Medical Xpress

Prying open the black box of the brain

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BRAIN is designed to finally reveal how the brain records, process, uses, stores, and retrieves vast volumes of information, all at the speed of thought. Credit: Thinkstock

The human brain is the most complex biological structure on Earth. It has about 100 billion neurons—each of which has thousands of connections to other neurons.

Moreover, brains change with time for a variety of reasons. For example, as we age, our brains lose nerve cells (neurons). In addition, the wiring of our brains is continually altered as we learn, socialize, undergo stress and encounter varied environmental conditions. That's right: Our brains are anatomically and physiologically changed by normal intellectual and physical experiences.

So each of us—continually subjected to new and different brain -changing experiences—has a unique brain. In fact, even the brains of identical twins differ from one another. What's more, brain injuries may trigger various types of changes in the anatomy and physiology of the brain to compensate for lost function and/or maximize remaining functions.

Largely because the brain is so complex and dynamic, it is still akin to a locked black box—three pounds of mystery lodged between our ears. Indeed, our understanding of the brain remains downright rudimentary compared to our understanding of other organs.

Desperately seeking a theory

Despite major technological advances in brain research during recent decades, scientists have yet to describe all of the various types of cells that comprise the brain and determine their functions. Complicating matters further, the brain is more than the sum of its parts. That is, the various components of the brain do not operate in isolation from one another; they must communicate with one another and work together to process information and produce memories, thoughts and behaviors.

But scientists still don't understand how information is processed in any organism, whether it be a lowly worm whose nervous system is comprised of only a few hundred neurons or a complex vertebrate. We simply do not know what happens in the brain when an organism thinks, maneuvers through the world, takes in sensory information or sleeps.

In other words, scientists lack a basic, overarching theory about healthy brain function that would explain how memories, thoughts and behaviors emerge from dynamic activities in the brain—any brain.

This theoretical vacuum has persisted even though molecular, cellular and neuronal activities in the brains of many species have been well studied, as has behavior in many species, including humans. Nevertheless, the relationships between these two types of phenomena and the sequence of events that translates one to the other remain mysterious.

By providing a framework for predicting how micro events in the brain produce behaviors, and vice-versa, a theory of healthy brain function would contribute as much to neuroscience as the theory of evolution contributes to the tree of life, the theory of plate tectonics contributes to geology and the theory of relativity contributes to cosmology.

But still unable to explain how a normal brain functions, scientists cannot yet explain how traumatic injuries and brain diseases, such as Alzheimer's, schizophrenia, autism, and epilepsy impair function. Nor can they determine how brain injuries and diseases should be treated. By comparison, imagine a mechanic trying to fix a car's engine without a parts list and/or understanding how it runs!

It is even difficult for scientists to so much as agree on which neurological variables should be studied. Such disagreement, however, would probably be reduced by a viable theory of healthy brain function because it would likely reveal particularly promising areas of future research. It could do so by, for example, helping scientists identify important neuronal nodes that warrant more attention than do thickets of rank-and-file neurons.

The new BRAIN Initiative

Responding to the need for a comprehensive understanding of the brain, President Obama launched the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative on April 2, 2013. Led by the National Science Foundation (NSF), the National Institutes of

Health (NIH) and the Defense Advanced Research Projects Agency (DARPA), BRAIN is a bold new research effort.

Extending beyond mere mapping of the brain, the BRAIN initiative is aimed at producing an array of tools that are needed to establish an integrated theory of how the healthy brain functions over an organism's life. This theory will provide a fundamental framework for interpreting new information on brain science and will change existing paradigms for explaining "who we are."

"When scientists do ultimately figure out how the brain works—however long it takes, this accomplishment will probably be considered the greatest scientific achievement in all of human history," said John Wingfield, NSF's Assistant Director for the Biological Sciences.

NSF'S role in BRAIN

Brain processes are multidisciplinary phenomena, incorporating the principles of biology, chemistry, physics, engineering and mathematics. Therefore, efforts to understand these processes under BRAIN require multidisciplinary approaches. "The kinds of challenges we are facing in the study of neuroscience require contributions from a wide range of scientific and engineering disciplines," said Denise Caldwell, NSF's division director for Physics.

Needed basic research: Examples of the types of multidisciplinary advancements that are needed to advance BRAIN include:

- Basic studies conducted by biologists, in collaboration with physicists, chemists, mathematicians and engineers, on the healthy functioning of the nervous systems of many types of species, from those with simple nervous systems to complex vertebrates—not just on humans and organisms that have

traditionally served as model organisms in brain studies. Such studies would be based on a species comparative approach.
- Theoretical and computational models created by physicists, mathematicians and computer scientists that will help reveal and predict complex neural activities in the healthy brain that drive thoughts and behavior.
- New materials developed by materials scientists and engineers that are needed to create innovative types of brain probes that can be used to monitor and manipulate the brain.
- Optical and electrical tools developed by physicists and engineers to better image the brain and brain activity.

NSF's key contributions: NSF is uniquely positioned to foster these and other types of needed innovations because the agency supports basic research across the scientific and engineering disciplines. What's more, NSF has already helped lay the groundwork for BRAIN by supporting many game-changing innovations in brain research, including the development of the following:

- Optogenetics: A bioengeering technique that enables scientists to selectively turn on and off particular neurons and neuronal circuits in living organisms so that resulting behavioral changes can be observed in real time. Optogenetics is currently being used to help identify the functions of neurons and neuronal circuits and to help identify appropriate targets for drugs or technologies that address brain dysfunction. (See an NSF article about the contributions of optogenetics to research on Parkinson's disease and an NSF article on its contributions to research on anxiety.)

  A crucial prerequisite to the development of optogenetics was a discovery that was produced by research on a seemingly unrelated topic: algae. Specifically, this research identified the presence and molecular structure of light-sensitive proteins in algae. Turned on by light, these proteins help algae find light that is needed by the algae to produce energy through photosynthesis.

After the light-sensitive algae proteins were discovered, brain researchers found that they could impart the brain neurons and neuronal circuits of various species with light sensitivity by inserting into them the light-sensitive algae proteins. Once made light sensitive, the neurons and circuits could be turned on merely by shining a light on them, and turned off by other types of simple light manipulations.

The basics of optogenetics were thus developed. This pivotal application of algae research to neuroscience underscores the importance to BRAIN of NSF-funded basic research—including basic research in seemingly far-flung disciplines.

- CLARITY: A new brain imaging technology, announced on April 10, 2013, that can be used to generate detailed, three-dimensional images of intact brains that highlight specific neuronal networks. These images can be produced without slicing the brain and disrupting its biochemistry, as previously required.

Potential applications of NSF-funded BRAIN research

By supporting additional multidisciplinary research under BRAIN, NSF will help produce a deep foundation of fundamental information of healthy brain function. This foundation will help reveal "how the car is designed, rather than just how it might be fixed." It may thereby open up entirely new avenues for NIH's research on brain diseases and DARPA's research on traumatic brain injuries.

This foundation may also offer applications to important issues that are unrelated to health. For example, this research may help explain differences in individual learning styles, reveal the origins of cultural mores, and provide insights into what makes people "tick" as individuals. It may also inspire the development of new "smart" technologies that mimic the information processing capabilities of the human brain.

NSF-funded BRAIN research may also help improve resource management. For example, this research may help scientists identify environmental conditions that promote the development of the nervous systems and metabolic systems of animals, such as fish and livestock. Resulting insights may help resource managers design aquaculture and livestock facilities to maximize the growth and productivity of their animals.

Brain studies may also help scientists figure out why many species of endangered vertebrates do not reproduce well in captivity—and explain why some species easily adapt to climate change, while other, closely related species cannot do so.

"We think that these [and other] phenomena are related to how an organism perceives its environment, which, in turn, is related to its brain function," said Wingfield. "Therefore, advancements in our basic understanding of the brain may have important implications for conservation and—by extension—our quality of life."

The kick-off of BRAIN: A meeting of the minds

NSF set the stage for producing such advancements by sponsoring the first BRAIN event: A workshop called, physicsoflivingsystems.org/bra

… tructureandfunction/">*Physical and Mathematical Principles of Brain Structure and Function*, which was held in Arlington, Va., on May 6 and 7, 2013.

The workshop drew 150 leading researchers from varied disciplines including physics, mathematics, and neurobiology. These researchers represented more than 60 institutions including NIH, DARPA, and other federal agencies; research institutions; academic journals; and the private sector.

Good timing: *Physical and Mathematical Principles of Brain Structure and Function* was fortuitously timed to tap into the sense of possibility generated by the coincidental release of CLARITY just weeks before the conference began, and by the recent development of optogenetics and various other new technologies for creating high-resolution images of brains with electron microscopes and for recording electrical impulses from brains.

"This conference was particularly timely because the community has realized that technologies for brain research have advanced to the point where we can now make a real leap in knowledge," said Caldwell.

Discussions about salient past and future multidisciplinary contributions to neuroscience also helped to generate an air of excitement, esprit de corps and sense of purpose at the workshop.

Developing research priorities: Various workshop activities, including presentations, break-out sessions and an invitation to participants to submit white papers, were designed to solicit input from participants on technical topics. These topics included important challenges in brain research, the types of computational approaches and tools that are most needed for advancing brain research, best practices for integrating data to produce knowledge, and methods for methods for incentivizing multidisciplinary brain research.

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The workshop culminated with the development of consensus by participants on the following priorities for future neuroscience research:

- Identifying signatures in neural activity that can be used to predict complex behaviors. These signatures may be identified through studies involving large-scale recordings from representative sets of neurons in multiple species and through high-resolution studies of neuro-anatomy in many species.
- Developing theoretical and computational models that can be used to understand and analyze data produced by large-scale neural recordings.
- Promoting unprecedented levels of international sharing of data on brain research and education. Doing so will involve developing standardized cyber tools and standards for data collection, analysis and integration—tasks that require solving complex "Big Data" problems.

"This initial set of over-arching priorities will set the stage for future detailed quantitative research," said Caldwell. "Results from this future research will drive advances in theoretical understanding that will, over the coming years, bring scientists closer to achieving the ultimate goal of understanding how the brain works and using this understanding to benefit human health."

More information: physicsoflivingsystems.org/

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