OPINION ARTICLE

Grand challenges for global brain sciences [version 1; referees: 1 approved, 1 approved with reservations]

Global Brain Workshop 2016 Attendees[1-5]

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Abstract

The next grand challenges for science and society are in the brain sciences. A collection of 60+ scientists from around the world, together with 15+ observers from national, private, and foundations, spent two days together discussing the top challenges that we could solve as a global community in the next decade. We settled on three challenges, spanning anatomy, physiology, and medicine. Addressing all three challenges requires novel computational infrastructure. The group proposed the advent of The International Brain Station (TIBS), to address these challenges, and launch brain sciences to the next level of understanding.

This article is included in the Neuroinformatics channel.

Open Peer Review

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Understanding the brain and curing its diseases are among the most exciting challenges of our time. Consequently, national, transnational, and private parties are investing billions of dollars (USD). To efficiently join forces, the *Global Brain Workshop 2016* was hosted at Johns Hopkins University's Kavli Neuroscience Discovery Institute on April 7–8. A second workshop, *Open Data Ecosystem in Neuroscience* took place July 25–26 in Washington D.C. to continue the discussion specifically about computational challenges and opportunities. A third conference, *Coordinating Global Brain Projects,* took place in New York City on September 19th in association with the United Nations General Assembly. So vast are both the challenges and the opportunities that global coordination is crucial.

To find ways of synergistically studying the brain, the kick-off workshop welcomed over 60 scientists, representing 12 different countries and a wide range of brain science subdisciplines. They were joined by 15 observers from various national and international funding organizations, including NIH, NSF, IARPA, the Kavli Foundation, and the Simons Foundation. Participants were engaged weeks before the conference and charged with coming up with ambitious projects that are both feasible and internationally inclusive, on par with the International Space Station (i.e., worthy of a global, decade-long effort). Over the course of 36 hours, scientists discussed, debated, and gathered feedback, ultimately proposing several "grand challenges for global brain sciences" that were refined by working groups. The workshop was covered in a media piece in *Science* April 15, 2016[1].

The group began with 60+ ideas, each forged independently by one of the scientific participants. Each participant proposed a unique challenge that was designed to meet the following desiderata:

1. *Significant*: it will yield tangible societal, economic, and medical benefits to the world.
2. *Feasible*: it can achieve major milestones within 10 years given existing funding opportunities.
3. *Inclusive*: nations throughout the world can meaningfully contribute to and benefit from each challenge, and the collection of challenges are collectively scientifically diverse.

Interestingly, a lot of the proposed ideas were similar to one another and others were complementary. This allowed the group to converge on three grand challenges for global brain sciences, each depending on a common universal resource. As each of these four projects gain momentum, we encourage readers to get in touch (details provided below).

Challenge 1: What makes our brains unique?

Both within and across species, brain structure is known to exhibit significant variability across many orders of magnitude in scale, including Anatomy, Biochemistry, Connectivity, Development, and gene Expression (ABCDE). It remains mysterious how and why the nervous system tightly regulates certain properties, while allowing others to vary. Understanding the design principles governing variability may hold the key to understanding intelligence and subjective experience, as well as the influence of variability on health and function.

This grand challenge is a global project to coordinate the construction of comprehensive multiscale maps of the ABCDE's of multiple brains from multiple species using multiple cognitive and mental health disease models. Within a decade, we expect to have addressed this challenge in brains including, but not limited to, *Drosophila*, zebrafish, mouse, and marmoset, and to have developed tools to conduct massive neurocartographic analyses. Indeed, many existing datasets will play a crucial role in seeding this project, including data from the Human Brain Project, IARPA's MICrONS project, and Z-Brain to name a few. The result will be a state-of-the-art "Virtual NeuroZoo" with fully annotated data and analytic tools for analysis and discovery. This virtual NeuroZoo can be utilized by neuroscientists and citizens alike, both as a reference and for educational materials. By incorporating disease models, we explicitly link this challenge with the third challenge. Global discussions around this project are now beginning via the tags "neurostorm" and "neurozoo" at the neuroinformatics discussion forum NeuroStars (https://neurostars.org/).

Challenge 2: How does the brain solve complex computational problems?

Brains remain the most computationally advanced machines for a large array of cognitive tasks - whether navigating hazardous terrain, translating languages, conducting surgery, or recognizing emotional states - despite the fact that modern computers can utilize millions of training samples, megawatts of power, and tons of hardware. While the ABCDEs establish the "wetware" upon which our brains can solve such computations, to understand the mechanisms we need to measure, manipulate, and model neural activity simultaneously across many spatiotemporal resolutions and scales - including wearables, embedded sensors, and actuators - while animals are exhibiting complex ecological behaviors in naturalistic environments.

This grand challenge is a global project to investigate a single naturalistic behavior that is ecologically relevant across phylogenies, such as foraging, and measure brain and body properties across spatial, temporal, and genetic scales. The challenge differs from previous efforts in three key ways. First, it requires studying animals in complex and naturalistic environments. Second, it requires coordinated attacks at many different scales by many different investigators while the animals are performing the same complex behaviors. We envision groups of 20–30 investigators all operating together on shared data and experimental design. Third, the richness of the mental repertoire of cognition suggests that deciphering its codes will require many parallel investigations to uncover different facets of brain function. These experiments in turn will produce multiscale models of neural systems with the potential to accomplish computational tasks that no current computer system can perform. Mechanistic studies, guided by theoretical models, will help to ask how perturbations of those systems lead to aberrant function, linking this challenge with the next one. Global discussions around this project are now beginning via the tags "neurostorm" and "GlobalBrainLab" at NeuroStars.

Challenge 3: How can we augment clinical decision-making to prevent disease and restore brain function?

Psychiatric and neurological illnesses levy enormous burdens upon humanity: impairment, suffering, financial costs, and loss of productivity. Despite a growing awareness of the challenges, clinicians consistently battle the lack of objective tests to guide clinical decision-making (e.g., diagnosis, selection of treatments, prognosis). Compounding these limitations are societal stigmas regarding mental illness that increase the suffering of patients and their families. The ABCDEs of neurobiological variability, when coupled with multiscale mechanistic models of cognition, will provide new approaches to neurobiologically informed clinical decision making.

This grand challenge is a global project to transform clinical decision-making via incorporating neural mechanisms of dysfunction. This will require collecting, organizing and analyzing human and non-human anatomical and functional data. These data (such as ADNI and ADHD-200), and the tools developed to explore and discover novel treatment therapies, will be the foundation upon which the next decades of experiments and clinical decisions will be based. The distributed and multimodal nature of these datasets further motivate the need for an all-purpose computational platform, upon which models of disease can be developed, deployed, tested, and refined.

A universal resource

All three of the grand challenges for global brain sciences represent severe methodological challenges, both technological and computational. The technological developments required for each of the challenges are non-overlapping. In contrast, regardless of the nature of the scientific questions or data modalities involved, each project will require computational capabilities including collecting, storing, exploring, analyzing, modeling, and discovering data. Although neuroscience has developed a large number of computational tools to deal with existing datasets (for example, resources in http://www.nitrc.org/), the datasets proposed here bring with them a whole suite of new challenges, including scale and complexity.

This resource would be a comprehensive computational platform, deployed in the cloud, that will provide web services for all the current "pain points" in daily neuroscience practice associated with big data. This resource will realize a new era of brain sciences, one in which the bottlenecks to discovery transition away from data collection and processing to data enriching exploring, and modeling. While science has always benefitted from standing on the shoulders of giants, this will enable science to stand on the shoulders of everyone. Today, essentially every practicing neuroscientist's productivity is limited due to computational resources, access to data or algorithms, or struggling with determining which data and algorithms are best suited to answer the most pressing questions of our generation. This resource will create a future where those limitations will feel as archaic as fitting the data with paper and pencil feels today. For further details, see an article written by the Neuro Cloud Consortium called called "To the Cloud! A Grassroots Proposal to Accelerate Brain Science Discovery"[2].

Societal considerations

Each nation affords different opportunities and restrictions, owing to ethical, policy, and cultural considerations. Because these grand challenges are inherently inclusive, manifesting them will require understanding and mitigating issues that arise in cross-cultural endeavors. Indeed, addressing the vast diversity of partnerships in such an endeavor is a challenge in itself. We therefore recommend the following. First, form a 'cultural sensitivity committee' to consider and investigate potentially sensitive issues. Second, bolstered by their research, establish cross-cultural collaboration education materials, including written guidelines and videos, which will be recommended to all participating scientists. Third, to deepen the understanding of transnational collaborations, develop trainee exchange programs in which participating trainees will spend six months to a year working and training in a foreign country. This will also facilitate cross-cultural knowledge dissemination and fertilization. Fourth, require frequent assessments to ensure maintenance of cultural sensitivities. These assessments will feedback into the educational material and be used to modify the exchange programs.

Next steps

Crucial to the success of this endeavor is a sequence of actionable steps that the community can follow. Because we are not proposing any additional funding, realizing the eventual goals of these grand challenges will rely on marshalling existing funds. Due to the incoming leadership changes, both on national and transnational levels, quick action is of the essence. Therefore, we have taken the following steps:

We have created a webpage, http://neurox.io, containing a bibliography of reports that resulted from this conference, as well as a list of all scientific participants and observers who attended the original brainstorming meeting in April that led to this document. We will also be monitoring comments on NeuroStars (https://neurostars.org/), a community forum for neuroscience and neuroinformatics related queries, with the tag "neurostorm" for further discussion. Finally, we held an outpost at the NeuroData booth #4126 at the 2016 Society for Neuroscience conference (https://www.sfn.org/annual-meeting/neuroscience-2016) to discuss these issues further. We were encouraged by visitors who felt inspired by this idea to join the discussion, engage.

Author contributions

JTV and BM organized the event and the writing of the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

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PubMed Abstract | Publisher Full Text

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Version 1

Referee Report 14 March 2017

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✓ **Sten Grillner**
Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden

I have been asked to comment on the opinion article "*Grand challenges for global brain sciences*". I was not present in the meeting at Johns Hopkins in April 2016, which provides the basis for the report, but at the follow-up meeting at Rockefeller in September 2016, and in the meeting at United Nations in February 2017.

The reason for this global initiative is the fact that great investments in neuroscience have been made through primarily the Human Brain Project of the EU, the US Brain Initiative, and the Japanese Brain Mind Initiative. In addition, there are advanced plans in a similar vein in several countries, including China, Korea, and Australia. The report argues for collaboration between the different initiatives, and it would seem clear that one should strive for complementarity between the initiatives. Essentially, what would seem important is to create a collaborative spirit, rather than a competitive mind set.

The conclusion as presented is that the different projects chosen should be *feasible* in a 10-year perspective, be *significant* in the context of basic and clinical neuroscience, an *inclusive*, that is involved as many research communities worldwide as possible. With a global perspective it is clear, that the human and infrastructure capabilities vary markedly in different parts of the world. It may be worthwhile to consider that some aspects of neuroscience (like computational neuroscience) can be conducted even under conditions when advanced experimental equipment is not available.

The members of the Johns Hopkins meeting ended up supporting three main challenges (original text in italics), as summarized below:

"Challenge 1: What makes our brains unique?
Both within and across species, brain structure is known to exhibit significant variability across many orders of magnitude in scale, including Anatomy, Biochemistry, Connectivity, Development, and gene Expression (ABCDE). It remains mysterious how and why the nervous system tightly regulates certain properties, while allowing others to vary. Understanding the design principles governing variability may hold the key to understanding intelligence and subjective experience, as well as the influence of variability on health and function."

I suppose the title infers that the question of what makes the human brain unique in comparison with that of other vertebrates should be in focus. What appears central in this context is the capacity to acquire language, because this allows us not only to interact regarding what goes on at a given moment, but also to discuss what happened many years ago, or different plans for the immediate or distant future. This

possibility is something that other primates and mammals cannot enjoy (in some species, there is a complex behavioral repertoire for communication that can be individualized, but it is far from the human language). We can, however, assume that the neural circuits involved in motor learning in mammals have been tinkered with to provide this novel skill to produce the different words as in speech, and not unlikely there may have been a gradual development of this skill on the evolutionary line from the chimps to humans (Cro-Magnon). The language capability has been extended through the ability to transmit information in the written form, a critical addition for transmission of culture. Another aspect is the human cognitive ability to reason, which is unmatched among vertebrates. The many different areas mentioned in the quote above seem to include almost any type of neuroscience, rather than what makes the human brain unique. I believe focus is needed.

"Challenge 2: How does the brain solve complex computational problems?
Brains remain the most computationally advanced machines for a large array of cognitive tasks - whether navigating hazardous terrain, translating languages, conducting surgery, or recognizing emotional states - despite the fact that modern computers can utilize millions of training samples, megawatts of power, and tons of hardware."

The human brain is unique in many aspects, but at the same time, we must realize that many of our fellow vertebrates are much more skillful in a variety of tasks. Consider for instance a bird navigating back to its nest of last year in the Northern hemisphere starting near the South Pole, the motor skills of a cheetah hunting for a prey, or an owl hunting down a mouse when it is pitch dark, a monkey swinging itself from branch to branch in an arboreal environment, an eagle identifying a prey from very high altitude, or a dog sniffing for detecting explosives. In understanding the neural bases of these complex behavioral skills, a variety of animal models will be useful. They are interesting in their own rights, but they may also unravel the neural bases of similar mechanisms in humans. What may characterize the human nervous system is the ***versatility*** in inventing novel skills like those of a piano virtuoso or juggler or just writing in long hand. The astounding energy efficiency is another unexplained fact – the brain with its billion of cells does only demand some 30 watts or so.

"Challenge 3: How can we augment clinical decision-making to prevent disease and restore brain function?
Psychiatric and neurological illnesses levy enormous burdens upon humanity: impairment, suffering, financial costs, and loss of productivity."

Clearly, the whole medical area is important, and no less than one third of the costs for health care in Europe are due to diseases of the brain, whether psychiatric, neurological, or geriatric in nature. This entire field is of course of crucial importance, and any solution to the many chronic diseases will of course be a gift to mankind. Consider for instance the possibility that we would find a therapy for Alzheimer's in an early stage, or treatment of MS or Parkinson's! However, also for this challenge no 3, there is a lack of focus.

To summarize
I find these different challenges to represent very important aspects of basic or clinical neuroscience, but on the other hand, the areas are formulated in so broad general terms that they actually represent the larger part of the current research panorama. This would mean that the initiatives would primarily provide additional research support for neuroscience in general.

Progress results, however, often from focused initiatives regarding particular functions of the brain or disease mechanisms. The current initiatives in Europe, the US and Japan have so far mainly focused on

developing tools and infrastructure for research. ***This can be important in itself, but it is only when these tools are used for research that scientific progress is made.*** It would therefore be important, in the reviewer's mind, that a set of crucial and solvable scientific problems will become in focus for the Brain initiatives in a ten year perspective.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 20 January 2017

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? **Stephen J. Eglen**
Department of Applied Mathematics and Theoretical Physics, University of Cambridge, Cambridge, UK

This opinion article lists three grand challenges for global brain sciences. It concisely summarises discussions from workshops held in 2016 to outline collaborative challenges for brain sciences. I found the paper interesting to read as I had not heard about these initiatives before, and I think others in the field would also find them of interest.

As an opinion piece, there is no original research contained in this piece that requires technical evaluation.

I do have some comments that I would like to see responses to before recommending the article getting indexed.

1. The abstract is not informative enough. I think it should describe the three scientific challenges (perhaps a sentence each) so that those readers just seeing the abstract on Pubmed will see the challenges.

2. The last sentence of the abstract notes that the group proposed the "TIBS", but this is not elaborated on in the paper. Is the TIBS the same as the GlobalBrainLab?

3. Very similar earlier versions of this paper are already available, on the front page http://brainx.io/ and https://arxiv.org/pdf/1608.06548v3.pdf -- I think this should be noted somewhere to help link up the literature.

4. A key point of this paper seems to be to communicate the grand challenges to a wide audience. Tags (neurostorm, neurozoo, GlobalBrainLab) are listed for people to use on a website (neurostars.org), but when I just searched, I could find no hits for either neurozoo or GlobalBrainLab (there is one hit for neurostorm; I am aware however that neurostars lost large amounts of data last year so perhaps earlier discussions have vanished). It seems a bit premature to say that discussions are "now beginning". Perhaps simply say that you encourage people to go to neurostars and use those tags if they wish to discuss them?

5. No tag for discussion grand challenge 3 has been listed.

6. The paper describes three challenges, but page 1 describes "As each of these four projects gain momentum". What is the fourth project? Is it the cloud-computing proposal described in reference 1 (the NeuroView article)? If so, it looks like since the workshops in Summer 2016 there has been sufficient momentum gained in this area to write a large article on this challenge. What has happened in the last six+ months to the last three challenges -- are people actively working on them? Having a bit more up to date information on the progress since the workshop would help the reader.

7. How might these global challenges interact with the research agendas of other large scale initiatives? There is brief mention of other large scale projects in challenge 1, but I see no strategy for ensuring how these large scale initiatives (Human Brain Project, and other National Brain projects) can work together with these challenges. As recognised in the article, there is no extra funding yet for these challenges, so interacting with these other initiatives is likely to be required (Huang and Luo, 2015). From my part, such coordination of large scale initiatives and challenges might best be led via the INCF (www.incf.org), as otherwise might end up with the creation of another INCF. (Full disclosure: I am co-chair of the UK neuroinformatics node, which is a national node of the INCF.)

8. I'm surprised to see only two references in the paper; at the very least I think Huang and Luo should be cited to give the reader some context of other large-scale initiatives. References to other projects would also be appropriate (e.g. ADNI, ADHD-200, Z-Brain, MICrONS).

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1. Huang ZJ, Luo L: NEUROSCIENCE. It takes the world to understand the brain.*Science*. 2015; **350** (6256): 42-4 PubMed Abstract | Publisher Full Text

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: I am a co-chair of the UK Neuroinformatics node, which is affiliated to the INCF.