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BRAIN @ 10: A decade of innovation

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Abstract

Now entering its second decade, the National Institutes of Health Brain Research Through Advancing Innovative Neurotechnologies Initiative, or the NIH BRAIN Initiative, has yielded remarkable success, accelerating research on the neural circuit basis of behavior and breaking new ground toward the treatment of complex human brain disorders.

Introduction

> *We stand on the verge of a great journey into the unknown—the interior terrain of thinking, feeling, perceiving, learning, deciding, and acting to achieve our goals—that is the special province of the human brain … No single researcher or discovery will solve the brain's mysteries.*—from the preamble to "BRAIN 2025: A Scientific Vision"

The mission of the National Institutes of Health (NIH) Brain Research Through Advancing Innovative Neurotechnologies Initiative (BRAIN Initiative) is to revolutionize our understanding of the human brain, with the goal of applying this knowledge to develop cures for human brain disorders. Spanning 10 of NIH's 27 institutes and centers, the initiative's efforts have been guided by two visionary strategic plans, "BRAIN 2025: A Scientific Vision" (https://braininitiative.nih.gov/vision/nih-brain-initiative-reports/brain-2025-scientific-vision) and the "BRAIN 2.0 Working Group Reports" (https://braininitiative.nih.gov/vision/nih-brain-initiative-reports). Over the past 10 years, the BRAIN Initiative has changed the neuroscience landscape by supporting the development and application of powerful new analytical tools and resources for mapping, monitoring, and modulating neural circuits. Among the many resources now widely available to the scientific community are an expanded collection of genetically encoded sensors and actuators of cellular activity and neurotransmitter signaling pathways (https://www.addgene.org/collections/brain-initiative/); high-density electrodes and imaging platforms capable of monitoring the activity of thousands, if not millions, of neurons simultaneously; and comprehensive cell atlases and connectivity maps of entire brains.

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DECLARATION OF INTERESTS

The author declares no competing interests.

What sets the BRAIN Initiative apart from other programs in the neuroscience research ecosystem, past and present? A technology-driven and disease-agnostic enterprise at its core, the BRAIN Initiative is uniquely situated to drive discovery across the entire neuroscience spectrum. With an emphasis on technology and embracing the value of diverse perspectives as drivers of innovation and creativity,[1] the BRAIN Initiative has attracted researchers with backgrounds in the physical, mathematical, and engineering sciences to work with neuroscientists on projects of all sizes. Collaboration across disciplines, a firm commitment to open science and resource sharing, and an intentional focus on integrating ethics and science[2] have built a scientific culture conducive to disruptive innovation that stretches existing disciplinary boundaries and forges new fields of inquiry. The accomplishments and pace of discovery enabled by the BRAIN Initiative over its first decade portend even greater advances in the next 10 years at the interfaces of the experimental, theoretical, computational, and data sciences.

Toward understanding the neural circuit basis of behavior

The human brain is the body's most complex organ, and in many respects, it is the most powerful and energy-efficient computer known to humankind. The human brain is capable of computations and flexibility surpassing those of non-biological machines. Yet for the most part, we still do not understand the brain's underlying computational logic. Research funded by the BRAIN Initiative has provided novel insights into how information is processed by neural circuits driving phenomena such as memory storage and retrieval, spatial navigation, sensory and motor processing, speech and language, mating and aggression, and intra- and interspecies communication, to name just a few.[3] Importantly, the initiative has made significant strides based on strategic investments in relatively simple and experimentally tractable model systems. This body of research has illuminated fundamental principles that can be generalized to inform and constrain hypotheses about how neural circuits underlie complex behaviors in multiple species, including humans. Moreover, the BRAIN Initiative's team-based approach is atypical in neuroscience and decidedly bold,[4] embodied by projects conceived and conducted by diverse groups and, in some programs, comprising large, multi-institution consortia of theoretical and experimental scientists. The initiative thus creates new opportunities for gaining insights into neural circuit function that might otherwise prove inaccessible via more narrowly focused efforts.

Enabling new opportunities in human neuroscience

An overarching goal of the BRAIN Initiative—and, indeed, of the broader neuroscience research endeavor—is to unravel the mysteries of the human brain. While research on non-human models has taught us many lessons about neural circuit function, they can only go so far to explain—on a mechanistic level—what about this organ makes us uniquely human. To address this challenge, the BRAIN Initiative's Research Opportunities in Humans program has built a vibrant ecosystem for rigorous and ethical research with human research participants as partners.[5] This program addresses questions ranging from formation and retrieval of memories to the computational principles underlying speech generation. These studies are made possible by the generosity of patients undergoing often invasive surgical treatments for unrelated neurological conditions. They adhere to a strong commitment to the many ethical issues suffusing this research, such as the implications of probing a human's seat of thought.[6] Investigations with our highly valued human research partners have led to ground-breaking discoveries into the neurobiological basis of human cognition and behavior, bringing us a few small but critical steps closer to understanding the inner workings of the human brain.

Through innovative and ethically sound collaborations with medical device manufacturers, in the past few years, we have seen an explosion of new personalized neural recording and neuromodulation approaches in humans, many of which have been supported by the BRAIN Initiative either directly or during their earlier, formative stages.[7] These studies have provided proof-of-principle demonstrations for a diversity of clinical interventions, such as restoring motor function after injury or stroke, neural prostheses that allow paralyzed individuals to communicate via brain-computer interfaces, and treatments for a growing list of neurologic and neuropsychiatric conditions including treatment-resistant depression, obsessive-compulsive disorder, post-traumatic stress disorder, binge-eating disorder, traumatic brain injury, and opioid use disorder. Successes in this domain have been enabled by advances in precision circuit mapping, invasive recording and stimulation technologies, and artificial intelligence (AI) to interpret brain activity patterns either to control neural prostheses or to derive biomarkers of mood states that can be used in adaptive or closed-loop designs to optimize stimulation for the individual patient. Considered science fiction just a decade ago, these first-in-human early-stage clinical trials offer unparalleled opportunities to develop desperately needed treatments for the millions of people living with brain disorders. Challenges moving forward include validating these preliminary successes in larger clinical trials. It will also be important to find ways to scale neuromodulation therapies, such as by transitioning them to less invasive modalities that can be made more readily available to populations that historically have had limited access to state-of-the-art medical care. The BRAIN Initiative is poised to meet these challenges by promoting and coordinating forward and reverse translation between fundamental research and mechanistically grounded clinical studies.

The BRAIN Initiative Cell Census Network: A triumph of team science

A full understanding of how the brain's neural circuits underpin behavior ultimately requires an understanding of their constituent cells' intrinsic properties and how they communicate with each other, the body's organs, and the outside world to receive, process, and convey information. The task of creating an accurate inventory of cell types in mammalian brains is particularly daunting, considering the number and complexity of cells predicted since the early days of Ramon y Cajal. A major achievement from the first decade of BRAIN Initiative research is a "parts lists" of mouse, non-human primate, and human brains provided by the BRAIN Initiative Cell Census Project. To maximize potential while managing risk, the project was conducted in phases with a mindset of "think big, start small, scale fast." Started in 2014 at the inception of the initiative, the BRAIN Initiative Cell Census Consortium (BICCC) was a collection of 10 pilot projects designed to develop and validate technologies that could be scaled to create a cell atlas of an entire mammalian brain.[8] In 2017, the BICCC gave way to the scaled-up BRAIN Initiative Cell Census Network (BICCN), which was charged with developing a comprehensive cell census and atlas of the entire mouse brain and laying the foundation for future efforts on non-human primate and human brains. In 5 short years, the BICCN developed and applied an impressive array of cutting-edge single-cell RNA and DNA sequencing technologies, statistical tools, and other approaches to produce a cell atlas of the entire mouse brain (https://www.nature.com/collections/fgihbeccbd) and draft cell atlases of the non-human primate and human brains (https://www.science.org/toc/science/382/6667). These comprehensive cellular inventories provide a census of brain cell types based on multimodal characterization of their transcriptomic, epigenomic, electrical, anatomical, and connectivity properties. Among the many discoveries from these landmark studies are the identification of more than 5,000 transcriptomically distinct cell types in the mouse brain (based on sequencing of more than 32 million cells!), their spatial locations in cortical and subcortical structures, the identification of gene regulatory networks specifying brain cell type diversity, and the organizing principles of neuronal diversification during development and over evolutionary time. Armed with these molecular, physiological, and anatomical signatures of the multitude of brain cell types, researchers can now ask more targeted questions about the roles that specific cell types play in underpinning behavior.

The success of the BICCN is a testament to the power of team science to produce resources at a scale that is simply beyond the reach of any one research group. The aforementioned brain cell atlases and the pilot “mini-atlas” of the primary motor cortex that preceded them (https://www.nature.com/collections/cicghheddj) were direct products of a carefully coordinated effort involving an international team of more than 250 researchers. Soon after the project began, researchers saw the true potential to transform neuroscience, and competition quickly gave way to a collaborative ethos that allowed individual groups to accomplish far more than they could have imagined on their own. In addition to providing invaluable resources that will spur many incisive investigations for years to come, the BICCN serves as a model for organizing large and diverse teams to generate similarly scaled resources for the benefit of the broader neuroscience community.

Bending the arc of neuroscience

Building on a decade of remarkable innovation and discovery, the BRAIN Initiative has set its sights on the future with four large-scale projects that hold promise to change the trajectory of neuroscience research. Inspired by the BRAIN 2.0 Working Group Reports, the BRAIN Initiative launched three transformative projects: the BRAIN Initiative Cell Atlas Network (BICAN), the BRAIN Initiative Connectivity Across Scales (BRAIN CONNECTS) project, and the Armamentarium for Precision Brain Cell Access program.[9]

BICAN, the third phase of the BRAIN Initiative Cell Census Project, continues to build brain cell atlases across multiple species, now with a major emphasis on mapping the human brain. These rich collections will define and characterize the wide diversity of brain cell types across mammalian species and thus will provide a framework for studying normal brain function, animal models of human disease, and, ultimately, human brain disorders. Indeed, tools and resources generated by the BICCN are already being applied directly to Alzheimer’s disease,[10] providing a cellular basis for understanding disease progression that may lead to new approaches with diagnostic and therapeutic promise. It is also important to note that creating cell atlases across the lifespan and representing the diversity of humans introduces additional logistical challenges and ethical considerations not encountered with projects focused on homogeneous animal models such as adult inbred mice. In this regard, lessons learned by the BICCN will provide BICAN researchers with the know-how and experience to navigate these complexities.

BRAIN CONNECTS, a consortium of scientists and engineers, was charged with developing scalable technologies to generate detailed wiring diagrams of whole mammalian brains. Meeting this challenge will require advances in tissue preparation and microscopy, as well as breakthroughs in data science and AI to store, manage, and analyze exascale datasets and make them accessible to the broader research community.[9] Dovetailing with BICAN and BRAIN CONNECTS, the Armamentarium for Precision Brain Cell Access program is developing state-of-the-art cell-targeting technologies to enable researchers to deepen our understanding of neural circuit function. Approaches include vector engineering, in some cases leveraging powerful directed evolution techniques, to facilitate transport across the blood-brain barrier and avoid uptake by other organs, allowing for a more facile delivery route than direct injection into brain tissue while minimizing toxicity. Additional cell-type-specific targeting is being pursued using gene regulatory elements identified through the genetic and epigenetic characterization of brain cell types by the BICCN and BICAN projects. These novel cell access tools will enable precisely targeted delivery of payloads to cell types of interest for both research and therapeutic applications.

A fourth large-scale project, the recently launched Brain Behavior Quantification and Synchronization program (BBQS), aims to develop and integrate highly precise quantitative behavioral readouts with neurophysiological measurements in both human and non-human models. The overarching goal of BBQS is to establish and validate causal relationships between neural circuit activity and behavior, information that can be used in the development of advanced closed-loop neuromodulation strategies to treat human behavioral disorders.

Together, these four projects will provide ground truth information about brain cell types and their connectivity, develop technologies to advance our understanding of neural circuit function and behavior at unprecedented levels of detail, and lay the groundwork for future precision circuit therapies—including precision gene therapies—for human brain disorders.

BRAIN data at scale: A new frontier for understanding natural and artificial intelligence

The next decade is expected to generate massive amounts of data across multiple experimental modalities that will outstrip current capabilities for data management and analysis. Accordingly, the BRAIN Initiative's ethos of innovation will inspire new experimental methods, AI technologies to convert data into knowledge, and more energy-efficient "neuro-inspired" or neuromorphic computer architectures that are urgently needed to reduce the exponentially increasing energy demands driven by the widespread adoption of AI technologies themselves. As a first step in this journey, the BRAIN Initiative's informatics program has established a federated network of data archives tasked with organizing data from multiple modalities (e.g., molecular, physiology, human imaging, electron microscopy, human brain recordings) and making datasets available and accessible to the wider scientific community. This rapidly expanding trove of brain data will provide valuable training sets for developing neural foundation models or more task-constrained representations to infer the computational principles embodied by the neural circuits underlying natural intelligence. To take full advantage of this opportunity, the BICAN, BRAIN CONNECTS, and BBQS consortia—each expected to generate voluminous amounts of complex data—will rely upon embedded data coordination centers, whose activities will include developing new AI-based approaches for data analysis and data dissemination. These efforts will help underpin a neuroscience data ecosystem in which big data—traditionally the domain of well-resourced institutions and investigators—becomes a powerful equalizer through knowledgebase frameworks that lower the barriers to data reuse and secondary analysis. Importantly, through its firm commitment to understanding and addressing the ethical, legal, and societal impacts of the research it supports, the BRAIN Initiative is positioned to provide critical leadership as the scientific community navigates the exciting opportunities, but also potential pitfalls, of rapidly evolving AI technologies.

Conclusion

In its first decade, the NIH BRAIN Initiative has supported the development of paradigm-shifting tools and resources that have accelerated the pace of discovery and provided new directions for neuroscience inquiry. While investing in fundamental research and the development of technologies that are opening doors to future breakthroughs, the initiative has also enabled remarkable advances in the clinical realm. Newly developed human neuroscience and human neuromodulation treatment strategies provide a path to address currently intractable and devastating human brain disorders within our lifetime. By fostering a culture that embraces collaboration and the interdependence of technology and discovery, the BRAIN Initiative has set the stage for scientific progress for generations to come.

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