Title

Worldwide initiatives to advance brain research

Journal

Nature Neuroscience, 19(9)

ISSN

1097-6256

Authors

Grillner, Sten
Ip, Nancy
Koch, Christof
et al.

Publication Date

2016-09-01

DOI

10.1038/nn.4371

Peer reviewed

Published in final edited form as:

Nat Neurosci. 2016 August 26; 19(9): 1118–1122. doi:10.1038/nn.4371.

Worldwide initiatives to advance brain research

Sten Grillner,
Department of Neuroscience, Karolinska Institute, Stockholm, Sweden

Nancy Ip,
Division of Life Science, Hong Kong University of Science and Technology, Hong Kong, China

Christof Koch,
Allen Institute for Brain Science, Seattle, Washington, USA

Walter Koroshetz,
National Institute of Neurological Disorders and Stroke, Bethesda, Maryland, USA

Hideyuki Okano,
Department of Physiology, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan and the Laboratory for Marmoset Neural Architecture, RIKEN Brain Science Institute, Wako, Saitama, Japan

Miri Polachek,
Israel Brain Technologies, Ramat HaSharon, Israel

Mu-ming Poo, and
Institute of Neuroscience, Chinese Academy of Science, Shanghai, China

Terrence J. Sejnowski
Salk Institute for Biological Studies, La Jolla, California, USA

Abstract

To highlight worldwide efforts to fund neuroscience research and address the growing threat of brain disorders, *Nature Neuroscience* asked leaders of six global brain initiatives to write about their programs.

In April 2016, the science academies of the G7 nations as well as seven additional academies issued a statement calling on world leaders to cultivate global brain resources and address the growing threat of brain disorders[1]. The statement proposed four objectives: (i) fundamental research with international collaboration; (ii) global programs for the diagnosis, prevention and treatment of brain disorders; (iii) theoretical modeling of the brain and the development of brain-based artificial intelligence; and (iv) integration of neuroscience with the social and behavioral sciences to improve education and life management as components of a brain-aware society.

H.O. acknowledges the contributions of T. Fujita, A. Miyawaki, K. Kasai, T. Yamamori, T. Shimogori, N. Kishi, J. Hata, T. Kaneko, Y. Yamaguchi and A. Iriki.

Paramount to addressing all of these objectives is government and/or private foundation commitment to supporting basic and clinical research in the brain sciences. Many nations around the globe have already made concerted efforts to develop research and funding initiatives that focus on understanding the brain in health and disease. *Nature Neuroscience* asked leaders of these initiatives to respond to questions (see Supplementary Table 1) about their aims, impact, achievements, data and resource sharing plans, and challenges they foresee in integrating worldwide efforts. Websites may be found in Box 1.

BOX 1

Where to find up-to-date information on funding opportunities and news about the worldwide brain initiatives

Allen Institute for Brain Science: http://www.brain-map.org/

China Brain Project: not available

European Union Human Brain Project: http://www.humanbrainproject.eu/

Israel Brain Technologies: http://israelbrain.org/

Japan Brain/MINDS: http://brainminds.jp/en/

US BRAIN Initiative: http://www.braininitiative.nih.gov/

BRAIN Initiative Alliance: http://www.braininitiative.org/

Human Brain Project

Sten Grillner

The European Union's Human Brain Project (HBP) started in 2013.

Aims—The original emphasis of the HBP was on simulations and modeling of the brains of mice and humans, based on a detailed neurobiological knowledge of the different parts of the brain. This required the development of multidimensional neuroinformatics databases, which is central to HBP. Complementary aspects of cellular systems and cognitive neuroscience are included that should serve as a background for simulations and modeling. In addition there are infrastructure platforms for high performance computing (to allow very large simulations), medical informatics, neuromorphic engineering and robotics. During the first 30 months the focus has shifted somewhat to emphasize the infrastructure development of six separate platforms.

Achievements—The major thrust of the HBP is to emphasize the need to use simulation and modeling in addition to biological experiments. We argue that the microcircuits of the brain, as well as more global aspects, cannot be understood without modeling and simulation, since a great number of interacting processes take place in parallel. The six different platforms for neuroinformatics, simulation, high performance computing, medical informatics, neuromorphic engineering and robotics are a major resource for the research community.

Measuring 10–15 year impact—The impact of the HBP will depend entirely on what critical new insights into brain function will have been obtained and how useful the different infrastructure platforms are for the broader neuroscience community as well as HBP researchers.

Challenges—The different brain initiatives complement each other in many respects. What is critical is that these initiatives interact openly to facilitate progress in the understanding of brain function and to avoid competition. My personal feeling is that collaboration between the different projects will come naturally, particularly if encouraged, and that a coordinating overarching administrative body is not needed. However, workshops and symposia including members of the different initiatives are, of course, very helpful to promote interaction.

Efforts to address reproducibility, data availability and resource sharing—The neuroinformatics platform of HBP is critical in this respect, and its goal is to facilitate data availability and data sharing and to provide curated information to HBP and the neuroscience community.

China Brain Project

Nancy Ip and Mu-ming Poo

The China Brain Project is expected to start in late 2016 or early 2017.

Goals—The China Brain Project will support three research areas in a ‘one body, two wings’ framework. The central body of the project will be the study of the neural basis of cognitive functions, with two wings addressing two translational aspects of brain science. The first is to improve and develop diagnoses and therapies for major brain disorders, with emphasis on early diagnosis and early intervention. The second is to develop brain–machine intelligence technologies, including brain–machine interfaces, and brain-inspired computing methods and devices. This framework reflects the consensus reached after many meetings among neuroscientists, clinicians and intelligence technologists over the past two years. The project was eventually approved by the central government and formally named “Brain Science and Brain-like Intelligence Technology” (“ “脑科学与类脑智能” ”).

Achievements—The China Brain Project has not started yet, but in the core area of primate models for brain disorders, many institutions have made substantial progress in establishing primate facilities and in developing genetic manipulation methods in macaque monkeys. In fact, the first macaque model that expresses autism-like phenotypes was recently generated at the Institute of Neuroscience of Chinese Academy of Sciences in Shanghai[2].

Measuring 10–15 year impact—With sustained government investment, together with new mechanisms in funding and team organization, we believe the China Brain Project will produce results that will complement those achieved by the US Brain Initiative, the European Union’s HBP and Japan’s Brain/MIND project. For example, it is likely that, through more extensive use of macaque monkeys as an animal model, Chinese teams will

obtain new insights into the neural mechanisms underlying higher cognitive functions and generate monkey models for brain disorders that could be used for developing new therapeutic treatment. It is also likely that, through modernization of Chinese herbal medicine, innovative drugs for treating brain disorders will be developed.

Challenges—A big challenge facing the China Brain Project is the effective integration of basic brain science with translational research for brain disorders and intelligence technology. This calls for new, innovative mechanisms for promoting cross-disciplinary, cross-institutional teamwork. Chinese leaders have repeatedly emphasized the importance of forging international collaborations in major frontier research areas. The urgency of finding solutions to the increasing societal burden caused by brain disorders is a global issue that requires integrative efforts across the globe, not unlike the problem of global warming, for which major nations are now mobilized to work together. A critical challenge facing international collaboration is to devise mechanisms that ensure appropriate recognition and benefit to all participants for their respective contributions.

Efforts to address reproducibility, data availability and resource sharing—A well-recognized goal of the Chinese Brain Project is to set up national clinical and technology platforms with uniform standards in reproducibility, as well as data and resource sharing. As opportunities arise for global collaboration, the Project's effort could be further directed toward international standards and global sharing. The issues facing domestic collaborations, such as credit allocation and data sharing, are similar to those facing international collaborations. While international collaborations involving individual Chinese institutions have been ongoing for decades and will continue in the future, the hope is that the China Brain Project can provide the driving force for more unified efforts that would have a strong international impact.

Allen Institute for Brain Science

Christof Koch

The Allen Institute for Brain Science (AIBS) started in 2003.

Aims—The AIBS seeks to understand the biological and biophysical properties of a speck (roughly 1 mm^3) of the most complex piece of highly excitable matter in the known universe: cerebral cortex. We are engaged in three large, interrelated projects. (i) Periodic Table of Cell Types: we are deriving an ontology of neuronal cell types in mouse and human cortex using a combination of single-cell transcriptional, morphological, electrophysiological, connectional and functional properties. (ii) Cortical Microcircuit: we are constructing detailed biophysical models of the local columnar microcircuit across cortical depth on the basis of dense, light- and electron-microscopic connectional reconstructions of one cubic millimeter of mouse and human cortex in conjunction with knowledge of cell types and their connectional probabilities. (iii) Brain Observatory: we are measuring dense cellular-level activity across many regions in behaving mice using a combination of wide-field and cellular optical physiology and electrophysiology under

highly standardized conditions and comparing these against expected responses from detailed models of cortical processing.

Achievements—Over our first decade, our signature achievements were the conception and successful execution of the Allen Mouse Brain Atlas, a comprehensive, cellular-level atlas of gene expression in the adult laboratory mouse. Together with our 3D reference atlas, it serves as the *de facto* standard for the field. We followed this up with brain atlases for the developing mouse and for the adult and developing nonhuman primate (*Macaca mulatta*), as well as transcriptional atlases for the adult and developing human brain. In 2015, we released the Allen Cell Type Database, a growing collection of single neurons from mouse primary visual cortex whose dendritic and local axons have been reconstructed, in conjunction with electrophysiological data and distinct point and biophysical models of these cells, complemented by single-cell transcriptional data. In June of 2016, we released the first massive data sets from the Allen Brain Observatory, characterizing and analyzing, in a highly standardized manner, the functional responses—using two-photon calcium imaging—of more than 10,000 cells in the visual cortex of behaving wild-type and transgenic mice in response to a battery of visual stimuli.

Measuring 10–15 year impact—We have always defined, and continue to define, our impact by a combination of factors, including wide use of our freely available data and research tools. We have specific milestones to achieve for our 10-year plan, including large-scale public data releases and other products, publications, and evaluations by external advisory boards. We hope to be able to provide a standardized and widely used framework and data repository of neuronal cell types, models and observatories for mammalian neocortex.

Challenges—Our biggest institutional challenge is organizational: assembling, managing, enabling and motivating large teams of diverse scientists, engineers and technicians to operate in a highly synergistic manner in pursuit of a few basic science goals. This is quite different from the mode of operation of independent laboratories typical for academic or independent research institutions. These challenges require developing trust in the team as a whole, alignment upon goals and constant inter-group communications and meetings.

Efforts to address reproducibility, data availability and resource sharing—We work hard to standardize all of our products and make our standard operating procedures (SOP) and our software publicly available. We developed, with multiple partners, an open source, common data format for recordings and metadata for cellular electrophysiological and optical imaging experiments called Neurodata without Borders (http://www.nwb.org/). Most importantly, we have shown that all data and tools can be freely and publicly released and shared without any intellectual property restrictions (except for commercial use), typically one or more years before publication, without any adverse effects. About 20,000 mice from our more than 100 different transgenic mouse lines have been shipped to users via Jackson Laboratory. We see no reason why everybody cannot adopt the same radical, open-science policy now. Indeed, this ethos was emphasized by the father of fly genetics, Thomas Hunt Morgan, in a letter he wrote in 1917 to his sponsor: “We make a point of supplying any

individual or group of individuals with any material in stock, not only material that has been studied by ourselves but also material as yet unpublished if it can be utilized. The method of locking up your stuff until you have published about it, or of keeping secret your ideas and progress has never appealed to me personally, and I think as a simple matter of policy that such a procedure is as injurious to the student as it is to the progress of science, which we profess to have most at heart."

Brain Research through Advancing Innovative Neurotechnologies

Walter Koroshetz and Terrence J. Sejnowski

The United States's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative program started in 2013.

Goals—The immediate goals of the BRAIN Initiative are to accelerate the development and application of innovative technologies and to construct a dynamic picture of brain function that integrates neuronal and circuit activity over time and space. The ultimate goal is to understand how our brain and body create our thoughts, motivations and feelings and how to help those whose brains are failing. While the initial years of the BRAIN Initiative will focus on tool development, we are also funding discovery projects with the goal of increasing our fundamental knowledge of brain circuits.

Achievements—A few of the notable products that have emerged from the push to develop new tools and techniques for high throughput transcriptomic classification of brain cell types[3,4]; DREADDs, a tool that uses designer drugs to turn on and off selected neurons via genetically engineered neural receptors[5]; photoacoustic imaging, a technique that blends the speed of precision of light with the penetrating ability of sound to interrogate neural activity[6]; Z-brain, an open-source anatomical atlas of the entire zebrafish brain; and miniaturized and highly sensitive electrophysiology and optical imaging instruments[7]. More generally, the achievements of the BRAIN Initiative will be highlighted by the Brain Alliance, a new website that will be launched later this year, which will bring together stories about the latest research advances from all the agencies and private foundations that are supporting BRAIN Initiative research.

Measuring 10–15 year impact—Success has many dimensions: (i) large-scale recordings and reconstructions that will enable scientists to 'crack the code' by which information is processed in neural networks, (ii) dramatic improvements in our ability to stimulate and record from human brains (most apparent to the public) and (iii) the birth of a vibrant neurotechnology startup industry (similar to that in the early days of biotechnology and genomics startups).

Challenges—It is very encouraging that the science community has come together around the multiple, complementary international brain initiatives. The challenge is finding ways to optimize the investments being made at this unique time in neuroscience history and to leverage the complementarity of the various efforts. A user-friendly, innovative data sharing platform could be a game-changer in bringing the global scientific community to join in the science of the Brain Initiative. The tools being developed by the US BRAIN Initiative, the

transgenic nonhuman primates being generated by the Japan Brain/MINDS project, the advances in nonhuman primate research by the China Brain Project and the computer pipeline for data and modeling being put together by the European Human Brain Project will be disseminated to neuroscientists around the world, who are already beginning to collaborate with each other across many areas of research. Additionally, the US National Institutes of Health (NIH) has entered into agreements with Brain Canada Foundation, the Australian National Health and Medical Research Council and the Lundbeck foundation of Denmark to cofund foreign investigators who are part of BRAIN teams, and the NIH is eager to partner with additional funding organizations to ensure that we maximize the opportunities for all researchers to join in the BRAIN Initiative.

Efforts to address reproducibility, data availability and resource sharing—This was a major recommendation in the BRAIN 2025 report. At the Alpbach Keystone Symposium on “The State of the Brain” in May, W.K. announced that data collected from forthcoming BRAIN Initiative grants will become open access. This will become more and more the norm as data standards are put into place and data platforms are created to make it easier to upload and curate data. The NIH BRAIN Initiative is planning to set up three major data platforms to serve investigators in projects around the following: (i) identifying the cell types in the brain; (ii) understanding information processing in recordings from human brain; for example, from patients undergoing deep brain stimulation or electrical recordings to identify seizure foci and/or patients with brain–computer interfaces; and (iii) understanding information processing in studies that apply advanced recording and stimulation technologies to variety of neural circuits. We plan to focus first on developing an informatics resource for cataloging the myriad cell types in the brain, which will require coordinated data production and rigorous standards for data quality. Investigators from our initial pilot projects are working to establish these data standards, and in fiscal year (FY) 2017 we will solicit proposals for a major data-coordinating center that will host these data and make them available to the research community. The NIH BRAIN Initiative is also committed to investing in technology dissemination. Dissemination allows the tools to reach new laboratories and also allows new users to provide feedback to the laboratories developing the tools, accelerating optimization of these tools. In FY2016 we released a funding opportunity announcement, BRAIN Initiative: Technology Sharing and Propagation (https://grantfundingresources.wordpress.com/2015/08/25/brain-initiative-technology-sharing-and-propagation-r03/) and we plan to support alternative strategies for dissemination in FY2017.

Brain Mapping by Integrated Neurotechnologies for Disease Studies

Hideyuki Okano

Japan’s Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) program started in 2014.

Goals—A key goal of Brain/MINDS is mapping the brain of a small New World monkey, the common marmoset (*Callithrix jacchus*), which represents an important step toward gaining a better understanding of the human brain and toward developing knowledge-based

strategies for the diagnosis and treatment of human psychiatric and neurological disorders. Within this general framework, we have categorized the objectives of Brain/MINDS into the following three major groups. (i) The Structural and Functional Mapping of Marmoset Brain group will undertake macro-, meso- and microscale mapping of the marmoset brain by MRI-based diffusion tensor imaging (DTI), stereotactic tracer injections followed by light microscopy, and a new method of serial electron microscopy. Transgenic techniques will be developed to achieve cell-type-specific mesoscale mapping. The group will also conduct functional mapping by analysis of resting-state functional MRI (fMRI) and will establish behavioral and cognitive test batteries as indicators of brain function. (ii) The Development of Innovative Neurotechnologies for Brain Mapping group will develop high-resolution, wide-field, deep, fast and long imaging techniques for brain structures and functions, new techniques for controlling neural activity and new neuroinformatics tools for integrating heterogeneous and multi-scale data. (iii) Finally, the Human Brain Mapping and Clinical Research group will map patient-derived human brains and will work with the marmoset brain-mapping group to create ‘translatable brain markers’ that bridge the gap between human and non-human primates. One of the most important aims of the clinical research teams is to develop translatable brain markers that are useful in research on neuropsychiatric disorders.

Achievements—A number of labs receiving funding from the Brain/MINDS project, supported by the Japan Agency for Medical Research and Development (AMED), have contributed to the marmoset brain mapping project. Hideyuki Okano’s lab at RIKEN/Keio University has been working on high-resolution structural and diffusion imaging of the marmoset brain[8,9] and has also developed an eight-channel phased array coil to record visually evoked functional blood-oxygen-level dependent (BOLD) responses in awake animals. Efforts from Noritaka Ichinohe’s lab at RIKEN to develop methods for tracer injection and from Tetsuro Yamamori’s group to study the prefrontal cortex are being integrated with the macroscopic MRI-based brain model. Atsushi Iriki’s lab at RIKEN created the first marmoset atlas using histology (Nissl staining) and stereotaxic coordinates[10,11]. The brain model is accessible at http://brainatlas.brain.riken.jp/marmoset/modules/xoonips/listitem.php?index_id=66.

One of the major achievements of the Brain/MINDS project is a gene mapping project using *in situ* hybridization. Tomomi Shimogori’s lab at RIKEN has generated a database for a marmoset whole-brain *in situ* hybridization atlas of over 400 genes as of July 2016, which provides detailed spatiotemporal gene expression information to improve our understanding of the mechanisms underlying primate-specific brain development, function and dysfunction caused by altered gene expression.

Following the Okano lab’s initial success in generating transgenic marmosets[12], they have been generating genetically modified marmosets that model neurodevelopmental and neurodegenerative diseases, such as autism spectrum disorders and Parkinson’s disease in collaboration with Erika Sasaki’s lab at CIEA and Keio University. These models have begun to show several behavioral and neuronal phenotypes typical of human disease symptoms.

Research groups have also produced an array of new tools and techniques for visualizing brain tissue and activity, including the Sca*l*eS method that was developed by Atsushi Miyawaki's group[13] and methods for robust expression of genetically encoded calcium indicators in the marmoset (developed by Yamamori's lab at RIKEN and Matsuzaki's lab at Japan's National Institute of Basic Biology).

At the Japan node of the International Neuroinformatics Coordinating Facility, Yoko Yamaguchi's lab is improving database construction in corporation with other worldwide initiatives, including the Human Brain Project and the Allen Institute. These efforts will lead to platforms for obtaining Brain/MINDS data that will be available for public use.

Finally, the clinical research team led by Kasai Kiyoto at the University of Tokyo has recently conducted a large-scale multisite study of subcortical volumetric differences between patients with schizophrenia and healthy controls[14] that suggests the possibility of aberrant laterality in neural pathways and connectivity patterns related to the pallidum in schizophrenia.

Measuring 10–15 year impact—We plan to measure the impact of Brain/MINDS in each of three areas: development of a microscopic atlas of marmoset brains, multiscale modeling and structure–function mapping of marmoset brain activity, and improvements in diagnosis and treatment of human psychiatric and neurological disorders based on outputs of Brain/MINDS, such as identification of translatable brain markers.

Challenges—We need to develop a consensus for assigning landmarks to areas that are likely to be homologous in nonhuman primates and humans (or in other species). Brain/MINDS will make efforts to promote international cooperation to develop these, as well as other tools and strategies for integrating heterogeneous and multiscale data, such as microcircuit, cortico-cortical projections, neural activities and behavioral data for various species.

Efforts to address reproducibility, data availability and resource sharing—Brain/MINDs is making efforts to construct neuroinformatics databases and develop methods for large-scale simulations that will be openly shared. For the sake of reproducibility and reuse of data obtained in Brain/MINDS, RIKEN has launched a research platform and a publication platform on cloud servers. The research platform is provided to store, share and analyze heterogeneous big data in collaboration among researchers. The Brain/MINDS project will share transgenic marmosets and the technologies needed to generate them upon request.

Israel Brain Technologies

Miri Polachek

Israel Brain Technologies (IBT) started in 2011.

Goals—IBT's mission is to accelerate brain-related innovation and commercialization. This is based on Israel's academic and clinical excellence in neuroscience combined with our

leadership in entrepreneurship and technological innovation. We are leveraging these strengths in order to turn Israel into a leading international hub for brain technologies and a major contributor of solutions to understanding and treating brain disease.

Achievements—IBT organizes one of the leading international brain technology conferences, which is attended by leaders from academia and industry worldwide. We have also launched one of the world's first brain technology accelerators for neuroscience startups.

Measuring 10–15 year impact—We will measure our impact by the growth in number and funding of Israeli brain technology projects and companies. Today Israel is considered a top-ten brain technology cluster worldwide, and we hope to see this cluster grow in the next decade.

Challenges—We see many opportunities ahead and are making efforts to bring leaders of brain initiatives together to discuss them. The main challenge in accelerating early stage brain technologies is obtaining sufficient funding. We at IBT are working hard to engage government, philanthropy and industry to join forces and increase the funding that is dedicated to both platforms such as IBT as well as direct support to the early stage projects.

Efforts to address reproducibility, data availability and resource sharing—IBT maintains a database of all brain researchers, companies and organizations in Israel to facilitate international collaborations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. G-Science Academies. Understanding, Protecting, and Developing Global Brain Resources 2016http://sites.nationalacademies.org/cs/groups/internationalsite/documents/webpage/international_172183.pdf
2. Liu, et al. Nature. 2016; 530:98–104. [PubMed: 26808898]
3. Habib N, , et al. Science 2016
4. Macosko EZ, et al. Cell. 2015; 161:1202–1214. [PubMed: 26000488]
5. Vardy E, et al. Neuron. 2015; 86:936–946. [PubMed: 25937170]
6. Yao J, et al. Nat Methods. 2015; 12:407–410. [PubMed: 25822799]
7. Randlett O, et al. Nat Methods. 2015; 12:1039–1046. [PubMed: 26778924]
8. Hikishima K, et al. Radiology. 2015; 275:430–437. [PubMed: 25602507]
9. Fujiyoshi K, et al. J Neurosci. 2016; 36:2796–2808. [PubMed: 26937016]
10. Hashikawa T, Nakatomi R, Iriki A. Neurosci Res. 2015; 93:116–127. [PubMed: 25817023]
11. Iriki A, , Okano HJ, , Sasaki E, , Okano H. The 3D Stereotaxic Brain Atlas of the Common Marmoset (*Callithrix jacchus*) Springer; in the press
12. Sasaki E, et al. Nature. 2009; 459:523–527. [PubMed: 19478777]
13. Hama H, et al. Nat Neurosci. 2015; 18:1518–1529. [PubMed: 26368944]
14. Okada N, , et al. Mol Psychiatry 2016