americans of all ages are living with the disease; it is currently the sixth leading cause of death in the United States. In 2018, Alzheimer's and other dementias will cost the nation $277 billion, with costs rising as high as $1.1 trillion by 2050.

- The Centers for Disease Control and Prevention report that 1 in 59 children have autism-spectrum disorders that cause mild to severe social challenges and communication difficulties, as well as physical and medical issues.

The Biggest Dataset Ever

Given the enormous benefits a better understanding of brains could provide, one could ask why we have not made more progress. Part of the problem is the sheer complexity of the human brain. The human brain contains around 100 billion cells, or neurons, which make thousands of connections with each other called synapses. The complexity of this intricate communication web cannot be overstated. Parts of our nervous system beyond our brain, some just mere atoms wide, extend from foot to spine. The quest to understand how the brain works requires more cooperation across academic disciplines than any other human endeavor.

The good news is that we have defined the underlying hardware, so to speak. Every nervous system is based on the same principle—all representations, computations and actions mediated by the brain depend on neurons that are connected by synapses in highly complicated directional networks. Each neuron receives information from synapses that affect its dendrites (branches) and sends information via its axon, which connects to dendrites of other neurons. One neuron might receive thousands of separate messages and convey the integrated information to thousands of other neurons.

You can picture each neuron as a hub that sends and receives signals to and from many thousands of other neurons. Neuroscientists propose that the map of how those 100 billion neurons make 1 quadrillion connections with each other, what we call the “connectome,” is a map of everything about you: your skills, your memories, your fears, and your personality. Disruptions or alterations in these maps—“mis-wirings” between neurons—are the basis of many neurological and psychiatric disorders. The raw data for the “Atlas of Human Connections” (i.e. the human connectome) would require approximately 1 trillion gigabytes (an exabyte) and could not fit in the memory of any current computer. By way of comparison, the entire Human Genome Project requires only a few gigabytes and all the written material in the Library of Congress, all the movies and audio that humans have produced since the dawn of civilization equate to a small fraction of the data in the human connectome.

We believe that the payoff these maps will provide for neuroscience will be enormous. Many neuroscientists understand that the fundamental unit of organization of neural tissue is the synaptic connections linking neurons together. Neurons in various mammalian species seem quite similar, despite the obvious differences in behavior. The ‘magic' that makes one species different from another is in how these very similar neurons connect with each other. For humans, these maps would have special significance because an “Atlas of Connections” would represent a blueprint of ourselves, including imprints of all those things that are not in our genome, such as all the things we have learned throughout our lives. In addition, it is possible that many neurological disorders, such as the Autism spectrum disorders or schizophrenia, may be the result of misrouting of neuronal wires. Detailing these ‘connectopathies' may provide insights into the underlying abnormalities in what are presently quite mysterious cognitive illnesses. Finally, as with all first glimpses into aspects of the natural world previously hidden, we imagine that a considerable number of surprises await us. For example, we do not fully understand how much the pattern of connections in one brain resembles the pattern in another. Are there deep organizing principles behind the ordering of our brains, or is each brain fundamentally unique? We predict that this effort will span many decades and just as the Hubble Telescope peers into a mysterious outer space, this effort will provide the first deep look into the inner space of our minds.

The “Mind-Meld” Between Computer Science and Neuroscience

In the quest to understand the brain, one of the most important scientific collaborations is the “mind meld” between computer science and neuroscience. Given the complexity of the brain that I just described, no matter how neuroscientists analyze the brain—whether we use laser beams, genetic engineering, fluorescent proteins, pharmaceuticals, virtual reality, metamaterials or robotics—tremendous computing power and big data will always be a necessity. For these reasons, the DOE and the resources within its national laboratories are critical.

Scientists, including those at Argonne National Laboratory and the University of Chicago, and collaborators around the United States, are already working toward a human connectome by mapping smaller brains of other animals, such as mice. To create even the smallest neural map, teams of neuroscientists and computer scientists must work side by side, using the latest artificial intelligence technology, to analyze the enormous brain datasets. Interestingly, we have discovered that although this collaboration clearly furthers neuroscience, this work is mutually beneficial to advancing computer science as well.

First, it turns out that problems to which computer scientists are eager to apply artificial intelligence—understanding pedestrian behavior to ensure the safe operation of a self-driving car or automatically interpreting changes in satellite images over time for strategic intelligence—involve the rapid analysis of large datasets at the same scales sought by neuroscientists. The only difference is that brain datasets are already orders of magnitude larger than any datasets humans have ever collected and are guaranteed to grow even larger. Deciphering the human brain by creating a new generation of artificial intelligence that is capable of analyzing the largest datasets ever created will inevitably aid every other field of human endeavor that struggles with big data.

Second, and perhaps even more importantly, understanding the brain more deeply could lead to a revolution in computing. Even as they herald recent gains in the computational abilities of artificial neural networks, computer scientists remain concerned that conventional approaches will soon plateau in performance. Almost every human brain possesses fundamental skills that even the most sophisticated algorithms do not: reasoning, humor, learning, and creativity. If we can find the physical basis of these abilities in the brain, we can transform the landscape of computing.

Increasing Collaborations between the Neuroscience Community and DOE National Laboratories

Although neuroscientists and computer scientists are making remarkable progress, an unfortunate reality still prevents us from fully understanding the human brain and leveraging these discoveries for society—that is, most neuroscientists lack access to the tools and resources needed to test their ideas about the brain. The enduring success of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative—a public-private collaborative effort aimed at developing new experimental tools to revolutionize the understanding of the brain—will depend on widespread access to the technological advancements, computational tools and datasets the initiative creates.

However, there are no existing mechanisms for providing national access to the increasingly technologically and computationally oriented investigations of the brain. Researchers encounter both financial and structural barriers to entry. Not only is technologically intensive neuroscience costly, it also requires investments in physics, engineering, and computer science, which are often beyond the scope of a single university or institute. Consequently, the neuroscience community is unable to efficiently utilize current technological capabilities, limiting the types of questions and hypotheses we can test to drive the next generation of innovation. We must counteract the widening gap between the small fraction of laboratories utilizing the most recent technology and the remaining majority of neuroscientists. A sophisticated national clearinghouse will ensure that the physics, engineering, and computer science are vetted and freely accessible to measure brain structure and functions.

The DOE National Laboratories are uniquely suited to convene leading researchers across the various scientific disciplines to overcome these barriers. At the forefront of discovery and innovation in fundamental sciences, the Laboratories are stewards of large-scale scientific user facilities, including light sources, accelerators, and supercomputers that support advancements in a range of disciplines from astrophysics to chemistry to material science. Given these unique capabilities increased collaboration between the DOE National Laboratories and the neuroscience community could further accelerate brain research. In a September 22, 2016 Task Force on Biomedical Sciences report, the Secretary of Energy Advisory Board (SEAB) noted the importance of DOE involvement and the expertise that resides within the Department's laboratories:

> *"Brain research is supported across many institutes of the NIH, but the opportunities for DOE involvement is perhaps most effective in the context of the recent BRAIN Initiative. This collaborative, public-private research initiative started a concerted effort to improve the methods available for brain research, both for experimental work and in the domain of theory and analysis. The ultimate goal is to understand pending questions of large circuits of nerve cells: What are all the types of neurons involved? What is the structure and connectivity of the circuit? What are the signals flowing through the circuit? How do these circuit functions relate to behavior and cognition? DOE laboratories clearly have expertise that relates to these goals."*

The Mouse Connectome Project

In order to advance the collaboration between DOE and NIH, a "moon-shot" approach is needed to accelerate progress in this area. This coordinated approach could derive the complete synapse-level wiring diagram (i.e., connectome) of a mouse's brain. The project will generate a dataset nearly a thousand times larger than any previous biology project, equivalent in size to 1.38 billion human genomes. Success will require harnessing advanced technologies in imaging, computation and biology. It will require a team of expert personnel from academic, data science, governmental and industrial entities forged into a close working partnership. It is a project that only DOE and NIH could successfully complete together and the resulting datasets will benefit scientists from throughout the U.S. The infrastructure we build to create that dataset will be used by neuroscientist throughout the country to develop new ideas about how brains work.

Creating the next generation of AI and neuroscience leaders

In 1962 at Rice University, Texas, President John F. Kennedy announced that the United States would put a man on the moon before any other nation. Seven years later, Neil Armstrong walked on the face of the moon. While some may say that the endeavor was a failure—where are moon bases now?—it is worth noting that at the time of the landing, the average age of a NASA scientist was 29 years old. Seven years earlier, at the time of Kennedy's announcement, these scientists were college students seeking inspiration. The "moon shot" changed their lives and focused their passion so that they could change society in innumerable ways. It is no surprise or coincidence that many of the leaders in artificial intelligence, like Yann LeCun and Geoff Hinton, where once students seeking inspiration for the next wave of artificial intelligence from the architecture of the brain. If we seize the opportunity for a national moon shot for the mouse connectome, we will inspire the next generation of students working at the intersection of brain science, computer science and big data. We will lead the world in training the next generation of computer scientists who penetrate the boundaries between biology and computation, and create the next generation of computers and robots based on the brain, transforming our society and assuring U.S. leadership in these vital areas for the future.

Leveraging World-Class DOE National Laboratory Facilities to Advance Neuroscience Research

The state-of-the-art user facilities across the DOE National Lab complex like Argonne National Laboratory's Leadership Computing Facility (ALCF), Advanced Photon Source (APS) light beam and Center for Nanoscale Materials, are helping develop biomedical breakthroughs to solve some of humanity's most intractable healthcare challenges.

The imaging technologies and advanced data-analysis techniques available through ALCF and the APS enable me to map the intricacies of brain function at the deepest levels and describe these processes in greater detail than ever before. These tools will be even more powerful in the future. The upgrade to the APS will create the ultimate 3-D microscope, producing the world's brightest hard X-rays and transforming our ability to understand and manipulate matter—including brains—at the nanoscale.

These world-class user facilities—particularly when leveraged together—are and will continue to be critical to my efforts. For example, current recording and imaging methods can sample only a limited number of neurons or limited brain volumes, which constrains neuroscientific discovery. However, when data from imaging facilities like the APS is later modeled, simulated and analyzed on a DOE supercomputer, neuroscientists can image and analyze every cell and blood vessel in a series of complete mammalian brains. Using one of world's fastest supercomputers – located at Argonne—I can quickly and efficiently analyze the millions of gigabytes of data this will produce. Imagine the game-changing possibilities of a resource where neuroscientists around the U.S., and ultimately around the world, utilize such technologies and infrastructure.

Every day, Argonne researchers are working with pharmaceutical companies on drug discovery and precision medicine, as well as the manufacturing of healthcare devices and wearables, all of which intersect with the NIH. DOE and NIH can, and should, continue to work together to solve these challenges. Present generation machines, like those that we have at Argonne, can get us part of the way there. With the support of DOE, Argonne is building the new machines that will move us much father along toward understanding the brain and the goal of curing mental illness.

Maintaining U.S. Leadership in Neuroscience

Continued and increased federal support is critical to maintain U.S. leadership in neuroscience. American competitiveness depends on our capacity to achieve pivotal discoveries, lead the research and development community, and apply our most powerful scientific tools and facilities. Remarkable healthcare and technological breakthroughs are possible with advances in biomedical science. The National Laboratories, working together with DOE and NIH, can accelerate our understanding of the brain and thus develop better treatments for the millions of people worldwide affected by neurological disorders. More importantly, they can together achieve generational science, removing boundaries between fields of science and creating transformative moments that shape society for generations to come.

A Team of Scientists Dedicated to Neuroscience

Finally, I would like to acknowledge the small group of dedicated scientists working throughout the United States and the world who have dedicated their time and effort to mapping brains at the finest scale. It is their work that makes this potential collaboration between the DOE and NIH possible.

Jeff Lichtman, Harvard University; Viren Jain, Google; Sebastian Seung, Princeton University; Gerry Rubin, Janelia Farms, Howard Hughes Medical Institute; R. Clay Reid, Allen Institute for Brain Science; David Tank, Princeton University; Kristen Harris, University of Texas- Austin; T Winfried Denk, Max Planck Institute, Germany; and Joshua Vogelstein, Johns Hopkins University. The testimony above is the direct result of many conversations I have had with them and my readings and extensive quoting of white papers, grant applications, and papers by the scientists above.

Thank you again for the opportunity to be here today to discuss these issues. I look forward to any questions that you may have.