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It Takes the World to Understand the Brain

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Inquiry into the brain basis of mental faculties and disorders dates back to antiquity (1). Yet the investigation of the cellular basis of brain organization and function lay dormant until the detailed structural studies and formulation of the neuron doctrine by Ramón y Cajal in the late 19th century (2), which ushered in more than a century of remarkable progress. Over the past decade, spectacular technological advances in multiple disciplines have accelerated that progress, bringing us to the verge of a fundamental leap toward understanding the brain as a set of sophisticated, powerful computational processes. New tools for visualizing, recording, and manipulating nerve cells (neurons) and neural circuits are enabling researchers to acquire much deeper insight into how the brain processes information and guides behavior than even just a decade ago. Advances in computer science have exponentially increased the capacity for analyzing, curating, and sharing the enormous datasets that have resulted. And genome-wide mapping has identified a large set of genetic variants that contribute to a wide spectrum of human brain disorders. Recognizing a truly unprecedented opportunity for understanding the brain and the profound implications of such understanding for human health and society, large-scale brain projects have been launched or are being planned in multiple continents and countries (2-4) (Table 1). On June 19–22, 2015, about 50 leading scientists from the United States, Europe, Japan, Korea, and China gathered under the same roof for the first time—at the Cold Spring Harbor Asia Conference Center in Suzhou, China—to discuss the opportunities and challenges of international coordination and collaboration on brain research.

Despite the remarkable technological advances of the past decade, the challenge of understanding the brain remains monumental. The human brain is 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. To put this challenge in perspective, it is informative to compare the brain projects with the Human Genome Project launched in the late 1980s, the first large-scale international bioscience collaboration. 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,

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Supplementary Materials: www.sciencemag.org/content/350/6256/42/suppl/DC1 sequence composed of just 4 discrete nucleotides (A, C, G, T); the ~20,500 protein encoding genes comprise 1-2% of this sequence. In contrast, the brain is vastly more complex in multiple aspects. The human brain contains $\sim 10^{11}$ neurons, the basic elements of brain circuits that are linked by $\sim 10^{14}$ 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. To make this significantly more complex, the connectome is not static—both the connectivity pattern and connection strengths among neurons change across life stages and are modified by an individual's experience and learning. Furthermore, mapping the connectome is only one step towards 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 more directly generate perception, cognition, and action.

Neuroscientists largely agree that in order to achieve a deep understanding of how the brain processes information and orchestrates mental functions, we need substantial progress on at least six fronts: 1) identifying the basic components of the brain circuits—classes of neurons that share similar properties and perform similar functions (belong to the same cell types); 2) deciphering the neuronal wiring diagrams integrated across multiple scales, from individual synapses (microscopic) to the entire brain (macroscopic); 3) 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; 4) manipulating neuronal firing patterns with spatiotemporal precision so as to establish the causality between neuronal activity and circuit function that contributes to behavior; 5) inventing computational tools for integrating and analyzing large complex datasets; and 6) formulating overarching brain theories that transcend levels and scales, conceptualize experimental findings, and predict novel circuit properties that underlie brain function. Finally, while most experiments are performed in animal models, we need to integrate this knowledge with valuable insights gained from recording, stimulating, and imaging the human brain. A bi-directional translation of animal and human studies will be crucial to facilitate understanding brains, especially the human brain and mental functions, and to treat brain disorders.

It will take a concerted global scientific effort to accomplish these daunting tasks (6). At the Suzhou meeting, participants reviewed brain projects that are in progress or in planning in their respective countries. They covered a wide range of brain science topics, from cells, circuits, neural development, and behavior to brain theory, tool development, and applications to human neuroscience and brain disorders. They further discussed data standardization and sharing, training and education, and funding mechanisms at the international scale, as well as research ethics. The meeting also heard about global consortia focused on identifying genetic risk factors for brain disorders that will rely on the results of brain projects to render their findings maximally interpretable and useful.

The current brain projects launched or planned in different countries have different emphases (Table 1). The United States BRAIN (Brain Research through Advancing Innovative Neurotechnologies) initiative is currently in the second year of its 12-year plan.

Its initial phase emphasizes developing new tools; these tools are expected to catalyze discoveries about neural circuit function in health and dysfunction in disease in later phases and beyond (3). The European Union's Human Brain Project (4), 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 potentially benefit from data acquired from brain projects around the globe. Japan's Brain/MINDS (Brain Mapping by Integrated Neurotechnologies for Disease Studies) project (5), launched at the end of 2014, features primate—in particular the marmoset, a relatively new genetic primate model—for basic research and for modeling human brain disorders. Canada has launched Brain Canada, which supports collaborative, multidisciplinary, multi-institutional neuroscience research. Korea is starting 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 underway that likely include neural circuits of cognition, brain disorders, and brain-inspired intelligence technologies. Non-human primate studies including the macaque monkey, a long-standing primate model for neuroscience research, is likely a significant feature in China's brain project. Taiwan is planning a modest scale Brain Project, focusing on neurodegeneration and chronic pain, with emphasis on interdisciplinary studies and development of novel neurotechnologies. Australia and Israel have established collaborative effort with the US BRAIN initiatives. In addition to government funded brain projects, the Seattle based Allen Institute for Brain Science, funded by philanthropist Paul Allen, has initiated a 10-year brain circuit project focusing on the study mouse and human visual system using comprehensive approaches and on building open, public shared data and tools.

A major consensus of the meeting was that international coordination and collaboration are necessary, feasible, and potentially highly productive. The participants recognized that no single country or brain project is equipped with the collective intellectual, technological, financial, and human power that is necessary to achieve the task of understanding the brain. In addition to this general agreement, scientists identified several areas where the needs for international coordination are particularly acute and likely to be effective and profitable. They further discussed collaboration opportunities that may leverage the unique strength in different countries to achieve highly strategic and challenging goals that will have sweeping impact across different levels of brain organization and neuroscience research.

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 prerequisite to mapping the wiring diagram, recording and manipulating cell type-specific activity, and deciphering circuit operations that underlie information processing and behavior. Recent convergence of neural developmental studies from invertebrates to mammals, as well as genetic and genomic technologies, has made it increasingly 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. Scientists around the globe can coordinate their efforts in identifying cell types in different brain regions and from different model organisms. Cell type-specific datasets, although enormous, are likely to prove the most readily standardizable. Cell transcriptomes can be acquired with a defined format, deposited into a common database, and analyzed similarly to the genome data. Datasets on cell location, morphology, and projection patterns (where in the brain the cells send information) can also be standardized. Comparisons of cell types across multiple model organisms, including humans, will reveal common principles as well as key differences on 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 serves as a foundational tool that will greatly facilitate and integrate multiple levels of neural circuit studies.

Coordination and, when appropriate, standardization of data and metadata acquisition, curation, and analysis is more challenging in other 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 that neuroscientists strive to explain. Because behaviors result from the integration of sensory inputs, internal brain states, cognitive decision making, and 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, meeting participants debated vigorously 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. Despite these challenges, there was general agreement on the pressing need for data sharing and on creating an infrastructure to make it feasible, a formidable task whose funding and personnel requirements are often underestimated. Success does not only depend on the goodwill of individual investigators but also the availability of tools and coordinating entities to accomplish the goal. 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 (7). INCF or other similar organizations may be positioned to support data sharing and cooperation with the international brain projects by providing seed funding and matchmaking of scientific, clinical, technical, industry and funding partners.

Meeting participants called for resource sharing that is clearly necessary and feasible. For example, primate research is highly valuable especially for disease biology but is also hugely expensive and time-consuming, with associated ethical issues. Primate genetic engineering and genetic modeling of human brain disorders should be coordinated and can greatly benefit from sharing and exchange. Establishing international primate centers in different continents may facilitate these research efforts, and may also maximize the amount of information that can be gained from each valuable experimental animal. Likewise, genetic data from human patients suffering from brain disorders can be shared around the globe—such data sharing has resulted in recent advances to identify genetic variants contributing to disorders such as schizophrenia and autism (8, 9).

Another consensus among the participants is the need to expand the field of theory and computational modeling, 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; computational neuroscience also provides a necessary bridge between neurobiology and brain-inspired intelligence. In particular, meeting participants generally agreed upon the importance of educating and training a new breed of young scientists who will be equipped with knowledge and tools of multiple disciplines for exploring the brain. In particular, a consensus emerged that analyzing and conceptualizing large datasets from brain projects will require a new generation of talents who can better integrate experimental neuroscience with computational analyses, modeling, and theory. To leverage brain projects at the international scale, participants discussed the possibility of establishing a set of "hybrid" interdisciplinary degree programs and training centers across different nations that offer theoretical and computational, as well as experimental courses. Another useful mechanism is to support sustained programs of exchange students to learn specific experimental techniques or data analysis tools in collaborating research groups.

A prerequisite for the success of any brain project is the proper level of funding. Even in nations where brain projects are already ongoing, continual and steady support is essential but is not guaranteed. For example, while the working group of the US BRAIN initiatives 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 will need to be crafted to support international coordination and collaboration. In addition to securing government support, additional resources from private organizations and philanthropists can significantly boost the brain projects by targeted investment toward strategic goals. For example, the Allen Institute of Brain Science, launched ~10 years ago, has generated large datasets such as murine gene expression and neuronal projection maps that have benefited the neuroscience community world-wide. Likewise, the Janelia Farm Research Campus of the Howard Hughes Medical Institute, established also ~10 years ago with focuses on understanding information processing principles in neural circuits and developing new tools, has made important contributions to the foundation of nearly every brain project. The Simons Foundation launched a "Global Brain" collaboration for studies of population neural data at cellular resolution and application of advanced statistical modeling, and the Kavli foundation has actively supported neuroscience centers and the initial discussion of the US brain project. Strategic collaborations that capitalize on the unique expertise of small research groups on the one hand, and high throughput, large data capacity of private research institutes on the other, may achieve milestone advances that are not possible by working separately. In addition, the meeting participants agree that continued and effective communication and engagement with the public and society is critical to gather and maintain the momentum for brain projects.

The most important outcome of the Suzhou meeting is the unanimous agreement and enthusiasm among participants that international coordination and collaboration are necessary and feasible, even though specific implementation mechanisms remain to be worked out. In the formative period of genome sequencing, a series meetings organized by the Cold Spring Harbor Laboratory significantly shaped the foundation and international collaboration of the Human Genome Project. The success of the Human Genome Project has revolutionized biology and medicine, and has produced exceptionally high returns on the investment (10). In contrast to the Human Genome Project and other large scale national or international physics (e.g., CERN for European Organization for Nuclear Research) and engineering programs (e.g., the space program), all characterized by well-defined goals and more definable strategies, a unique challenge of an international brain project is that its overarching goal may only be achieved by solving a large set of multi-faceted and inter-related problems in multiple organisms including human, 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 at the Suzhou Cold Spring Harbor Asia meeting will continue in future meetings as the national brain projects evolve. The collective success of international brain projects will be as significant as, if not more than, the Human Genome Project: it will yield greater insight into the inner working of the human brain – often considered the last frontier of scientific inquiry, help treat devastating brain disorders which are major burdens on current and future society, inspire brain-like computer design and intelligent 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hippocrates (~400 BC) On the sacred disease. http://classics.mit.edu/Hippocrates/sacred.html
2. Ramón y Cajal, S. Histology of the Nervous System of Man and Vertebrates (1995 translation of the 1911 French version). Oxford University Press; 1995.
3. Jorgenson LA, et al. The BRAIN Initiative: developing technology to catalyse neuroscience discovery. Phil Trans B. 2015; 370:20140164. See also http://www.braininitiative.nih.gov/2025/BRAIN2025.pdf.
4. https://www.humanbrainproject.eu/
5. http://brainminds.jp/en/overview/organization
6. http://www.kavlifoundation.org/science-spotlights/it-takes-world-map-brain#.VZl8-fkbIz0
7. http://www.incf.org
8. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014; 511:421–427. [PubMed: 25056061]

9. De Rubeis S, et al. Synaptic, transcriptional and chromatin genes disrupted in autism. Nature. 2014; 515:209–215. [PubMed: 25363760] Iossifov I, et al. The contribution of de novo coding mutations to autism spectrum disorder. Nature. 2014; 515:216–221. [PubMed: 25363768]

10. http://battelle.org/docs/default-document-library/economic_impact_of_the_human_genome_project.pdf

Table 1

Brain Projects Summary

Brain Projects	**Major goals and focus**	**Funding characteristics**	**Duration and funding**
US BRAIN (Brain Research through Advancing Innovative Neurotechnology) Initiative	- develop novel tools to enable abrain cell census, recording andmodulation of brain circuit activity linked to behavior - acquire multi-level brain data - develop new computational models and theory	- set strategic priorities - initially decentralized funding of small groups of investigators - may include larger projects atlater phase	- 12 years - starts at $100 million, proposed to ramp up to $500 million by 2019 and remain steady thereafter
Japan Brain/MINDS (Brain Mapping by Integrated Neurotechnologies for Disease Studies)	- non-human primate brain - collaboration between clinicians and researches toward knowledge based diagnosis andtreatment of brain disorders	- centralized at Riken Brain Science Institute - decentralized participation by other universities and institutes	- 10 years - $30 million per year - a parallel project withemphasis on circuit functionis under consideration
Europe HBP (Human Brain Project)	- big data integration, analysis - computation modeling	- more centralized - participating groups throughout Europe	- 10 years - € 1 billion total
Allen Institute for Brain Science	- mouse visual system - human cortex - building open, public shared the database and tools	- funded by philanthropist Paul Allen; also recruits NIH funding	- 10 years - $50-80 million/ year
Korea Brain Project	- systems neuroscience of cognition and brain disorders - neural circuits and brain imaging	- centralized at Korean Brain Research Institute, Institute of Brain Science, Korean Institute of Science and Technology	- 10 years - $50 million/ year
Brain Canada: supports collaborative, multidisciplinary research across neurosciences	- increase brain research funding - widen scope for collaboration to produce insights for treating brain disorders		
China Brain Science Project (under planning)	- neural circuits of cognition - brain disorders		

Brain Projects	Major goals and focus	Funding characteristics	Duration and funding
	- brain-inspired intelligence technologies		