DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of the Director

The BRAIN Initiative

Lawrence A. Tabak, D.D.S., Ph.D.
Principal Deputy Director, NIH

Table of Contents

INTRODUCTION

The Joint Explanatory Statement accompanying the fiscal year (FY) 2024 appropriations for the U.S. Department of Health and Human Services (HHS) stated:

> *"Brain Research through Advancing Innovative Neurotechnologies (BRAIN)— The agreement directs NIH to provide a report within 90 days of enactment of this Act on the progress and achievements of the key projects and studies it is supporting with these funds. Such a report should include the objectives and anticipated/actual outcomes for each activity and be made available on NIH's website."* (Conference Report, Page 45)

This report has been prepared by the National Institutes of Health (NIH), HHS, in response to this request.

BACKGROUND

The *Brain Research Through Innovative Neurotechnologies®* Initiative, or The BRAIN Initiative®, has revolutionized neuroscience by accelerating the development and application of innovative technologies to advance our understanding of the human brain, allowing us to apply this knowledge to inspire and advance new treatments for brain circuit disorders. Spanning 10 Institutes and Centers (ICs) at NIH, the BRAIN Initiative is uniquely positioned for cross-cutting and accelerated discoveries in neuroscience that go beyond the mission and capability of any single IC. The BRAIN Initiative builds on progress in the neurosciences and advances in optics, engineering, chemistry, mathematics, genetics, nanoscience, computer science, and other disciplines, to move science closer to a more holistic understanding of the human brain and brain disorders.

Given the complexity of the human brain, the BRAIN Initiative is not specifically focused on one primary disease or condition; instead, the BRAIN Initiative is working to build a toolkit of knowledge and technology that will enable researchers to understand the brain at unprecedented levels of detail. Indeed, the major focus of the BRAIN Initiative is on better understanding the brain by focusing on its circuitry – which includes the components that make up the brain, how they are connected, how they process information to enable our thoughts and actions, and how they malfunction in neurological, psychological, and substance use disorders. This unique approach ensures that the work of the BRAIN Initiative can be applied to myriad brain disorders and conditions. At the same time, innovations supported by the BRAIN Initiative are already having an impact in the clinic, making important inroads into treating neurologic and neuropsychiatric conditions, including Parkinson's disease, major depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, binge-eating disorder, traumatic brain injury, stroke, chronic pain, and opioid use disorder. This report highlights some of the collaborative, cross-cutting research, made possible by the BRAIN Initiative, that is enabling discovery in neuroscience, moving the field closer towards understanding the human brain in health and disease, and advancing cures for human brain disorders previously thought to be intractable.

ADVANCEMENTS IN NEUROSCIENCE

New Insights into the Brain

The BRAIN Initiative continues to provide new, unparalleled insights into the human brain. In addition to the benefits and potential applications to the treatment of brain disorders this provides, the level of detail resulting from BRAIN-supported work serves as a catalyst for the entire field of neuroscience. The research highlighted below demonstrates how BRAIN-funded investigators are working toward the BRAIN Initiative's goal of revolutionizing our understanding of the human brain.

The BRAIN Initiative Cell Census Network (BICCN)[1] is an effort to understand and create an atlas of brain cell types. By better understanding where cells are located in the brain, their functional properties, and how they develop, work together, and regulate their activity, research can move closer to a clearer picture of how brain circuits malfunction in disease and how to potentially develop new treatments. Recently, scientists from teams around the world published a suite of more than 20 research papers in *Science*, *Science Advances*, and *Science Translational Medicine,* detailing the creation of the first cellular, genetic, and structural maps of both the human and nonhuman primate brain.[2] The research teams examined more than one million cells from over 100 brain regions and identified more than 3,000 distinct brain cell types. The map that results from the BICCN depicts a never-before-seen level of detail into the human brain. As a result, researchers will be able to use the map to learn more about brain function and how to better treat neurological disease.

The BICCN has also recently produced, for the first time ever, a complete cell atlas of a whole mammalian brain. Described in a collection of 10 papers published in *Nature*, the international research team created an atlas of the mouse brain. Based on an analysis of more than 32 million cells, the team described at unprecedented levels of detail the type, location, and molecular information of the 5,000-plus cell types comprising the mouse brain, and provided information on connectivity between these cells.[3] The mouse is the most commonly used vertebrate experimental model in neuroscience research; this map lays the foundation for a greater understanding of the human brain and a new generation of precision therapeutics for individuals living with mental and neurological disorders. Further, these recent findings follow the first suite of the BICCN's results, published in 2021, which are described in 27 papers in the *Nature* family of journals.[4]

Already, the BICCN technologies and cell census data are being adopted by researchers and clinicians studying brain tissue in brain disorders. For instance, a team of scientists is building on the research and tools developed through the BICCN to map the cellular landscape of alterations in brain cell types in individuals living with Alzheimer's disease. Alzheimer's disease, a fatal form of dementia marked by progressively worsening memory loss, is characterized by significantly atrophied brains. However, identifying which cells are lost in the

---

[1] braininitiative.nih.gov/research/tools-and-technologies-brain-cells-and-circuits/brain-initiative-cell-census-network
[2] science.org/collections/brain-cell-census
[3] nature.com/collections/fgihbeccbd
[4] nature.com/collections/cicghheddj/

brain and how this contributes to disease progression has been a challenge. Through a multi-institutional consortium funded by the National Institute on Aging, researchers have identified a preliminary list of cells from the brains of those with Alzheimer's that may differ significantly from healthy brain cells. This finding could provide a pathway for the development of better therapies.[5]

In other work building on the BICCN, researchers have revealed the human brain cell types that first stop functioning in Parkinson's disease, another chronic and progressive neurological disease. A hallmark of Parkinson's disease is the progressive loss of a class of neurons located in a brain region called the substantia nigra. Identifying which class of neurons located in that brain region go awry in Parkinson's disease raises the possibility of discovering more effective treatments and long-term prevention strategies. Through this work, the investigators established a link between a candidate gene for Parkinson's disease and the disease-susceptible neurons in the brain.[6] Understanding these molecular roots offer the best options for developing treatments and cures and potentially ways to prevent the disease completely.

In addition to developing a highly detailed map of the brain, investigators supported by the BRAIN Initiative also are making strides to better understand how these brain regions work together and communicate. For instance, an international team of researchers published the first completed wiring map of an insect brain.[7] This work represents the most complex and detailed brain diagram to date. The team identified 93 distinct neuron types and where they connect to form hubs. The research teams also traced input and output neuron pathways to better understand how these neurons function. By establishing new foundational technologies and biological principles, such work holds great promise to guide future research on human brain wiring and its role in human brain disorders.

BRAIN Initiative in the Clinic

The BRAIN Initiative, within a decade since its inception, is already influencing treatment and care for individuals living with neurologic and neuropsychiatric disorders and conditions. BRAIN Initiative-funded researchers have developed life-changing personalized treatments. The following examples highlight important advances and how BRAIN Initiative-supported work is bringing promising approaches to patients, caregivers, and healthcare providers today.

In a recent BRAIN Initiative-funded study, investigators found a new potential therapy for people with arm or hand paralysis, which can occur following a stroke.[8] Using electrical impulses on the spine, the researchers were able stimulate the spinal cord's neural circuits and improve range of motion and strength in both the arm and hand. The results are a promising part of an ongoing clinical trial aimed at restoring arm and hand function following subcortical stroke. In other work aimed at stroke recovery, a clinical trial supported by the BRAIN Initiative

[5] portal.brain-map.org/explore/seattle-alzheimers-disease
[6] pubmed.ncbi.nlm.nih.gov/35513515/
[7] pubmed.ncbi.nlm.nih.gov/36893230/
[8] pubmed.ncbi.nlm.nih.gov/36807682/

has released early results suggesting that deep brain stimulation therapy on a part of the brain called the cerebellum may help recover upper limb function after a stroke.[9]

Understanding how pain is represented in the brain and whether that can be targeted to relieve suffering from chronic pain has been a long sought-after goal of pain and neuroscience research. Through research jointly supported by the BRAIN Initiative and the NIH Helping to End Addiction Long-term (HEAL) Initiative, scientists were able, for the first time, to identify biomarkers associated with chronic pain.[10] The research involved recording electrical activity from two brain regions using implanted electrodes and a monitoring device that participants could use to track their experience of pain. The work is emblematic of how the BRAIN Initiative can work across diseases, disorders, and conditions to synergize with other priority programs and accelerate progress on long-standing challenges in treating neurological disorders. Crucially, by understanding brain activity patterns related to pain, this work represents an important step in the development of better treatments for chronic pain that do not carry the risk of addiction associated with opioids – a major goal of the NIH HEAL Initiative.

BRAIN Initiative-supported work is also leading to progress in the treatment of mental health conditions. For example, researchers have been able to use a new device to measure the electrical activity of the nervous system to uncover a brain activity pattern, or biomarker, associated with episodes of treatment-resistant depression.[11] After targeting the biomarker with deep brain stimulation, nine out of ten patients in the study reported symptom improvement. This work demonstrates the benefit of identifying and implementing personalized treatments for conditions where other, more common approaches have not been effective.

TRANSFORMATIVE PROJECTS

Many of the clinical advances previously noted are a result of the BRAIN Initiative's continued investment in and focus on improving existing technologies while also developing the next generation of tools to better understand the brain and advance the search for better treatments and cures. To support this effort, the BRAIN Initiative recently launched three large-scale transformative projects – the BRAIN Initiative Cell Atlas Network (BICAN), the BRAIN Initiative Connectivity Across Scales (BRAIN CONNECTS) Network, and the Armamentarium for Precision Brain Cell Access – that together promise to change the trajectory of foundational neuroscience research and the treatment of human brain disorders.

BRAIN Initiative Cell Atlas Network (BICAN)

The BRAIN Initiative Cell Atlas Network (BICAN) is a collaborative research network working to create comprehensive brain cell atlases across multiple species, with an emphasis on humans.[12] BICAN builds on the groundbreaking work of the BRAIN Initiative Cell Census Network (BICCN) that unveiled a comprehensive description of cell types in the mouse brain and a draft atlas of the larger nonhuman primate and human brains. The focus of BICAN is to

---

[9] /pubmed.ncbi.nlm.nih.gov/37580534/
[10] pubmed.ncbi.nlm.nih.gov/37217725/
[11] pubmed.ncbi.nlm.nih.gov/37730990/
[12] braininitiative.nih.gov/research/tools-and-technologies-brain-cells-and-circuits/brain-initiative-cell-atlas-network

generate complete reference atlases of brain cell types in humans, nonhuman primates, and mice. These atlases can then be shared and used throughout the research community. In addition, BICAN aims to map the cellular interactions that underly a wide range of human brain disorders.

BRAIN Initiative Connectivity Across Scales (BRAIN CONNECTS) Network

The BRAIN Initiative Connectivity Across Scales (BRAIN CONNECTS) Network is designed to develop the research capacity and technical capabilities to generate whole brain "wiring diagrams," which will be indispensable for understanding how brain circuits function and operate.[13] BRAIN CONNECTS supports grantees from dozens of research institutions and universities around the world, promoting scientific collaboration in the realm of brain mapping. Each research project supported by BRAIN CONNECTS will develop a technological approach for imaging and reconstructing brain connectivity that ultimately will be used to map with high precision all the connections in whole mammalian brains. This will allow scientists to test new hypotheses about human brain circuit function, potentially laying the foundation for more precise diagnostics and therapeutics for devastating brain diseases.

Armamentarium for Precision Brain Cell Access

The Armamentarium for Precision Brain Cell Access aims to create powerful new tools to monitor and modulate activity of specific cell types in neural circuits that underlie complex behaviors.[14] More specifically, this transformative project is developing tools to aid neuroscientists studying neural circuits and will allow researchers to not only map circuit components but also monitor and manipulate neural activity. The Armamentarium will lay the groundwork for future research that uses precision targeting tools to access human disease-relevant circuits to deliver new therapies.

CONCLUSION

The BRAIN Initiative is making impactful contributions to the entire neuroscience ecosystem through an innovative approach that combines the development of cutting-edge tools and technologies and their application to better understand brain circuits, with the goal of developing treatments that will benefit individuals living with brain disorders. The Initiative is simultaneously pursuing emerging opportunities across all mission areas and leveraging the results of the large-scale transformative projects to significantly change the trajectory of neuroscience research and the treatment of human brain disorders. The research examples highlighted throughout this report demonstrate the unique and outsized value of this approach to NIH ICs that are already building on the tools, technologies, and findings made possible through the BRAIN Initiative.

---

[13] braininitiative.nih.gov/research/neuroimaging-technologies-across-scales/brain-initiative-connectivity-across-scales

[14] braininitiative.nih.gov/research/tools-technologies-brain-cells-circuits/armamentarium-precision-brain-cell-access