# ***National Centers* for innovative neurotechnology development are now *essential*.**

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Since its official announcement in 2012, the Obama Administration's **BRAIN Initiative** has jump-started the development of a variety of new neurotechnologies in an effort that could have an historic impact. In our original proposal to OSTP of a *Brain Activity Map Project* that helped nucleate this Initiative [1], we emphasized that understanding the brain has been hampered by the limitations of traditional methods for recording neuronal activity one neuron at a time. As a solution to this challenge, we pointed to efforts in nanotechnology, molecular reporters, optical/photonic systems, and semiconductor large-scale integration that are now sufficiently mature to permit their concatenation into powerful neurotechnologies that could fundamentally transform neuroscience research. To enable this transformation, we argued that it is essential for interdisciplinary teams of physical scientists and engineers to engage with neuroscientists to develop new, large-scale experimental tools for neuroscience. Our ideas formed the basis of what has become the BRAIN initiative, which currently involves more than one hundred laboratories and is widely perceived as a successful example of our country tackling a grand challenge of science and technology.

In this current document, we revisit one important aspect of these original arguments, which we believe can significantly leverage the progress that is being achieved within the BRAIN initiative. Specifically, we wish to take this opportunity to emphasize an essential, but as yet unrealized, component of our original vision. This is the creation of a coordinated network of four to six *National Neurotechnology Development Centers*. While present BRAIN Initiative efforts are beginning to yield accomplishments that will serve as important *elements* for next-generation neurotechnology, achieving the full spectrum of potentialities we envisaged will only become possible within such *Centers*. The essential goals transcend what is possible via present single- or few-investigator funding models; the technological challenges that must be surmounted are sufficiently complex that they can **only** be achieved through *highly coordinated* multi-investigator and cross-disciplinary efforts. We believe it is critical that these efforts be synchronized across a spectrum of requisite technologies, spanning novel molecular and nanoparticle reporters, nanotechnologies, instrumentation, computational hardware, data mining and numerical and theoretical analysis. Below, we expand on our original vision of this coordinated assemblage of effort – which we term the *Center paradigm* [2].

We cite three recent and monumental scientific achievements to illustrate our point. First, **gene sequencing technology** has enabled the modern era of genomics. *Components* that contributed to the development of gene sequencing instrumentation were initially developed within individual laboratories: Sanger sequencing, fluorescent labeling, capillary electrophoresis, *etc*. However, it was only through coordinated efforts within a *Center* at Caltech and at Applied Biosystems that these could be successfully concatenated, and assembled into a technological *system* that eventually became the first automated gene sequencer. Passing through several models, it was eventually robust production *en masse* of the **Prism 3700 Sequencer,** and its deployment at the hundred-fold scale in sequencing *Centers* worldwide, that powered efforts culminating in the unraveling of the human genome [3]. In the ten years that followed this achievement, an even more aggressive "next-generation sequencing" technology push (started by the NIH in 2004) resulted in a million-fold improvement in the cost and quality of gene sequencing. Incidentally, this technological breakthrough unexpectedly also resulted in an economic bonanza, since the $3.8 billion federal investment in the genome project generated an economic output of $796 billion after it was completed; this is a return of $141 for every $1 invested.

Beyond the realm of biomedical sciences, for example in physics and in space exploration, the *Center* paradigm has long been understood to be the means for technologically ascending what is termed the *TRL Index* (Technical Readiness Level) [4]. Coordinated *Center* efforts enable extremely complex projects to culminate in systems that are sufficiently mature that sophisticated experiments and cutting-edge exploratory missions can be launched with a high probability of success. **IceCube** is a prominent example of such a project [5]. It is a km-scale neutrino observatory at the South Pole that, in 2013, first achieved detection of neutrinos that originate outside of our solar system. Its underlying technology was developed, perfected and assembled by a highly-coordinated network of contributing laboratories – distributed at points nationwide, yet coordinated by a *Center* at the University of Wisconsin, Madison. Another example is **NuStar**, 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 [6]. It also followed this paradigm – through a *Center* led by Caltech astrophysicists. In these and many other areas, the *Center* paradigm has harnessed the immense power of interdisciplinary teams of scientists to help solve critical problems and propel the frontiers of science forward.

Could similar *National Centers* play a vital role in the future of neurotechnologies? We emphatically believe the answer is yes. As examples of what *Centers* could catalyze, we outline four areas of critical importance to the BRAIN Initiative where significant technology development may not be realized unless anchored within such a framework.

- **Connectomics** is the systematic ultrastructural reconstruction of neural circuits. Today, what is arguably the most advanced platform for large-scale electron microscopy based connectomic reconstructions involves the use of a 61-beam instrument, manufactured commercially. This instrument is far too expensive for individual laboratories to develop or even to maintain. Since connectomics is an enterprise requiring automation and massively-parallel data acquisition and analysis, it would be sensible for such an instrument, or even larger future machines, to be hosted within one such *National Center* to facilitate research for the entire community. Also important in this context is novel instrumentation capable of integrating connectomics with transcriptomics and cell history (developmental lineage and activity); candidate technologies may involve specialized super-resolution fluorescent microscopy that, again (given complexity, requisite operator expertise, and cost), is appropriate for deployment within the *Center* paradigm.

- Realizing the next-generation of massively-multiplexed, implantable **electrical or photonic neural nanoprobes** require large-scale integration and nanofabrication, which are processes far too complex to be carried out by individual laboratories with sufficient robustness and scale of production. To drive next-gen experimental neuroscience, emerging proof-of-concept sub-systems must be transferred to production at industrial foundries, which maintain sophisticated instruments and process tolerances at a precision and scale that make traditional "home made" (university scale) fabrication obsolete. These must be coupled to custom-designed chips permitting high-channel count signal acquisition and processing, which are again generally beyond the scope of what individual investigators can produce. The cost and scale of the coupled development challenges here are far beyond what is possible within the single-investigator model.
- State-of-the-art **optical and magnetic imaging technologies** necessitate more powerful lasers or magnets which, again, stretch the limit of what individual laboratories or universities can acquire and, then, maintain at peak operating levels. In the optical microscopy realm, progress is also presently limited by the lack of commercially-available high-speed modulators, large-scale objective lenses and specialized optical components. All of these require very specialized design knowledge, precision engineering, and micro- and nanofabrication facilities. Individual neuroscience laboratories, university facilities, and research institutes almost always lack the full range of capabilities required.
- Next-generation **data storage and computational data mining** will be essential for employing these novel neurotechnologies. The amount of data we estimate will be collected with these new instruments and approaches will soon completely dwarf the output of all previous neuroscience applications. Individual laboratories with traditional servers and cluster-based IT will be overwhelmed with a data deluge unless assisted by a *National Center* with skilled personnel, supercomputers, and appropriate storage to enable that these valuable new data sets are appropriately stored, protected and shared.

Progress in these four critical technological areas will be stymied if the BRAIN initiative limits itself to the present single-investigator paradigm.

To realize future neurotechnology that many of us believe is achievable within the next decade, jumpstarting the *Center* paradigm is essential, as the aforementioned examples well illustrate. The new technology we envisage will completely transform how neuroscience is carried out, and how neuromedicine will be practiced in future. **To achieve these transformational, high-TRL neurotechnologies we must now transcend the single-investigator research paradigm.** While the efforts of individual laboratories working in these critical areas will continue to provide the bedrock of independent creativity and exploration of innovative approaches that the nation needs, these *National Centers* will nurture this creativity, transition them into the context of regularized interoperability with other advances, and thereby enhance the productivity and output of individual laboratories by taking away the burden of systematic tool development in favor of creative question-posing and exploration. Centers will also provide sustained coordinated technological support that can enable greater synergy and long-term planning for independent research groups. In fact, it is well proven that *Centers* are the ideal venue to provide the focal points for dialog, planning, execution, and deployment of complex technology. It is increasingly clear that individual labs cannot handle the entire spectrum of challenges in next-gen neurotechnologies – given the requisite personnel, scope of efforts, and costs involved. In the absence of a *Center* paradigm, the otherwise uncoordinated constellation of funded laboratory researchers will solely provide proof-of-concept demonstrations of what *could* constitute sub-components of the potential technological systems. But such an approach does not provide the infrastructure for achieving the eventual coordination and concatenation of these proof-of-concept achievements into complete, next-generation instrumentation *systems*. We emphasize that the sheer diversity of requisite component technologies makes their concatenation impossible without overarching *coordination* and *standardization* of approaches and interconnections. Standardization of platforms is essential and will be a natural consequence of the creation of *National Centers*. They will permit coordinated pursuit and evolutionary optimization of innovative system elements by separate laboratories, but within a context permitting their subsequent assembly to create complete neurotechnology platforms. Absent *Center*-based efforts, we may never emerge from the present “neuro-craft” era – cobbled together by today’s albeit-skilled single investigator “artisans” – to realize the potentialities of a true neurotechnology revolution.

Centers alone also can provide the overarching and galvanizing mission *vision* to sustain the elemental operations that, by their nature, must range from the exalted to the pedestrian. Across this span of efforts, each individual contribution plays its own critical role toward realizing overall *system* technology. For some of the essential system elements (that is, *sub*-components), their requisite optimization and specialization to tasks at hand may not be sufficiently cutting-edge to be separately fundable. Further, they may also not be appropriate fodder for building the careers of graduate or postdoctoral researchers; hence, these activities must be carried out by professional, skilled staff because it is imperative to insure their reliable execution. However, this in no way diminishes the central importance of *all* such specialized sub-components; when integrated into the entire systems envisaged – these elements and their reliability provide the critical functionality enabling the transformative neurotechnology. Again, this paradigm of effort is beyond the scope of traditional single-investigator science funding.

We must also emphasize that next-gen neurotechnology development cannot be pursued in an experimental vacuum. *At all stages* of its evolution it must be directed towards concrete experimental neuroscience research goals (so as to avoid a devolution into self-serving "widgetry"). Hence, it must be co-directed by close partnerships between experimental neuroscientists and technologists. In fact, it is essential that *Centers* include a cohort of experimental neuroscientists – not simply as beta adopters, but as intimately integrated, alpha *co-developers* [2]. Together with instrument developers, the necessary neurotechnological advances will be driven forward through closed-loop, iterative cycles of development, validation, neuroscience experimentation, and subsequent optimization.

Although we have discussed and developed possible approaches to realizing a coordinated network of *National Neurotechnology Centers*, here we provide only a bare sketch of how they might be realized and what the goals of these *Centers* might be. Again, the overarching mission of these *Centers* will to coalesce new innovations to develop and standardize next-gen technologies, regularize protocols with them, and to transfer the technology to permit robust instrumentation systems production *en masse*. Of course, **the ultimate goal is to achieve standardized next-gen instrumentation platforms and to make them available for wide deployment to the neuroscience community.** These neurotechnological systems will be developed to permit *brain activity mapping* with sufficient uniformity of data acquisition to permit standardized cross-comparison between output of individual laboratories. We have previously outlined the spectrum of cross-disciplinary efforts and technology that is essential to this mission, which *National Neurotechnology Centers* must coordinate [7]. We envision these *Centers* would be independent, yet strongly interacting, not just at the outset – but throughout their lifespan. They would leverage ongoing single-investigator-scale BRAIN Initiative work, already embarked upon with federal funding, and also single-investigator efforts that will be funded and pursued in future. The strong connections between these *Centers* might themselves be facilitated and coordinated at a national scale by a single "hub" – for example by a national laboratory (as was the case for the public efforts in the Human Genome Project). Such a hub will be especially important to facilitate the large-scale computation and the unprecedented scale of "big data" that *brain activity mapping* will engender, as previously mentioned. **Moreover, by serving as foci, these *Centers* could synergize and interconnect the full spectrum of diverse and innovative research activity funded as individual investigator grants within the BRAIN Initiative.** Finally, as it occurs with national centers in other disciplines, these *Centers* could serve as the natural "watering holes" (points of convergence) to accelerate progress and to ensure the open and effective dissemination of the technology.

In summary, we congratulate the OSTP on the BRAIN initiative and celebrate this Initiative's nascent achievements; here we aim to further help to massively amplify and accelerate its impact. Accordingly, we believe it is now urgent that a national and *public* effort be mounted to create a small cluster of *National Neurotechnology Centers* with federal funding. These Centers would form an ideal partnership with the hundreds of individual laboratories funded by the BRAIN initiative. Center-like efforts in neuroscience have been recently embarked upon by private research foundations, such as the HHMI and Allen Institute. While important participants, the efforts of private research foundation are necessarily limited in scope and focus – and, hence, they cannot sustain the large-scale levels of effort that are essential for achieving the true neurotechnology revolution now possible. In fact, because the *Centers* we propose will ultimately benefit society at large (through subsequent translation of their benefits to neuromedicine), they should squarely be in the public domain as a national resource. We acknowledge that it is difficult to create these *National Centers* without the wide consensus among researchers, which is often hard to achieve. Here, inspired leaders have an essential role to play in galvanizing public and federal and private organizations to this end. As a nation, it is critical that we act now. If the BRAIN Initiative is to succeed as a national effort of historic proportions, we must treat it as such!

**REFERENCES**


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2. Here, by "Center" we do not necessarily mean to connote *localization* – although likely coordinated at a single institution for efficiency, *Center* efforts can indeed the coalesce cross-disciplinary efforts from disparate laboratories, corporate partners, and public and private research institutions.
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