VIEWPOINT

# Neuroscience thinks big (and collaboratively)

*Eric R. Kandel, Henry Markram, Paul M. Matthews, Rafael Yuste and Christof Koch*

Abstract | Despite cash-strapped times for research, several ambitious collaborative neuroscience projects have attracted large amounts of funding and media attention. In Europe, the Human Brain Project aims to develop a large-scale computer simulation of the brain, whereas in the United States, the Brain Activity Map is working towards establishing a functional connectome of the entire brain, and the Allen Institute for Brain Science has embarked upon a 10-year project to understand the mouse visual cortex (the MindScope project). US President Barack Obama's announcement of the BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies Initiative) in April 2013 highlights the political commitment to neuroscience and is expected to further foster interdisciplinary collaborations, accelerate the development of new technologies and thus fuel much needed medical advances. In this Viewpoint article, five prominent neuroscientists explain the aims of the projects and how they are addressing some of the questions (and criticisms) that have arisen.

**Q** *What are the (long-term) goals of these projects? Why is now the right time to invest in them?*

**Eric R. Kandel.** The long-term goal of these highly ambitious projects is to gain a better understanding of the anatomical, molecular and circuit bases for the logical operations carried out by the human brain. The Human Brain Project (see Human Brain Project), based in Europe and led by H.M., aims to understand the human brain by simulating its functions through the use of supercomputers. The Brain Activity Map, with which I am more familiar, will be based in the United States and coordinated by Francis Collins, Director of the US National Institutes of Health (NIH), and Story Landis and Tom Insel, Directors of the US National Institute of Neurological Disorders and Stroke (NINDS) and the US National Institute of Mental Health (NIMH), respectively.

These projects may be early for the human brain, but it is a good time to undertake these ambitious tasks in experimental animals for two reasons. First, in both simple invertebrate animals, such as worms and flies, and in vertebrates, we have begun to understand how the brain processes sensory information and how the brain initiates movements. We have also gained insight into the neural basis of learning, memory, emotion and even decision-making. These findings position scientists, especially in the Brain Activity Map project, to be able to begin to tackle the overall organization of brain structure and function.

Second, in recent years, scientists have developed a range of new technological, molecular and computational tools that allow for more efficient and accurate recording from many nerve cells at the same time, for mapping of connections between neurons in the brain, for correlating structure and neural activity with function and for manipulating neural activity to test the causal role of defined neuronal elements in behaviour.

**Henry Markram.** The Human Brain Project is building the foundations that we need to reconstruct and simulate the human brain and its diseases, and to develop related computing technologies. This is terribly urgent. Today, we are failing to translate our rapidly improving knowledge of the brain into benefits for society. Very soon the cost of brain disease will reach 10% of the world's gross domestic product (GDP), yet the development of new treatments is grinding to a halt. There is still a massive gap between the neuroscience laboratory and the clinic. In the same way, we still do not know how to use our knowledge about the brain to build new computing technologies. Neuroscience is like the infant brain — it is flooded with data and theories but lacks the ability to bring them together in a unified view. We pin our hopes on more and more data without realizing that experiments can only give us a small fraction of what we need. The attempt to reconstruct the human brain as a computer model can provide a new focus for neuroscience and for clinical and technological research. It will help us to 'clean up' conflicting reports and teach us how to apply knowledge from animal studies to understanding the human brain. Ultimately, it will allow us to discover the fundamental principles governing brain structure and function and to predictively reconstruct the brain from fragments of experimental data. Without this kind of understanding, we will continue to struggle to develop new treatments and brain-inspired computing technologies.

**Paul M. Matthews.** The Human Brain Project will engage a consortium of 80 neuroscience centres across Europe to aggregate brain functional data on an unprecedented scale, use data-mining techniques to derive an understanding of the way the human brain is constructed and then apply what is learned to revolutionize computing and to develop new approaches for the diagnosis and treatment of brain disease. This is a hugely ambitious remit. A strength of this project is the focus on multilevel integration. However, at this early stage, the project is more aspirational than scientifically well targeted. It emphasizes a massive scaling up of activities in many areas of neuroscience rather than exhaustively exploring a specific question or innovation challenge.

The BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies Initiative; see BRAIN Initiative) is still more of a commitment than a reality. The specific goals are not set but will be considered over 2013 by an advisory committee to the US NIH Director. However, a vision for the BRAIN Initiative, which focused attention on the challenge of developing tools able to describe activity across every cell in a functional unit to characterize 'emergent properties', was set out in a 2012 *Neuron* paper[1] from a group led by R.Y. Specific opportunities offered by voltage-sensitive optogenetic probes, wireless (nano) electrophysiological sensors and synthetic biology were highlighted.

Why are these initiatives coming now? Politically, we need them to help real science funding grow. They both emphasize

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how neuroscience can be an exciting area of blue skies discovery research and an engine of economic recovery. We also need them to change the way we do neuroscience. The 'big' problems of the brain demand interdisciplinary approaches. There is so much in the present system that creates barriers between investigators and institutions and that slows (or even impedes) free flow of information. We need examples that show how to change this.

**Rafael Yuste.** The BRAIN Initiative will promote the development of novel technological platforms for neuroscience. The exact focus is being decided by the three funding agencies involved and their panels of experts and will become clear in a couple of months. I expect it will focus on technologies to perform systematic measurements and manipulations of the activity of large numbers of neurons in animal models and in human patients.

The time is ripe now because of the development of different areas of associated technologies, such as optogenetics, synthetic biology, nanotechnologies, microelectronics and computational analysis of large-scale datasets.

**Christof Koch.** To understand the cerebral cortex, we must bring all available experimental, computational and theoretical approaches to focus on a single model system. In particular, it is of the essence to move from correlation — this neuron or brain region is active whenever the subject does this or that — to causation — this set of molecularly defined neuronal populations is causally involved in that behaviour. The power of optogenetics has given us unprecedented power to rapidly, specifically, delicately and reversibly turn specific connections or groups of neurons on and off. The time is ripe for a concerted project combining these precise tools with large high-quality genomic and cellular databases and atlases, multiple physiological observatories to track the spiking activity of large ensembles of neurons in behaving animals under highly standardized conditions, and anatomically and biophysically accurate computer simulations and theoretical studies.

**Q** *What are the challenges facing these projects? Are there lessons to be learned from other large-scale biology projects (the Human Genome Project, for example)?*

**E.R.K.** There are enormous challenges facing these projects because the human brain is so complex. These projects are unlike anything undertaken before. It therefore is essential that we first study the terrain to be covered and begin with more tractable goals — for example, understanding the logic of the worm and the fly brain, and understanding sensory, motor and cognitive systems in the mammalian brain. In parallel, we need to improve imaging capabilities for the human brain and to develop more precise methodologies for measuring neural activity in humans. What I gather is being planned for the BRAIN Initiative, which has a superb advisory committee, is a series of study groups to outline the tasks to undertake and the sequence in which to undertake them.

As I indicated, there are no precedents for this. The Human Genome Project was important and successfully executed, but it was much simpler. We knew exactly what the end point was. We needed to obtain the whole sequence of nucleotides that makes up the human genome. Further, we knew how to reach this end point. It therefore became a challenge of organization and production: to develop sequencing methods that were quicker and less expensive. For these large neuroscience projects, we do not have a genetic code. Indeed, we must discover the code of information and the logical transformations of that information. Although it might be tempting to push the analogy with the genetic code and transcription, the logic of neuroscience will be far more complex and diverse.

**H.M.** The Human Brain Project is a technology-driven project with set milestones and deliverable outcomes. We have promised to develop information computer technology platforms that will give us a new foundation for studying the brain. The Human Brain Project's platforms will give scientists a single point of access to neuroscience data, multiomic clinical data and analysis tools from all over the world. The platforms will allow them to reconstruct and simulate the brain on supercomputers coupled to virtual bodies acting in virtual environments (*in silico* behaviour), and provide them with pipelines to develop simplified brain models for implementation in neuromorphic computing systems. We are confident that we can deliver what we have promised. This does not mean that one automatically understands the brain; it means we have a better chance to do so. Of course, there are obvious challenges in any big science project: the Human Brain Project will coordinate some 150 research groups distributed across 86 institutions in 22 countries. But the biggest challenge for our project will be to trigger a phase shift in the way we do neuroscience. Our goal is to promote a radically new collective, synergistic and integrative approach that allows neuroscientists to pool the data, knowledge and expertise that they are generating — this is the only way we are going to understand the human brain. Another major challenge will be 'translation' — working with industry to translate research results into new treatments for brain disease and new technologies.

**P.M.M.** The BRAIN Initiative and the Human Brain Project both face a fundamental challenge: we do not have a strong paradigm to guide inquiry. It is striking that both the BRAIN Initiative and Human Brain Project are 'big data' collection exercises from which meaningful relationships are anticipated to emerge. By contrast, the Human Genome Project — a success of biology 'big science' with which the BRAIN Initiative has been compared — was simply an engineering project: what needed to be done was precisely defined and the principles established. It was matter of scaling the effort up and making it affordable.

The lessons that I draw are that, if the BRAIN Initiative and the Human Brain Project are to succeed, they need to provide a clarity of vision and to enunciate well-defined, achievable goals from the start. They also need to maintain coordination and rigour in approach without limiting the openness to new directions necessary for discovery science.

**R.Y.** In this difficult funding climate, the BRAIN Initiative can be perceived as a 'zero-sum game', in that it will automatically result in the diminishing of other funding for current neuroscience projects. This perception is wrong, as it is precisely these type of novel proposals that could help to highlight the importance of neuroscience research to the public and lead to an increase in neuroscience research funding overall. For example, the Human Genome Project led to the unexpected development of a new industry, with an enormous impact on the economy. The lesson learned is that investing in technology development opens new areas of economic benefit.

**C.K.** The comprehensive brain observatory project that we initiated last year will involve several hundred scientists, engineers and technicians, and can be thought of as an experiment in the sociology of neuroscience with unique organizational challenges. It requires rewarding the team for the collective effort rather than a few lead investigators. It signals the arrival of large-scale science in a field populated by small groups. By assembling a large team of specialists focused on a common set of goals, techniques and standards, MindScope will be able to achieve much more than any one scientist can on their own. High-energy physics and astrophysics have successfully carried out projects involving hundreds to thousands of scientists, engineers and technologists over several decades, and we are learning from their experience. In a manner comparable to how physical scientists build instruments to gaze at distant events at the edge of the universe, brain scientists must build observatories to peer at proximal events inside the skull that give rise to the mind that wonders.

**Q** *When will we begin to see the fruits of these endeavours (short-term goals), and what effects are they likely to have on neuroscience research?*

**E.R.K.** A serious concerted effort on the worm and fly brain could lead to a dramatic increase in the understanding of the human

## Glossary

**Allen Institute for Brain Science**
The Allen Institute for Brain Science is an independent non-profit medical research organization. Launched in 2003 with a seed contribution from founder and philanthropist Paul G. Allen, it uses a big science approach to generate comprehensive mouse, monkey and developing and adult human brain atlas resources. In 2012, Allen committed an additional US$300 million for the first 4 years of a 10-year plan to further propel and expand the institute's scientific programmes, bringing his total commitment to date to $500 million. The Allen Institute's data and tools are publicly available online.

**Brain Activity Map**
The Brain Activity Map project was proposed by an independent group of American researchers sponsored by the Kavli Foundation. The project's goals — to develop novel tools to measure, manipulate and model the activity of neurons in living brains — came about from a meeting in 2011 held by private philanthropic organizations (the Kavli Foundation, the Allen Institute for Brain Science and the Gatsby Charitable Foundation). The project aims to generate a dynamic map of the brain — that is, a 'functional connectome' — and to achieve systematic measurements of neural activity in complete neural circuits. This will require the development of novel imaging or nanoelectronic technologies that can capture the activity of every individual neuron, and will be complemented by techniques to systematically manipulate and computationally analyse the activity of these circuits. The Brain Activity Map was endorsed by the US government and subsumed by the BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies Initiative), after the official announcement of the BRAIN Initiative by the US government.

**BRAIN Initiative**
(Brain Research through Advancing Innovative Neurotechnologies Initiative). The BRAIN Initiative is a proposed collaborative research initiative that aims to accelerate the development and application of new technologies that will enable researchers to examine how individual cells and complex neural circuits interact in both time and space. The BRAIN Initiative has been projected to cost more than US$100 million per year for 10 years and will be led by the US National Institutes of Health (NIH), the Defense Advanced Research Projects Agency (DARPA), and the National Science Foundation (NSF). An advisory group is in the process of developing a scientific plan that will identify areas of high priority and develop some principles for achieving the goals of the BRAIN Initiative.

**Human Brain Project**
The Human Brain Project involves over 80 European and international research institutions and aims to bring together existing knowledge about the human brain to develop supercomputer-based models and simulations. Such digital brains may be able to represent the inner workings of a single neurons or even the whole brain. The project is planned to run for 10 years and will be coordinated at the Ecole Polytechnique Fédérale de Lausanne (EPFL) in Switzerland.

brain in the next decade. I believe that rapid developments in the parallel fields of neuroscience, molecular biology, immunology and cell biology (for example, stem cell biology) could accelerate the impact that the fundamental discoveries in model systems such as worms, flies, mice and monkeys have on the development of treatments in human patients. So while the total impact will require a long-term investment, there are likely to be important dividends along the way.

The potential impact of these projects is enormous. The most important would be to better understand, and therefore be able to treat, the devastating diseases of the brain that haunt human kind: schizophrenia, depression, bipolar disorder, post-traumatic stress disorder, addiction, Alzheimer's disease, amyotrophic lateral sclerosis, parkinsonism — the list goes on. In addition, insights from these projects will give us a better understanding of what is unique about the human mind, for example, by shedding light on how we make decisions and the nature of consciousness, free will and creativity.

**H.M.** The Human Brain Project will start on 1 October 2013. Just 18 months later we plan to deliver a first-draft version of our platform for use by researchers within the Consortium. In month 30, we will make the platforms available to the world scientific community. Over 10 years, the Human Brain Project will dedicate €200 million to fund independent research projects using the Human Brain Project platforms. The platforms will allow scientists from outside the Consortium to hunt for, organize and analyse neuroscience data. It will give them access to clinical data from huge numbers of patients with every possible brain disease. It will offer them the tools and data that they need to develop predictive algorithms: for instance, to predict neuron morphologies from patterns of gene expression. Researchers will be able to reconstruct brain models of the healthy and diseased brain and perform *in silico* experiments with the models and compare the results with those from biological experiments. They will be able to couple brain models to virtual robots acting in virtual worlds and perform *in silico* behavioural studies. They will also be able to implement simplified versions of brain models in neuromorphic devices that are suitable for integration in robots and other kinds of devices.

Scientifically, we want to open the road to a new form of accelerated neuroscience in which we identify basic principles spanning multiple levels of brain organization and exploit these principles to fill the large gaps in our current data and knowledge. For instance, we can use principles about the way neurons connect to predict the connectome. Hypothetical reconstructions of the brain can guide and accelerate experimental mapping of the brain, turning it from a dream into a practical reality.

**P.M.M.** These projects are at an early stage — the grand vision for the Human Brain Project was only released at the end of 2012, and the BRAIN Initiative is still in a consultation stage. My guess is that it will take a couple of years to see what form they will take. What I expect from the Human Brain Project in the short term is an acceleration of current human brain neuroscience efforts already undertaken in Europe but with a greater spirit of common purpose and more movement of people between laboratories and countries. There will be an increase in training and a 'step change' in opportunities in theoretical neuroscience. I am more sceptical about the delivery of the novel computing architectures or the *in silico* human brain that they propose, even within the decade, but I would be delighted to be proved wrong!

The BRAIN Initiative may be expected to deliver new tools for functional analyses of circuit activity in animal models, initially within a limited community in 3–4 years and then more widely over 5-plus years. The sensor systems engineered could be at the core of a new approach to design brain–machine interfaces. Perhaps we could expect to see practical translation of the latter as real devices even within 5–7 years. I hope that new principles might emerge from this effort and its spin-offs within the decade.

Together, these projects could deliver a mechanistic model for elements of cognition before 2025. New technologies and exploitation opportunities will emerge. They will also foster a new, bigger (and I hope even bolder) generation of neuroscientists.

**R.Y.** There will probably be technologies (such as novel optical methods for imaging large-scale neuronal activity) that could be released to the community in 3 years, but it of course depends on the exact focus of the BRAIN Initiative's funding.

**C.K.** We are milestone-driven. Our goals over the next 3 years are: first, to construct massive online databases of the meso-scale connectivity of genetically identified cell types throughout the brain in thousands of mice sampled at the sub-micrometre level; second, to systematically classify cell types by linking the electrophysiological properties of single cortical neurons with their dendritic and axonal projection patterns and the genes that they express in their cell bodies; third, to describe the functional properties of genetically identified neurons throughout the ten or more cortical regions of behaving mice; and fourth, to generate *in silico* models of their spiking behaviour. As in the past, all of this data will be freely available via dedicated web tools.

**Q** *Could you envisage these projects sharing information and informing the direction of each other?*

**E.R.K.** It would be valuable for the American and the European projects to continuously inform and enrich one another for the mutual benefit of both and for society at large. To the extent that the Human Brain Project exposes principles of computation, it could provide insights that bear on the interpretation of the facts about the brain that will be furnished by the Brain Activity Map. Of course, the computational efforts of the Human Brain Project will be both nourished and challenged by the data generated by the Brain Activity Map.

Finally, we may begin to see, in fundamental terms, the principles underlying the organization of the brain, what aspects of brain functioning are preserved and what is unique to higher primates and to humans.

**H.M.** Definitely. The Human Brain Project is developing both bottom-up (biologically based) and top-down (theory-based) models. Both approaches are data-driven. The more data we have, the more biologically accurate the models will become. From the Human Brain Project perspective, the data generated by the BRAIN Initiative will provide benchmarks for validating the models we build. Conversely, Human Brain Project models will make it possible to perform *in silico* experiments that are impossible to perform on biological tissue. If the BRAIN Initiative project manages to record from all the neurons in the human brain simultaneously, researchers will eventually need to use biologically accurate human brain models to help understand the machinery that gives rise to the vast spectrum of spiking patterns one should expect to observe. Spiking of neurons is just one out of thousands of dimensions that could be recorded in the whole brain. The model can hopefully help to fill in the missing dimensions. We are at the stage in the history of neuroscience in which experiment, theory and simulation will start to merge. Exciting!

**P.M.M.** These projects are highly complementary. They individually address 'tools and rules' in the United States (new sensors and circuit characterization) and Europe (new approaches to massive data integration and mining), respectively. Linking the American reductionist and European more holistic approaches seems like a good strategy. Each should inform directions for the other.

Importantly, both are committed to open sharing of data, tools and ideas. This is not the US–Soviet space race! I can only hope that there will be no barriers between the projects. Each needs the other's success to realize their own. I would urge the leaders to actively incentivize cross-fertilization.

**R.Y.** Yes, I think it will be natural and desirable for this to happen. These large-scale projects should aim to coordinate efforts.

**C.K.** Yes, the Allen Institute for Brain Science collaborates with the Human Brain Project, and we are coordinating work at a number of levels. Indeed, we just jointly published a paper in *Neuron*[2] on large-scale biophysical modelling of the local field potential. The cerebral cortex is the most complex sheet of organized matter in the universe. If we want to understand it, all of us need all the help we can get from related efforts.

**Q** *Given the amount of resources and therefore funding that both projects will require, do they represent the best way to conduct neuroscience research?*

**E.R.K..** If they are to be successful, the monies necessary for these huge projects are great. But they will only be productive if they come from new sources and not reduce the modest funds now available for the powerful existing programmes for individual research — which are still, far and away the most useful method we have to encourage new innovations and new insight.

**H.M.** In 2012, the worldwide community of neuroscientists published about 100,000 peer-reviewed papers on the brain. Meanwhile global investment in neuroscience research amounts to about US$7 billion. The annual cost of the Human Brain Project will add up to about 1.4% of that figure. The idea that Human Brain Project will drain funds from neuroscience research is a very narrow one. It has already put the human brain on the horizon as a serious target for research, and it will further raise awareness of the extreme urgency of intensifying our research and increase funding. As world populations age, the burden of brain disease is rising to unsustainable levels. We cannot continue with business as usual.

Today, investment in neuroscience research is growing exponentially. This is good news. But we are still talking about research by individual groups and scientists. What is missing is a strategy to integrate the data and knowledge that we are producing. Without such a strategy, we could generate millions more papers, make many great discoveries and win many more Nobel prizes without ever getting closer to a unified understanding of brain function and the way it breaks down in disease.

We are hampered by the general belief that we need an Einstein to explain how the brain works. What we actually need is to set aside our egos and create a new kind of collective neuroscience. Over the next 10 years, the Human Brain Project will fund about 5,000 Ph.D. students. Other large neuroscience projects are moving in the same direction. All the signs indicate that this new generation of neuroscientists will be far more ready to work in teams than the current generation. This is our true hope for the future — Brain 2.0.

**P.M.M.** Is big science also best science? These are large projects, with a €1.1 billion investment for the Human Brain Project over 10 years. The US government has pledged an initial $100 million in spending over the course of 2014 to the BRAIN Initiative, with a $3 billion spend over 10 years envisioned. I cannot think of major new conceptual advances that have come directly from such big science in the past, although there is no question that such efforts have enabled conceptual advances made by individuals or smaller groups, with data or tools arising from them. While this is an unfair comparison, recall that it was Peter Higgs — a single creative scientist — whose theory 'discovered' the Higgs boson. The big science effort of CERN (European Organization for Nuclear Research) was important, but it tested a hypothesis rather than developing it. Similarly, the Human Genome Project has provided the data for discovery of the genetic architecture of disease. It did not lead to the individual discoveries themselves. Nonetheless, publically high-profile, sustained, big-project funding is an effective way of championing a discipline. Pulling together a new level of public and political support for science demands an exciting vision — and in these days of austerity, the vision needs not only to be seen to push the frontiers of knowledge but also to deliver on economic, social or health needs. These projects have the potential to do this. In general, there is no 'best way' of conducting research because 'research' does not have only one kind of objective. However, I strongly believe that at the basis of all of the best research is an openness to new ideas, transparency of approach and a commitment to the most rapid communication.

**R.Y.** I think that developing novel methods for monitoring and manipulating the activity of neuronal circuits is the best investment one can make today for the future of neuroscience.

**C.K.** The standard, principal investigator-driven approach, operating in small laboratories on 3-year grants, has significant drawbacks. Because students must write first-author papers to graduate, and faculty must publish in high-impact and hyper-competitive journals to obtain grant support and tenure, the academic research enterprise encourages maximal independence among experiments and groups. Selection bias is rampant, and many experiments are not reproducible. Neuroscience is a splintered field, with circa 10,000 laboratories worldwide pursuing distinct questions with a dizzying variety of tools in a multiplicity of animal species, behaviours and developmental time points. Indeed, when attending the annual Society for Neuroscience meeting, I am struck by the speed with which its 60,000 or more practitioners are heading away from each other in all possible directions in a sociological Big Bang. While this is necessary in the romantic, exploratory phase of any new science, a more systematic and thorough exploration is called for as our field enters a more mature phase. This orthogonality among groups has prevented the emergence of common standards. To gain a competitive edge (and due to lack of funding to manage and curate online repositories of data), hard-gained structural or functional information is hoarded and rarely made accessible online. Molecular compounds and transgenic animals are only shared after the initial papers describing them have appeared in print. All of this has made comparison across laboratories difficult, replication of specific experiments almost impossible and has significantly slowed progress. Big brain science offers an alternative approach to address many of these shortcomings.

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**Competing interests statement**
The authors declare competing financial interests: see Web version for details.

**FURTHER INFORMATION**
**Allen Brain Atlas:** http://www.brain-map.org/
**BRAIN Initiative:** http://www.nih.gov/science/brain/
**Human Brain Project:** www.humanbrainproject.eu

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