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# The BRAIN initiative: a pioneering program on the precipice

Cory T. Miller, Xiaoke Chen, Zoe R. Donaldson, Bianca Jones Marlin, Doris Y. Tsao, Ziv M. Williams, Moriel Zelikowsky, Hongkui Zeng & Weizhe Hong

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Launched in 2013, the BRAIN Initiative (BRAIN) in the United States aimed to unlock the mysteries of the brain and develop new treatments for neurological and neuropsychiatric disorders. The success of this program is evidenced by the accelerated discoveries and development of interventions that are happening in real time. However, a recent 40% cut in funding for BRAIN threatens this once-in-a-generation opportunity to solve fundamental mysteries of the brain and achieve treatment breakthroughs that we once thought impossible.

The BRAIN Initiative — Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) — launched in 2013 with the vision of unraveling the mysteries of the most complex organ in our body — the brain — and leveraging these discoveries to develop better treatments for a range of neurological and neuropsychiatric disorders[1–3]. After all, treatment of brain disorders costs $1.5 trillion annually in the United States alone, and one in three Americans will be affected in their lifetime. Inspired by other successful scientific initiatives, this moon-shot program sought a different strategy to understand brain systems, one that has now proven more successful than even its founders might have envisioned. Not only has BRAIN accelerated the rate of discovery, but we are seeing new interventions being developed in real time, with potential cures for some of the most devastating brain disorders within our grasp[3]. However, the recent reduction in funding by $278 million (~40%)[4] for BRAIN in 2024 risks squandering this once-in-a-generation opportunity not only to solve keystone mysteries of the brain, but also to see more effective treatments for brain disorders in our lifetime that we never thought possible. The weight of this loss to science funding will be felt by every reader of this article, either directly or through a loved one. Sadly, almost no-one escapes the devastating impacts of brain diseases and disorders in their lives. This is even more so the case for the brave men and women who protect our country, because the incidence of these afflictions and related mental health challenges are significantly higher in our veterans, as many of their families know all too well.

This funding cut was particularly acute for systems and circuit neuroscience research — an integral area of research for understanding the complexities of neural systems and circuits in humans and animal models. After funding had been substantially increased in recent years for the Targeted BRAIN Circuits Projects — the funding programs that supported this area of research — new applications are no longer being accepted, effectively halting momentum for an important portion of the BRAIN grants portfolio.

Restoring funding for BRAIN is not as simple as increasing the overall NIH budget[4]. To understand this, one must consider how this program is funded. Base appropriations to support BRAIN are provided to the ten participating NIH Institutes and Centers (ICs), with additional funding authorized through the 21st Century Cures Act following a predetermined schedule (Fig. 1a). In 2024, the predetermined funding for BRAIN through the 21st Century Cures Act decreased substantially, but the base appropriations were not increased to offset this anticipated decline and were held flat at the 2023 funding level. As funding through the Cures Act is scheduled to decline further in the coming years and to end completely in 2026, the most direct way to restore funding for BRAIN is through increased funds appropriated directly for this program by Congress. If the base appropriations to BRAIN are not increased, by 2026 the program will be left with approximately one-third of its peak funding levels, amounting to a loss of nearly $1 billion for critical neuroscience research, which will have a debilitating effect on this pioneering program. It is important to point out that the success of the program has been the product of a collective effort by researchers throughout the country (Fig. 1b). The shortfall in funding will be felt not only by the principal investigators but also by the many trainees and staff that are cornerstones to the scientific enterprise.

## BRAIN is unique

What sets BRAIN apart from other NIH funding mechanisms, and how has it achieved its unparalleled success? The unprecedented growth in understanding of the brain that has occurred since the inception of BRAIN a decade ago is not simply the result of throwing more money at the problem. Instead, it is in large part the product of at least five unique — ultimately prescient — strategic decisions made about how to structure this program that laid the foundation for the progress we see today.

**Targeted research efforts.** A decade ago, it was obvious that we lacked not only a detailed understanding of many of the core functional units (cell types, circuits and so on) within the brain, but also methods to study them, particularly in living organisms. BRAIN set out to bridge this considerable gap by offering targeted grants to develop the tools needed to both identify and investigate the core building blocks of the brain[3] (for example, mapping neuronal and non-neuronal cell types and their connectivity in the brain, and monitoring and perturbing them in a cell-type-specific manner). This strongly motivated unique groups of investigators from different disciplines to work together to solve the engineering and biological challenges that had until then been seemingly insurmountable.

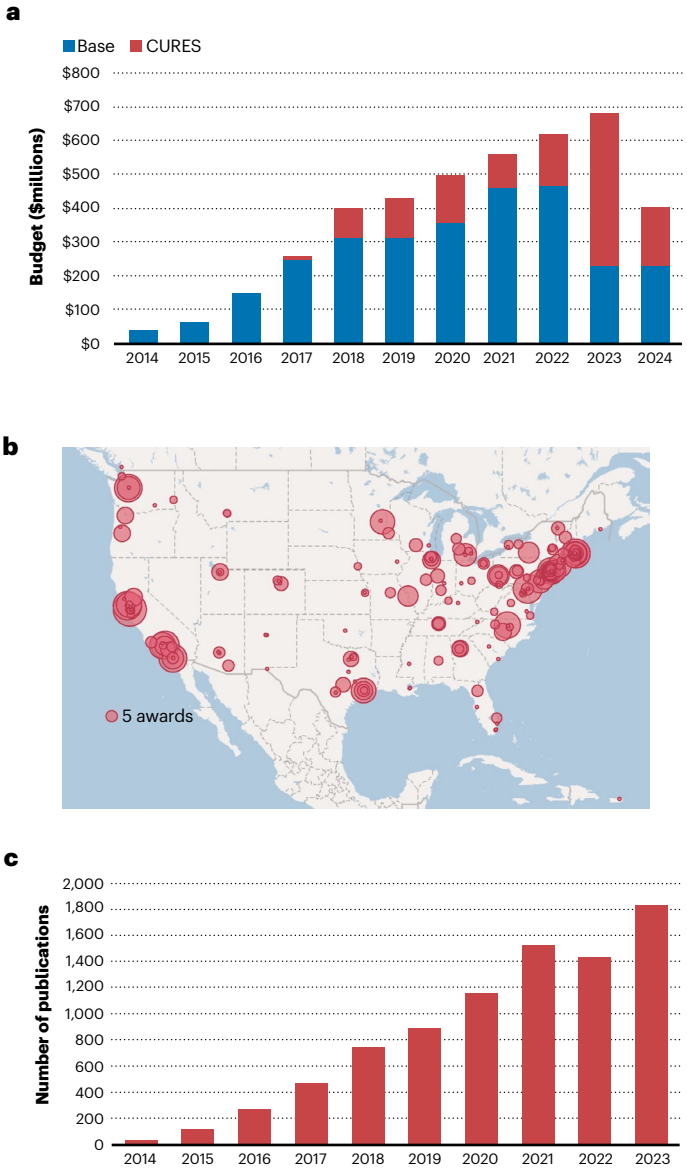


**Fig. 1 | Budgets, awards, and publications of BRAIN Initiative. a**, BRAIN Initiative budget for fiscal years 2014–2024 for base allocations and 21st Century Cures Act authorization[4]. **b**, 1,705 PIs across 265 institutions have been supported by 1,575 BRAIN awards[15]. **c**, Number of publications directly supported by BRAIN Initiative awards[15]. **a**, Reproduced from ref. 4, NIH. **b**, **c**, Reproduced from ref. 15, NIH.

**Discoveries through interdisciplinary team science.** BRAIN recognized at an early stage that the necessary keystone discoveries would be unlikely to come from a single lab or even a single scientific discipline. Rather, expertise from chemistry, biology, mathematics, engineering and other scientific disciplines would be needed. The practice of 'team science' emphasized in early funding opportunities at BRAIN has expanded to nearly all of these research endeavors, and because of its success is now influencing funding initiatives at the NIH more broadly[5].

**Complex computational tools are needed to understand complex systems.** One of the challenges faced when investigating brains is that they operate at all levels of the system – cells, circuits, systems and behaviors – in accordance with dynamic nonlinear principles that are almost impossible to characterize with low-dimensional analytic approaches. BRAIN recognized this challenge and pushed the development of cutting-edge computational tools and approaches to understand systems. Additionally, BRAIN had the prescience to understand the importance of theory-driven approaches in generating hypotheses for experiments, fostering collaborations between experimentalists and theorists to tackle these complex issues. Although these types of analysis were rare a decade ago, they have become common throughout neuroscience today.

**More species means more discoveries.** In the decades before BRAIN, neuroscience had increasingly limited its scope of inquiry to studies in a handful of 'model' organisms. A primary motivation for this myopic focus revolved around the powerful genetic tools that were originally deployed exclusively in a small number of laboratory species. Yet many of the core principles of neural function were discovered in species outside this small group – the pioneering discovery of the action potential using the giant squid axon is just one example. BRAIN recognized the limitation of working with only a handful of species, most of which are far removed from their wild counterparts owing to domestication and inbreeding. BRAIN has promoted the need for a wide variety of species to be studied and has critically fostered the development of tools needed to bring these species into the modern age of neuroscience. Indeed, the use of species including cephalopods, voles, bats and more has continued to advance our understanding of brains in just the past few years alone. Yet we have only just begun to explore the tremendous diversity of form and function that exists among the panoply of brains in nature.

**A holistic approach to the fundamental questions of brain function.** Before we can fix something, we need to understand how it works. BRAIN has placed a special emphasis on fundamental research questions without needing to directly link them to specific diseases, as is common at other funding agencies. Although core neuroscience research, such as uncovering the functions of neural circuits in the healthy brain, might not seem immediately critical to public health, it is an essential step toward eventually understanding brain disorders and diseases. For example, many psychiatric illnesses, such as schizophrenia and depression, are likely to result from large-scale circuit imbalances and can affect phenomena as foundational and mysterious as personal identity; only through much deeper understanding of how different brain areas interact to generate conscious perception and self-awareness can we gain traction to develop effective treatments when these processes do not function properly.

## What is BRAIN's return on investment?

Funding from BRAIN has led directly to countless discoveries about brains and thousands of related scientific publications on diverse topics ranging from molecular, computational, systems and cognitive neuroscience to biology, psychology, engineering and mathematics (Fig. 1c). The early stages of BRAIN focused on generating the tools and data needed to elucidate the cellular building blocks of the brain. The BRAIN Initiative Cell Census Network (BICCN), a main consortium within BRAIN, rapidly adopted, validated and scaled up the latest single-cell genomics technologies and has used them to create a

comprehensive transcriptomic, epigenomic and spatial cell type atlas for the entire mouse brain, the first in any mammalian species[6], as well as a draft cell census of the human[7] and non-human primate brains[8,9]. The identification of these molecular and cellular properties of the brain has led directly to improvements in the translational approaches that are needed to overcome brain diseases[10,11]. These range from identifying cell-type-specific signatures and biomarkers for brain diseases to the remarkable progress made with brain–computer interfaces (BCIs), which allow patients to perform dynamic motor tasks using only their thoughts to control prosthetics (including, recently, to speak[12]), and personalizing deep brain stimulation for major depression[13], and to innovations in delivering genes to brain cells intravenously that will transform how we treat numerous brain disorders and diseases[14].

What will be lost if BRAIN funding is not restored? BRAIN has brought a paradigm shift to neuroscience and moved the goalposts closer by showing what is possible with technological innovations. This BRAIN-inspired revolution is related not only to what has been discovered, but also to how we study the brain. The early investment by BRAIN in developing an expansive collection of tools aimed at precisely quantifying the foundations of neural systems has paid off at every level of the system and helped launch the BRAIN 2.0 Transformative Projects (BICAN, CONNECTS, Armamentarium) and the Brain Behavior Quantification and Synchronization Program (BBQS), which hold great promise to reimagine the field by elucidating the complex relationship between brain and behavior, including for the dynamic challenges that brains were optimized to overcome during evolution[2].

The dramatic reduction in funding has occurred at a critical juncture, right as the program is poised to leverage these prodigious tools and datasets to investigate the more complex questions about how cells and circuits interact to give rise to the complex behaviors and cognitive faculties that make us who we are. Within the framework of BRAIN, we are more likely to unlock keystone discoveries that have been enigmatic for generations but are critical to understanding brain disorders and diseases. The investment over the past decade has brought us to a tipping point; if this investment is continued, it could lead to unparalleled discoveries that will bring tremendous benefits to society. Rather than dementia being a decades-long emotional and financial burden for families, what if it could be treated?

The abrupt cut to funding is equivalent to your football team being on the 15-yard line with 20 s to play and the coach deciding to bench the star quarterback. While there are other funding mechanisms, BRAIN is simply different. It is perhaps unsurprising that such an iconoclastic program has been sorely needed because, after all, the brain itself is unlike any other organ in our body. If we are to understand not only what cells and circuits are in the brain, but also how they function as a cohesive system to support complex behavior and cognition in the healthy brain, as well as the process through which they deteriorate in disease, we need BRAIN. Notably, BRAIN recognized the essential importance of systems neuroscience research in diverse species to achieve this goal and — before the funding cut — had substantially increased funding to support this research in recent years through the Targeted BRAIN Circuits Projects mechanism. Reducing new grants in systems and circuit neuroscience research could limit our progress in functional understanding of the brain as a whole, if the enormous resources of cell type atlases and connectivity maps are not integrated with systems neuroscience research. It is at the functional brain systems level of scientific inquiry that transformative discoveries are so tantalizingly close.

To realize its full potential to fundamentally change the lives of countless people and families in our society — now and for future generations — not only must we reverse the reductions to funding outlined above, but it is imperative that funding for the BRAIN Initiative be increased above its peak levels (Fig. 1a). From the current precipice, the potential of a new frontier lies ahead, where we could bridge the gap between what is currently known about the brain and the development of broad-ranging treatments for brain diseases and disorders. Rather than squandering this investment and progress, let us take full advantage of what we have already learned and champion BRAIN to lead a renaissance of discoveries that will unlock the many remaining mysteries about our most complex organ.

**Cory T. Miller [1,13] ✉, Xiaoke Chen [2] ✉, Zoe R. Donaldson [3,4] ✉, Bianca Jones Marlin [5,6] ✉, Doris Y. Tsao [7] ✉, Ziv M. Williams [8] ✉, Moriel Zelikowsky [9] ✉, Hongkui Zeng [10] ✉ & Weizhe Hong [11,12,13] ✉**

[1]Cortical Systems & Behavior Lab, University of California, San Diego, La Jolla, CA, USA. [2]Department of Biology, Stanford University, Stanford, CA, USA. [3]Department of Molecular, Cellular & Developmental Biology, University of Colorado Boulder, Boulder, CO, USA. [4]Department of Psychology & Neuroscience, University of Colorado Boulder, Boulder, CO, USA. [5]Department of Psychology, Columbia University, New York, NY, USA. [6]Department of Neuroscience, Columbia University, New York, NY, USA. [7]Department of Molecular and Cell Biology, Howard Hughes Medical Institute, University of California, Berkeley, Berkeley, CA, USA. [8]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. [9]Department of Neurobiology, University of Utah, Salt Lake City, UT, USA. [10]Allen Institute for Brain Science, Seattle, WA, USA. [11]Department of Neurobiology, University of California, Los Angeles, Los Angeles, CA, USA. [12]Department of Biological Chemistry, University of California, Los Angeles, Los Angeles, CA, USA. [13]These authors contributed equally: Cory T. Miller, Weizhe Hong.
✉e-mail: corymiller@ucsd.edu; xkchen@stanford.edu; zoe.donaldson@colorado.edu; bjm2174@columbia.edu; dortsao@berkeley.edu; zwilliams@mgh.harvard.edu; moriel.zelikowsky@neuro.utah.edu; hongkuiz@alleninstitute.org; whong@ucla.edu

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## References

1. The BRAIN Initiative Working Group. *BRAIN 2025: A Scientific Vision* https://braininitiative.nih.gov/vision/nih-brain-initiative-reports/brain-2025-scientific-vision (NIH, 2014).
2. Ngai, J. *Cell* **185**, 4–8 (2022).
3. Ngai, J. *Neuron* **18**, 3003–3006 (2024).
4. *Understanding the BRAIN Initiative Budget* https://braininitiative.nih.gov/funding/understanding-brain-initiative-budget (NIH, 2024).
5. David, K. K., Fang, H. Y., Peng, G. C. Y. & Gnadt, J. W. *Neuron* **108**, 1020–1024 (2020).
6. Tosches, M. A. & Lee, H. J. *Nature* **624**, 253–255 (2023).
7. Siletti, K. et al. *Science* **382**, eadd7046 (2023).
8. Krienen, F. M. et al. *Sci. Adv.* **9**, eadk3986 (2023).
9. Chiou, K. L. et al. *Sci. Adv.* **9**, eadh1914 (2023).
10. Shirvalkar, P. et al. *Nat. Neurosci.* **26**, 1090–1099 (2023).
11. Provenza, N. R. et al. *Nat. Med.* **27**, 2154–2164 (2021).
12. Silva, A. B., Littlejohn, K. T., Liu, J. R., Moses, D. A. & Chang, E. F. *Nat. Rev. Neurosci.* **25**, 473–492 (2024).
13. Sheth, S. A. et al. *Biol. Psychiatry* **92**, 246–251 (2022).
14. Chen, X. et al. *Neuron* **110**, 2242–2257.e6 (2022).
15. *The BRAIN Initiative Overview* https://braininitiative.nih.gov/about/overview (NIH, 2024).

## Competing interests

H.Z. is on the scientific advisory board of MapLight Therapeutics, Inc. All other authors declare no competing interests.