The impact of the NIH BRAIN Initiative

The NIH BRAIN Initiative is currently in its fifth year. We reflect on its impact on methods development at a time when the program's future direction is under discussion.

In 2013, US president Barack Obama announced the National Institutes of Health Brain Research through Advancing Innovative Neurotechnologies Initiative, or NIH BRAIN Initiative. By the anticipated close of the high-profile program in 2026, it will have provided about $5 billion of funding. Although this sum seems enormous, it encompasses only about 5% of the funding that the NIH distributes to awardees in the field of neuroscience. Can the program's impact keep up with its high profile?

The overarching goals of the BRAIN Initiative are to markedly increase understanding of the human brain and to treat and possibly cure brain disorders. The BRAIN Initiative focuses on research aimed at neural circuitry, the level at which many disorders arise or manifest themselves, and it is in this area that the program is poised to make a major impact.

Nobel laureate Sydney Brenner argued that progress in science "depends on the interplay of techniques, discoveries and new ideas, probably in that order." Though its long-term goal is to improve human health, during its first five years, the BRAIN Initiative centered on the development of tools for monitoring, manipulating and analyzing neural activity. In this regard, the BRAIN Initiative was inspired by the Human Genome Project, which also initially focused on developing technology.

The NIH has defined several high-priority areas, such as cataloguing and defining cell types, establishing circuit diagrams, monitoring neural activity and developing interventional tools, in addition to theory and data analysis, human neuroscience and integrative approaches. So far, more than 500 publications have arisen from BRAIN Initiative projects in these areas. A large proportion of these publications report new or refined tools, as well as fundamental insights into the structure and function of neural circuitry in model organisms such as the mouse. The BRAIN Initiative has had a particularly strong impact on basic research into cell types and circuitry, tools for monitoring and manipulating activity, and computation.

Genetic access to the different cell types that make up the brain is a prerequisite for in-depth studies of the brain. The Cell Census Network is a large-scale community effort to generate a mouse brain atlas through molecular profiling of single cells. The project is expected to be completed by 2021 or 2022. The human and nonhuman primate counterpart is currently in a pilot stage and should be ready by 2026. These resources can then be mined to identify cell-type-specific marker genes, which serve as the basis for the generation of driver lines that can express functional tools in specific cell types.

Knowledge of the structural architecture of the brain is relevant for both basic and clinically oriented research. To this effect, BRAIN Initiative–funded projects map neural circuits in different organisms, from *Drosophila* to humans. The teams involved use technologies as diverse as electron microscopy, light microscopy and magnetic resonance imaging. The datasets produced by these projects will provide a rich resource for in-depth studies of neural connectivity.

The ability to monitor and manipulate neural activity is at the core of functional studies of the brain. Optical and electrophysiological approaches are the most widely used. In addition to well-established calcium sensors and optogenetic tools, sensors for neurotransmitters and improved voltage sensors are currently being developed. Because optical methods are sensitive to light scattering, approaches that facilitate the illumination of deeper brain regions will be crucial, and several BRAIN Initiative–funded projects have made inroads into this problem. On the electrophysiological front, electrodes that reduce damage associated with their implantation will benefit both research and clinical applications.

Large-scale efforts such as the Cell Atlas and connectomics projects generate unprecedented amounts of data to be stored and analyzed, thus necessitating the development of computational infrastructure. In particular, accessible file formats and standards for structuring and annotation of data, which differ across subdisciplines, will facilitate data reusability. Projects such as Neurodata Without Borders and Brain Imaging Data Structure address these issues in domains such as neurophysiology and magnetic resonance imaging. While the former has yet to be broadly adopted by the community, the latter already has a large user base.

The influence of the BRAIN Initiative has already extended beyond the tools, methods and infrastructure developed in its funded research projects, as it may have at least in part inspired similar neuroscience projects in other countries. For example, the Japanese Brain/MINDS project promotes mapping of the marmoset and human brains, as well as tool development. The Chinese counterpart focuses on cognition and the early diagnosis and treatment of brain disorders. The European Human Brain Project aims to understand the brain by modeling its function. Finally, there are numerous other brain projects in Israel, Korea, Australia and Canada, to name just a few.

As the first phase of the BRAIN Initiative approaches its end, stakeholders are discussing directions for the second phase and soliciting input from the neuroscience community at town halls and in discussion groups. While the initial idea was to transition to funding more discovery-based science, we believe that tool development should not be phased out. More technological advances and long-term investments are needed to translate the tools that have been developed into clinical practice. Funding for the next three years has already been allocated in legislation and is stable at around $400–450 million per year. Given that brain disorders are the leading cause of disability in the US, there is reason to hope that funding for the BRAIN Initiative will be maintained at its current level or higher until 2026.

Has the BRAIN Initiative's impact kept up with its promise? Cures for many brain disorders are still a far reach. But it is unlikely that the large-scale collaborative projects funded under the BRAIN Initiative's auspices would have been possible or have progressed as rapidly otherwise. Thus, the investments made already will have a lasting impact, and continued commitment should ensure steady progress into the future. ❐

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