NEUROSCIENCE

It takes the world to understand the brain

International brain projects discuss how to coordinate efforts

By **Z. Josh Huang**[1] *and* **Liqun Luo**[2]

We are on the verge of a fundamental leap toward understanding the human brain, and the implications for health and society are profound. Large-scale brain projects have been launched or are being planned in multiple continents and countries (*1–4*). In June, about 50 leading scientists from the United States, Europe, Japan, Korea, and China gathered in Suzhou, China (organized by Cold Spring Harbor Asia) to discuss the opportunities and challenges in brain research (*5*). The benefits of international coordination and collaboration were recognized, and the discussions laid a foundation for future meetings aimed at fleshing out details related to specific goals.

COMPLEXITY. The human brain is arguably the most complex entity in the known universe, and this complexity is best reflected by the fact that the brain strives to understand itself—how its molecules, cells, circuits, and systems enable perception, cognition, memory, emotion, thought, language, art, and contemplation of humanity's place in the natural world. Inquiry into the origins of mental faculties and disorders in the brain dates back to antiquity (*6*). Since the formulation of the neuron doctrine and detailed structural studies by Ramón y Cajal more than a century ago (*7*), there has been great progress in understanding the cellular basis of brain organization and function. In the past decade, technological advances in multiple disciplines have accelerated that progress. New tools for visualizing, recording, and manipulating neurons and neural circuits are enabling deeper insight into how the brain processes information and guides behavior. Advances in computer science have exponentially boosted the capacity for analyzing, curating, and sharing enormous data sets. And genome-wide mapping has identified genetic variants that contribute to a wide spectrum of human brain disorders.

To better appreciate the challenges of understanding the brain, it is informative to compare the brain projects with the first large-scale international bioscience collaboration launched in late 1980s—the Human Genome Project. The Human Genome Project aimed to determine the complete sequence of the human genetic blueprint encrypted in ~3 billion nucleotides organized along 23 chromosomes. The genome is a largely static linear sequence composed of just four discrete nucleotides; the ~20,500 protein-encoding genes constitute 1 to 2% of this sequence. The project provided the foundation for an explosion of biomedical research.

Brain projects summary

BRAIN PROJECTS	MAJOR GOALS AND FOCUS
U.S. BRAIN Initiative	•Tools to enable a brain cell census and for recording/modulating brain circuit activity linked to behavior •Multilevel brain data •New computational models and theory
Japan Brain/MINDS	•Nonhuman primate brain •Collaboration between clinicians and researchers toward knowledge-based diagnosis and treatment of brain disorders
Europe HBP (Human Brain Project)	•Big data integration and analysis •Computational modeling
Allen Institute for Brain Science	•Mouse visual system •Human cortex •Open, public, shared database and tools
Korea Brain Project	•Systems neuroscience of cognition and brain disorders •Neural circuits and brain imaging
China Brain Science Project (in planning)	•Neural circuitry of cognition •Brain disorders •Brain-inspired intelligence technologies
Brain Canada	•Increased brain research funding •Collaboration related to brain disorders
Taiwan	•Neurodegeneration •Chronic pain
Australia	•Collaboration with U.S. BRAIN

The human brain can be considered vastly more complex in multiple aspects. It contains ~10^{11} neurons, linked by ~10^{14} synaptic connections. As any one neuron on average receives inputs from, and delivers outputs to, thousands of other neurons distributed over local and distant brain space, delineating the wiring diagram of these neurons (the connectome) alone is an immense challenge. Moreover, the connectome is not a static network; both the connectivity pattern and connection strengths change across life stages and are modified by an individual's experience and learning. Furthermore, mapping the connectome is only one step toward understanding the brain—it is the dynamic firing of neuronal ensembles and their communication across local and global networks, which are layered onto the structural framework of the connectome, that generate perception, cognition, and action.

SIX FRONTS. Neuroscientists largely agree that to achieve a deep understanding of how the brain processes information and orchestrates mental functions, substantial progress is needed on at least six fronts: (i) identifying the basic components of brain circuits—classes of neurons that share similar properties and perform similar functions (belong to the same cell types); (ii) deciphering the neuronal wiring diagrams integrated across multiple scales, from individual synapses (microscopic) to the entire brain (macroscopic); (iii) recording the firing patterns—the common vocabulary of neuronal communication—of large numbers of neurons across different brain regions while an animal or human subject performs well-characterized behavioral or cognitive tasks; (iv) manipulating neuronal firing patterns with spatiotemporal precision so as to establish the causality between neuronal activity and circuit function that contributes to behavior; (v) inventing computational tools for integrating and analyzing large and complex data sets; and (vi) formulating overarching brain theories that transcend levels and scales, conceptualize experimental findings, and predict novel circuit properties that underlie brain function. In addition, because most experiments are performed in animal models, knowledge gleaned from animal experiments must be integrated with insights gained from recording,

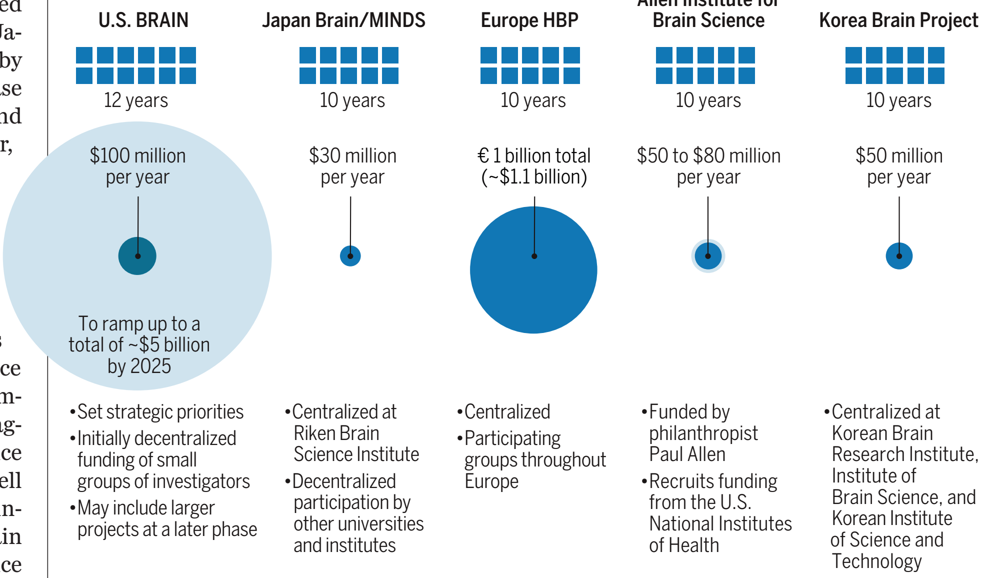
---

[1] Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA. [2] HHMI/Department of Biology, Stanford University, Stanford, CA 94305, USA. E-mail: huangj@cshl.edu; lluo@stanford.edu

stimulating, and imaging the human brain to understand human mental functions and to treat brain disorders.

OVERVIEW OF PROJECTS. The current brain projects launched or planned in different countries have different emphases (see the table and figure). The U.S. BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative is now in the second year of a 12-year plan. Its initial phase emphasizes developing new tools that are expected to catalyze discoveries in later phases about neural circuit function in health and disease (*1*, *2*). The European Union's Human Brain Project (*3*), started in 2013 and financed by the Future Emerging Technologies Program of the European Community, focuses on large-scale computational modeling and building neuroinformatics standards for brain databases, and could benefit from data acquired from brain projects around the globe. Japan's Brain/MINDS (Brain Mapping by Integrated Neurotechnologies for Disease Studies) project (*4*), launched at the end of 2014, features primates—in particular, the marmoset, a relatively new genetic primate model—for basic research and for modeling human brain disorders. Brain Canada was announced this year, supporting collaborative, multidisciplinary, multi-institutional neuroscience research. Korea also just started its brain project on the systems neuroscience of cognition and brain disorders, with emphasis on neural circuits and brain imaging. China has yet to officially announce its brain project, but discussions are well under way, and its scope will likely include neural circuits of cognition, brain disorders, and brain-inspired intelligence technologies. Nonhuman primate studies including the macaque monkey, a long-standing model for neuroscience research, are likely to be part of China's brain project. Taiwan is planning a modest-scale brain project on neurodegeneration and chronic pain, with emphasis on interdisciplinary studies and development of novel neurotechnologies. This year, Australia established a collaborative effort with the U.S. BRAIN Initiative. In addition to these government-funded brain projects, the Seattle-based, privately funded Allen Institute for Brain Science launched a 10-year brain circuit project that intends to create a system of publicly shared data and tools to study mouse and human visual systems.

Funding characteristics



GRAPHIC: C. SMITH/SCIENCE

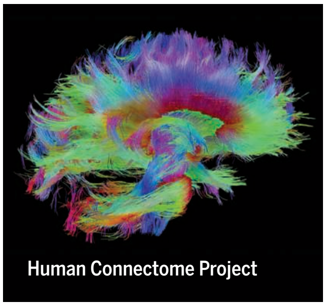
STANDARDIZATION. No single country or brain project alone is equipped with the collective intellectual, technological, financial, and human power needed to achieve the task of understanding the brain. The Suzhou discussions identified several areas where the needs for international coordination are particularly acute but likely to be high-yielding if particular strengths of the different brain projects are leveraged and standardization is implemented.

Take the problem of cell type as an example. The brain consists of a large diversity of nerve cell types that serve as working units of widely distributed neural networks. Systematic identification and classification of this parts list is a prerequisite to mapping the wiring diagram, recording and manipulating cell type–specific activity, and deciphering circuit operations that underlie information processing and behavior. The recent convergence of neural developmental studies from invertebrates to mammals, as well as genetic and genomic technologies, has made it possible to systematically identify distinct cell types. Single-cell transcriptome profiling (quantitative determination of the expression levels of all genes) promises to refine cell type definition and enhance precision of genetic access to individual cell types (using genetic tools to label, record, and manipulate activity in a cell type–specific manner). Thus, the cell type problem is fundamental and challenging, yet well-defined and solvable by leveraging the collective power of individual brain projects.

What should be standardized in this context? Cell transcriptomes can be acquired with a defined format, deposited into a common database, and analyzed similarly to the genome data. Data sets on cell location, morphology, and projection patterns (locations in the brain where cells send information) can also be standardized. Comparisons of cell types across multiple model organisms, including humans, should reveal common principles as well as key differences concerning the organization of the brain's working units. With this parts list in hand, scientists can systematically establish experimental access to specific cell types, which will greatly facilitate and integrate multiple levels of neural circuit studies.

Coordination and standardization of data (not to mention metadata acquisition, curation, and analysis) are more challenging in certain domains of neuroscience research such as neurophysiology and brain imaging. An extreme example is behavior, the final output of neural circuit operation and ultimate manifestation of brain function. Because behavior results from the integration of sensory inputs, brain states, and cognitive decision-making, and because it manifests as high-dimensional motor output, it is inherently complex and variable even in highly constrained experimental conditions, let alone more naturalistic paradigms. To understand the neural basis of behavior, scientists use many different and often highly specialized experimental designs to record and manipulate neuronal activities in different brain regions while animals or human subjects perform tasks of varying sophistication. Thus, not only the behavioral data themselves but also simultaneous recording and manipulation of neural activity can be difficult to standardize. Indeed, the Suzhou discussions included vigorous debate as to whether it is possible, or even beneficial, to standardize a few sets of agreed-upon behavioral paradigms for data acquisition and comparison across different labs, and for comparison across species.

SHARING. There is pressing need for an infrastructure that makes sharing data among the brain projects feasible. But creating such a system is a formidable task, and funding and personnel requirements are often underestimated. However, the benefits of data sharing make this an important issue. For example, genetic data from human patients suffering from brain disorders can be shared around the globe; such data sharing thus far has spurred the identification of genetic variants contributing to disorders such as schizophrenia and autism (*8–10*). In 2005, the International Neuroinformatics Coordinating Facility (INCF) was initiated by the Global Science Forum of the Organization for Economic Cooperation and Development to help advance data reuse and reproducibility in brain research through the development of global standards, best practices, tools, and infrastructure (*11*). INCF and other similar organizations may be best positioned to support data sharing (as well as draw partnerships among scientific, clinical, technical, industrial, and funding arms).


Human Connectome Project

Another need is for resource sharing. For example, nonhuman primate research is highly valuable for disease biology but is expensive and time-consuming, with associated ethical issues. Genetic engineering and genetic modeling of human brain disorders in nonhuman primate models could greatly benefit from coordinating research on shared experimental animals. Establishing international primate centers as hubs for such collaborations could move this forward.

TRAINING. In response to the avalanche of big data on multiple scales, and in recognition of the extraordinary complexity of neural circuits endowed with an abundance of feedback loops, there is a need to expand the field of theory and computational modeling. Computational neuroscience provides a necessary bridge between neurobiology and brain-inspired intelligence. In particular, the Suzhou discussions noted the importance of equipping a new generation of scientists with the knowledge and tools of multiple disciplines for exploring the brain. In particular, a consensus emerged that analyzing and conceptualizing large data sets from brain projects will require talents that can better integrate experimental neuroscience with computational analyses, modeling, and theory. To leverage brain projects at the international scale, "hybrid" interdisciplinary degree programs and training centers across different nations are needed that offer theoretical, computational, and experimental courses. Another useful mechanism is to support sustained programs of exchange students among collaborating research groups to learn specific experimental techniques or data analysis tools.

FUNDING. Even in nations where brain projects are already ongoing, steady support is not guaranteed. For example, although the working group of the U.S. BRAIN Initiative has made specific, conservative budget recommendations for 12 years, the actual funding requires congressional approval each year and is subject to short-term fluctuations of the political process. All brain projects at present are organized to primarily fund research groups within individual countries or a continent. Thus, innovative funding strategies and mechanisms are needed to support international collaboration. Here, support from private organizations and philanthropists can boost the brain projects. For example, the Allen Institute for Brain Science, launched ~10 years ago, has generated large data sets (such as murine gene expression and neuronal projection maps) that have benefited the neuroscience community worldwide. Likewise, the Janelia Farm Research Campus of the Howard Hughes Medical Institute, also established ~10 years ago (focused on information-processing principles in neural circuits and developing new tools), has made key contributions to the foundation of brain projects. The Simons Foundation launched a "Global Brain" collaboration for studies of population neural data at cellular resolution and advanced statistical modeling, and the Kavli Foundation has supported neuroscience centers and the initial discussion of the U.S. BRAIN project. Strategic collaborations that capitalize on the unique expertise of small research groups on the one hand, and the high-throughput, large data capacity of private research institutes on the other, may achieve milestone advances that are not possible by working separately. Of course, continued and effective engagement with the public is critical to gathering and maintaining support for brain projects.

NEXT STEPS. The most important outcome of the Suzhou discussions is the unanimous agreement and enthusiasm that coordination of the world's multiple brain projects is necessary and feasible, even though specific implementation mechanisms remain to be worked out. In the formative period of genome sequencing, a series of meetings including those organized by Cold Spring Harbor Laboratory profoundly shaped the foundation and international collaboration of the Human Genome Project. The success of this project has revolutionized biology and medicine and has produced exceptionally high returns on the investment (*12*). Unlike this and other large-scale national or international physics (e.g., CERN) and engineering programs (e.g., space programs), all characterized by well-defined goals and more definable strategies, a unique challenge for the brain projects is that the overarching goal may only be achieved by solving a large set of multifaceted and interrelated problems in multiple organisms (including humans), with highly interdisciplinary approaches carried out in many laboratories across the globe. There are few precedents for such a large-scale and highly sophisticated scientific endeavor. We envision that the discussions initiated in Suzhou will continue in future meetings as the national brain projects evolve. The collective success of these projects will be enormous: It will yield greater insight into the inner working of the human brain, often considered the last frontier of scientific inquiry; help to treat devastating brain disorders that are major burdens on current and future society; inspire brain-like computer design and intelligence technologies; spawn new industries and stimulate new economies; build foundational links from science to the humanities; and ultimately achieve a deeper understanding of what makes us human. ■

REFERENCES AND NOTES

1. L. A. Jorgenson *et al.*, *Philos. Trans. R. Soc. London Ser. B* **370**, 20140164 (2015).
2. www.braininitiative.nih.gov/2025/BRAIN2025.pdf
3. www.humanbrainproject.eu/
4. http://brainminds.jp/en/overview/organization
5. Cold Spring Harbor Asia Conference on International Brain Projects, 19 to 22 June 2015, Suzhou, China (see the supplement).
6. Hippocrates, *On the Sacred Disease* (~400 C.E.); http://classics.mit.edu/Hippocrates/sacred.html.
7. S. Ramón y Cajal, *Histology of the Nervous System of Man and Vertebrates* (Oxford Univ. Press, Oxford, 1995; translation of 1911 French version).
8. Schizophrenia Working Group of the Psychiatric Genomics Consortium, *Nature* **511**, 421 (2014).
9. S. De Rubeis *et al.*, *Nature* **515**, 209 (2014).
10. I. Iossifov *et al.*, *Nature* **515**, 216 (2014).
11. www.incf.org
12. http://battelle.org/docs/default-document-library/economic_impact_of_the_human_genome_project.pdf

ACKNOWLEDGMENTS

We thank all meeting participants (see the supplement) for their contributions to the discussion, and W. Newsome, T. Bonhoeffer, W. Koroshetz, S. Hyman, G. Buzsaki, and Y. Fregnac for comments. We acknowledge Suzhou Industrial Park for generously supporting the meeting.

SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/350/6256/42/suppl/DC1
Supplementary Text

10.1126/science.aad4120

CREDIT: HUMAN CONNECTOME PROJECT/NIH

Science AAAS

It takes the world to understand the brain

Z. Josh Huang and Liqun Luo

Science **350**, 42 (2015);
DOI: 10.1126/science.aad4120

This copy is for your personal, non-commercial use only.

If you wish to distribute this article to others, you can order high-quality copies for your colleagues, clients, or customers by clicking here.

Permission to republish or repurpose articles or portions of articles can be obtained by following the guidelines here.

The following resources related to this article are available online at www.sciencemag.org (this information is current as of October 14, 2015):

Updated information and services, including high-resolution figures, can be found in the online version of this article at:
http://www.sciencemag.org/content/350/6256/42.full.html

Supporting Online Material can be found at:
http://www.sciencemag.org/content/suppl/2015/09/30/350.6256.42.DC1.html

A list of selected additional articles on the Science Web sites **related to this article** can be found at:
http://www.sciencemag.org/content/350/6256/42.full.html#related

This article **cites 4 articles**, 1 of which can be accessed free:
http://www.sciencemag.org/content/350/6256/42.full.html#ref-list-1

This article appears in the following **subject collections:**
Neuroscience
http://www.sciencemag.org/cgi/collection/neuroscience

Downloaded from www.sciencemag.org on October 14, 2015

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published weekly, except the last week in December, by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. Copyright 2015 by the American Association for the Advancement of Science; all rights reserved. The title *Science* is a registered trademark of AAAS.