The Brain Observatory: A National Laboratory of Neurotechnology

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Summary:
We propose the creation of a national laboratory of neurotechnology to tackle critical technological challenges that individual laboratories or universities cannot face alone. Such a center could catalyze novel efforts in an interdisciplinary environment, and, by serving as a "brain observatory", also provide researchers with access to unique and transformative technical infrastructure. Organized in five technological thrusts, a national brain observatory would become a natural home for neuroscience-related FROs, ensuring their intellectual and technical synergy enabling sharing of common infrastructure. Besides propelling to the future existing single-investigator research programs by the generation of next generation methods, and hosting teams of extramural researchers to carry out specific instrument development, a national brain observatory would also facilitate the introduction of novel neurotechnologies into the clinical setting, by facilitating collaborations for preclinical and clinical trials, and into the industry, by seeding neurotechnology startups.

Challenge and Opportunity:
Understanding how the brain works is likely one of the most important scientific challenges of our times, as it would have three revolutionary impact in three areas: i) science, providing a rigorous understanding of the inner workings of our mind, ii) medicine, enabling the deciphering of the pathophysiology and the design of effective therapies for mental and neurological diseases and iii) economy, by fueling novel areas of enterprise for the tech and AI industry. But, in spite of this great promise, and after a hundred years of sustained effort, we still lack a general theory of brain function. This is due to the lack of technology to approach the enormous complexities of the nervous system ("the impenetrable jungles where many investigators have lost themselves"), composed of circuits with close to 100 billion neurons, each connected with tens of thousands of other neurons, far surpassing the number of nodes and connections in the entire internet of the earth. To tackle this technological deficit, the Obama administration launched the BRAIN Initiative, a 12-year, multibillion dollar project, that currently involves over 500 laboratories in the US and the world, and whose main purpose is to create advanced neurotechnological tools. The US BRAIN initiative, and similar large-scale neuroscience programs inspired by it in the EU, China, Japan, South Korea, Australia and Canada, are generating novel optical, magnetic, electrical, molecular and computational methods to record, manipulate and interpret the activity of brain circuits in laboratory animals and humans. While this global effort is of historic proportions, funding in these initiatives are dispersed into individual laboratories, normally composed of a small group of researchers trained in one discipline, and therefore do not allow for the design and fabrication of large scale instruments, which appear necessary for the enormous challenges ahead. In addition, to successfully generate methods to record and manipulate the activity of large neural circuits in living animals or humans, it seems necessary to engage a multidisciplinary team of researchers and engineers, with combined expertise in physical and biomedical sciences.

Proposed Action: National Laboratory for Neurotechnology
A time-tested successful recipe to face major technological challenges is building national research centers. Many examples abound: from particle accelerators to astronomical observatories, genome centers, to space exploration centers, national laboratories or centers have enable the generation of game-changing technologies which have propelled humanity forward, revolutionized entire field of sciences and also physically and intellectually anchored those communities by providing common instruments for individual investigators to share collectively. This lesson could be applied to neurotechnology. A national center of neurotechnology could enable the assembly of interdisciplinary teams of researchers, focused on solving specific technological challenges, with the mandate of building

instruments to be shared by the larger community. In fact, as it happened in Astronomy a century ago, shared cutting edge-instruments will make it unnecessary for individual laboratories to purchase and maintain expensive equipment with lesser perfomance, which will become obsolete, so such a center could eventually become cost effective for federal funding agencies. As has been proven over and over, technology drives science and large-scale instruments will revolutionize neuroscience.

For neurotechnology, there are five areas that are critically dependent on significant technology developments **–** and that could profit directly from a center-based approach. To cover them, we envision the following thrusts:

- **Connectomics**, the systematic ultrastructural reconstructions of the wiring diagram of neural circuits using electron microscopy, is essential milestone towards understanding brain function. Today, some of the most advanced platforms for large-scale electron microscopy involves multibeam instruments, far too expensive even for individual universities to acquire or maintain. Like with particle accelerators or telescopes, this is a size game: advanced instruments acquire not only technically superior data but do it larger quantities, more effectively and faster than dozens of standard ones.
- **Molecular Brain Mapping.** This describes a host of novel technologies that are emerging from the systematic application of genomics and proteomics to the nervous system. The ultimate goal here is to provide single-cell-level atlases of brain tissue, with detailed genomic, transcriptomics and proteomic datasets, while preserving the structure and positional information of the tissue. These technologies should be robust enough so they can be applied to post-mortem samples of human brain, or brain banks.
- **Nanoelectrical/Photonic Probes** are silicon-based multielectrodes with electrical and optical properties. whose fabrication requires large-scale semiconductor integration, nanofabrication and foundry-scale production. Individual laboratories, or even large universities, are not equipped to carry out these tasks with the reproducibility, robustness, and scale of production needed to generate game-changing truly powerful multielectrode arrays. Industrial foudnries, which do have the right scale of resources, are understandably focused on semiconductor industry, not on neuroscience. A national center could have specialized fabrication facilities with tooling that would allow commercial CMOS and photonic technologies to be adapted for the development of a new generation of implantable and wearable devices. This will include facilities for prototyping and assembling devices for initial animal and human studies.
- **Optical and magnetic imaging** technologies require powerful lasers, magnets, and instrumentation that exceeds what individual laboratories or universities can typically build, acquire, or maintain at cutting-edge performance. In fact, current progress in optical microscopy is limited by the lack of commercially available lasers, high-speed modulators, large-scale objective lenses, or optical components specifically engineered for neuroscience applications. This involves specialized design knowledge, precision engineering, and micro- and nanofabrication expertise and infrastructure, constraining researchers to the use of existing, commercially-available components from the optics or microscopy industries that are designed for other, more broadly-marketable applications. A similar case can be made for development of magnetic resonance imaging technology; it is primarily driven today by the needs of hospital-based imaging systems, rather than by the research community in cognitive neuroscience.
- **Computational data mining and storage,** is another critical thrust, as it underpins all emerging neurotechnologies. The amount of data collected with the new neurotechnologies, from connectomics, to imaging datasets or multiprobe recording, will dwarf the output of all previous methodologies in biomedicine. Hence, individual laboratories with traditional servers and cluster-based IT will likely become overwhelmed with an unprecedented deluge of data without

assistance from state-of-the-art computational centers with skilled personnel, supercomputers, and storage to curate the valuable public datasets that will be amassed. While some of this could possibly be carried out by commercial enterprises – as is increasingly done in diverse fields of science – the access, control and analysis of large-scale neuroscience databases should, as a public resource, remain in the hands of a national center. Finally, as important as the storage is the need to develop the analysis tools to handle the datasets. From novel algorithms, to flexible computational strategies, to information-theory based preprocessing, all the way to theoretical models of the data, these are examples of the types of computational tools that need to be systematically developed, to enable the true connection of these neurotechnologies with the users, researchers, clinicians and entrepreneurs.

Vision: The National Brain Observatory (NBO)

Our vision is a national center that, as a mid-size national laboratory, would serve to anchor the development of large-scale neurotechnologies. High-end instruments, like telescopes in astronomical observatories, would then become available for individual investigators from around the country and the world. But, instead of focusing on the stars, they would focus on the neurons of our brain, the biological matter than makes us human.

***Size**:* A hundred researchers, working on the five target areas, would provide approximate 20 PhD level researchers per thrust, which seem like an ideal critical mass, as it still maintains a "small village" size that is viewed as key for successful group dynamics. The computational thrust will likely need fewer positions than the experimental thrusts, the remaining FTEs, counting towards the 100, would be necessary for administration and general infrastructure.

***Funding**:* The burdened costs of 100 FTEs per year results in an annual core operating budget of approximately $50M. Higher start-up costs will characterize the first year. An existing building is assumed. This budget would guarantee that each of the four areas have enough resources and time for transformative work. It is not anticipated that the NBO will seek to obtain government funding in federal grant programs, but operate with relative independencies of the vagaries of academic research funding. This could be supplemented by revenue from licensing and other commercial engagements. Governmental funding should be secured, and guaranteed for a decade, by bipartisan support. An interesting model would be to seek buy-in from local or regional political bodies, as the German Max-Plank Institutes, where the federal government provides half of the resources whereas the regional governments provide the other half.

***Location**:* We think that it is critical that the NBO should be created at a major US research node, in partnership with an existing university or research institution, in order to capitalize and leverage existing talent and infrastructure, and also as a critical step towards recruitment of high end experts. As a beneficiary of this partnership, the university or research institute would provide and maintain the building, as well as generate intellectual and technical synergies with the existing communities. Location near a large metropolitan area seems also desirable to enable clinical collaborations and facilitate entrepreneurship and attract venture capital to startup projects, as well to facilitate finding positions for spouses in the area.

***Logistics**:* The NBO would require an agile administrative structure, with independence comparable to a startup company, and it would be accountable to a scientific advisory board, which would be responsible for the recruitment and periodic reviews of the leader and the NBO. These reviews will be based on se milestones and timelines. Each of the four thrust will have a coordinator with independence to pursue the goals and individual milestones.

***Outcome**:* The NBO will generate datasets, tools or instruments which will be shared with the scientific, clinical and private industry communities. To ensure the dissemination of the technologies in critical areas, the NBO will have two translational offices, one targeting clinical applications and the other technological applications. The clinical translation office will help plan, organize and run clinical trials, which will be carried out with collaborating hospitals and research centers. The startup office will be responsible for IP protection and distribution and will also serve as an incubator, providing space, infrastructure support and seed funding for those project that are deemed to have potential commercial applications.

***Collaboration with academia and extramural researchers**.* Besides a vibrant intramural technology development program, the NBO will have a program in place to host extramural research groups, as it happens fluidly in existing national laboratories. Teams from universities, hospitals or research institutions could block allocated time, from weeks to months, to either develop specific technologies, where the NBO could provide critical infrastructure, or simply to make use of NBO instruments for the acquisition of data.

***Collaboration with industry**.* We expect that the NBO will form collaboration with industry to foster technology translation. This includes both established players such as Medtronic and the growing body of start-up ventures focused on brain-computer interfaces, including Kernel and Neuralink.

FAQs:

Wouldn't the NBO overlap with the US BRAIN Initiative?

The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, now in its 5th of 12 years, is aimed at revolutionizing our understanding of the human brain by building neurotechnology. It currently employs 500 laboratories around the country in the world, funded with individual grants. It is widely seen as a success, as it harnesses the ingenuity and creativity of individual laboratories in developing neurotechnological methods that are starting to have an impact in research, in medicine and in the industry. At the same time, the BRAIN Initiative focuses exclusively on funding individual laboratories, or groups of them, and lacks an intramural program or a national center. Because of this, major challenges, such designing large-scale instruments and addressing major technological challenges, as described above, will remain unmet. Moreover, the recent mid-point review of the goals of the BRAIN Initiative that occurred earlier this year has refocused it on the application of technology to the translation setting, steering it further away from its initial focused mission on neurotechnology development.

Why can't existing research institutes do this?

Each of the five thrusts would aim at challenges that are outside the scope of existing research teams in universities and research institutes. There are three main reasons for this: i) size of the necessary teams, iii) large cost of the equipment and iii) necessity of interdisciplinary collaboration. It is essentially impossible to assemble, direct and maintain an institute like the one describe with the existing funding structure afforded by programs like the BRAIN Initiative, NIH, NSF or DARPA-style grants. While private research centers as Janelia Farm or the Allen Institute of Brain Science could step in and fill this void, they are either not focusing in neuroscience anymore (Janelia) or are explicitly not developing technology, but deploying it (Allen Institute).

What is the exact goal of the lab?
The main goal of the NBO is strictly to develop large-scale instruments to be shared with the community. Two addition It is to provide the means by which this technology reaches the clinical setting and the industry, generating startups. The NBO will not carry out fundamental neuroscience research, and thus will not compete with existing universities or research institutes, funded with multibillion dollar federal grants in neuroscience programs, but instead complement them by developing transformative instruments. This technological revolution would be analogous to the one that happened in Astronomy and Astrophysics, where individual instruments and individual university became obsolete once large scale telescopes were developed.

Could there be synergy with other FROs?
The NBO would naturally synergize with centers aim at human brain disease biology with proteomics and human brain sample banking but it would overlap (or subsume) FROs devoted to brain computer interface development. Examples of specific projects are listed in the Appendix.

How would this relate to priorities on competitiveness in AI?
Through its fifth thrust, focused on the development of novel computational approaches and mining of brain data, the NBO could have a significant impact on AI, through the generation of novel bio-inspired algorithms that could then be ported to the computer and AI industry. This algorithmic pipeline, providing potentially novel computational approaches to “hard” computer science problems, is avidly sought after by the tech industry, whose workhorse deep neural network) was actually directly inspired by the mathematical analysis of neural circuits.

What data do we expect this lab to produce?
The NBO will generate three types of data: structural (connectomes), functional (high throughput recordings of neural activity and molecular (chemical or genetic maps of nervous system) these data will be hosted, distributed and mined by the computational thrust of the NBO.

What specific staff does it need?
The core of the NBO will be highly specialized scientists and engineers, with a background in different fields, and assembled into multidisciplinary teams. These teams will be topic focus, as in a startup, and recruit researchers with different skills as needed.

What external relationships does it need?
The NBO will seek to establish external relation with several groups of stakeholders. This will include Fab foundries, microscope companies and lens manufacturers, medical imaging magnet manufacturers. In addition, there will be strong relationships with clinical hospitals to facilitate the establishments of preclinical follow-up and clinical trials of the methods developed.

Would the lab commercialize some innovations? How?
Yes, a core mission of the NBO will be the generation of neurotechology startups. We view this as a critical aspect of the NBO, which should be setup from the beginning to facilitate the path towards the commercialization of the technology. As mention, a dedicated section of the NBO will be devoted to this.

sAPPENDIX: EXAMPLE KICK-OFF PROJECTS

Our proposal is project-agnostic, as it aims to provide an institutional framework where different projects could be developed. Key to the success of the NBO will be in identifying a few key projects that are beyond the scope and risk profile of traditional funding sources. We also hope that many of them will have translational potential in being able to influence human health. In the following we detail some potential examples of projects to be worked on by the NBO, organize by thrust.

Thrust 1. Connectomics.

- Connectomes from the mouse to the human
- Rosetta 3D molecular physiology
- Epiconnectomics.

Thrust 2. Molecular Brain Mapping.

- Single cell proteomics.
- Human brain disease molecular mapping.
- Human brain banking.
- Multiplex stimulated Raman imaging.

Thrust 3. Nanoelectrical, acoustic, and photonic neural probes. These will be projects that will leverage commercial foundries, CMOS and photonic. These will produce new electronic and photonic devices, far beyond that is available commercially. NBO resources would be engaged for additional process steps and packaging not supported for commercial applications. Human clinical translation envisioned for severa. Projects here can include:

- Implantable plenoptic imagers, both surface and penetrating.
- Novel imager designs with various approaches to lensless imaging and integrated spatial light modulation.
- Devices that integrate piezoelectric transducers or CMUTs for acoustic interfacing for photoacoustic or acoustophotonic techniques.
- Other imagers and devices in support of Area 4.
- Large-scale, active implantable CMOS MEA designs including wireless design

Thrust 4. Optical and magnetic imaging. Approaches here will push the state-of-the-art in both invasive and noninvasive imaging and will have strong synergy with the techniques employed in the implantable of thrust 3. This include optical probes/reporters.

- NIR optical tomography technique for noninvasive imaging.
- Holographic brain imaging.
- Optically pumped MEG.
- Photoacoustic and acoutophotonic imaging.
- Probes including infrared functional probes, genetic voltage indicators, optochemical probes.
- Design and fabrication of plasmonic nanoparticles for imaging and photostimulation.

Thrust 5. Computational data analysis.

- Connectome assembly and data mining.
- Multiplexed spike sorting analysis.
- Circuit inference modelling.
- Large scale neural network simulations.
- Complete biophysical models of neurons and circuits.

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