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A National Network of Neurotechnology Centers for the BRAIN Initiative

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We propose the creation of a national network of neurotechnology centers to enhance and accelerate the BRAIN Initiative and optimally leverage the effort and creativity of individual laboratories involved in it. As "brain observatories," these centers could provide the critical interdisciplinary environment both for realizing ambitious and complex technologies and for providing individual investigators with access to them.

> Progress in science depends on new techniques, new discoveries, and new ideas, probably in that order.
>
> —Sydney Brenner

The BRAIN Initiative Today

In our original proposal for a Brain Activity Map (BAM) Project (Alivisatos et al., 2012), we emphasized that the scientific understanding of the brain has been hampered by the limitations of traditional methods for recording neuronal activity. These methods largely measure one neuron at a time and thus remain ill-suited for probing complex neural circuits that likely operate at higher, emergent levels of functionality. To solve the challenges of observing and interacting with neural circuitry at these higher levels of complexity we pointed to the recent advances in nanotechnology, molecular reporters, advanced optical and photonic systems, and large-scale semiconductor integration. These fields are now sufficiently mature to permit their concatenation into powerful neurotechnologies that will fundamentally transform how neuroscience research is carried out. To enable this technological coalescence, we encouraged interdisciplinary teams of physical scientists and engineers to closely unite with neuroscientists in order to jointly develop new experimental and computational tools for neuroscience. Our ideas formed the basis of what became the BRAIN Initiative (Insel et al., 2013), a national White House Grand Challenge that currently involves more than one hundred U.S. laboratories and numerous regional offshoots. The collective tackling of this grand challenge in science and technology is already widely perceived to be a national success and an example of U.S. leadership in science and technology. Indeed, since its inception, similar initiatives have been launched by other countries; this indicates global consensus about the scientific value and potential of the Initiative.

In this NeuroView perspective, we revisit an important component of our original BAM proposal—one that, if realized, will significantly leverage the progress achieved by the BRAIN Initiative. Specifically, we wish to reemphasize the development of a coordinated, national network of neurotechnology centers, devoted to the creation and dissemination of next-generation tools for neuroscience, neuromedicine, and brain-inspired engineering. While the single- or few-investigator efforts now supported by the BRAIN Initiative are yielding significant accomplishments that can serve as important elements for future neurotechnology, we believe that achieving the project's full potentiality—that is, creating large-scale tools—requires efforts anchored within the well-validated center paradigm. It is our view that the technological challenges that must be surmounted are sufficiently complex that they are beyond the reach of single-investigator efforts; we believe they can only be tackled through highly coordinated, multi-investigator, cross-disciplinary efforts. Below, we expand on this proposition, outlining our reasons and evidence that implementing a network of neurotechnology centers can ensure the success of the BRAIN Initiative.

National Centers Enable Complex, Transformational Science

To illustrate the power of the center paradigm, we cite three recent and significant scientific achievements in the biomedical and physical sciences that have been enabled by center-scale efforts. First, we point to gene-sequencing technology, which has enabled the modern era of genomics. Based on previous successes with particle accelerators, chromosome sorting, and development of computer infrastructure, the U.S. Department of Energy first envisioned a national center-based approach for genomics in the mid-1980s (Cook-Deegan 1989). It then proceeded to fund individual technology-oriented laboratories' efforts to build the many initial components essential for developing genome sequencing instrumentation—including improvements to Sanger sequencing enzymes, fluorescent labeling, capillary electrophoresis, etc. Indeed, it was through subsequent, coordinated efforts and partnerships that evolved between two national centers, one at Caltech and the other at Applied Biosystems, that these individual components were ultimately concatenated into an integrated technological system comprising automated gene sequencing instruments, reagents, and software. After evolving through several models, the Prism 3700 Sequencer was eventually upscaled for robust mass production. Its subsequent acquisition by sequencing centers worldwide powered the efforts that culminated in the elucidation of the human genome (Springer, 2006). In the ten years following this achievement, the U.S. National Institutes of Health supported an even more aggressive push toward "next-generation sequencing" that ultimately resulted in a million-fold improvement in the cost and quality of gene sequencing technology. These breakthroughs resulted in an unanticipated economic bonanza: the $3.8 billion initial federal investment in the Human Genome Project, followed by an additional $10.7 billion through 2012, has since generated an economic output of $965 billion and more than 4.3 million job-years of employment (Battelle Technology Partnership Practice for United for Medical Research, 2013). This represents an impressive return on investment of $65 for every $1 invested.

In physics and astronomy, the center paradigm has long been understood to be the means for technologically ascending what is termed the technology readiness level (TRL) index (Moorehouse, 2002). Coordinated, center-scale efforts have enabled complex projects to culminate in systems that are sufficiently mature to permit the launching of sophisticated experiments and cutting-edge exploratory missions with a high probability of success. A prominent example of such a project is IceCube (Shi et al., 1998), a kilometer-scale neutrino observatory at the South Pole that, in 2013, first achieved detection of neutrinos originating outside of our solar system (Aartsen et al., 2015). Its underlying technology was developed, perfected, and assembled by a highly coordinated network of contributing laboratories. These efforts in this network were distributed at various points and institutions nationwide but were coordinated by a National Science Foundation-funded center at the University of Wisconsin, Madison. Another example is NuStar (Harrison et al., 2013), the satellite-based X-ray telescope that is now beginning to provide astounding new images and insights into black holes and violent events in the universe's evolution (Perez et al., 2015). NuStar followed a paradigm similar to that of IceCube, in this case through a NASA-funded center led by Caltech astrophysicists. In these, and many other similar examples, the center paradigm has harnessed the collaborative power of interdisciplinary scientific teams to solve critical problems and advance the frontiers of science. We ask: why should 21st-century neuroscientists continue to operate in isolation, when they could powerfully organize to tackle major outstanding problems in concert?

Scientific Need for National Centers for Neurotechnology

We strongly believe that a coordinated national network of neurotechnology centers can play a vital role, both primary and catalytic, in enhancing neuroscience in general, and the progress of the BRAIN Initiative in particular. To support this, we outline four primary areas of the BRAIN Initiative that are crucially dependent on significant technology developments—ones that could profit critically from a center-based framework.

- *Connectomics* is the systematic ultrastructural reconstructions of neural circuits (Lichtman and Denk, 2011). Today, some of the most advanced platforms for large-scale electron microscope-based connectomics involves the use of instruments with 61 or more beams (Lichtman et al., 2014), which are far too expensive for individual laboratories to acquire, implement, or even maintain. Since connectomics is an enterprise that requires automation and massively parallel data acquisition and analysis, it is sensible for such instruments, or even larger future machines, to be hosted within one such center to facilitate research for the entire neuroscience community. To this could be added complex future instrumentation capable of integrating connectomics with transcriptomics and cell history, that is, with developmental lineage and activity (Marblestone et al., 2014). Here, candidate technologies may also involve specialized super-resolution fluorescent microscopy (Chen et al., 2015), plus in situ identification of molecular profiles and barcodes (Crosetto et al., 2015). These complex technologies are, again, perhaps most appropriate for deployment within a center-based context.
- Assembly and deployment of massively multiplexed, implantable *electrical or photonic neural nanoprobe systems* will require large-scale semiconductor integration, nanofabrication, robust foundry-scale production, and big-data computational resources. If left to individual laboratories, these tasks cannot be carried out with the level of reproducibility, robustness, and scale of production needed to drive next-generation experimental neuroscience. We believe the technology underlying proof-of-concept subsystems must follow well-validated protocols to permit their coordination and transferral to state-of-the-art industrial foundries, which maintain sophisticated instruments and process tolerances for mass production at a precision and scale that renders university- or national-laboratory-based fabrication obsolete. During their initial phases of development, the requisite integration and production of advanced tools for fundamental neuroscience discovery are unlikely to be sustained by venture funding or the commercial sector. We believe that bringing coherence to

the process of creating individual neurotechnology elements, and then integrating them into complex and robust instrumentation systems, can only be optimally pursued through the center-based paradigm.

- Likewise, state-of-the-art *optical and magnetic resonance 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. For example, progress in optical microscopy is limited to the use of commercially available infrared lasers and optics, high-speed modulators, large-scale objective lenses, and optical components. This equipment is not specifically engineered for neuroscience applications. To do so involves specialized design knowledge, precision engineering, and micro- and nanofabrication expertise and infrastructure; in general, neither individual neuroscience laboratories nor university facilities and research institutes are equipped for this. This presently constrains 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.
- Finally, advanced *storage and computational data mining* are inextricable elements that underpin all emerging neurotechnologies. The amount of data collected with the new neurotechnologies is expected to dwarf the output of all previous methodologies (Alivisatos et al., 2012). 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 data sets 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—we believe that access, control, and analysis of large-scale neuroscience databases should, as a public resource, remain in the hands of a national center. Here, the Human Genome Project points to a potential path forward, as it has solved similar data and privacy challenges.

Neurotechnology Centers Will Amplify Single-Investigator Achievements

The initial steps of the BRAIN initiative have laid the groundwork for the next critical stages: enabling the development of integrated neurotechnology systems and, subsequently, the broad dissemination of newly created tools. There could be tremendous opportunity for rapid progress in the four areas mentioned above if the BRAIN Initiative expands beyond its current portfolio of single- and few-investigator projects. Efforts of individual laboratories—driven by independent creativity and the exploration of diverse approaches—will remain critical and will be powerfully enabled by this new network. Rather than drawing away resources from individual laboratories, a national network of neurotechnology centers will both anchor and nurture this PI-scale creativity. In particular, a center-based model will enhance the productivity and output of individual laboratories: removing the essential burden of systematic engineering—an absolutely essential yet technical and time-consuming piece of the process—thereby permitting individual labs and scientists to redirect their focus and energies toward activities at the frontiers: question-posing, problem-exploration, and concept-inventing. Centers will complement this by providing sustained and coordinated technological support to enable greater synergy and coherence in long-term planning for independent research groups. Realizing high-TRL neurotechnologies requires the disciplined approach that only a highly coordinated, center-based research network can provide.

The sheer diversity of requisite component technologies makes their concatenation impossible without overarching coordination and standardization of approaches and interconnections. Centers can provide the galvanizing vision necessary to coordinate the pursuit and optimization of innovative elements by the separate laboratory participants. Centers are ideal for preserving mission coherence and for sustaining the complete ecosystem of elemental operations that, by nature, range from the exalted to the pedestrian. Many of these essential operations may not be perceived, in isolation, as sufficiently cutting-edge to be fundable. Further, many will also be inappropriate for graduate or post-doctoral researchers; instead, to ensure their reliable execution, these activities could be better carried out by professional scientists and engineers. Yet it is generally impossible to sustain skilled and experienced technical personnel through short-term single-investigator funding.

We also emphasize that neurotechnology development cannot be pursued in an experimental vacuum. At all stages in project evolution, the coordinated technological efforts must be directed toward high-profile experimental neuroscience goals. Hence, they must be co-directed by close partnerships between experimental neuroscientists, physical scientists, and engineers. Centers must therefore include an inextricable cohort of experimental neuroscientists—not simply as beta adopters, but as integrated alpha co-developers. The essential technological development must be driven forward by iterative, closed-loop cycles of development, technical validation, neuroscience experiments, and subsequent optimization.

Finally, in addition to coalescing new innovations to develop and standardize next-gen technologies, centers are ideally positioned to enable both technology transfer (to enable robust mass production of instrumentation systems) and regularization of experimental neuroscience protocols (to permit deployment of standardized, next-generation instrumentation platforms to the laboratories of individual users).

Toward a National Network of Neurotechnology Centers

As a starting point to promote further discussion, we briefly sketch how a network of neurotechnology centers might be implemented and what might constitute their goals. In a way, these centers could be similar to existing astronomical observatories, where large-scale technology development and deployment is carried out in a centralized fashion, and where facilities are then shared by the entire community. We envision centers that, as "*brain observatories*" (Yuste and Church, 2014), are independent while being strongly interactive and collaborative—not just at their outset, but throughout their lifespan. Such centers could be created in existing academic laboratories or national facilities or implemented de novo. Although ideally coordinated at a single location or institution for efficiency, the term "center" need not connote localization. Efforts could, in principle, coalesce cross-disciplinary efforts from a spectrum of participants: disparate laboratories, corporate partners, and public and private research institutions. These centers could optimally leverage ongoing single- and few-investigator-scale projects supported with federal BRAIN Initiative funding; yet they would also enable larger, coherent technological and research programs to emerge. Strong connections between the various "nodes" of a national network of centers might be facilitated and coordinated by a single "hub"—perhaps orchestrating a network of several national laboratories, for example, as was the case for the public efforts of the Human Genome Project. We believe that such a hub will be especially important for facilitating the unprecedented scale of "big data" tasks that brain activity mapping will certainly engender. Finally, as occurs with national centers in other disciplines, neurotechnology centers could serve as the natural points of human convergence and interaction, accelerating, as "watering holes," progress and ensuring the open and effective dissemination of the technology.

In summary, in celebrating the nascent achievements of the BRAIN Initiative, we also aim to amplify and accelerate its impact. We think it is important that a national, public effort be mounted to create a national network of neurotechnology centers, supported with federal funding. These centers would unite and synergize the hundreds of individual laboratories funded by the BRAIN Initiative. Several center-scale efforts in neuroscience have recently been embarked upon by private research foundations, such as the Allen Institute for Brain Science and the Howard Hughes Institute Janelia Farm campus; in certain respects, these initiatives might serve as potential models. However, while private-sector efforts will no doubt remain important participants in national efforts, they are necessarily limited in scope and focus. They are unlikely to assemble, manage, and sustain the deep and wide efforts needed for nucleating the technological revolution that we believe is possible. In fact, because the neurotechnology centers we advocate will ultimately benefit society at large, we believe they should exist within the public domain and be managed as a national resource. Jump-starting such national centers will require consensus among researchers, federal officials, and private organizations; to achieve this, inspired public leadership will be essential.

The BRAIN Initiative has laid the groundwork for success, and it is poised to engender a new and exciting phase of neuroscience with immense potential for societal benefit and scientific discovery. The rapid establishment of a vital national network of collaboratively-minded neurotechnology centers is the surest path to this goal. If the BRAIN Initiative is to succeed as a national effort of historic proportions, it must be treated as such.

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