National Institutes of Health
The BRAIN Initiative®

# NIH BRAIN Initiative Report

## Research Roadmap

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The BRAIN Initiative®

# Inventing the Future:

## NIH BRAIN Initiative Research Roadmap

The human brain is capable of abstract reasoning, creativity, and self-awareness – with the ability to continuously learn, adapt, and innovate. Deep, mechanistic understanding of the human brain's complexity and broad function is one of the greatest challenges of our generation. Meeting this challenge is an urgent call to action since one-third of all Americans live with a chronic brain disorder; the U.S. health investment is staggering at $1.5 trillion per year.

For 10 years, the NIH BRAIN Initiative (BRAIN) has met this challenge through a deliberate focus on disease-agnostic neurotechnology and a full embrace of transparency, ethical rigor, and interdisciplinary collaboration. As a result, we are now beginning to understand the core building blocks of the brain and can watch and control brain activity at "the speed of thought." Early examples of personalized neural recording and neuromodulation strategies are showing dramatic success treating severe neurologic and neuropsychiatric conditions.

Meeting this moment, looking back and looking ahead, requires strategic investments to arrive at a future state that i) defines unifying brain function principles that integrate the brain's complexity; ii) explains the seamless integration of brain and body to sense, understand, and engage with the world; and iii) uses unique neural fingerprints to develop individualized therapies that safely adapt to use in real-world settings.

In consultation with the participating NIH Institutes and Centers (ICs), the Initiative has identified four Innovation Domains that chart a course to achieving these goals (**Figure 1**, see Innovation Domain Summaries for more detail). Each poised for rapid growth, these four areas merge the fruits of the BRAIN investment to date with cutting-edge opportunities in biomedical and data science. All will require attendant development and adaptation of the neuroscience workforce. Importantly, development and implementation of the Innovation Domains commits to integrated exploration of the ethical, legal, and societal implications of this research as it proceeds. Parallel consideration of potential impacts on autonomy, privacy, safety, and fairness will ground new findings in ethical rigor. Unique issues related to brain data also require special attention, including those related to privacy, ownership, consent, accountability, and sovereignty, among others.

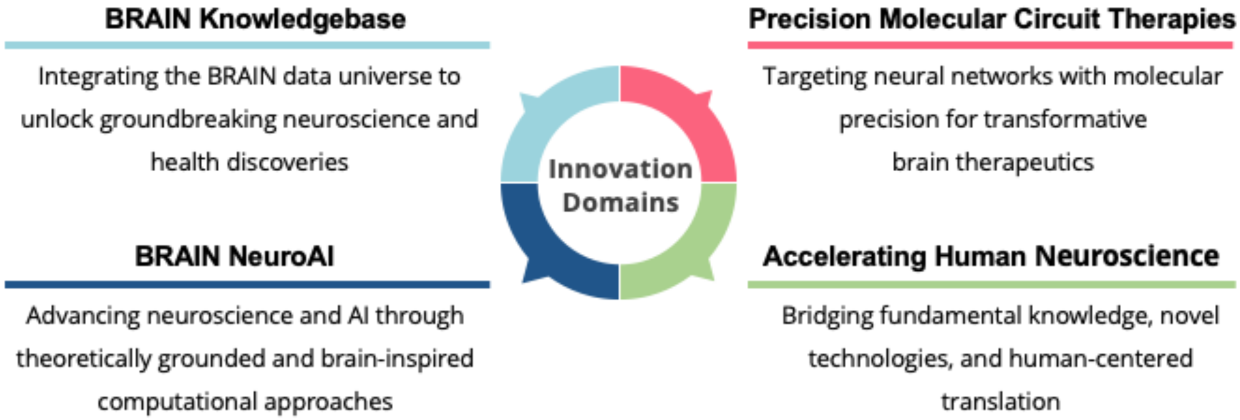


***Figure 1. BRAIN Innovation Domains***

This strategy intends to yield the following deliverables within 10 years:

- A plug-and-play, user-friendly, and secure artificial intelligence (AI)-powered BRAIN knowledge ecosystem
- Therapeutic platforms that safely modulate neural circuits with molecular precision, enabling targeted treatment of a range of chronic brain conditions
- Clear translational pathways from foundational knowledge and de-risked neurotechnologies to therapeutic interventions in real-world settings
- Fundamental principles of brain function that reciprocally inform natural intelligence and AI responsibly and without bias
- Brain-inspired technological applications for adaptable, secure, resilient and energy-efficient health monitoring devices and interventions

As an incubator for technology-driven innovation, BRAIN will take many steps, but not every step, to realize this strategic vision. Collaboration across the U.S. neuroscience ecosystem must involve partnerships and opportunities for technology hand-offs for further scaling and commercialization. Continued, transparent partnerships with people living with brain disorders is paramount to addressing fairness, accessibility, and safety for development of new technologies and sharing of personal data.

# Research Roadmap

## Innovation Domain Summaries

# BRAIN Knowledgebase

## Innovation Domain Summary

## Strategic Vision

The BRAIN Knowledgebase Innovation Domain establishes a unified, federated system that integrates multiple infrastructure components while preserving domain expertise. This framework leverages BRAIN's specialized data platforms to enable transdisciplinary advances across neuroscience: from molecular mechanisms to cognition and behavior. Four interconnected components include a nascent BRAIN Data Commons, which will federate existing data repositories using shared metadata standards; the BICAN Brain Cell-Atlas Knowledgebase, which incorporates ontologies and spatial frameworks for cellular and functional data; the BRAIN Initiative Connectivity Across Scales (CONNECTS) Knowledgebase, focused on integrating connectivity maps across scales and species; and the Brain Behavior Quantification and Synchronization (BBQS) Knowledgebase, which links behavioral data with neural activity to explore brain-behavior relationships.

## Value Proposition

The BRAIN Knowledgebase Innovation Domain will transform data into discovery by addressing critical challenges that currently limit progress:

- **Data Volume & Complexity**: BRAIN data archives have reached nearly 12 petabytes across 9 specialized repositories, with large-scale, transformative projects pushing data volumes to the exascale
- **Fragmentation & Inaccessibility**: Key relationships between molecular, cellular, circuit, and behavioral data remain undiscoverable when data are stored in disconnected repositories
- **Cross-Modal Integration Barriers**: Differences in data standards, metadata schema, and access protocols force researchers to spend more time wrangling data than advancing science
- **Sustainability Concerns**: Grant-cycle funding creates uncertainty about long-term maintenance of critical data infrastructure

The BRAIN Knowledgebase Innovation Domain will empower researchers to explore complex, cross-modal, and cross-scale questions that are not currently possible. This approach transforms the scientific value of BRAIN's massive data investments by connecting previously isolated information domains into a cohesive knowledge ecosystem that protects privacy and adheres to consent and data sovereignty principles.

## Scientific and Operational Strategy

The BRAIN Knowledgebase Innovation Domain will involve a three-phase implementation strategy that progressively achieves integration. This phased approach will build workforce capacity throughout via short courses, workshops, and other training opportunities.

**Phase 1: Building the Foundation (Years 1-2)**

- Develop common metadata standards and application programming interfaces (APIs) across existing data archives
- Implement unified authentication and cross-archive search capabilities
- Address practical implementation concerns related to privacy, fairness, transparency, and accessibility across diverse populations and research contexts
- Build specialized infrastructure for BICAN, CONNECTS, and BBQS Knowledgebases

**Phase 2: Deployment & Scaling (Years 3-5)**

- Deploy cross-domain search and analysis capabilities
- Implement secure and sustainable governance models
- Establish cross-species, ethically sound frameworks linking cell types, connectivity, and behavior

**Phase 3: Advanced Integration (Years 6-10)**

- Implement AI-powered search and exploration across the entire BRAIN Knowledgebase ecosystem
- Create comprehensive translational frameworks linking animal models to human cognitive functions and brain health improvement
- Establish long-term sustainability through community governance and strategic partnerships

## Impact

- **Accelerated Discovery Timelines** by reducing data preparation burden, allowing researchers to focus on science rather than data wrangling
- **Cross-Scale Integration** that reveals relationships between molecular mechanisms and behavioral outputs
- **Translational Pathways** from fundamental neuroscience to clinical applications

# Precision Molecular Circuit Therapies

## Innovation Domain Summary

## Strategic Vision

The Precision Molecular Circuit Therapies BRAIN Innovation Domain envisions a future in which neuroscience treatments move beyond broad neural modulation to safe and precise targeting of dysfunctional circuits that characterize a variety of neurological and neuropsychiatric indications. Within 10 years, the goal is to deploy optogenetic, chemogenetic, and other neural effector technologies with unprecedented spatial, cellular, and temporal resolution. This Innovation Domain will create platforms and resources that translate molecular genetic technologies into circuit therapies by combining two powerful technical approaches into clinically viable strategies: i) precision access to circuit components using genetic delivery and ii) engineered control of neural activity using effector molecules.

## Value Proposition

Current neuroscience treatments offer only limited specificity that by design affect both healthy and dysfunctional neural tissue. This Innovation Domain addresses these limitations with:

- **Targeted Precision**: Engaging only those specific neural circuits implicated in disease
- **Temporal Control**: Providing on-demand modulation of neural activity
- **Cell-Type Specificity**: Accounting for the complex diversity of brain cell types
- **Cross-Scale Integration**: Bridging molecular, cellular, and circuit-level interventions

### Leveraging BRAIN's Successes and Strengths

The Precision Molecular Circuit Therapies Innovation Domain builds strategically upon multiple transformational achievements and ongoing efforts made possible by the BRAIN Initiative:

- Foundational knowledge about brain cell types and multi-scale connectivity achieved through the BICCN/BICAN and CONNECTS programs, respectively
- Sophisticated tools and technology for experimental access to defined cell types and for neural recording/modulation through the Armamentarium for Precision Brain Cell Access and Neural Recording and Modulation programs, respectively

- Multimodal understanding of circuit dynamics at high spatiotemporal resolution through the Systems Neuroscience program

## Scientific and Operational Strategy

A Working Group, comprising NIH scientific staff, are developing a three-pronged implementation plan:

1. **Technology Integration Pathways**
    - Coordinate with BRAIN and relevant NIH IC programs to define complementary and synergistic opportunities
    - Leverage BRAIN Armamentarium research developing precision brain cell access reagents
    - Survey industry progress and identify opportunities for public-private collaboration
    - Explore infrastructure needs for preclinical discovery and lead identification
    - Foster skills training and collaboration via short courses and professional development

2. **Neurobiological Opportunities**
    - Identify optimal circuit targets for therapeutic engagement by leveraging BRAIN circuit exploration programs.
    - Foster integration between neuroscientists and technology developers
    - Encourage interaction of circuit therapy researchers and trainees from across BRAIN consortia/groups to promote pre-competitive knowledge sharing

3. **Regulatory and Ethical Considerations**
    - Consider and evaluate issues such as autonomy, privacy, control, and consent related to the use of novel molecular- and circuit-based interventions
    - Collaborate with the Food and Drug Administration (FDA) to address regulatory science gaps
    - Establish handoff points to NIH and other translational programs

## Impact

- **Translation** of cutting-edge neurotechnology tools into safe and efficacious therapeutic applications
- **Precision Treatment Paradigms** that target underlying circuit dysfunction rather than broad symptom management
- **De-risked Early Development** to catalyze pharmaceutical industry engagement

# Accelerating Human Neuroscience

## Innovation Domain Summary

## Strategic Vision

The Accelerating Human Neuroscience Innovation Domain aims to advance and integrate BRAIN-supported research to enhance fundamental knowledge of human brain function, leading to transformative treatments, cures, and preventive interventions. While benefiting from significant investments, human neuroscience research has nonetheless been dispersed across the BRAIN portfolio. This Innovation Domain will create a more unified scientific ecosystem to catalyze knowledge flow seamlessly from basic discovery to clinical applications, while ensuring that translation does not outpace ethical considerations and oversight. It will establish clear pathways for technologies and insights to transition to NIH IC-specific programs and external partners, including industry.

## Value Proposition

Due in large part to sophisticated BRAIN-enabled tools and technologies to investigate and modulate the human brain, the human neuroscience ecosystem is now at an inflection point. To meet its full potential, this Innovation Domain will address critical gaps in the current human neuroscience research landscape:

- **Bridge Knowledge Translation:** Create systematic connections between non-human models and human neuroscience studies, as well as between invasive and non-invasive neuromodulation approaches
- **Enable Cross-Scale Integration:** Facilitate the comparison and combination of data across experimental approaches to advance basic discovery and speed clinical translation
- **Accelerate Technology Development:** Advance tools from concept to clinical application through coordinated, strategic investments, including cross-training researchers
- **Harmonize Data Standards:** Develop common data elements, platforms, and protocols to maximize the value of more than 10 years of BRAIN investments

By focusing on these strategic priorities, the Accelerating Human Neuroscience Innovation Domain will empower researchers and funding organizations to explore complex questions about human brain function that currently remain out of reach due to fragmented approaches and lack of coordination.

## Scientific and Operational Strategy

The Human Neuroscience Innovation Domain will execute its vision through three interconnected scientific objectives:

**1. Generate Fundamental Knowledge**

- Translate brain circuit knowledge from non-human animal studies to humans
- Bridge invasive and non-invasive research methods
- Understand mechanisms of neuromodulation
- Embed neuroethical exploration and clinical research principles across the human neuroscience ecosystem

**2. Develop New Technologies & Platforms**

- Assess and optimize translation of technologies across species
- Identify barriers to progress, including ethical challenges
- Target specific brain mechanisms for technology development
- Create secure shared resources and platforms for human neuroscience research

**3. Test Next-Generation Technologies**

- Advance first-in-human and early feasibility studies
- De-risk promising approaches for subsequent NIH IC-specific funding
- Develop less-invasive devices, sensors, and combination technologies for improved stakeholder accessibility
- Establish clear criteria for success and pathways to translation

## Impact

- **Leveraged Existing Investments** by connecting disparate research efforts
- **Common Standards & Tools** that benefit research across all NIH ICs
- **Bridged Knowledge Gaps** between non-human animal models and human applications
- **Accelerated Technology Translation** through clear development-to-testing pathways that firmly embed neuroethics principles
- **Skilled Workforce** that applies advances in human neuroscience

# BRAIN NeuroAI

## Innovation Domain Summary

## Strategic Vision

The NeuroAI Innovation Domain establishes an ethically grounded framework that creates a transdisciplinary bridge in which biological insights inform the development of more brain-like AI models that in turn drive new approaches to resolve longstanding obstacles in neuroscience. A NeuroAI ethical framework emphasizes active stakeholder engagement that prioritizes fairness, transparency, privacy, and autonomy, ensuring responsible innovation and evolving data protections as technologies advance. Interdisciplinary training programs will involve collaborations with academia, industry, and government.

## Value Proposition

The NeuroAI Innovation Domain addresses three fundamental challenges that currently limit progress at the intersection of neuroscience and AI:

- **Biological-Computational Translation Gap:** Few frameworks translate biological mechanisms into computational principles while maintaining both biological relevance and engineering feasibility
- **Embodiment & Adaptation Gap:** Current AI approaches rely predominantly on statistical learning from massive datasets rather than the structured, brain-body learning characteristic of biological systems, resulting in technologies that excel at narrow tasks but lack adaptability and may harbor or amplify bias
- **Disciplinary Integration Gap:** Traditional boundaries between neuroscience, AI, cognitive science, and engineering create barriers to progress that require coordinated, cross-disciplinary approaches

The human brain achieves remarkable cognitive flexibility while consuming only 15-20 watts of power: orders of magnitude lower than current AI systems. BRAIN's unique combination of biological understanding, ethical rigor, technological capabilities, computational resources, and team science culture enable an approach to NeuroAI that maintains biological relevance while advancing computational capabilities.

## Scientific and Operational Strategy

The NeuroAI Innovation Domain will implement a three-phase innovation pipeline advancing promising approaches from exploration to implementation, considering infrastructure, workforce development, and strategic partnerships throughout. Training programs across phases will emphasize blending technical, scientific, and collaborative skills.

**Phase 1: Innovation Incubator (Years 1-2)**

- Broad exploration through data challenges, seed grants, and collaborative platforms

**Phase 2: Community-Driven Pipeline (Years 3-5)**

- Selection and refinement of Phase 1 outcomes through benchmarks and integration with BRAIN programs

**Phase 3: Transition to Impact (Years 6-10)**

- Scaling successful approaches with a deliberate focus on health applications

This pipeline addresses three core scientific priorities:

- **Computational Models & Mechanisms:** Develop interpretable models that elucidate biological mechanisms while maintaining cross-scale integration
- **Learning & Adaptation:** Advance energy-efficient neuromorphic platforms that adjust to individual variations for research and health applications
- **Brain-Body Systems:** Establish new paradigms for understanding embodied intelligence as it emerges through the interaction of brain and body in complex biological systems

## Impact

- **Maximal BRAIN Data Value**, creating frameworks to interpret complex multi-modal datasets
- **Bridged Disciplinary Divides** between neuroscience and AI
- **Energy-Efficient Computing** through brain-inspired architectures
- **Adaptive Health Technologies** that learn and adjust to individual variation
- **Skilled Workforce** conversant in the ethics of both neuroscience and AI