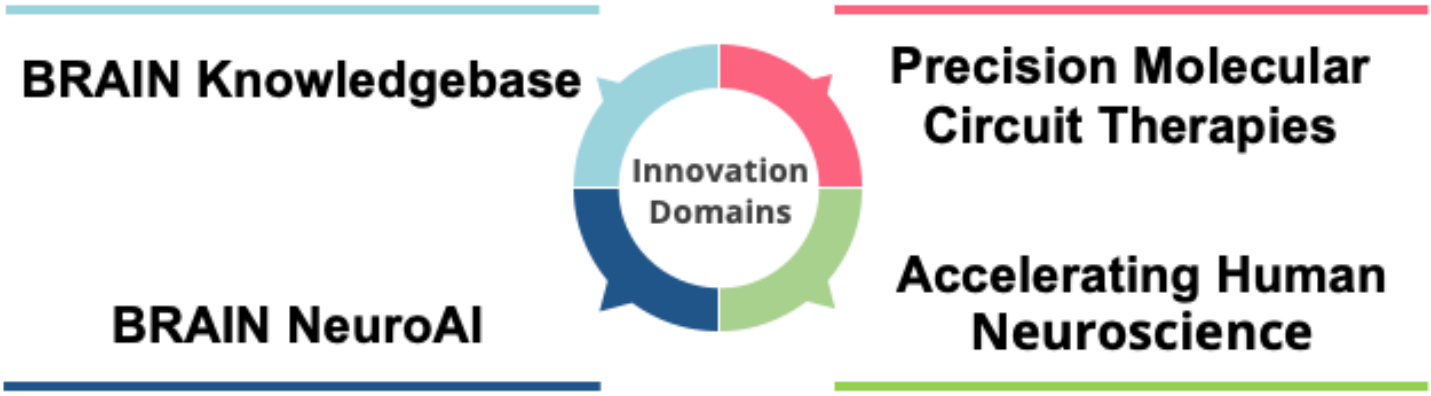
National Institutes of Health
The BRAIN Initiative®



NIH BRAIN Research Roadmap

Innovation Domains: Detailed Scoping Plans

August 2025

The BRAIN Initiative®

NIH National Institutes of Health
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NIH BRAIN Initiative Research Roadmap

Overview of Innovation Domains

Introduction

The National Institutes of Health (NIH) Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative Research Roadmap is a strategic effort coordinated by the Office of the BRAIN Director to develop a forward-looking vision to drive innovation, capitalizing on the unique role of BRAIN in the neuroscience ecosystem. It builds on progress to date and identifies opportunities that recently emerged or are ripe for accelerated pursuit. Developed in close collaboration with the BRAIN scientific program teams, the Research Roadmap will be reviewed and refined by the Committee of BRAIN Institute and Center (IC) Directors, BRAIN Multi-Council and Neuroethics Working Groups, NIH leadership, and relevant National Advisory Councils. The Research Roadmap has identified four BRAIN Innovation Domains (**Figure 1**) that harness BRAIN's progress and unique technology-driven approach to maximize research impact across neurologic and neuropsychiatric disorders. Embedded throughout the BRAIN Innovation Domains are plans to address cross-cutting issues including workforce capacity and ethically responsible neurotechnology development and implementation.

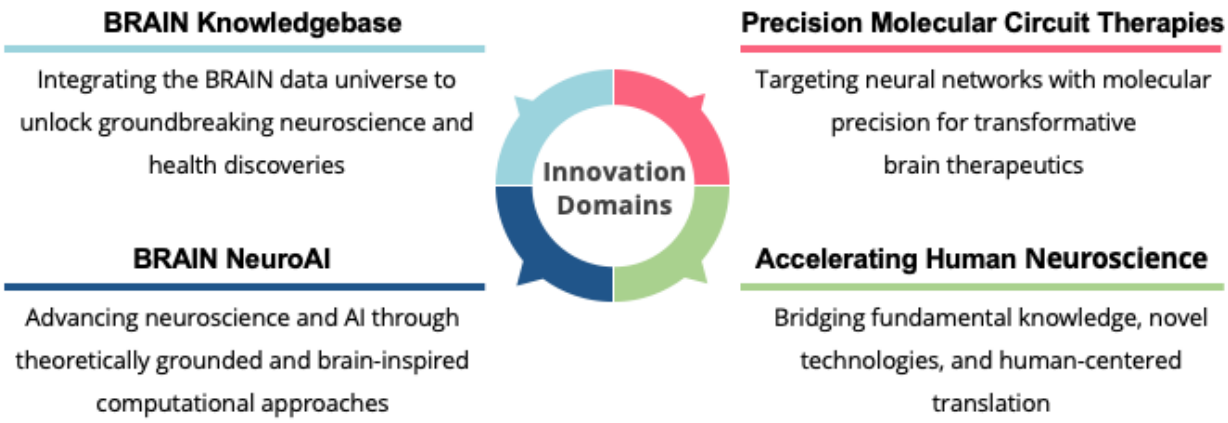

Figure 1. BRAIN Innovation Domains

Guiding Principle: Staying True to the BRAIN Mission

BRAIN's technology-driven and disease-agnostic approach has been the cornerstone of its success during its first decade. Innovation Domains will continue this foundational philosophy, strategically positioning BRAIN's efforts to address critical unmet needs while leveraging the Initiative's distinctive role within the neuroscience and neurotechnology ecosystem. A brief description of each Innovation Domain appears below, followed by detailed scoping plans. Cross-cutting issues – notably training, dissemination, and neuroethical principles – apply to all Innovation Domains.

Innovation Domains

The **BRAIN Knowledgebase** Innovation Domain aims to accelerate neuroscience discovery through integrated knowledge management. Central to this framework are four interrelated knowledgebases: the BRAIN Data Commons, which federates 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 CONNECTS Knowledgebase, focused on integrating connectivity maps across scales and species; and the BBQS Knowledgebase, which links behavioral data with neural activity to explore brain-behavior relationships. Through this Innovation Domain, BRAIN aims to empower researchers to explore complex, cross-modal, cross-scale questions that are currently not possible due to fragmented data systems that to date collectively host nearly 12 petabytes of BRAIN-generated data. BRAIN will simultaneously consider neuroethics principles that balance potential risks and benefits of this integrated knowledge.

The **Precision Molecular Circuit Therapies** Innovation Domain envisions a future in which therapies target dysfunctional brain circuits with increased precision and specificity to treat many neurologic and neuropsychiatric conditions. Achieving this vision requires that therapies operate at high spatial, cellular, and temporal resolution, accounting for the complexity of brain cell types and circuit dynamics. Through this Innovation Domain, BRAIN will drive early-stage technology development and integration, laying the groundwork for future therapeutic breakthroughs through disease-targeted investments by NIH ICs and the private sector. Proactive engagement with the Food and Drug Administration (FDA) will identify regulatory science gaps, and alignment with neuroethics expertise will position future therapeutics for long-term success in collaboration with external partners conducting clinical development.

The **Accelerating Human Neuroscience** Innovation Domain aims to enhance fundamental understanding of the human brain while setting the stage for translation to clinical technologies that can be adopted by the broader neuroscience and neurotechnology ecosystem. Through this Innovation Domain, BRAIN will focus on i) reciprocally applying circuit

insights between non-human animal models to humans to reveal underlying mechanisms, ii) advancing invasive and non-invasive methods, and iii) identifying new neuromodulation targets for treating human brain disorders. The Innovation domain will assess existing BRAIN tools to determine successful approaches and barriers to adoption, while prioritizing human testing of next-generation devices that offer less-invasive alternatives for recording and stimulation. Ethical considerations will be essential for the responsible development and implementation of technologies and approaches to understand mechanisms of human brain function.

The **BRAIN NeuroAI** Innovation Domain establishes a framework for advancing both neuroscience and artificial intelligence (AI) through bidirectional advances and knowledge exchange. The BRAIN NeuroAI vision centers on developing brain-inspired computational approaches that are theoretically grounded, ethically sound, and inherently adaptable. Through this Innovation Domain, BRAIN aims to create a transdisciplinary bridge in which biological insights inform the development of more brain-like AI models. In turn, such models will drive new computational and neuromorphic approaches that integrate cognition with physical interaction, helping to close the embodiment gap (how humans or systems interact with and experience the world) and resolve longstanding obstacles to progress in neuroscience.

The Path Forward

Importantly, BRAIN will take many steps, but not every step, to realize the vision of the Research Roadmap. A key role for the Initiative will be as an incubator for innovation and as a nexus for cross-cutting issues like training, dissemination, and ongoing consideration of neuroethical principles. Strategic collaboration across the U.S. neuroscience ecosystem must involve shared resource development and opportunities for technology hand-offs for further scaling and commercialization. The evolving scoping plans in the next section will be used to stimulate discussions toward innovative and efficient use of BRAIN resources now and in future years.

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BRAIN Knowledgebase

Research Roadmap Innovation Domain

Integrating the BRAIN data universe to unlock groundbreaking neuroscience and health discoveries

BRAIN Knowledgebase:

NIH BRAIN Research Roadmap Innovation Domain Scoping Plan

Strategic Vision & Objectives

The BRAIN Knowledgebase Innovation Domain is a strategic proposal for building a unified, federated framework that addresses emerging data challenges by integrating multiple data infrastructure components. The envisioned BRAIN Knowledgebase framework leverages BRAIN's domain-specific and consortium-scale data platforms to preserve expertise while enabling transdisciplinary advances across the full spectrum of neuroscience from molecular mechanisms to cognition and behavior in a sustainable and ethical manner.

- **BRAIN Data Commons:** Federation of specialized BRAIN data archives through common metadata standards and protocols while preserving crucial domain expertise
- **BICAN Brain Cell-Atlas Knowledgebase:** Integration of formal ontologies, cell-type taxonomies, and spatial reference frameworks across cellular, anatomical, and functional dimensions
- **CONNECTS Knowledgebase:** Interoperability and integration with whole-brain connectivity maps from multiple species and scales, from molecules to circuits
- **BBQS Knowledgebase:** Integration of behavioral quantification, neural activity, and environmental context to establish mechanistic links between circuits and behavior across species, providing a critical translational bridge to brain health

The Challenge:

Connecting Data to Accelerate Knowledge and Discovery

As neuroscience data expands across modalities and scales of brain organization, exponential growth in data volume threatens to overwhelm our scientific data platforms. BRAIN's data archives, which service investigator-led research data, have reached nearly 12 petabytes across nine specialized repositories, with some individual datasets exceeding 300 terabytes. BRAIN's transformative projects are currently pursuing the collection and integration of whole-brain cell-type atlases, trillion-cell analyses, and multi-species connectomes, which will push data volumes to the exascale and beyond. Current approaches face growing challenges on

multiple fronts, from computational capacity requirements for analyzing massive multimodal datasets to enabling broader researcher communities to find, access, and capably investigate cross-domain hypotheses to advance knowledge and discovery.

Key relationships between molecular, cellular, circuits/systems, and behavioral data remain undiscoverable when stored across a disconnected set of repositories. Fragmentation in "data ecosystems" obscures the scientific value of NIH and BRAIN funded research. Cross-modal insights – such as linking gene expression to connectivity patterns or circuit function – require integration capabilities that don't currently exist. Developing data standards (see details in *Appendix A: Data Standards in Neuroscience Research*), metadata schema and data processing pipelines (*Appendix B: Metadata Standards, Data Processing Pipelines, and Identifier Schema*), and analytical tools and references (*Appendix C: Ontologies, Coordinate Frameworks, and Reference Atlases*) impose significant challenges for data producers as well as consumers. BRAIN-funded researchers (current and future) must navigate multiple platforms to access and analyze related datasets, forcing investigators to spend more time wrangling data than working toward scientific advances and discoveries.

The BRAIN Knowledgebase will address critical privacy and re-identification risks through a comprehensive framework (*Appendix D: Data Access Controls and Privacy Protection for Human Data*). This framework will support tiered access controls to ensure that genomic sequences, anatomical imaging, and multimodal brain data are shared responsibly. The integration of data across many scales – from genomic sequences to neural circuitry to behavioral outcomes – requires careful consideration of how combined datasets might enable re-identification of donors or their relatives. This approach balances open science principles with robust privacy protections through informed consent processes and appropriate access restrictions based on data sensitivity.

Grant-cycle funding of critical infrastructure creates uncertainty about the sustainability and adaptability of the current data ecosystem. Looking ahead, the next generation of data platforms must be modular, maintainable, and built on shared, evolving standards and protocols to ensure continuous security, accessibility, and compatibility. The long-term value of BRAIN-funded research investments will depend on planning for technical, financial, and governance sustainability.

The Vision:

A Unified Knowledgebase Framework for BRAIN

BRAIN envisions a unified BRAIN Knowledgebase framework that coordinates the federation of three interlocking components, preserving crucial domain expertise in each module. The first

component is a multidomain Data Commons that unifies and enhances BRAIN's existing network of data archives through common metadata standards and protocols while maintaining their specialized capabilities and data sharing functions. The second component learns from and leverages the BRAIN Initiative Cell Atlas Network (BICAN) transformative project to integrate formal ontologies, cell-type taxonomies, spatial reference frameworks, automatable pipelines, and reproducible analysis tools across cellular, anatomical, and functional dimensions of brain-scale data. The third component supports knowledgebase development for the BRAIN Initiative Connectivity Across Scales (CONNECTS) transformative project to ensure interoperability and integration with whole-brain connectivity maps from molecular to circuit scales. The fourth component establishes the Brain Behavior Quantification and Synchronization (BBQS) Knowledgebase to integrate behavioral quantification with neural activity, providing data and tools to understand complex brain-behavior relationships across species and environmental contexts.

These BRAIN Knowledgebase components – the BRAIN Data Commons, BICAN Brain Cell-Atlas Knowledgebase, CONNECTS Knowledgebase, and BBQS Knowledgebase – will build upon shared infrastructure guided by a set of core principles emphasizing sustainable, modular architecture and research community engagement. The core principles, formulated as four strategic imperatives, will be critical to the success of the BRAIN Knowledgebase framework: i) Adopt modular architectures with well-defined user interfaces and data protocols to ensure compatibility between components and adaptability as scientific priorities, community needs, and information technologies evolve; ii) Implement progressive data maturity models for levels of processing and cross-modal integration, from raw data to fully annotated datasets and validated derivative resources; iii) Balance centralized coordination with distributed domain expertise by establishing common standards and an open ecosystem of tools for interoperability and cross-domain analysis; and iv) Foster coordination and collaboration with NIH, domestic, and international science infrastructure platforms while maintaining BRAIN's unique focus on integrating multimodal, multiscale neuroscience data within a framework of neuroethical and sustainable knowledge management. The BRAIN Neuroethics Working Group (NEWG) has provided crucial guidance in this area through workshops addressing the ethics of sharing human brain data and multimodal data integration. A July 2023 NEWG workshop on the ethics of sharing human brain data examined potential risks to individuals and communities when integrating diverse data types. These insights directly inform BRAIN's approach to building ethical knowledge systems.

The BRAIN Knowledgebase framework will only succeed if it is used and trusted by BRAIN researcher communities and other users. To promote organic engagement beyond data sharing mandates, knowledgebase platforms should systematically lower barriers to accessing high-quality, curated datasets. To gain community trust, knowledgebase platforms should provide and support the development of formal ontologies and validation tools that enhance data

integrity through metadata, provenance, and reproducibility. User interfaces, including centralized portals and data hubs, will provide progressively revealed complexity for different use cases and users, from specialized neuroscientists to broader biomedical researchers. The transparency of the BRAIN Knowledgebase should borrow best practices and conventions from the AI/machine learning (AI/ML) communities, such as knowledge cards, model cards, and standardized vocabularies for expressing taxonomies and ontologies.

Why BRAIN is Uniquely Positioned

BRAIN stands uniquely positioned to address challenges of large-scale neuroscience data integration as a result of a decade of innovation and leadership in establishing specialized data archives and integrated consortium-scale data infrastructure. Since its inception, BRAIN has implemented its "think big, start small, scale fast" approach to enable progressive scientific advances while managing the risks inherent in pursuing ambitious goals. This philosophy has established BRAIN as the driving force behind recent neuroscience and neurotechnology innovations, exemplified by the BRAIN Initiative Cell Census Network (BICCN), which mobilized more than 250 researchers to create the first comprehensive brain cell atlases. BRAIN is positioned to address the urgent need to move from centralized to federated data platforms to ensure sustainability in the face of increasing scale and complexity of brain data.

BRAIN has consistently supported the development of community data standards, and it has integrated those standards into the data sharing platforms that form the backbone of the BRAIN data ecosystem. The continuing widespread adoption of open standards like Neurodata Without Borders (NWB) and Brain Imaging Data Structure (BIDS) has significantly improved access to reproducible data-driven research across the field. BRAIN's specialized data archives house nearly 12 petabytes of high-quality datasets submitted by individual BRAIN investigators, demonstrating that open data standards can be flexible enough to accommodate multiple modalities and data types. Community-driven maintenance of open data standards has shown how to preserve domain-specific expertise while enabling broader adoption as needs evolve. The BRAIN Data Commons will build upon this established foundation, leveraging experience from transformative projects like BICAN and BBQS that have already launched data platforms subserving cellular, circuit, and behavioral domains.

BRAIN's commitment to integrating behavioral neuroscience with cellular and circuit-level research is exemplified by the BBQS program that launched in 2023 (see details in *Appendix E: BBQS Infrastructure, Synchronization Challenges, and Integration Tools*). By developing standardized approaches for quantifying behavior and synchronizing it with neural recordings, BBQS fills a significant gap in neuroscience knowledge by connecting cellular and circuit mechanisms to functional behavioral outputs. The BBQS program's emphasis on cross-

species behavioral homologies and environmental context provides an essential translational bridge to potential clinical advances through fundamental neuroscience.

Most importantly, BRAIN builds, supports, and engages active researcher communities spanning domains and scales of brain investigation. BRAIN researchers at all career levels, current and future, are the producers and consumers of the BRAIN data ecosystem who collect, validate, analyze, model, and apply data. These communities bring wide-ranging perspectives and expertise to questions, hypotheses, and approaches to disentangling brain function. A unified BRAIN Knowledgebase framework will support a BRAIN-focused ecosystem in which data-driven discovery can flourish. BRAIN's commitment to open science and the core principles described above will ensure that investments in data generation and knowledge integration will collectively accelerate discovery while maintaining rigorous scientific standards. By building on this critical expertise, infrastructure, and community engagement, BRAIN is uniquely positioned to lead the transformation of how data becomes knowledge that advances human health.

Working Group Organization

A Working Group (WG) has been formed to spearhead the development and implementation of the BRAIN Knowledgebase Innovation Domain strategy. As planning matures, additional members with adjacent and relevant expertise will be added at key milestones of Innovation Domain development to ensure that the overall plan considers the appropriate breadth of perspectives and addresses cross-cutting issues like training, dissemination, and ongoing consideration of neuroethical principles.

Relevant Expertise	Name
Data Science, Data Management and Sharing, Data Standards, & Informatics Infrastructure	**Joseph Monaco* (NINDS/OBD)**, **Ming Zhan* (NIDA)**, Brad Bower (NIH/OD), Amanda Price (NIMH), Roger Miller (NIDCD), Natalia Volfovsky (NINDS), Adi Cymerblit-Sabba (NINDS), Eunyoung Kim (NIMH, Team T liaison), David Panchision (NIMH, Team N liaison), Elizabeth Powell (NIAAA), Mauricio Rangel Gomez (NIMH), Saskia Hendriks (NIH/CC/BEP)
Computational Neuroscience & AI	**Joseph Monaco* (NINDS/OBD)**, Michele Ferrante (NIMH), Elizabeth Powell (NIAAA), Mauricio Rangel Gomez (NIMH)
Genomics & Multi-omics	Amanda Price (NIMH), **Ming Zhan* (NIDA)**, **Yong Yao* (NIMH)**, Emrin Horgusluoglu (NCCIH), Natalia Volfovsky (NINDS), Erin Quinlan (NICCH)

Brain Imaging & Neuroimaging	Laura Reyes (NIMH), Mauricio Rangel Gomez (NIMH), Megan Frankowski (NINDS), Emrin Horgusluoglu (NCCIH), Erin Quinlan (NICCH), Courtney Pinard (NIMH)
Statistical Methods & Data Analysis	**Joseph Monaco* (NINDS/OBD)**, Jasenka Borzan (NIMH), Emrin Horgusluoglu (NCCIH)
Consortium-scale Data Coordination	**Yong Yao* (NIMH)**, Laura Reyes (NIMH), David Panchision (NIMH, Team N liaison), Kari Johnson (NINDS, Team T liaison)
Developmental & Molecular Neurobiology	David Panchision (NIMH, Team N liaison), Elizabeth Powell (NIAAA), Courtney Pinard (NIMH)
Electrophysiology & Neural Circuits	Jasenka Borzan (NIMH), Mauricio Rangel Gomez (NIMH), Qi-Ying Liu (NIAAA)
Bioethics & Data Governance	Saskia Hendriks (NIH/CC/BEP), David Panchision (NIMH, Team N liaison)
Connectomics & Network Analysis	Emrin Horgusluoglu (NCCIH), Kari Johnson (NINDS, Team T liaison)
Neurotechnology & Engineering	Roger Miller (NIDCD), Elizabeth Powell (NIAAA), Courtney Pinard (NIMH)

*** Working Group Leads**

Landscape Analysis

State of the Science: Neuroscience Data Management

Current best practices in neuroscience data management emphasize Findability, Accessibility, Interoperability, and Reusability (FAIR) principles, with specialized data standards like BIDS and NWB gaining widespread adoption by establishing common formats for neuroimaging and neurophysiology data, respectively. The field is shifting from traditional data repositories toward data commons models that combine storage with computational resources, visualization capabilities, and integrated analysis tools to address the extreme scale and heterogeneity of neuroscience datasets. Formal ontologies and common coordinate frameworks (CCFs) have become essential infrastructure components, enabling spatial registration of data across modalities and species while providing controlled vocabularies that enhance metadata quality and searchability. Metadata standards remain inconsistent across

neuroscience subfields, despite being crucial for making data truly FAIR, with many datasets lacking detailed experimental context for meaningful reuse.

As noted above, ethical considerations for large-scale brain data sharing have been extensively examined by the BRAIN Neuroethics Working Group, particularly in a July 2023 workshop, which identified key challenges in multi-modal data integration and provided recommendations for responsible data governance that inform the BRAIN Knowledgebase design.

BRAIN Informatics Portfolio Analysis

BRAIN's current data archives span 9 specialized repositories housing nearly 12 petabytes, demonstrating significant adoption of data sharing practices but with limited cross-archive integration. While specialized archives excel at handling specific data types, researchers face significant barriers when attempting to combine and analyze data across multiple archives and modalities, limiting the scientific return on BRAIN's substantial data generation investments. The exponential growth in data volume from transformative projects like BICAN and CONNECTS is pushing existing archive architectures to their limits, particularly for applications requiring cross-modal analysis of datasets that individually can exceed 300 terabytes. Current approaches would benefit from cross-archive integration of molecular, cellular, circuits/systems, and behavioral data, which would enable researchers to test new hypotheses and potentially discover key relationships to advance our understanding of brain function across scales.

Relevant Players and Potential Partners

Cross-NIH Data Programs

Multiple cross-NIH data initiatives and programs demonstrate the impact of well-designed platforms for advancing scientific discovery. For example, the NCI Genomic Data Commons serves 50,000 researchers monthly who access 1.5 PB of curated, harmonized data to enable new discoveries. Molecular cell type information from BICAN provides a natural bridge from future CONNECTS connectivity maps to well-established genomic databases, enabling broader integration with NIH biomedical data resources. Establishing such a connection would represent a strategic opportunity to leverage existing NIH data infrastructure while extending to neuroscience applications for BRAIN.

In addition, the NIH Common Fund Data Ecosystem has prioritized connecting NIH biomedical data resources through unified discovery portals to enable researchers to address cross-disciplinary health questions. Other NIH-wide programs like the Helping to End Addiction Long-term® Initiative, Adolescent Brain Cognitive Development℠ Study, and All of Us℠ Research Program have each showcased approaches to managing sensitive data with appropriate levels

of access control. The NIH Office of Data Science Strategy (ODSS) coordinates critical data science activities across NIH ICs, including the STRIDES Initiative which provides cost-effective access to cloud-computing resources. These NIH-wide efforts complement BRAIN's specialized data platforms and offer potential synergies for BRAIN Knowledgebase activities, enhancing the long-term sustainability of NIH and BRAIN data ecosystems.

Other Governmental Data Programs

Beyond NIH, the National Science Foundation's (NSF) Proto-OKN program, launched in 2023, supports public data infrastructure projects that connect knowledge graphs across fields to create a unified platform for evidence-based policymaking and scientific discovery. International initiatives such as the EBRAINS infrastructure program, originally developed to serve the large-scale data needs of the European Union Human Brain Project, emphasize open access to cloud data and computing resources, digital twin methodologies, and cross-scale modeling capabilities. EBRAINS efforts could inform BRAIN's Knowledgebase integration strategy or enhance it via partnership, potentially by serving as a bidirectional North American node of the growing international EBRAINS network. Other international projects are exploring different approaches to data governance, such as the International Neuroinformatics Coordinating Facility (INCF) which is working to establish cross-border standards for neuroscience data sharing.

Private Sector Vendors and Capabilities

Commercial entities including tech startups, large companies, and small businesses (such as DataJoint and CatalystNeuro, which currently operate within the BRAIN ecosystem) are increasingly involved in neuroscience data infrastructure. Commercial offerings include on-premise, turnkey, and cloud-based solutions for research data management, FAIR sharing implementation, and AI-based analytics capabilities that complement and potentially compete with public research infrastructure.

Implementation Strategy

From Federation to Sustainable Integration

Phase 1 (Years 1-2)

This phase will build a strong foundation for a federated BRAIN data ecosystem. This includes developing shared metadata standards, APIs, and authentication systems across data archives, while maintaining their domain-specific strengths. Infrastructure will support cross-archive searches, data quality metrics, and interoperability. Specialized inventories of datasets and AI/ML assets will be catalogued, and training programs will be created in relevant neuroscience concepts and data structures. The CONNECTS initiative will set standards for connectomics data, develop cloud-based platforms, as well as integrate molecular and

connectivity data with BICAN. Similarly, the BBQS effort will enhance behavioral data archives, create behavioral ontologies, and synchronize neural-behavioral recordings across timescales and species.

Phase 2 (Years 3-5)
This phase aims to move from foundational efforts to full-scale deployment and integration. The Data Commons will expand with cross-domain search and analysis tools, sustainable financial and governance models, and Phase 1-guided broader federation. BICAN will transition to a knowledge framework with automated cell-type annotation, unified visualization, and published taxonomies. CONNECTS will scale up to produce cross-species analytic frameworks for 3D map-based visualization and circuit motif discovery. BBQS will develop comprehensive ontologies for multi-timescale behavioral processes and cross-species homologies and launch AI-powered tools for behavioral analysis and link behavior to neural and cell-type data.

Phase 3 (Years 6-10)
This phase aims to create a unified knowledgebase framework that emphasizes advanced integration and enables AI-powered exploration and automated hypothesis testing across the knowledgebase. A key goal is seamless, cross-scale analysis from molecular to behavioral levels, with sustainable international partnerships, translational frameworks for human health, and a comprehensive training ecosystem to ensure long-term impact. Validated translational pathways will advance fundamental neuroscience knowledge to clinically relevant applications for human health.

To achieve this transformation, BRAIN aims to implement a phased approach to training that builds workforce capacity. Phase 1 will develop introduction programs for data access, metadata standards, and basic analytics while cross-training software developers in relevant neuroscience concepts. Phase 2 will partner with institutions to expand training programs, develop specialized courses for visualization and analysis, and host workshops to encourage collaboration. Phase 3 will disseminate educational materials for integration into formal programs and promote mentoring to sustain the data ecosystem.

Assessments:

Impact, Opportunities, Socialization, and Transformative Projects Integration

Impact Assessment

Scientific Value Proposition

The BRAIN Knowledgebase Innovation Domain represents a transformative opportunity to accelerate neuroscience discovery through integrated knowledge management. By creating a unified framework that connects currently siloed data archives, the effort will enable researchers to trace relationships between molecular, cellular, circuit, and behavioral data in ways previously impossible. The proposed Knowledgebase's value extends beyond data integration, potentially enabling new forms of hypothesis generation through AI-assisted exploration of cross-modal relationships. This capability is particularly critical for BRAIN's large-scale projects, where understanding relationships between cell types, connectivity, and function requires synthesizing massive datasets across different scales and modalities.

Technical Feasibility Assessment

The technical foundation for the Knowledgebase Innovation Domain builds upon demonstrated successes while acknowledging significant challenges. BRAIN's existing network of specialized data archives provides a strong base for federation, with established standards like NWB and BIDS enabling interoperability. Recent advances in AI foundation models and knowledge graph technologies offer promising approaches for cross-modal data integration. However, the scale of data integration required – from single-cell genomics to whole-brain connectivity – presents technical challenges requiring careful staging of development phases. Success will depend on balancing immediate practical needs with longer-term infrastructure development.

Resource Requirement and Sustainability

Implementing the BRAIN Knowledgebase Innovation Domain demands sustained investment in both technical infrastructure and human expertise. Beyond initial development costs, long-term sustainability requires stable funding for data curation, tool maintenance, and user support services. Experience from existing repositories demonstrates that successful data ecosystems need dedicated professional staff for software development, data curation, and community engagement. The distributed nature of the proposed system helps manage costs through shared resources while maintaining specialized expertise at individual archives, but coordination overhead must be carefully considered in resource planning.

Risk Evaluation

Primary risks fall into three categories: technical, organizational, and strategic. Technical risks include challenges in scaling integration across vastly different data types and volumes, while organizational risks center on maintaining coordination across distributed teams and archives. Strategic risks involve balancing comprehensive data inclusion with quality standards and ensuring long-term sustainability. These risks can be mitigated through careful staging of

development, clear governance structures, and strong community engagement, but require ongoing attention throughout implementation.

The integration of multiscale and multimodal brain data presents unique ethical challenges that require dedicated attention:

- Re-identification risks from combined genomic, imaging, and behavioral datasets
- Need for ethical subject matter expert input to manage large-scale brain data integration risks
- Challenges in harmonizing consent across different data types and collection protocols
- Potential for unintended insights about donors when combining previously separate datasets

Mitigating these risks requires the need to:

- Implement the tiered access framework detailed in Appendix D
- Engage neuroethics expertise throughout development and operation phases
- Establish clear protocols for handling potential re-identification scenarios
- Maintain ongoing dialogue with the BRAIN Neuroethics Working Group
- Ensure Federal Information Security Modernization Act of 2014 (FISMA) compliance for all human data management systems

Technical Opportunities

Advanced AI foundation models are transforming the extraction of knowledge from large-scale brain data. Large language models (LLMs) can already automate traditionally manual processes like cell type annotation and literature curation. More sophisticated foundation models, trained on billion-cell datasets, could enable prediction of cell types, integration of molecular profiles, and analysis of cellular changes across health and disease states. These models can help bridge gaps between different data modalities while maintaining clear provenance to source data.

Visual intelligence tools represent another crucial opportunity, particularly for the integration of spatial data across scales. New approaches combining computer vision with biological knowledge can enable automated analysis of complex brain imagery, from cellular morphology to circuit connectivity. These tools will be essential for projects like CONNECTS that generate massive imaging datasets requiring sophisticated pattern recognition and structural analysis. The integration of visual and semantic understanding could revolutionize how we navigate and understand brain architecture.

The BRAIN Knowledgebase framework offers a transformative opportunity by integrating specialized repositories for different brain research domains while maintaining interoperability through common standards. The BRAIN Knowledgebase will be able to support a unified, yet flexible knowledge ecosystem. This approach allows for domain-specific optimization while enabling cross-domain discovery through AI-powered search interfaces and knowledge graphs. The framework must emphasize maintaining detailed provenance tracking and clear attribution while supporting novel combinations of data and analyses previously impossible.

These technical opportunities align with BRAIN's "think big, start small, scale fast" approach by leveraging existing capabilities while pushing toward transformative goals. Success will require careful attention to both technical excellence and usability, ensuring these advanced tools remain accessible to the broader neuroscience community.

Socialization & Engagement

Workshop Planning

Developing the BRAIN Knowledgebase Innovation Domain will require a coordinated series of workshops to address both immediate integration needs and longer-term strategic planning. An initial workshop plans to focus on "Digital Brain – When Brain Cell Atlas Meets AI," establishing a foundation for AI-driven integration across the three major knowledge components. This workshop will explore how foundation models, LLMs, and visual intelligence tools can enhance data federation, knowledge integration, and research resource management across BRAIN's distributed data archives.

Future workshops will address specific technical challenges for each Knowledgebase component while maintaining cross-cutting themes. For BICAN Knowledgebase integration, sessions will focus on billion-cell genomics models and automated annotation systems. CONNECTS Knowledgebase workshops will emphasize scalable technologies for managing exascale connectivity datasets. Data Commons sessions will address federation architecture and cross-modal integration frameworks. Each workshop will include concrete deliverables aligned with both immediate project needs and longer-term strategic objectives.

Community Engagement

A socialization strategy will employ a phased approach, beginning with internal alignment across BRAIN scientific teams and expanding to broader community engagement. An initial focus will be to coordinate work across Teams A, C, and Data to ensure alignment of knowledge infrastructure with the needs of BRAIN large-scale projects. Internal discussions aim to establish clear roles and responsibilities while developing unified standards and protocols for broader adoption.

External engagement will systematically expand through advisory board consultations, stakeholder feedback sessions, and partnership development. This strategy emphasizes maintaining balance between specialized needs of individual Knowledge components while ensuring interoperability and shared resources across the data ecosystem. Regular communication channels will be established to keep the broader neuroscience community informed and engaged, with particular attention to ethical considerations and sustainable governance models for long-term knowledge infrastructure management.

Integration with BRAIN's Large-Scale Projects

Project-Specific Integration

The BRAIN Knowledgebase framework will interconnect and integrate multiple components of BRAIN's data ecosystem and transformative projects while maintaining specialized focus areas.

1. The Data Commons provides a foundational infrastructure, implementing a federated approach across nine distributed archives with common metadata standards. This central framework enables unified querying while preserving original data integrity and maintaining comprehensive provenance tracking throughout the research workflow. The system's AI-powered search interface and interactive exploration capabilities serve as shared resources across all BRAIN projects.

2. The BICAN Brain Cell-Atlas Knowledgebase, developed in conjunction with BICAN, processes approximately 100 petabytes of cell atlas data across five BRAIN archives. This specialized component creates versioned cell type taxonomies and spatial maps while leveraging billion-cell foundation models for prediction and analysis. Integration with the broader Knowledgebase framework occurs through standardized coordinate systems and cross-species ontologies.

3. The CONNECTS Knowledgebase will manage massive data volumes to be generated through whole-brain connectivity mapping by 40+ institutions based in specialized data collection centers. This component implements rigorous quality control and standardization processes while developing automatable systems for processing exabyte-scale datasets. Integration with other Innovation Domain components occurs through common coordinate frameworks and unified analysis platforms.

4. The BBQS Knowledgebase addresses a critical gap by integrating behavioral quantification, neural activity, and environmental contexts across species. This component standardizes multi-dimensional behavioral measurements and neural-behavioral synchronization protocols while establishing cross-species frameworks for behavioral phenotyping. Integration with BICAN and CONNECTS creates comprehensive links between cell types, circuits, and behaviors, providing the

translational bridge essential for relating fundamental neuroscience to cognitive and behavioral functions relevant to human health.

Cross-Project Synergies

Common technical infrastructure elements include standardized APIs, metadata schema, and quality assessment frameworks that ensure interoperability while maintaining specialized capabilities for each domain. This approach allows flexible adaptation to emerging technologies while preserving consistent data management practices across all components.

Planned shared AI/ML resources will span the Knowledgebase, including foundation models for cross-modal integration, automated annotation systems, and advanced visualization tools. These tools can be developed with modular architectures that enable customization for specific use cases while maintaining core compatibility across projects.

Best practices and standards will be coordinated through systematic governance structures that balance specialized needs with overall integration goals. This includes unified approaches to data quality assessment, provenance tracking, and ethical considerations that apply across all components while accommodating domain-specific requirements.

Knowledge transfer mechanisms ensure that advances in a single component can benefit the entire ecosystem. This includes shared documentation systems, cross-training programs, and collaborative development of new integration capabilities. Regular coordination ensures that individual components evolve in complementary ways while maintaining their essential specialized functions.

BBQS Knowledgebase integration will enhance cross-project synergies by connecting neural mechanisms to behavioral outputs, establishing the critical final link in the knowledge chain. BBQS components bridge traditionally disparate fields including cognitive neuroscience, ethology, and behavioral sciences, creating new opportunities for translational insights. The integration of EMBER and DCAIC data platforms with other knowledge components enables multi-timescale analysis of brain-behavior relationships that would be impossible in isolated systems.

Federating and interconnecting BRAIN's large-scale project data platforms will ultimately establish a comprehensive BRAIN Knowledgebase framework that from molecules to behavior across species and environments.

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The BRAIN Initiative®

Precision Molecular Circuit Therapies

Research Roadmap Innovation Domain

Targeting neural networks with molecular precision for transformative brain therapeutics

Precision Molecular Circuit Therapies:

NIH BRAIN Research Roadmap Innovation Domain Scoping Plan

Strategic Vision

Within 10 years, this Innovation Domain expects to deliver precise deployment of optogenetic, chemogenetic, and other neural effector technologies to correct dysfunctional circuits for several classes of neuroscience indications. Precision molecular circuit therapies will combine the power of i) precision access to circuit components using genetic delivery tools, such as viral vectors, and ii) engineered control of neural activity using effector molecules, such as optogenetic and chemogenetic receptors. The main objective is to improve therapeutic potential with greater spatial, cellular, and temporal resolution, toward addressing the complexity of brain cell type identities and circuit dynamics. Optogenetic and chemogenetic strategies are beginning to be applied for genetic blinding diseases of the retina in humans and Parkinson's disease in preclinical models. The vision for this Innovation Domain is to expand upon these efforts and integrate refined access and actuator technologies. The molecular genetic approach to circuit intervention holds great potential to transform treatments for a range of neurologic and neuropsychiatric disorders.

Strategic Objectives

BRAIN will take many steps, but not every step, to realize this vision. For example, BRAIN can serve a critical role to support technology development and integration to accelerate preclinical discovery and lead identification of precision molecular circuit therapies. Substantial downstream investment from industry and others will be required to advance therapeutic development to regulatory approval and commercialization. BRAIN is well positioned to address several obstacles that are i) technological, ii) neurobiological, and iii) regulatory and ethical. These three areas form the strategic objectives for the scoping plan:

1. **Technology Integration Pathways**
   A. Delineate technology development and integration appropriate for BRAIN funding versus other sponsors, including NIH ICs and trans-NIH programs.
   B. Assess synergies of precision molecular circuit therapies (PMCTs) technology development with BRAIN recording and modulation research.

C. Engage BRAIN Armamentarium research developing precision brain cell access reagents and gauge readiness for PMCT efforts.
D. Survey industry progress in PMCT development and identify opportunities for non-dilutive interactions.
E. Explore infrastructure needed to support early-stage, preclinical discovery and lead identification for PMCTs.
F. Foster knowledge transfer and collaboration among circuit therapy researchers in different technological domains through short course-based training and professional development opportunities.

2. **Neurobiological Opportunities**
   A. Gain alignment of the PMCT effort with existing BRAIN human and organismal programs and BRAIN 2.0 projects.
   B. Identify "low-hanging fruit" targets for circuit engagement.
   C. Engage researchers to gauge interest in fostering integration of neuroscientists and technologists on molecular circuit therapies.
   D. Encourage interaction of circuit therapy researchers and trainees from across consortia/groups (NINDS translational training programs, BBQS, BICAN, CONNECTS, Armamentarium) to promote pre-competitive knowledge sharing.

3. **Regulatory and ethical Issues**
   A. Learn from FDA about regulatory science gaps for PMCTs related to evaluating delivery vectors and actuator products.
   B. Establish potential handoff points for technology support with NIH Blueprint translational programs.
   C. Engage BRAIN neuroethics researchers to integrate ethical considerations with PMCT investigation and product development.
   D. Propose plans to close gaps in support for technological, neurobiological, regulatory science areas.

Working Group Organization

A Working Group (WG) has been formed to spearhead the development and implementation of the Precision Molecular Circuit Therapies Innovation Domain strategy. As planning matures, additional members with adjacent and relevant expertise will be added at key milestones of Innovation Domain development to ensure that the overall plan considers the appropriate breadth of perspectives and addresses cross-cutting issues like training, dissemination, and ongoing consideration of neuroethical principles.

Relevant Expertise	Name
Expertise in technology development for gene-targeted therapies for rare diseases; clinical sub-team member for FNIH Bespoke Gene Therapy Consortium and NINDS URGenT working group member	**Jill Morris* (Program Director, NINDS)**
Expertise in molecular neurotechnologies; RFA lead for BRAIN Initiative Armamentarium for Precision Brain Cell Access project	**Doug Kim* (Program Officer, NIMH)**
Expertise in non-invasive neuromodulation and therapeutics; Team co- lead for BRAIN Initiative Brain Behavior Quantification and Synchronization (BBQS) team; Team N member	Lizzy Ankudowich (Program Officer, NIMH)
Expertise in neuroengineering and genetic approaches to interrogate and modulate circuit function; co-lead of BRAIN Team A	Olivier Berton (Program Officer, NIDA):
Expertise in preclinical neurotherapeutic biologics development; lead of the NINDS URGenT Program and member of Blueprint Biologics; working group member of Somatic Cell Gene Editing Common Fund Program	Chris Boshoff (Program Director, NINDS)
Expertise in the integration across scales to solve complex systems neuroscience questions and team science; co-lead of Team E; Team T member	Karen David (Program Director, NINDS)
Expertise in understanding the genetic, molecular, cellular, and circuit level changes that occur in aging and neurodegeneration; Team A and D member; Program Director managing NIA-funded Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD) program	Erin Gray (Program Director, NIA)
Expertise in developing and testing innovative targets and therapeutic candidates; Team E member	Sofiya Hupalo (Program Officer, NIMH):
Expertise in bioengineering and technology development efforts addressing retinal function and vision impairment caused by retinal diseases; Team B and D member	Paek Lee (Program Director, NEI)
Expertise in neural prosthesis development for deafness; Team B member	Roger Miller (Program Director, NIDCD)
Familiarity with experts in neuroethics of gene therapy and/or invasive brain interventions in humans	TBD

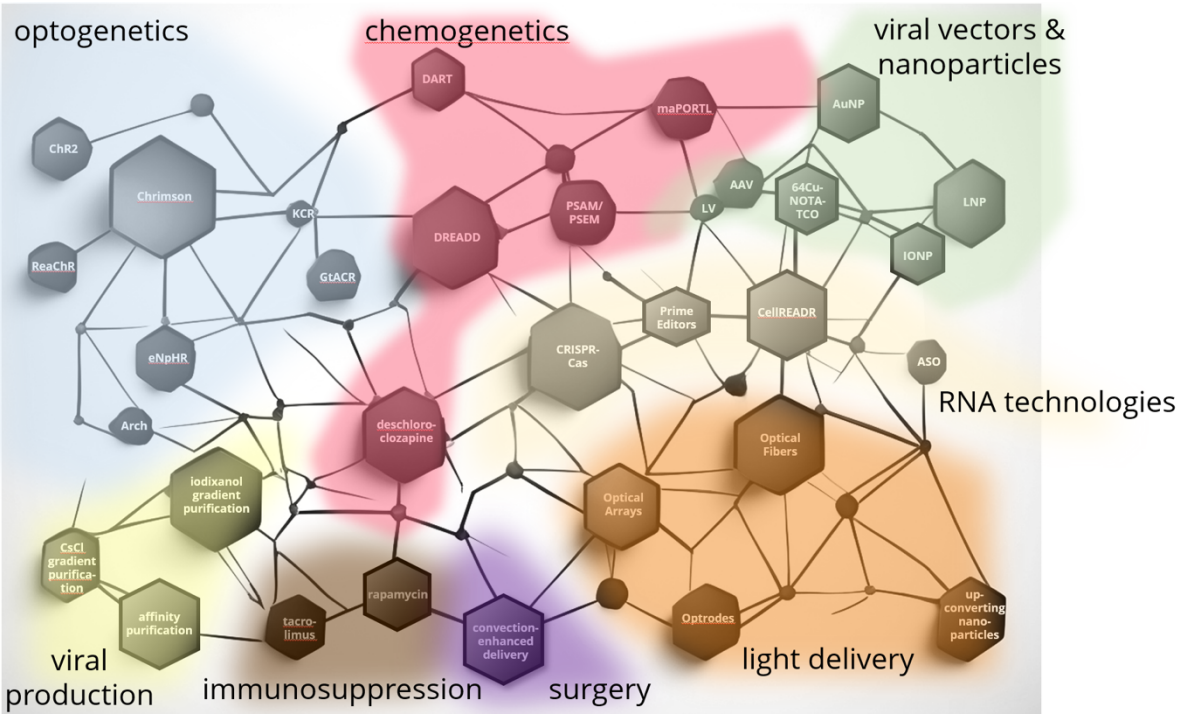
***Working Group Leads**

Landscape Assessment

The Precision Molecular Circuit Therapies Innovation Domain fits within a broad community of stakeholders in various frameworks. These frameworks will guide stakeholder engagement.

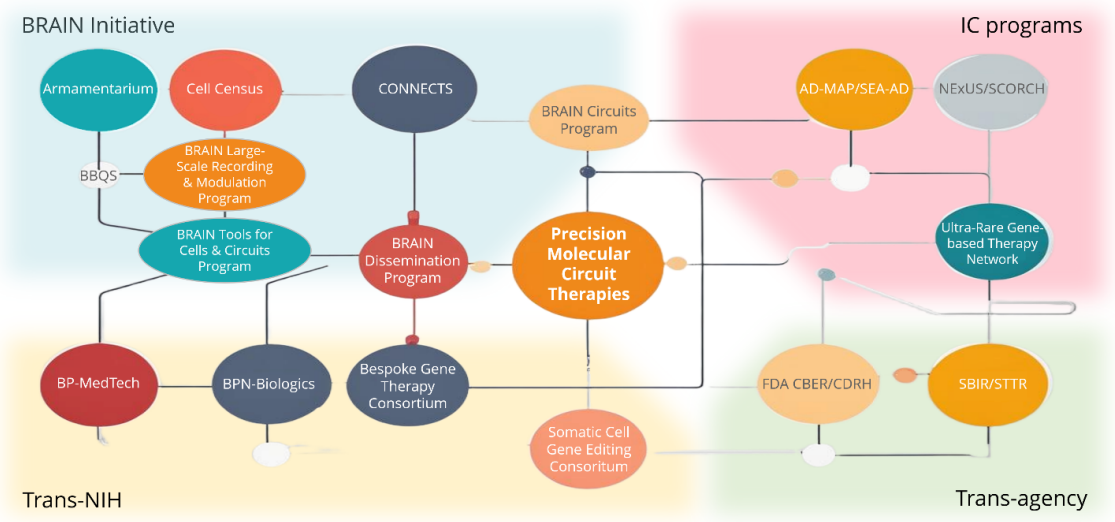
1. Consider researchers and programs with direct versus indirect PMCT relevance. Research areas with direct PMCT connections include gene therapy, precision brain cell access, optogenetics, chemogenetics, and vector production. Research areas with less direct but still impactful PMCT relevance include brain cell census efforts, basic brain circuit neuroscience, noninvasive neuroimaging, neuroethics, and connectomics.

Enabling Technologies to Integrate



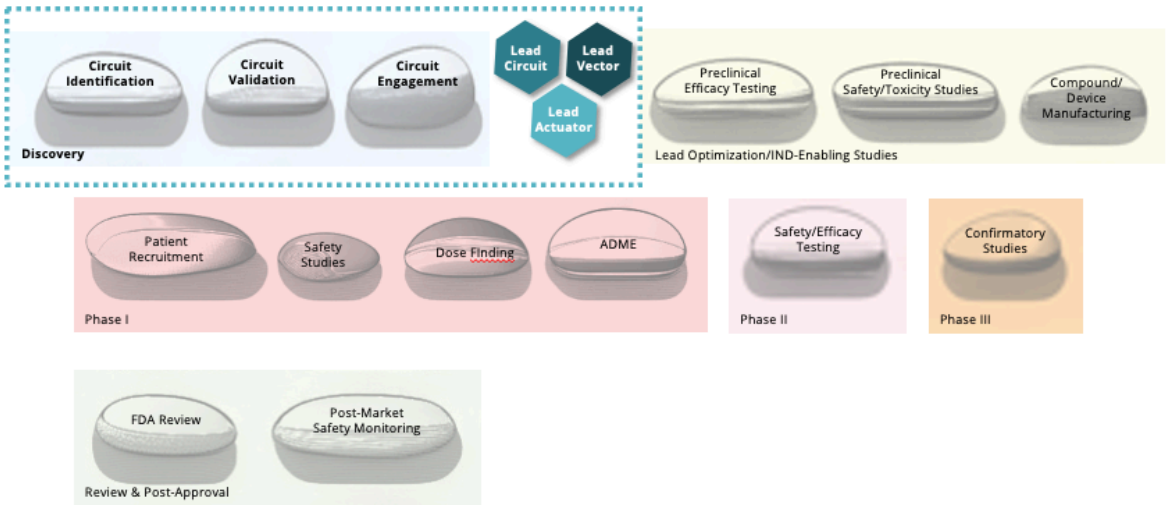
The Precision Molecular Circuit Therapies Innovation Domain will build on BRAIN's strong track record in technology development. It will draw upon prior experience supporting technologies such as precision brain cell access, optogenetics, and chemogenetics. It remains to be assessed through program evaluation and stakeholder dialogue i) how circuits and components can best be identified for engagement and targeting by PMCTs and ii) what regulatory hurdles need to be addressed to advance PMCT technologies toward translation.

Ecosystem of Circuit Therapeutic Development



2. Consider groups internal and external to NIH. Internal groups include the Cell and Circuits program, the Circuits program, the Large-Scale Recording and Modulation program, the Non-Invasive Recording and Modulation program, the Dissemination program, the Neuroethics Program, the Cell Census program, the Armamentarium program (see Precision Molecular Circuit Therapies Appendix A), the CONNECTS program, the BBQS program, individual Institutes/Centers, the Bespoke Gene Therapy Consortium (see Precision Molecular Circuit Therapies Appendix B), the Somatic Cell Gene Editing Consortium (see Precision Molecular Circuit Therapies Appendix C), the Blueprint Medtech and Biologics programs (see Precision Molecular Circuit Therapies Appendix D). External groups include industry and other research sponsors, patients and patient advocacy groups, and FDA.

Informing Discovery and Lead Identification



The Precision Molecular Circuit Therapies Innovation Domain grows from BRAIN's focus on new tools and methods and is well positioned to focus on preclinical discovery research. Support of preclinical technology development is critical for eventual adaptation to human therapeutic use. It remains to be assessed through program evaluation and stakeholder dialogue i) how circuits and components can best be identified for engagement and targeting by PMCTs, and ii) which regulatory hurdles need to be addressed to advance PMCT technologies toward translation.

Scoping Strategies

Technological Scoping

1A. Goal: Delineate technology development and integration appropriate for BRAIN funding versus other sponsors, including ICs and trans-NIH programs.

Strategy: BRAIN Director and program staff meet with individual BRAIN IC institute leaders and trans-NIH program leaders to understand how PMCT technology development fits with their programs. Target completion date: 11/30/2025.

1B. Goal: Assess synergies of PMCT technology development with BRAIN recording and modulation program.

Strategy: PMCT team meets with Team B to discuss potential opportunities to synergize. Target completion date: 2/28/2025.

1C. Goal: Engage BRAIN Armamentarium researchers developing precision brain cell access reagents and gauge readiness for PMCT effort.

1D. Goal: Survey industry progress toward PMCTs and opportunities for non-dilutive interaction.

1E. Goal: Explore the infrastructure needed to support early-stage, preclinical discovery and lead identification for PMCTs.

Strategy: PMCT team hosts public workshop to bring together precision brain cell access technologists, industrial researchers, and biologics infrastructure stakeholder to assess opportunities for the field. Target completion date: TBD

1F. Goal: Foster knowledge transfer and collaboration among circuit therapy researchers in different technological domains through short course-based training and professional development opportunities.

Strategy: Support community of practice initiatives for short courses or other forums to bring together technologists.

Neurobiological Scoping

2A. Goal: Gain alignment of PMCT effort with existing BRAIN human and organismal programs and BRAIN 2.0 projects. **Strategy:** PMCT team meets with Team E to discuss potential opportunities to synergize. Target completion date: 1/31/2025.
2B. Goal: Identify the low-hanging fruit targets for circuit engagement. **2C. Goal:** Engage researchers to gauge interest in fostering integration of neuroscientists and technologists on molecular circuit therapies. **Strategy:** See workshop strategy above. **2D. Goal:** Encourage interaction of circuit therapy researchers and trainees from across consortia/groups (NINDS translational training programs, BBQS, BICAN, CONNECTS, Armamentarium) to promote pre-competitive knowledge sharing. **Strategy:** Collaborate programmatically to engage trainees with knowledge of tools and circuits; support through Team T translational neuroscience training program.

Regulatory and Ethics Scoping

3A. Goal: Learn from FDA about regulatory science gaps for PMCTs in terms of evaluating vector and actuator products. **Strategy:** PMCT team holds roundtable discussion with FDA experts to present technological opportunities for future translational efforts and to examine key regulatory questions about technologies. Target completion date: TBD
3B. Goal: Establish potential handoff points for technology support with Blueprint translational programs. **Strategy:** PMCT team meets with Blueprint MedTech and Blueprint Biologics program leadership to discuss parameters of program entry. Target completion date: 5/31/2025.
3C. Goal: Engage BRAIN neuroethics program on supporting investigation of molecular circuit therapy ethical issues. **Strategy:** PMCT team meets with Team N to discuss potential opportunities to synergize. Target completion date: 3/31/2025.
3D. Goal: Propose plans to close gaps in support for technological, neurobiological, regulatory science areas. **Strategy:** PMCT team integrates above learnings and composes an innovation domain action plan for the BRAIN Research Roadmap. Target completion date: TBD

Future Public Workshop

The Precision Molecular Circuit Therapies Innovation Domain WG is planning a virtual public workshop. This workshop builds upon and extends topics explored in the 2021 "From BRAIN to Bedside: Translation of Next-Generation Circuit Therapies" Workshop.

The workshop aims to extend previous discussions by homing in on the specific bridging studies needed to build on what BRAIN has accomplished to date in order to advance circuit therapeutic approaches in humans. Although a complex nexus of considerations surrounds this Innovation Domain (e.g., precision access tools, circuit specificity, actuators, neuroethics), fully addressing these considerations is an essential step to identify the necessary studies to bridge research/knowledge gaps in the field toward advancing circuit therapies in humans.

Workshop Goals

1. Identify **pathways to technology bridging**, through discussion with precision access toolmakers, actuator technologists, and therapeutic developers.
2. Evaluate **feasibility of a stepwise PMCT approach**:
    - **First** precision CNS gene therapies, **then** precision CNS circuit actuator therapies.
3. Ascertain **disease areas ripe for PMCT** preclinical development.
4. Clarify **regulatory science issues** for PMCTs.

Tentative Agenda

- Session 1: Cell- or circuit-selective gene therapy
- Session 2: Cell-selective access tools for preclinical neuroscience
- Session 3: Identifying disease-relevant circuits using molecular actuators
- Session 4: Human applications of molecular circuit therapies
- Session 5: Technical and clinical feasibility of molecular circuit therapies

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Informing Precision Molecular Circuit Therapies Innovation Domain Scoping Goals: Workshop Outcomes and Follow-up

*Workshop goals
**Workshop follow-on activity

I. Technological	II. Neurobiological	III. Regulatory & ethical
A. Delineate technology development and integration appropriate for BRAIN funding versus other sponsors, including ICs and trans-NIH programs.	A. Gain alignment of PMCT effort with existing BRAIN human and organismal programs and BRAIN 2.0 projects.	**A. **Learn from FDA about regulatory science gaps** for PMCTs in terms of evaluating vector and actuator products.
B. Assess synergies of PMCT technology development with BRAIN recording and modulation program.	*B. Ascertain the **low-hanging fruit targets** for circuit engagement.	B. Establish potential handoff points for technology support with Blueprint translational programs.
*C. Engage **researchers developing precision brain cell access reagents** and gauge readiness for PMCT effort.	*C. Engage researchers to gauge interest in **fostering integration of neuroscientists and technologists** on molecular circuit therapies.	C. Engage BRAIN neuroethics program on supporting investigation of molecular circuit therapy ethical issues.
*D. **Survey industry progress** toward PMCTs and opportunities for non-dilutive interaction.		D. Propose plans for to close gaps in support for technological, neurobiological, regulatory science areas.
*E. Explore the **infrastructure needed to support early-stage, preclinical** discovery and lead identification for PMCTs.		

Accelerating Human Neuroscience

Research Roadmap Innovation Domain

Bridging fundamental knowledge, novel technologies, and human-centered translation

Accelerating Human Neuroscience:

NIH BRAIN Research Roadmap Innovation Domain Scoping Plan

Strategic Vision

The Accelerating Human Neuroscience Innovation Domain aims to advance and integrate BRAIN-supported research and training to enhance fundamental knowledge of human brain function, supporting the development of transformative treatments, cures, and preventative interventions. Despite significant investments, human neuroscience research has been conducted in a dispersed manner across the BRAIN portfolio, resulting in limited integration between non-human model systems and human research data. The rare cases in which this has been attempted have been challenging. This Innovation Domain will create a unified scientific ecosystem with clear synergies between basic and translational science, across species and levels of analysis. It will establish clear pathways for technologies and insights to transition to NIH IC-specific programs and external partners, including industry.

Strategic Objectives

Scientific Objectives

1. **Generate fundamental knowledge** about the mechanisms of human brain function that can be transformative across BRAIN NIH ICs, providing a pathway and environment for the integration of human and non-human model systems data to enhance knowledge of brain mechanisms that can support treatments and improve health.
2. **Develop new technologies and platforms** to advance human neuroscience from fundamental knowledge to technology translation and interventions, and in consideration of alternative approaches.
3. **Test next-generation technologies** in first-in-human and early-feasibility studies with the goal that successful projects can subsequently apply for IC-specific funding. Determine and implement the necessary neuroethical principles governing human neuroscience research, as well as the translatability of results from other model systems.

Organizational Objectives

1. **Support relevant training opportunities**, resources, and infrastructure to facilitate development of a BRAIN-wide human neuroscience framework. Foster research networks that bring together experts and trainees across fields. Incorporate neuroethics training into all levels of neuroscience research and education.
2. **Optimize the organization of BRAIN programs and teams** to develop, coordinate, and implement a cohesive framework for BRAIN human neuroscience.
3. **Consult with the BRAIN Neuroethics Working Group** on all major activities.
4. **Facilitate increased coordination and interdisciplinary collaboration** in the BRAIN-supported extramural human neuroscience community.

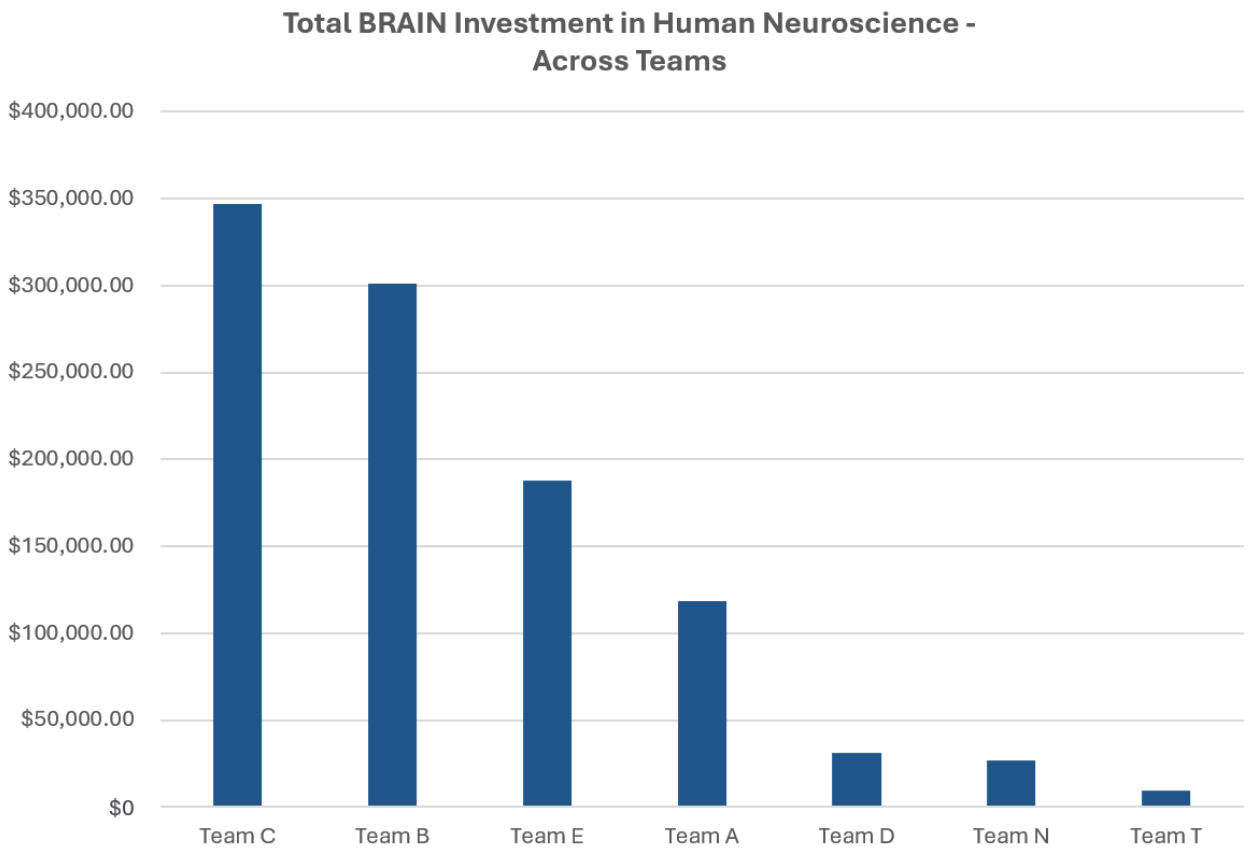


Figure 1.

Human neuroscience investments span BRAIN scientific program teams

- Team A: BRAIN Cells & Circuits Analysis
- Team B: Neural Recording & Modulation/ Technology Development & Human Studies
- Team C: Human Neuroimaging Technologies
- Team D: Dissemination
- Team N: Neuroethics
- Team T: Training

Introduction

BRAIN's overarching goal is to revolutionize understanding of the human brain, and substantial resources in human neuroscience have been invested to date. These investments span BRAIN scientific program teams (**Figure 1**) and scientific areas. These include tool/technology development for human application; use of advanced technologies to investigate the structure, function, and connectivity of the human brain; and first-in-human and early feasibility studies of novel technologies to address disorders of the central nervous system (**Figure 2**). These investments have yielded significant dividends for both basic and translational science.

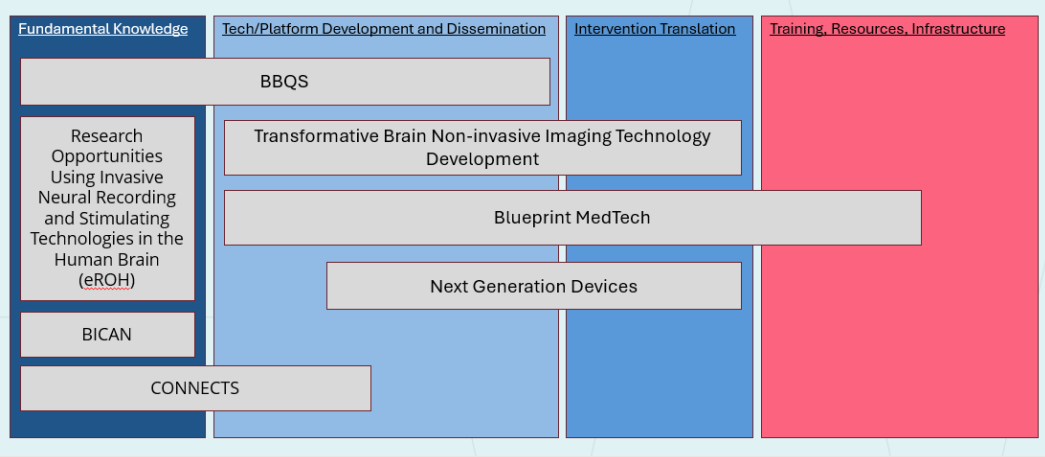


Figure 2.
Current and recent BRAIN programs with significant human neuroscience components. Colors represent the cross-cutting themes that each program addresses. Note: Human research was defined as projects with an IRB as part of the initial application.

Despite this substantial BRAIN investment, planning and implementation of human neuroscience research across the Initiative has been conducted in a dispersed manner across teams and planning groups, pointing to the need for a more cohesive guiding framework. There is also an important, and urgent, opportunity to expedite transformative progress by exploiting the tools, infrastructure, and conceptual foundations developed in the first 10 years of BRAIN. This urgency was an important criterion for selection of Accelerating Human Neuroscience as one of the four identified Innovation Domains.

The Accelerating Human Neuroscience Innovation Domain was charged with developing a cohesive scientific and organization framework, one that supports a continuum from tool and resource development to basic and translational research across investigator career levels, attendant to clearly defined neuroethics principles. This Innovation Domain will identify novel opportunities to promote translation and reverse-translation between foundational and clinical

studies. As well, it will develop explicit plans for effective hand-off points to NIH ICs and other external partners in the private and public sectors.

BRAIN is uniquely situated to tackle scientific opportunities that cross the boundaries of individual NIH IC missions, with potential to catalyze transformative science within BRAIN ICs. The Human Neuroscience Working Group compiled the scientific objectives below for further exploration, scoping, and refinement. These objectives were generated by analyzing consistent areas of emphasis and scientific gaps that BRAIN scientific program staff put forward as Research Roadmap concepts; through larger feedback at the September 2024 BRAIN retreat (for details, see *Appendix A: Cross-Cutting Themes from the Human Neuroscience Roadmap Concepts* and *Appendix B: Research Roadmap Retreat Feedback*; and through preliminary analysis of recent workshop and RFI outcomes relevant to BRAIN human neuroscience (such as the "Advancing Human Neuroscience through Neural Stimulation and Recording: Opportunities and Challenges for Coordinated Efforts" workshop and RFI NOT-NS-24-080). The scoping process described herein is designed to refine the broad scientific objectives below into i) a more holistic understanding of areas in which ongoing BRAIN programs are well situated to make continued progress, and ii) specific areas where new and/or reconceptualized programs are needed.

Scientific Objectives

Scientific Objective 1: Generate fundamental knowledge about the mechanisms of human brain function that can be transformative across BRAIN NIH ICs, providing a pathway and environment for the integration of human and non-human model systems data to enhance knowledge of brain mechanisms that can support treatments and improve health**.**

From its inception, BRAIN has recognized the importance of uncovering fundamental principles of human brain structure and function. The BRAIN 2.0 report noted that, despite the unique challenges of basic human studies, they are nonetheless critical because of the unique features of the human brain and the importance for relevant discoveries to improve health and develop cures for neurological and psychological/psychiatric conditions. The report also noted that it is increasingly possible to combine observations from noninvasive brain imaging with high-resolution cellular and physiological data in humans with implanted devices – enabling study of the human brain at multiple levels. Ongoing BRAIN programs are making progress in this area, but the Accelerated Human Neuroscience Innovation Domain Working Group identified areas for further scoping in which continued or increased emphasis could have significant impact.

- Translate brain circuit knowledge derived from non-human animal studies to humans.
    - **Scoping Question**: Are there opportunities from the BRAIN Circuits portfolio ready for exploration in humans?
- Identify how to bridge/map fundamental knowledge of brain structure and function gained from invasive methods to noninvasive methods (and vice versa), as well as across species.
- Understand the mechanism of action of a neuromodulation tool versus the specificity of targeting by the neuromodulation tool.
- Identify novel mechanisms/neural processes that could serve as targets for neural recording and modulation tools that do not yet exist.
    - **Scoping Question**: What should new tools look like to engage new previously unidentified mechanisms?

Scientific Objective 2: Develop new technologies and platforms to advance human neuroscience from fundamental knowledge to technology translation and interventions, and in consideration of alternative approaches.

Over the past 10 years the BRAIN Initiative has significantly (both directly and indirectly) invested in new tools, technologies, and platforms to improve understanding of brain structure and function in a range of species and at increasingly better spatial and temporal resolutions. Breaking through barriers of scale, enabling comparison and combination of data from distinct experimental approaches (and species), would yield substantial benefits for basic discovery about the human brain as well as for diagnosing and treating human brain diseases. However, there has not yet been a systematic assessment of what has been funded and the impact to date, particularly in the context of furthering our understanding of the human brain. We have identified this as a critical gap in its goal to *accelerate and integrate* the human neuroscience efforts supported by BRAIN.

- **Scoping Question**: What BRAIN-funded technologies have been developed so far? Where are they in the device development pipeline? Is more than one lab using the tool or technology? Identify the successes versus failures and identify/fund ways to train individuals to use them.
- **Scoping Question**: What is the landscape for translation of technologies or models developed in/for animal use to use in human neuroscience research?
- **Scoping Question**: What are the barriers to progress and dissemination of BRAIN-funded technologies to ultimately increase access and dissemination for both researchers and individuals with brain conditions?

- **Scoping Question**: What are brain mechanisms that could be targeted by optimizing existing technologies or developing new technologies?
- **Scoping Question:** How can current technologies help bridge human and non-human model systems data? Are there new technologies needed to optimize the connection of data across models?

Scientific Objective 3: Test next-generation technologies in first-in-human and early feasibility studies with the goal that successful projects can subsequently apply for NIH IC-specific funding.

Stimulation and recording technologies developed in part through BRAIN funding have had a profound impact both for neuroscience research and for people living with brain disorders. Both invasive and less-invasive forms of neuromodulation have shown therapeutic benefit for neurologic and neuropsychiatric disorders including Parkinson's disease, essential tremor, dystonia, obsessive compulsive disorder (OCD) and major depressive disorder. There is also new evidence pointing to potential therapeutic benefit for other disorders including Tourette's syndrome, eating disorders, and addiction. Currently, implantable stimulation and recording neuromodulation devices such as deep brain stimulation are only FDA-approved for Parkinson's disease, essential tremor, and dystonia with a humanitarian device exemption for OCD.

Except for the examples above, research and development of new stimulation and recording technologies is still in its infancy. There are several barriers contributing to the advance of stimulation and recording technologies, including limited knowledge of the neural circuitry underlying disorders that can guide targeting and monitoring; a lack of understanding of which physiologic changes resulting from stimulation are beneficial; and a need to understand how stimulation parameters (e.g., continuous stimulation, burst stimulation, intermittent stimulation, responsive stimulation) may be leveraged to increase efficacy and reduce side effects. These gaps in knowledge create a significant barrier to developing potentially life-changing treatments that could address the ultimate goal of NIH and BRAIN to cure human brain disorders and also gain a greater understanding of the human brain.

- **Scoping Question**: What are new technologies, such as less invasive devices, sensors, combination devices that can derisk projects for future funding?
- **Scoping Question**: What BRAIN-funded stimulation and recording technologies have been developed so far? Where are they in the device development pipeline? Is more than one lab using the tool or technology?
- **Scoping Question**: What constitutes a success or a failure in the development and translation of BRAIN-funded devices for humans?

- **Scoping Question**: What steps can BRAIN take to reduce risk and promote continued advancement of technologies in individual NIH ICs?
- **Scoping Question**: What is the landscape of translation for technologies or models developed for human neuroscience research?
- **Scoping Question**: What unmet needs can be targeted by future efforts from BRAIN for technology development in this space?

These Scientific Objectives consider opportunities to uncover causal explanations underlying brain function and behavior (e.g., new tools, technologies, conceptual advances).

Scientific Objective 4. Determine and implement the necessary neuroethical principles governing human neuroscience research, as well as the translation potential of results from other model systems.

Human neuroscientific research, using both invasive and non-invasive technologies, presents significant and unique ethical challenges. This Innovation Domain will aim to generate consensus and implement best practices that will guide future human neuroscience research.

The topic of neuroethics has been widely discussed both within and outside NIH in the context of new developments that allow for more naturalistic and continuous recordings of human data, focusing in particular on risks associated with privacy, consent, and data sensitivity. It is essential that all neuroethical elements are considered across BRAIN programs, projects, and future funding directions.

Working Group Organization

An Accelerating Human Neuroscience Working Group (WG) has been formed to spearhead the development and implementation of ID strategy. Initial members of the WG consist of the authors of those Concept Notes that informed the Accelerating Human Neuroscience Innovation Domain. As Innovation Domain planning matures, additional members with adjacent and relevant expertise will be added at key timepoints of Innovation Domain development to ensure that the overall plan considers the appropriate breadth of perspectives.

Working Group Members

The Accelerating Human Neuroscience WG will have representation from key scientific areas in support of its Scientific Objectives, including human systems/circuits neuroscience; organismal neuroscience; tool, technology, and platform development and dissemination; neuroethics; data; and training.

Knowledge and Interests	Name(s)
BRAIN Systems and Organismal portfolios with a strong interest in translating knowledge between animals and humans	**Mauricio Rangel-Gomez*(Team E Co-Lead)** **Andrew Breeden* (Team E member)**
Noninvasive Imaging portfolio with a strong interest in translating knowledge between noninvasive and invasive methods	**Erin Burke Quinlan* (Team C Co-Lead)**
Intracranial Recordings and/or Neuromodulation portfolio and interest in human clinical translational research	**Megan Frankowski* (Team B Co-Lead)** Yvonne Bennett (Team B Co-Lead) Merav Sabri (Team E member, ROH)
Device/tool development pipeline	Nick Langhals (Team B member) Brooks Gross (Team B member)
Training portfolios and generating training opportunities in human neuroscience	Kristin Brethel-Haurwitz (Team T member) Rachel Saré (Team T member)
Dissemination portfolio	Natalie Trzinski (Team D member) Jacky Durkin (Team D member)
Neuroethics portfolio and neuroethical considerations for human research	Lizzy Ankudowich (Team N member)
BBQS portfolio	Lizzy Ankudowich (Team BBQS co-lead)

***Working Group Leads**

Extended Working Group Meeting

To identify the most effective approaches to operationalizing the scoping of the three Strategic Objectives, the WG held a meeting March 17, 2025 (see Accelerating Human Neuroscience Appendix C), The meeting's purpose was to discuss long-term directions of the Accelerating Human Neuroscience Innovation Domain, including: i) a brief overview of relevant current programs, ii) research gaps to prioritize focused exploration, iii) identify needed targeted portfolio analyses, iv) discuss the potential formation of planning sub-groups and a timeline for WG activities. Overall, the meeting was collaborative and productive, culminating in several next steps. These include: i) three sub-groups will be formed around the Scientific Objectives in

the scoping plan, ii) core evaluation data elements will be agreed upon (see above), iii) each sub-group will conduct analyses relevant to their scientific areas/programs, iv) the full WG will assess all analyses to inform understanding of scientific gaps, v) the possibility of rapid turn-around “mini-workshops" to assess these gaps will be discussed and/or planned, and vi) new programs and/or re-envisioned existing programs will be proposed that address gaps most strategically.

Landscaping strategies

Landscaping activities with BRAIN scientific program teams, particularly Teams B, C, and E. Doing so will require additional resources, including both personnel and technology (e.g., AI tools).

- Assess portfolios for gaps across human neuroscience in the areas of the scientific objectives above (start with Teams B, C, E).
- Assess how aspects of the included concepts address gaps identified from the portfolio analysis and identify which can addressed in the nearer term (e.g., via reissued Notices of Funding Opportunities NOFOs) rather than included in the implementation plan.
    - **Refine short-, medium-, and long-term goals to address these gaps.**
      A “funnel” process will start with broad gaps, and will be narrowed according to the core guiding question: “which of these gaps is important to neuroscience across the BRAIN NIH ICs and can only be uniquely addressed by BRAIN?”
        - **Short-term:** Establish the Human Neuroscience Innovation Domain WG.
        - **Medium-term:** Identify high priority aspects of individual roadmap concepts that are ready for further development towards NOFOs, etc.
            - **Potential activities in service of this goal:** mini-retreat, coordination with Team scoping activities
        - **Long-term:** Identify gaps that are not adequately captured by the concepts but are important elements of a 10-year vision of what BRAIN can uniquely accomplish.
            - Examples of such potential gaps identified at the retreat include: i) the potential need for synergistic human-animal programs aimed at uncovering underlying mechanisms of human brain function,
              ii) the need for programs to elucidate the biophysical mechanisms and basic physiology of neurostimulation,
              iii) the need to identify/develop data standardization and data sharing practices.

- When addressing the Scientific Objectives via scoping strategies, the WG will consider the question, "What's ready for NIH ICs to carry forward?"
- The Human Neuroscience Innovation Domain WG will refine the goals above into a cohesive plan for short-, medium-, and long-term implementation

Socialization and Engagement Plan

As part of landscaping, this Innovation Domain will interact with NIH ICs to understand their needs for handoff of relevant funded BRAIN knowledge and tools. In the longer term, we will engage the research community. The WG will also learn from successful BBQS socialization efforts. This section of our scoping document will be expanded upon with more details and timelines as the scoping process unfolds.

Team Interactions

Alignment and integration with BRAIN scientific program team activities – which have already started – are crucial for the success of the Human Neuroscience Innovation Domain. For example, the Human Neuroscience Innovation Domain presented to Team E on 1/14/25. The working group will also consider appointing Team Liaisons (e.g., following the Team B model) and conduct "roadshow-like" presentations and other relevant activities in the spirit of the successful interactions and dissemination by the BBQS program. We envision that with regard to the BRAIN Teams/Research Themes, this Innovation Domain will serve as a locus of coordination and is not necessarily designed to replace or supersede Team activities.

National Institutes of Health
The BRAIN Initiative®

BRAIN NeuroAI

Research Roadmap Innovation Domain

Advancing neuroscience and AI through theoretically grounded and brain-inspired computational approaches

BRAIN NeuroAI:

NIH BRAIN Research Roadmap Innovation Domain Scoping Plan

Strategic Vision

The BRAIN NeuroAI Innovation Domain aims to establish a framework for advancing both neuroscience and artificial intelligence (AI) through bidirectional advances and knowledge exchange. The BRAIN NeuroAI vision centers on developing brain-inspired computational approaches that are theoretically grounded, ethically sound, and inherently adaptable. The NeuroAI Innovation Domain aims to create a transdisciplinary bridge where biological insights inform the development of more brain-like AI models, which in turn drive new computational and neuromorphic approaches to address the embodiment gap and resolve longstanding obstacles to progress in neuroscience. Building a community of NeuroAI researchers to achieve these reciprocal advances will require collaboration and cross-training between neuroscientists, engineers, roboticists, materials scientists, computer scientists, mathematicians, neuroethicists, and others. The envisioned approach takes advantage of BRAIN's unique position to bridge theory, embodiment, and technology transition by leveraging its massive neural and behavioral datasets, experience with large-scale team science and interdisciplinary training, and a decade of BRAIN's transformative advances in neurotechnologies for science and health.

Strategic Objectives & Scientific Priorities

1. Computational Models & Mechanisms for Theory-Experiment Integration

- Develop interpretable computational models that mechanistically elucidate how biobehavioral mechanisms give rise to emergent sensorimotor, cognitive, and affective functions, emphasizing biological plausibility over performance metrics.
- Create data-driven predictive models operating across multiple spatial and temporal scales that balance discovery with hypothesis testing while maintaining interpretability and biological relevance for forecasting neural dynamics.

- Establish bidirectional knowledge exchange between NeuroAI research communities through computational model-mapping with mechanistic understanding that integrates with experimental approaches for mutual advancement.
- Investigate fundamental principles of biological computation that can reciprocally inform both neuroscience and technology development, creating a virtuous cycle of discovery and innovation.

2. Learning and Adaptation through Energy-Efficient Neuromorphic Platforms

- Advance energy-efficient neuromorphic platforms that adjust and adapt to individual variations through real-time processing capabilities, enabling resilient systems that operate continuously for research applications and health monitoring.
- Develop new tools for measuring and implementing synaptic plasticity and neuromodulation in systems that learn from and adjust to individual variability to enable long-term monitoring and feedback control.
- Study adaptation mechanisms in natural contexts and real-world applications that can be integrated with BRAIN-scale data collection efforts to enhance biological understanding.
- Investigate the biological components of energy efficiency that can be transferred to technological applications while enhancing adaptability, functionality, and performance in complex environments.

3. Brain-Body Systems for Embodied Intelligence

- Establish new paradigms for understanding brain-body systems that address the circular causality inherent in complex biological systems, including neuronal and non-neuronal cell interactions with the environment.
- Develop platforms that integrate across multiple scales from cellular to organismal levels while focusing on natural behavior and environmental interactions to embrace real-world biological complexity.
- Investigate the combined role of neuronal and non-neuronal cells in biological systems to understand how embodied cognition emerges from integrated physiological processes.
- Create models and technologies that reflect the bidirectional relationship between internal biological processes and environmental contexts to better understand adaptive behaviors.

4. Interdisciplinary Collaboration and Cross-Cutting Elements

Infrastructure and Resources

- Establish standardized, accessible platforms through multi-agency collaboration that leverage existing infrastructure while creating new resources specifically designed for NeuroAI applications and data sharing.
- Develop shared computational resources and analysis tools that democratize access to advanced NeuroAI methods and facilitate reproducible research across laboratories and institutions.
- Create sustainable support mechanisms through strategic partnerships with academic institutions, industry collaborators, and government agencies to ensure long-term viability of NeuroAI resources.
- Enable broad access to specialized NeuroAI technologies by developing user-friendly interfaces and documentation that lower barriers to entry for researchers from diverse disciplinary backgrounds.

Training and Workforce Development

The BRAIN NeuroAI Innovation Domain recognizes that advancing brain-inspired AI requires a new generation of researchers comfortable working at the intersection of neuroscience, AI, and ethics. A comprehensive training strategy includes the need to:

- Create interdisciplinary educational programs combining neuroscience and computation that prepare the next generation of researchers to work at the intersection of these traditionally separate domains.
- Establish collaborations with academic institutions and non-profit organizations to develop NeuroAI curricula that integrate neuroscience, computational techniques, neuroethical frameworks, and engineering approaches from fields including neuromorphic computing, robotics, and materials science.
- Develop new mathematical frameworks for understanding biological complexity that can be incorporated into curricula and training materials for students and established researchers.
- Engage with the community through RFIs, workshops, and other forums to build pathways to interdisciplinary collaboration and identify emerging training needs.
- Support robust long-term workforce development through fellowships, career transition awards, and mechanisms for critical roles, like research software engineers, that recognize and support important skill sets for NeuroAI research.

NeuroAI Ethical Framework

- Address patient and user safety proactively by developing guidelines and best practices for NeuroAI applications in research and healthcare settings before deployment.
- Ensure responsible innovation practices through ongoing ethical review and stakeholder engagement throughout the development and implementation of the NeuroAI roadmap.
- Focus on practical implementation concerns related to fairness, transparency, and accessibility of NeuroAI tools and platforms across diverse populations and research contexts.
- Consider privacy and security implications of NeuroAI systems that may handle sensitive neural data or interface directly with biological systems to protect individuals and communities.
- Integrate neuroethics within training to ensure that ethical considerations guide technological developments.

Implementation Approach

- Emphasize health relevance over performance metrics to ensure that NeuroAI innovations subserve meaningful scientific and health advances rather than technological advancement for its own sake.
- Allow standards and best practices to emerge organically from the research community through iterative refinement rather than imposing rigid frameworks that may limit innovation.
- Enable translation of fundamental discoveries to applications without overpromising clinical outcomes by maintaining realistic timelines and expectations about technological readiness.
- Maintain focus on fundamental scientific understanding as the foundation for all NeuroAI activities, recognizing that breakthroughs in basic science drive transformative applications.
- Foster partnerships across sectors while preserving BRAIN's unique role as a catalyst for high-risk, high-reward research that might not be supported through traditional funding mechanisms.

The Challenge of NeuroAI

The central challenge of NeuroAI lies at the intersection of three critical gaps in the understanding of intelligence. First, despite impressive advances in neuroscience data collection, few frameworks can translate biological mechanisms into computational principles that maintain both biological relevance and engineering feasibility. The human brain achieves remarkable cognitive flexibility while consuming only 15-20 watts of power – a level of efficiency that remains orders of magnitude beyond current AI systems – yet it is still not known which biological features are essential versus incidental to efficient performance. Second, current AI approaches rely predominantly on statistical learning from massive datasets rather than the structured, embodied learning that characterizes biological systems, resulting in technologies that excel at narrow tasks but lack the adaptability and resilience of even simple organisms. Third, this divide is widened by disciplinary boundaries between neuroscience, AI, cognitive science, biocomputing, and device engineering, with few researchers possessing the cross-disciplinary expertise needed to bridge biological understanding with technological implementation.

These challenges are compounded by significant infrastructure and methodological limitations. Neuroscience data remains fragmented across modalities, scales, and repositories, with limited tools for integration and cross-scale analysis (for more details, see *Appendix A: Advances and Challenges in NeuroAI Data Integration*). Meanwhile, hardware implementations face a "chicken and egg" problem – developers need validation data to justify investment in novel architectures, but gathering this data requires investment in the devices themselves. This has led to incremental improvements rather than transformative approaches. The field also lacks standardized benchmarks and validation frameworks that can meaningfully compare the performance of biological and artificial systems across multiple dimensions, including energy efficiency, adaptability, and computational capability. Addressing these challenges requires a coordinated approach that can bridge disciplinary boundaries, integrate across scales and modalities, and create frameworks for translating between biological observations and computational implementation. These are the goals of the BRAIN NeuroAI Innovation Domain.

Why BRAIN is Uniquely Positioned

BRAIN is uniquely positioned to lead the BRAIN NeuroAI Innovation Domain through its unparalleled combination of transformative neuroscience data resources, established interdisciplinary research community, and proven track record of coordinating large-scale scientific endeavors. After investing more than $3.5 billion since 2014, BRAIN has created an integrated ecosystem spanning cell atlases (BICAN), connectivity maps (CONNECTS), specialized data archives, and advanced neural recording and modulation technologies. These

complementary resources collectively provide the comprehensive neural datasets across multiple scales and modalities that are essential for developing biologically informed computational models. BRAIN's distributed network of 9 specialized data archives already hosts nearly 12 petabytes of neuroscience data with standardized formats (NWB, BIDS) and cloud computing resources, creating an unparalleled foundation for NeuroAI development.

BRAIN's "think big, start small, scale fast" philosophy has demonstrated success in mobilizing scientific communities around ambitious goals, exemplified by transformative projects like the BRAIN Cell Census Network which engaged more than 250 researchers to create comprehensive brain cell atlases. BRAIN's open science experience building infrastructure for large collaborative teams provides the necessary foundation for the cross-disciplinary integration required by NeuroAI research. The planned BRAIN Knowledgebase and Human Neuroscience Innovation Domains will provide natural integration points for BRAIN's NeuroAI advances, with the former providing the data infrastructure foundation and the latter offering pathways for clinical translation of next-generation adaptive neurotechnologies.

BRAIN's combination of biological understanding, technological capabilities, computational resources, and team science culture enables a unique approach to NeuroAI that maintains biological relevance while advancing computational capabilities. Unlike purely commercial AI development or academic neuroscience research, BRAIN can bridge these domains through its focus on mechanistic understanding and health relevance. The planned innovation pipeline reinforces BRAIN's proven approach to high-risk, high-reward research, allowing exploration of new approaches while maintaining strategic direction toward transformative outcomes. BRAIN faces exciting opportunities to build on a decade of transformative discovery, while adapting to a rapidly changing landscape – the opportunity that the BRAIN NeuroAI Innovation Domain addresses through its structured, yet flexible approach to advancing this critical intersection of neuroscience and technology.

Working Group Organization

A Working Group (WG) has been formed to spearhead the development and implementation of the BRAIN NeuroAI Innovation Domain strategy. As planning matures, additional members with adjacent and relevant expertise will be added at key milestones of Innovation Domain development to ensure that the overall plan considers the appropriate breadth of perspectives and addresses cross-cutting issues like training, dissemination, and ongoing consideration of neuroethical principles.

Relevant Expertise	Name
Computational Neuroscience & AI	**Joseph Monaco* (NINDS/OBD)**, Jessica Mollick (NIDA), Michele Ferrante (NIMH), Jeffrey Kopsick (NINDS), Karen David (NINDS), Leslie Osborne (NINDS), Elizabeth Powell (NIAAA), Mauricio Rangel Gomez (NIMH)
Data Science & Management	Bo-Shiun Chen (NINDS), Clayton Bingham (NLM), Elizabeth Powell (NIAAA), Roger Miller (NIDCD), Mauricio Rangel Gomez (NIMH)
Neuromorphic Engineering & Computing	**Grace Hwang* (NINDS)**, Jeffrey Kopsick (NINDS), Jessica Falcone (NIBIB), Roger Miller (NIDCD)
Systems & Neural Circuits Neuroscience	Karen David (NINDS), Leslie Osborne (NINDS), Mauricio Rangel Gomez (NIMH), Yael Mandelblat-Cerf (NIMH), Holly Moore (NIDA), Bo-Shiun Chen (NINDS), Jay Churchill (NIMH, Team N liaison)
Brain-Body Interactions & Behavioral Science	Christina Hatch (NIDA), Fernando Fernandez (NIMH), Holly Moore (NIDA), Dana Schloesser (OD/OBSSR), Elizabeth Powell (NIAAA), Yael Mandelblat-Cerf (NIMH)
Biomedical Engineering & Technology	Jessica Falcone (NIBIB), Elizabeth Powell (NIAAA), **Grace Hwang* (NINDS)**, Roger Miller (NIDCD)
Neuroethics & Research Ethics	Courtney Pinard (NIMH, Team T liaison), Jay Churchill (NIMH, Team N liaison), Nina Hsu (NINDS), Elizabeth Powell (NIAAA)
Connectomics & Large-Scale Data Integration	Clayton Bingham (NLM), Jeffrey Kopsick (NINDS), Kari Johnson (NINDS)
Research Training & Career Development	Courtney Pinard (NIMH, Team T liaison), Jessica Mollick (NIDA), Elizabeth Powell (NIAAA)
Theoretical Neuroscience	Fernando Fernandez (NIMH), **Joseph Monaco* (NINDS/OBD)**, Jessica Mollick (NIDA), Michele Ferrante (NIMH)
Strategic Planning & Federal Coordination	Chris Kinsinger (OD/OSC), **Grace Hwang* (NINDS)**, Dana Schloesser (OD/OBSSR)
Neuroimaging & Neurophysiology	Courtney Pinard (NIMH, Team T liaison), Mauricio Rangel Gomez (NIMH), Merav Sabri (NIDCD)

*** Working Group Leads**

Landscape Analysis

State of the Science

The intersection of neuroscience and AI has reached an inflection point where technological capabilities can now support meaningful bidirectional exchange. Neuroscience data collection has expanded dramatically across scales from molecular to whole-brain levels, with recording technologies approaching petascale daily volumes within 3-5 years. BRAIN-funded transformative projects including BICAN, CONNECTS, and BBQS provide rich datasets on cellular diversity, connectivity patterns, and neural-behavioral functions in environmental context, offering crucial validation resources for computational models. Simultaneously, foundation models and neuromorphic computing systems have demonstrated remarkable capabilities in sensory processing and neural dynamics simulation with increasing biological fidelity, though most remain focused on performance metrics rather than mechanistic understanding.

Despite these advances, significant challenges persist in translating between biological mechanisms and computational implementations (for more details, see *Appendix B: Technical Approaches to Neural Computation and Validation*). The circular causality inherent in brain-body systems and the relationship between neural mechanisms and emergent computational properties remain poorly understood. Current models typically focus on either biological detail or computational performance, with few approaches successfully bridging this gap. Neuromorphic implementations in particular face a critical "chicken and egg" problem – developers need validation data to justify investment in novel architectures, but gathering this data requires investment in the devices themselves. This has led to incremental improvement of existing technologies rather than exploration of truly innovative designs that might better capture essential biological principles.

The intersection of neuroscience and AI has been the subject of intensive neuroethical examination across many recent workshops and meetings including:

- **National Academies Workshop (March 2024)**: The "Exploring the Bidirectional Relationship Between Artificial Intelligence and Neuroscience" workshop examined many aspects of brain-AI integration, including ethical and regulatory concerns.
- **International Neuroethics 2025 (April 2025)**: The "Neuroethics at the Intersection of the Brain and Artificial Intelligence" workshop focused on issues at the intersection of neuroethics and AI, including brain-computer interface technologies and beyond.
- **The BRAIN NEWG Meeting (May 2025)** focused specifically on ethical considerations for digital brain twins and other detailed AI models in clinical settings.

These meetings have identified key ethical considerations including data governance, adaptive or dynamic consent models, the potential for bias in AI tools, and the benefits of interpretability in more brain-like AI models.

Portfolio Analysis

The BRAIN ecosystem provides a strong foundation for NeuroAI advancement through its complementary teams and transformative projects. Team B's development of neural recording and stimulation tools enables new data collection modalities, while Team E's circuit-level insights inform computational implementations. The BBQS program's focus on behavior quantification provides essential context for embodied approaches. Team Data's infrastructure supports the data management needs of complex NeuroAI projects, and cross-cutting efforts in ethics (Team N) and training (Team T) address critical implementation considerations. However, gaps remain in integrating these components across the BRAIN portfolio, particularly in developing standardized validation frameworks that can evaluate computational approaches against biological benchmarks.

While these BRAIN resources represent significant assets, current portfolio allocations do not provide support hardware-software co-design approaches, exploratory neuromorphic implementations, or coordinated efforts to achieve cross-scale model development. The current funding landscape tends to separate tool development from computational modeling, limiting opportunities for integrated approaches that could accelerate progress. Additionally, while data generation has been well-supported, the infrastructure for integrating different data types and modalities across spatial and temporal scales remains underdeveloped.

Relevant Players and Potential Partners

Beyond NIH, key stakeholders include NSF (supporting theoretical frameworks and neuromorphic computing through programs like POSE and the THOR Neuromorphic Commons), the Department of Energy (providing high-performance computing resources and large-scale neuromorphic funding), and the Defense Advanced Research Projects Agency (advancing brain-inspired computing supported by multiple programs). Commercial partners range from established companies implementing neuromorphic architectures (Intel's Loihi, IBM's TrueNorth) to startups developing specialized applications (BrainChip, SynSense, Prophesee). International initiatives including Europe's EBRAINS and the International Brain Laboratory (IBL) offer complementary resources and collaboration opportunities. Academic institutions with neuromorphic computing centers (Georgia Tech, UTSA, UCSD, Yale) represent potential external partners for reducing access barriers to custom chips and computing capacity. For more details, see *Appendix C: Neuromorphic Computing and Hardware Implementation*.

Coordination gaps exist in data standardization, sustainable infrastructure development, and clear pathways for regulatory approval of adaptive neurotechnologies. While individual agencies have strong programs addressing aspects of NeuroAI research, the lack of coordinated funding mechanisms creates challenges for projects spanning biological understanding and technological implementation. The regulatory landscape for neuromorphic medical devices remains underdeveloped, particularly regarding adaptive systems that learn and change over time. BRAIN is uniquely positioned to address these gaps through its comprehensive datasets, interdisciplinary expertise, and focus on both basic science and technology transition toward health applications, particularly at the intersection of neural mechanisms of learning and adaptation.

Implementation Strategy:

NeuroAI Innovation Pipeline

The BRAIN NeuroAI Innovation Domain aims to implement a strategic innovation pipeline that advances promising approaches from early exploration through community refinement to practical implementation. This three-phase structure provides a clear pathway for transformative ideas to develop into mature technologies with significant scientific and health impacts while maintaining BRAIN's commitment to high-risk, high-reward research.

The NeuroAI Innovation Domain will develop interdisciplinary training programs through collaborations with academic institutions, industry partners, and government agencies. These programs will prepare researchers to work at the intersection of neuroscience, AI, and ethics through curricula encompassing neuroscience fundamentals, computational and engineering approaches, ethical frameworks, and hands-on projects. Mechanisms could include co-mentorship programs pairing neuroscientists with AI experts, summer schools focused on NeuroAI applications, funding for cross-disciplinary postdoctoral fellowships, and supporting the development of online educational resources. These efforts will cultivate a generation of researchers that can advance both fields.

Phase 1 (Years 1-2): Innovation Incubator
This initial phase aims to promote broad exploration of early-stage ideas at the intersection of neuroscience and AI, using flexible funding mechanisms and accessible infrastructure to encourage innovation without prematurely narrowing the field. Funding mechanisms may include thematic data challenges, cross-disciplinary seed grants, and supplements to existing BRAIN Initiative awards. Infrastructure investments will support cloud access, collaborative platforms, and technical workshops. Community engagement will be fostered through hackathons, seminars, and online training to build capacity in emerging NeuroAI methods.

Phase 2 (Years 3-5): Community-Driven Pipeline
This phase aims to refine and advance promising approaches from Phase 1 through structured community selection and benchmarking. Evaluation panels and progressive funding will prioritize models that demonstrate biological relevance, energy efficiency, scalability, and clinical potential. Integrations with BRAIN programs – such as BICAN, CONNECTS, and BBQS – will anchor research in established neuroscience frameworks. Clear advancement criteria will ensure that selected methods can span cellular to behavioral levels and contribute meaningfully to brain health applications.

Phase 3 (Years 6-10): Transition to Impact
The final phase aims to focus on scaling the most successful approaches into translational impact through large, collaborative efforts. Cooperative agreements, team science awards, and public-private partnerships will drive progress on adaptive neural interfaces, predictive health models, and energy-efficient monitoring. Long-term sustainability will be supported through shared computing infrastructure, open-source tool ecosystems, and educational programs to maintain innovation momentum.

Cross-Cutting Implementation Considerations

Ethical Framework Integration

- Ethics considerations will be integrated from the earliest stages of all phases
- Projects will develop and incorporate responsible AI/NeuroAI development practices
- Privacy and data security standards will evolve with technological capabilities
- Patient and user autonomy will remain central to all health applications

Partnership Development

- **Across BRAIN**: Close coordination with all Teams, particularly B (tools), E (circuits), and BBQS
- **Across NIH**: Integration with relevant NIH Common Fund programs, ODSS initiatives, and National Library of Medicine resources
- **Federal Partnerships**: Strategic collaborations with NSF (neuromorphic commons), DOE (computing infrastructure), and FDA (regulatory pathways)
- **International Coordination**: Alignment with global initiatives including EBRAINS and IBL

Training and Workforce Development

- Targeted opportunities for early-career researchers across all three phases

- Development of interdisciplinary curricula combining neuroscience and computation
- Support for specialized roles including research software engineers and data scientists
- Community-building activities to create a sustainable NeuroAI ecosystem

Assessments:

Impact, Opportunities, Socialization, and Team Integration

Impact Analysis

Scientific Value Proposition

The BRAIN NeuroAI Innovation Domain represents a transformative opportunity to advance both neuroscience understanding and technological innovation through a structured innovation pipeline approach. By creating bidirectional knowledge exchange between biological principles and computational frameworks, the NeuroAI Innovation Domain aims to catalyze discoveries across multiple domains. The phased implementation will enable development of cross-scale predictive models that integrate data from molecular mechanisms to system-level behaviors, creating new frameworks for understanding how biological elements give rise to cognitive functions and behavior.

Through exploration of wide-ranging approaches in Phase 1 and community refinement in Phase 2, BRAIN NeuroAI aims to bridge historically separate theoretical frameworks, developing unified models that balance biological plausibility with computational power. By Phase 3, mature BRAIN NeuroAI approaches will provide new tools for understanding neurological and psychiatric disorders, potentially leading to more precise diagnostics and adaptive therapeutic interventions based on biological principles. The innovation pipeline structure will maximize the value of BRAIN's investments in data collection and tool development by creating new computational frameworks to integrate and interpret complex multi-modal datasets from the BRAIN Knowledgebase BICAN, CONNECTS, and BBQS.

Moreover, as BRAIN's data ecosystem approaches petabyte-scale volumes across multiple modalities, the BRAIN NeuroAI Innovation Domain approach will leverage shared infrastructure and scalable computing to transform BRAIN data into actionable knowledge through computational models that maintain biological relevance while enabling new capabilities.

Technical Feasibility

The phased implementation strategy ensures technical feasibility by building systematically on existing capabilities while allowing for exploration of novel approaches. For example, large vision and language models have demonstrated scalable processing and interpretation of

massive quantities of multimodal data, indicating that neural foundation models are a feasible, promising approach to large-scale, multimodal integration of complex neural and behavioral data for neuroscience. Additionally, neuromorphic computing platforms are reaching scales and capabilities that can implement increasingly complex biological mechanisms; the remaining obstacles to wider adoption are related to limited access to customized research-specific technologies. The innovation pipeline structure specifically addresses technical feasibility concerns by starting with small-scale, lightweight explorations before committing to larger investments, ensuring that resources are directed toward approaches with demonstrated potential.

Resource Requirements and Sustainability

Infrastructure needs include cloud computing access for challenges and benchmarking, leveraging existing NIH resources where possible and establishing partnerships for specialized computing needs. Coordination with the proposed BRAIN Knowledgebase Framework will be crucial to provide streamlined access to BRAIN datasets for secondary users of data and data challenge participants. BRAIN NeuroAI activities will require development and deployment of knowledge exchange platforms, including code repositories, discussion forums, and documentation.

Risk Evaluation

A main technical risk for the BRAIN NeuroAI Innovation Domain is the difficulty translating biological principles into computational frameworks that maintain both biological relevance and computational efficiency. This risk is mitigated by the structure of the innovation pipeline implementation, which enables many parallel approaches in Phase 1 to ensure broad exploration of the solution space. There are technical challenges in validating computational models against biological data due to incomplete or inconsistent measurements. This risk will be mitigated by community solicitations to address gaps in data validation and benchmarks, as well as by coordination between the BRAIN NeuroAI Innovation Domain and the BRAIN scientific program teams.

A main strategic risk is a premature narrowing of focus that may overlook potentially transformative, but nascent, approaches. This risk is mitigated by the broad exploratory Phase 1 activities, backed by quantitative community-driven benchmarks, and by integrating BRAIN domain-expertise into evaluation processes between each phase.
Overall, the innovation pipeline structure inherently manages risk by allowing for broad exploration before making larger investments, with clear decision points between phases to assess progress and adjust direction as needed. This approach maintains BRAIN's commitment to high-risk, high-reward research while ensuring responsible stewardship of resources.

Data Management and Privacy Risks

NeuroAI systems present unique challenges for data collection, management, and storage:

- Adaptive learning systems may inadvertently capture sensitive neural patterns
- Brain-inspired architectures could reveal unexpected insights about cognition
- Integration of neural and behavioral data in AI systems raises consent complexity
- Potential for brain-like AI systems to infer protected characteristics

Mitigation strategies will potentially include:

- Implementing privacy-preserving machine learning techniques
- Establishing clear data governance frameworks for NeuroAI systems
- Regular audits of data collection and usage in brain-inspired AI models
- Ongoing consultation with neuroethics experts throughout development
- Transparent documentation of data flows and potential privacy implications

Scientific Impact and Technical Opportunities

The BRAIN NeuroAI Innovation Domain emerges at a pivotal moment when recent advances in the scale of neuroscience data collection and computational capabilities have created a unique opportunity for step-like progress toward understanding the brain. The convergence of petascale neural datasets from BRAIN-funded research programs, the maturation of foundation models with remarkable generalization capabilities, and the rapid advancement of neuromorphic hardware platforms collectively enable an innovation pipeline that was not previously possible. These developments allow researchers to implement complex biological principles – from dendritic computation and neuromodulation to distributed learning and neuronal mixed-selectivity – in computational systems that maintain biological relevance while achieving new capabilities.

The innovation pipeline structure specifically leverages these capabilities to address fundamental challenges in understanding brain function and developing next-generation health applications. Early-phase exploration will capitalize on cloud computing infrastructure and standardized interfaces to the BRAIN Knowledgebase, enabling diverse approaches to neural data interpretation and biological emulation. As promising approaches emerge through community-driven selection, advances in both digital and neuromorphic computing will support scaling these models to address increasingly complex problems in neuroscience discovery and health applications. This structured approach ensures that BRAIN investments drive progress across disciplinary boundaries, creating bidirectional knowledge flow that enhances both our understanding of natural intelligence and our ability to implement its principles in technologies that benefit human health.

Socialization & Engagement

Funder Engagement

- BRAIN hosted a government roundtable in June 2025 to establish an informal federal NeuroAI working group to align efforts across NIH, NSF, DARPA, and other agencies.
- Internal "roadshow" presentations to BRAIN program teams to discuss NeuroAI coordination are currently ongoing through Summer 2025.

Workshops & Challenges

- Implement a "roadshow" series presenting NeuroAI opportunities to BRAIN teams with direct synergies (Teams B, E, Data, N, T, and BBQS program) through Spring/Summer 2025.
- (*Defer pending budget clarity*) Host a government roundtable in 2025 to establish a coordinated "NeuroAI coalition" aligning initiatives across NIH, NSF, DOE, and DARPA.
- Organize a rotating series of targeted challenges addressing scientific priorities in cross-scale predictive modeling, brain-body system integration, and learning mechanisms, to begin in 2026.
- Co-sponsor specialized sessions at major conferences (Institute of Electrical and Electronics Engineers Engineering in Medicine and Biology Society / Neural Engineering Conference, Society for Neuroscience Annual Meeting, Conference on Neural Information Processing Systems (NeurIPS), Computational and Systems Neuroscience Meeting, Cognitive Computational Neuroscience Conference) to build community awareness and identify emerging research directions.
- Conduct an annual BRAIN NeuroAI summit bringing together researchers from Phase 1 projects to share progress and build collaborations.

Community Engagement

Internal Coordination

- Coordinate quarterly meetings with BRAIN team leaders to identify collaborative opportunities and align priorities across programs.
- Engage regularly with advisory bodies including the BRAIN Multi-Council Working Group and BRAIN Neuroethics Working Group to ensure strategic alignment.
- Establish specialized working groups addressing common technical challenges in multi-scale integration and validation frameworks.

- Create integration pathways with transformative projects (BICAN, CONNECTS, BBQS) through joint planning sessions and resource-sharing mechanisms.

External Outreach

- Develop strategic partnerships with national laboratories for computational resources and with federal agencies for complementary expertise.
- Build upon momentum from successful events including the BRAIN NeuroAI Workshop and presentations at NeurIPS and the International Neuroinformatics Coordinating Facility Assembly in 2024.
- Implement data challenges and hackathons that engage diverse research communities and lower barriers to entry for new investigators.
- Create interdisciplinary educational programs combining neuroscience and computation to prepare researchers for working at this intersection.

Communications Strategy

- Publish position papers defining BRAIN's unique vision for bidirectional NeuroAI research and knowledge exchange.
- Develop joint statements with partner agencies outlining complementary roles and shared goals for BRAIN NeuroAI advancement.
- Distribute regular updates through BRAIN channels highlighting progress and opportunities within the innovation pipeline.
- Document success stories demonstrating how NeuroAI approaches advance understanding of brain function and enable health applications.
- Emphasize communication of how BRAIN NeuroAI efforts align with and enhance BRAIN's existing investments in transformative neuroscience research.

Team Integration

BRAIN Team Synergies

- **Team A (Cell Types)**: Integrate cell atlas data into predictive models; explore organoid platforms for computational theory validation.
- **Team B (Tools)**: Co-develop adaptive neural interfaces; create validation frameworks for neuromorphic implementations in research applications.
- **Team C (Imaging)**: Leverage CONNECTS connectivity data for neuromorphic architecture design; develop multi-scale structural-functional models.

- **Team D (Dissemination)**: Establish frameworks for NeuroAI tool dissemination; coordinate with NIH SBIR/STTR programs for industry translation.
- **Team E (Circuits)**: Incorporate circuit mechanisms into adaptive learning systems; develop theory-experiment loops for computational hypotheses.
- **Team Data**: Prepare datasets for NeuroAI applications; create standardized pipelines for multi-modal data integration; support validation benchmarks.
- **Team N (Neuroethics)**: Integrate ethical frameworks throughout development; address unique concerns of adaptive learning systems.
- **Team T (Training)**: Develop specialized training in NeuroAI modeling; create educational resources for interdisciplinary and early-career researchers.
- **Team BBQS (Brain, Behavior, Quantification and Synchronization)**: Leverage behavioral data for embodied AI; improve neural-behavioral synchronization methods; develop validation frameworks; develop multimodal integration (hardware & software).

Cross-Team Resource and Knowledge Sharing

- Establish a centralized repository of BRAIN NeuroAI datasets, tools, and models accessible across teams and external collaborators.
- Institute regular seminars or events to showcases emerging BRAIN NeuroAI advances and technologies to facilitate cross-team knowledge exchange.
- Develop common evaluation frameworks for assessing progress toward strategic objectives and validating computational approaches.
- Create standardized interfaces between NeuroAI innovations and existing BRAIN resources to maximize impact of investments.

APPENDICES

BRAIN Knowledgebase Appendices

BRAIN Knowledgebase Appendix A: Data Standards in Neuroscience Research

Overview of NIH BRAIN Initiative Data Standards

BRAIN has fostered the development of several critical data standards to ensure that the massive quantities of neuroscience data generated can be easily shared, integrated, and analyzed. These standards form the foundation of a robust data ecosystem that enables collaboration and maximizes the scientific value of collected data. BRAIN has funded nine projects specifically focused on developing standards for neuroscience data, with three standing out as particularly successful and widely adopted within the scientific community.

The Brain Imaging Data Structure (BIDS) emerged as a solution to the long-standing challenge of inconsistent organization and sharing of neuroimaging experiment data. Before BIDS, there was no consensus on how to structure and share neuroimaging data, making collaboration difficult and complicating the application of automated pipelines and quality assurance protocols. The BRAIN Initiative supported the development of BIDS as a standard for organizing and describing MRI datasets using file formats compatible with existing software. The BIDS standard unifies previously disparate practices in the field and captures the metadata necessary for common data processing operations. By consulting a wide range of neuroscientists during its development, BIDS was designed to cover most common experiments while remaining intuitive and easy to adopt, factors that have contributed to its widespread acceptance within the neuroscience community.

Neurodata Without Borders (NWB) represents another significant advancement, functioning as a data standard specifically for neurophysiology. NWB enables neuroscientists to share, archive, and analyze neurophysiology data using common tools within a standard framework. The standard accommodates diverse neurophysiology data types, including data from intracellular and extracellular electrophysiology experiments, optical physiology experiments, and tracking and stimulus data. Beyond just establishing a data format, the NWB project provides comprehensive software tools for data standardization and application programming interfaces (APIs) for reading and writing data. Additionally, it offers high-value datasets that have been translated into the NWB standard as reference implementations.

The third major standard addresses the critical challenge of cell type classification with the development of a Community Framework for Data-driven Brain Transcriptomic Cell Type Definition, Ontology, and Nomenclature. This standard emerged in response to major investments in characterizing cellular diversity using single-cell transcriptomic methods, which

have rapidly generated maps of cell types across the whole brain in mouse, monkey, and human. This transformative resource required standardization of quantitative methods for cell type definition and the development of a formal data-driven cell ontology and nomenclature convention, similar in concept to the human genome reference in genomics. The project brought together experts in single-cell transcriptomics, informatics, ontology development, and computational biology who were also leaders and members of major cell type consortia. The initiative engaged the international cell type community in developing and refining standards and reference classifications to ensure widespread adoption and usefulness.

BICAN Standards and FAIR Data Principles

The BRAIN Initiative Cell Atlas Network (BICAN) project has demonstrated a strong commitment to the FAIR (Findable, Accessible, Interoperable, Reusable) data sharing principles through its implementation of community standards for data and metadata. BICAN adopts existing community standards where possible and develops additional standards as necessary through dedicated working groups. All standards used by BICAN undergo a rigorous governance process, including comprehensive review by consortium members, to ensure they meet the network's specific needs and adhere to best practices in data management.

BRAIN Knowledgebase Appendix B: Metadata Standards, Data Processing Pipelines, and Identifier Schema

Metadata Standards for Neuroscience Data

Metadata standards define guidelines for structuring, formatting, and using "data about data" within specific domains. In BICAN, these standards ensure that datasets are well-documented, discoverable, and interoperable. All metadata standards developed through BICAN working groups undergo review by the Metadata and Ontologies working group to ensure alignment across the network.

BICAN has established comprehensive metadata standards covering various aspects of research data. These include Donor to Alignment Metadata, which tracks information from the original biological donor through the data alignment process; Human Donor Metadata, capturing essential information about human research participants; Projects and Data Collections Metadata, which documents research project structures and data relationships; and Library Minimum Metadata, defining the core information required for data libraries. Additional species-specific metadata standards include HMBA Macaque Metadata, Marmoset Metadata, Developing Human Metadata, Developing Non-Human Primate Metadata, and Developing Tissue Metadata, each tailored to the unique requirements of these research areas.

The Data, Ontological, and Taxonomic Cell Type Standards provide guidelines for consistent description and classification of cell types across research projects. The Spatial

Transcriptomics Data Dictionary standardizes terms and definitions for spatial gene expression studies. Basic Metadata for Self-Registration of Subjects and Specimens outlines the minimal information needed when registering research materials. The NBB HBCAC Tissue Requirements specify the standards for tissue collection and quality that must be met for human brain samples.

Data Processing Pipelines

BICAN has developed numerous data processing pipelines to standardize the analysis of various data types. These pipelines ensure consistency in data processing across different research groups and projects, enhancing the comparability and integration of results.
For genomic data analysis, the BuildIndices Pipeline creates standardized reference indices for different species. The Common Reference Genomes standard defines the specific genomic references and annotations used for mouse, macaque, marmoset, human, and other species studied within BICAN, ensuring consistency in sequence alignment and gene identification. Specific pipelines for different assay types include the Paired-Tag Pipeline for processing 3' single-nucleus histone modification data and 10x gene expression data; the Multiome Pipeline for 10x 3' single-cell and single-nucleus gene expression and chromatin accessibility data; the Single Nucleus Methyl-Seq and Chromatin Capture Pipeline for processing single-nucleus methylome and chromatin contact sequencing data; and the ATAC Pipeline for processing 10x single-nucleus chromatin accessibility data.

Additional specialized pipelines include the Optimus Pipeline for processing 3' single-cell and single-nucleus count data from 10x Genomics assays; the Slide-seq Pipeline for spatial transcriptomic data analysis; the Smart-seq2 Single Nucleus Multi-Sample Pipeline for processing snRNAseq data generated by Smart-seq2 assays; and the Transcriptomic Clustering Pipeline for identifying cell types based on gene expression patterns. These pipelines represent significant advancements in standardizing complex data analysis workflows, making sophisticated analytical techniques accessible to the broader neuroscience community.

Identifier Schemes for Research Resources

Identifier schemes provide structured systems for assigning unique identifiers to entities such as genes, proteins, diseases, and clinical trials. These identifiers ensure unambiguous referencing across different databases and systems, facilitating data organization, access, and integration.

BICAN recommends using established external identifier systems, defined as well-accepted, globally unique, and persistent identifiers (PIDs) for key entities in information systems and publications. These PIDs are issued by external authorities and ensure that entities are uniquely identified, accompanied by standard metadata, and trackable across the BICAN

ecosystem. Using community standards for PIDs enables tracking within the biomedical literature and integration with data from other sources. BICAN recommends specific identifier systems for different entity types: ORCID for authors and collaborators, DOIs for datasets and code, RRIDs or DOIs for workflows and pipelines, RRIDs for biosamples, organisms, antibodies, plasmids, cell lines, and digital tools/databases, and DOIs for protocols and data underlying figures.

The NHash Identifiers system, implemented through the Neuroanatomy-anchored Information Management Platform for Collaborative BICAN Data Generation, provides unique identifiers across BICAN workflows. These identifiers ensure traceability for subjects (donors), brain slabs, tissues, histology, and libraries, with recorded provenance linkage using a blockchain-style approach. NHash identifiers are required for all subjects, brain slabs, tissues, histology, and libraries in BICAN. For some workflows, such as requesting tissue from a human subject via NIMP, identifiers are issued automatically during data ingestion. For others, such as non-human tissue, investigators may need to register subjects and samples manually. These identifiers facilitate subsequent data generation, ingestion, linkage, and curation processes, enabling comprehensive tracking of research materials throughout the research lifecycle.

BRAIN Knowledgebase Appendix C: Ontologies, Coordinate Frameworks, and Reference Atlases

Common Coordinate Frameworks in Neuroscience

Common coordinate frameworks (CCFs) provide standardized reference systems essential for describing and mapping brain structures and activities across different specimens, species, and studies. These frameworks facilitate comparison, integration, and analysis of brain data, enabling researchers to develop a comprehensive understanding of brain function and structure. BICAN has established several species-specific CCFs to support standardized spatial referencing of neuroanatomical data.

The Human Connectome Project (HCP) Template & Atlas for BICAN is derived from data collected through the HCP and serves as a core dataset for BICAN investigators. This resource includes structural MRI volumes and associated cortical surfaces based on 1,071 subjects scanned at 3T from the HCP S1200 data release. All surface-based datasets have been aligned using areal-feature-based registration (MSMAll). The HCP_MMP1.0 cortical parcellation comes from 210 validation subjects described in Glasser et al. (Nature, 2016). The T12/T2w cortical myelin maps feature improved bias field correction compared to earlier versions, and both task-fMRI and resting-state fMRI datasets have been enhanced through temporal ICA denoising

in addition to spatial ICA denoising, resulting in significant improvements over the original S1200 data release.

For non-human primates, the Mac30BS Macaque MRI-based Template serves as a key reference framework. This template is constructed from MRI scans of 30 adult macaque monkeys, including 16 rhesus macaques and 14 cynomolgus macaques, ranging in age from 3.25 to 9.8 years. Structural MRI scans include T1w and T2w images at 0.5mm isotropic resolution, along with a high-resolution group average volume at 0.15mm isotropic resolution. The template incorporates the SARM_6 subcortical atlas with 210 parcels, initially registered to the NMT v2 template and subsequently aligned to the Mac30BS template. A future iteration, the Mac25Rhesus template, is currently under development with a major focus on improving the fidelity of cortical surface reconstructions. Additional templates in development include the Mac25Cyno (a cynomolgus-specific template) and a hybrid rhesus/cynomolgus template. The MarmosetRIKEN20 Template for BICAN is based on MRI scans from 20 adult male marmoset monkeys with an average age of 5.5 years. Structural MRI scans include T1w and T2w volumes acquired at 0.36mm isotropic resolution and resampled to 0.2mm isotropic resolution. The stereotaxic atlas of Paxinos et al. (2012) provided the foundation for a 116-area neocortical parcellation and a subcortical parcellation into 23 structures on each side. For cortical parcellations, the original Paxinos surface parcellation was mapped onto the MarmosetRIKEN20 surface and manually corrected by an anatomist. Similarly, the subcortical parcellations of 23 regions were manually generated by an anatomist based on the Paxinos 2D atlas. Future plans include the development of a MarmosetRIKEN100 template, though the emphasis will be on high-quality cortical surfaces rather than increasing the number of subjects.

For rodent studies, the Allen Mouse CCF 2015 Release serves as a standard reference framework. The anatomical template of CCF v3 represents a shape and background signal intensity average of 1,675 specimens from the Allen Mouse Brain Connectivity Atlas. These specimens were imaged using a customized serial two-photon (STP) tomography system that combines high-speed two-photon microscopy with automated vibratome sectioning. This imaging approach produces inherently pre-aligned images ideal for precise 3D spatial mapping. The population average was created through an iterative process involving multiple cycles of averaging across many brains. To create a symmetric average, each specimen was flipped across the mid-sagittal plane, effectively doubling the input data to 3,350 hemispheres. The resulting anatomical template minimizes both the intensity difference between the average and each transformed specimen and the magnitude of all deformation fields used in the transformations. As a result, the template represents the average shape and appearance of the specimen population and displays remarkably clear anatomic features and boundaries for many brain structures.

Brain Ontologies in Neuroscience Research

Ontologies provide structured frameworks that represent concepts within specific domains and the relationships between those concepts. They serve as formal naming and definition systems for types, sub-types, and hierarchical relationships, facilitating knowledge sharing and reuse by establishing common vocabularies and well-defined structures. BICAN has developed several ontologies to standardize neuroanatomical and cell type classification.

The Developmental Anatomical Ontology is an application ontology constructed by combining ontologized versions of the Allen Institute Developing Human Brain Atlas (DHBA) StructureGraph mapped to Uberon. This ontology provides standardized terms and relationships for developmental neuroanatomy, facilitating the integration of data across developmental stages and between different research groups studying brain development. The Anatomical Structure Ontology offers a data model designed to represent types and relationships of anatomical brain structures. This model formalizes relationships between spatial definitions, names, and metadata of brain structures and the parcellations they collectively comprise. By providing this standardized framework, the ontology enables more consistent annotation and interpretation of neuroanatomical data across different studies and analyses.

The BICAN Application Ontology (BICANO) focuses specifically on research, subjects of research, and research results within BICAN. This ontology bridges scientific knowledge gained through experimentation with knowledge distribution and dissemination. Its primary goal is to help scientists annotate data and communicate about their work by defining a set of terms relevant to BICAN efforts. The development of BICANO builds on previous standardization work from BICCN and Brain Data Standards projects and aims to interoperate with the broader biomedical ontology community. The development team adheres to best practices in ontology development as outlined by the OBO Foundry, and team members review changes to ensure the ontology accurately reflects current understandings in brain science.

For cell type classification, the Cell Ontology (CL) serves as an OBO Foundry ontology covering biological cell types, with curation focused on animal cell types and interoperability with specialized ontologies. The Provisional Cell Ontology (PCL) complements CL by identifying cell types that are provisionally defined by experimental techniques such as single-cell transcriptomics rather than through conventional property-based definitions. All terms in PCL subclass conventionally defined terms in CL, with the understanding that terms may migrate to CL as more data emerges to support more conventional definitions.

The Techniques and Methods for Neuroscience Ontology captures information about techniques and methods supporting BICAN research. This ontology helps scientists

communicate about their experiments and results by defining terms for techniques, methods, modalities, assays, devices, tools, and related concepts. By standardizing the description of research methods, this ontology enhances the reproducibility and comparability of studies across different laboratories and research groups.

BRAIN Knowledgebase Appendix D: Data Access Controls and Privacy Protection for Human Data

BRAIN Initiative Data Access Framework

The BRAIN Initiative supports a distributed data-sharing ecosystem that offers significant advantages by adapting to specific research community needs. However, this approach creates challenges in harmonizing informed consent across repositories and maintaining consistent access controls for human subject data.

For human neuroscience data within the BRAIN Knowledgebase, effective management will require balancing scientific utility with appropriate privacy protections. Every barrier to data access reduces usage by approximately a factor of 10, making it essential to implement controls that are proportionate to actual privacy risks rather than imposing unnecessary restrictions that diminish scientific value.

Tiered Access Implementation for Human Data

The BRAIN Knowledgebase must implement a clear tiered access framework to accommodate varying sensitivity levels of human neuroscience data. Open access models are generally appropriate for fully anonymized data or synthetic datasets derived from sensitive data. Metadata should clearly document the anonymization procedures applied and any statistical limitations resulting from privacy-preserving modifications.

Registration-required access models are suitable for human data with minimal re-identification risk but requiring basic user-tracking. This tier enables collection of usage statistics while establishing a record of who has accessed data, without imposing significant barriers to legitimate research use.

Controlled access models are necessary for more sensitive human data where additional oversight is warranted. This typically involves Data Access Committee review of research proposals to ensure scientific merit and compliance with original consent limitations. The Knowledgebase should standardize application procedures across repositories to reduce researcher burden.

Consent Harmonization Challenges

A critical challenge for the BRAIN Knowledgebase involves harmonizing different informed consent models across multiple data archives. Current repositories face difficulties in consistently implementing consent-based access restrictions, particularly as data linking increases potential re-identification risks. The BRAIN Knowledgebase should develop standardized consent categories that can be mapped across different repositories to ensure consistent enforcement of participant preferences.

Future data collection should implement forward-looking consent models that anticipate sharing through the BRAIN Knowledgebase, clearly communicating with participants about potential data uses while maintaining appropriate protections. For legacy datasets with varying consent provisions, the Knowledgebase will need protocols for determining appropriate access levels that respect original agreements while maximizing scientific utility of the data.

Technical Privacy Solutions

For the BRAIN Knowledgebase to effectively manage privacy concerns while enabling scientific discovery, several technical approaches could be implemented.

De-identification Standards

The BRAIN Knowledgebase could establish consistent standards for de-identification of human neuroscience data, recognizing that brain recordings may contain unique patterns that could enable re-identification when combined with other datasets. These standards should address both direct identifiers and indirect identifiers specific to neuroimaging and neurophysiology data.

Synthetic Data Generation

Modern approaches like denoising diffusion probabilistic models (DDPMs) can generate realistic synthetic neurophysiological recordings that preserve key statistical properties while eliminating re-identification risk. The BRAIN Knowledgebase could incorporate tools for creating and validating synthetic datasets that can be shared with minimal restrictions while maintaining scientific utility.

Governance Implementation

Effective governance of human data in the BRAIN Knowledgebase requires transparent policies, clear accountability mechanisms, and ongoing ethical oversight. The Knowledgebase should establish a coordinated access review process across repositories, potentially implementing a federated committee structure that allows domain-specific evaluation while ensuring consistent application of access policies.

Systems must be implemented to track compliance with data use agreements, including technical measures to prevent unauthorized sharing while minimizing barriers for legitimate

research access. For human neuroscience data, metadata must document privacy protection methods, consent limitations, and access requirements. Without appropriate metadata, the BRAIN Knowledgebase cannot effectively implement access controls or enable researchers to discover suitable datasets while respecting participant privacy.

BRAIN Knowledgebase Appendix E: BBQS Infrastructure, Synchronization Challenges, and Integration Tools

The success of the BBQS Knowledgebase component depends on FAIR data sharing and innovative computational tools that interoperate with widely adopted neuroscience data standards. The BBQS Knowledgebase, and the BRAIN Knowledgebase Framework as a whole, will in turn enable researchers to develop and validate theories, models, and analyses that will advance scientific understanding of the relationships between molecular cell-type taxonomies, neural circuits and connection patterns, and cognitive/behavioral outputs across scales and species.

BBQS Data Infrastructure Components

The BBQS program is supported by two complementary data infrastructure components that will enable the integration of neural activity and behavioral data. EMBER (Ecosystem for Multi-modal Brain-behavior Experimentation and Research) serves as a specialized data archive tailored to the unique requirements of neurobehavioral research, featuring a scalable hybrid architecture optimized for diverse data modalities ranging from high-resolution video to complex environmental measurements. Launched with limited functionality in February 2025, EMBER provides secure storage for sensitive behavioral data, user-friendly interfaces for data ingest and discovery, and integration with cloud-based computational environments, positioning itself to become the gold standard for neural-behavioral data discovery, sharing, and access.

Complementing EMBER, the DCAIC (Data Coordination and Artificial Intelligence Center) functions as the BBQS consortium's hub for data management, standards development, and analysis resources. The center focuses on five key areas: comprehensive data management across projects, establishment of standards for novel sensors and multimodal integration, development of specialized AI/ML resources for behavioral analysis, creation of cloud-based computational platforms, and coordination of training and dissemination activities. By working closely with BRAIN data archives including EMBER and developing frameworks for neural-behavioral data integration, the BBQS DCAIC will provide critical infrastructure needed to transform fragmented behavioral recordings into cohesive, analyzable datasets that can be meaningfully connected to neural activity measurements across species, experimental paradigms, and environmental contexts.

Neural-Behavioral Data Synchronization Challenges

The data ecosystem for experimental behavior tracking data

Emerging tools for richly detailed tracking of human and animal behavior will enable transformative opportunities, but how do we integrate and make sense of all this data? Shared data pipelines will connect experimental and clinical data collection to cloud-based informatics infrastructure. That infrastructure – to be initially provided by established BRAIN data archives, including EMBER, and the BBQS DCAIC – will provide data standards, validation, integration, and computational tools for applications ranging from testing theory-driven models to optimizing individualized health interventions. A broad range of clinical applications for neurological and neuropsychiatric conditions will depend on translating detailed causal understanding of neural circuits and behavior from animal studies based on high-quality behavioral data.

Challenges synchronizing multimodal data streams

The promise of the BBQS program's approach is based on leveraging a variety of devices and sensors to capture intricate behaviors. However, that promise is equally matched by the potential technical challenge of synchronizing many data sources that may exhibit variable reliability, accuracy, sampling rates, latencies, or timing drift, which produce timing errors that can generally accumulate as recording continues. Mitigating synchronization errors will require robust methods for re-aligning and co-registering these heterogeneous data streams within the shared temporal reference frame of a single clock. An example of this technical challenge is synchronizing video footage from high-resolution cameras at typical rates of 30–60 frames per second with electrophysiological recordings from scalp or intracranial EEG with voltage sampling rates of 1 kHz or potentially much higher. In this case, the camera and the EEG acquisition board will emit timestamps based on internal clocks whose implementations in software and hardware can vary widely. Reasons for inter-device clock variability include the distinct sets of requirements presented by video and EEG modalities that guide the respective engineering designs as well as manufacturing variance, wear and tear, age, or usage conditions that otherwise affect the performance figures-of-merit of each device. Synchronization, by definition, is a process that operates across multiple independent oscillators or clocks and aligns them to shared temporal parameters. Ideally, joint multimodal time-series data of a behaving organism and its environment will be synchronized so that relative temporal offsets between distinct modalities will maximally reflect the ordering, rate, rhythm, and timing of events and sequences as they factually occurred in the organismal brain–body–environment system being observed.

Synchronization for closed-loop applications

To operate within closed-loop control systems, real-time synchronization is critical. For instance, the efficacy of closed-loop neurostimulation modalities may depend on high-throughput, real-time behavior detection as both a biomarker of organismal health and as a

concurrent or complementary readout of brain activity. However, once objectively quantified biomarkers are developed that measure underlying behavioral, cognitive, or health states, the use of those biomarkers as targets or set points for closed-loop control should be carefully considered and validated. Compensatory and homeostatic mechanisms can operate at many levels and cause unknown or counterintuitive off-target effects. Real-time approaches include, but may not be limited to, centralized hardware co-design that allows deep system integration and decentralized consensus methods based on distributed TTL (time-to-live) signaling or similar network-level protocols. The centralized approach may be more costly and less scalable, and thus more appropriate for highly controlled animal research labs compared to the decentralized, network-based approach. For open loop research or health applications, data pre-processing steps and validation tools for synchronizing heterogeneous sensor configurations will be critical to the ease and effectiveness with which data streams can be integrated and made interoperable.

Tools for Data Integration, Theory, and Modeling

Computational tools and data standards for quantified behavioral data

The original BRAIN 2025 Working Group report noted that it was vital that behavioral quantification methods apply quantitative, objective, and automated tools to identify and track cognition and behavior at the organismal level. State-of-the-art machine learning and computer vision techniques are advancing rapidly and will continue to enable pivotal tools for robust detection, tracking, and classification of a wide range of behavioral dynamics at multiple scales from raw data. For example, MoSeq is a software tool that automates the detection of repeated behavioral motifs called "syllables", complementing other tools that detect instantaneous poses or longer time-scale actions and sequences. Computational tools including data standards-based validation and interconversion software will enable data-driven analysis or modeling of causal relationships in datasets comprising jointly recorded neural, behavioral, and environmental factors. Additionally, the continued adoption of broadly used neuroscience data standards like NWB and BIDS can potentially support multiple stages of data collection, aggregation, and synchronization to help integrate multi-domain, multi-dimensional neural-behavioral datasets and allow researchers to effectively combine and compare findings from different studies. To support secondary analysis, model comparison, and aggregation, these computational tools for synchronization, quantification, validation, and modeling must be shared and easily accessible across the BBQS researcher community, including as cloud-based capabilities provided by data archives and other platforms.

Integrating theory and experiment to discover principles of behavioral control

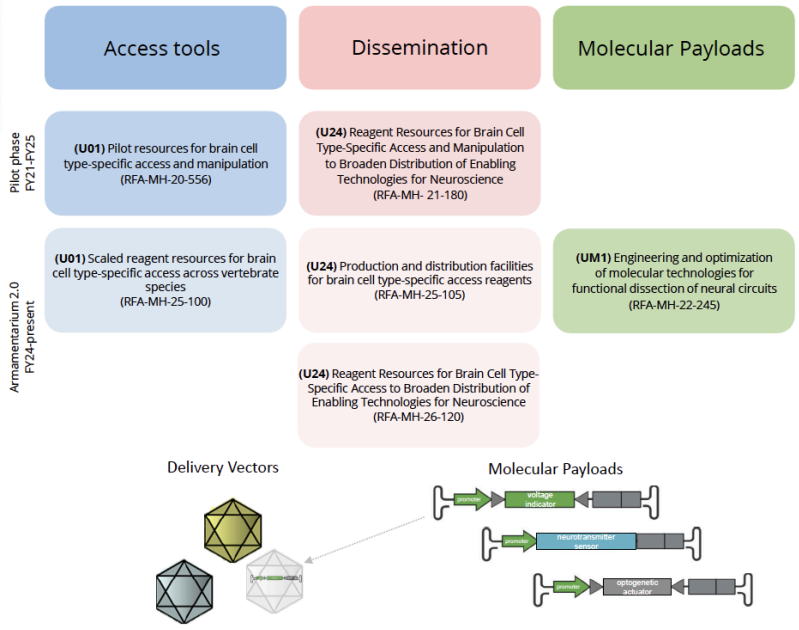
The nature of theory development differs starkly between biology and a more explicitly reductionist science like physics. Theoretical frameworks in organismal biology should be tested by a battery of convergent approaches ranging from idealized theory-driven models of general principles to large-scale, data-driven, and potentially individualized platforms, like

digital twins, neurorobotics, animal experiments, or trials in patient populations. Regardless of the approach, multiscale modeling will be integral to developing and validating theoretical principles for understanding complex brain–body relationships. Data sharing, secondary analysis, replication, and reproducible workflows will need to work in combination with data-driven modeling and validation tools to discover organismal principles of behavior that translate across domains. The integration of experimental and theoretical approaches will be crucial to apply these insights to understand behavior and treat neurological, movement-based, and neuropsychiatric disorders.

Precision Molecular Circuit Therapies Appendices

Precision Molecular Circuit Therapies Appendix A:

BRAIN Armamentarium for Precision Brain Cell Access

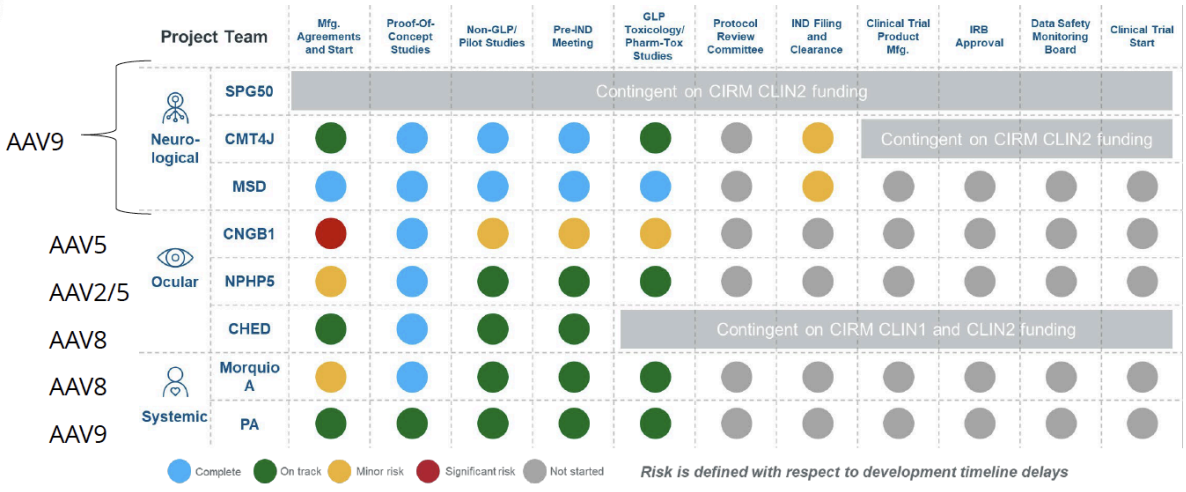


- **BRAIN 2.0** report transformative project.
- **Support access reagent development** for the diversity of molecularly defined brain cell types.
- **Scale up** generation of **brain cell type-selective access and manipulation reagents** in vertebrate species, including human ex vivo tissue and cells.
- **Support dissemination facilities** for distribution of brain cell type-specific access reagents.
- FY21-present
- 10 awards
- $42M TC

Precision Molecular Circuit Therapies Appendix B:

Bespoke Gene Therapy Consortium

- Partners from the public, private, and non-profit sectors to foster development of gene therapies intended to treat rare genetic diseases, which affect populations too small for viable commercial development.
- Focus is on generating a standard operational playbook for developing such gene therapies.



Precision Molecular Circuit Therapies Appendix C:
Somatic Cell Genome Editing Consortium

SCGE Phase 2 - Translating in vivo Genome Editing Therapies into the Clinic More Broadly & Efficiently

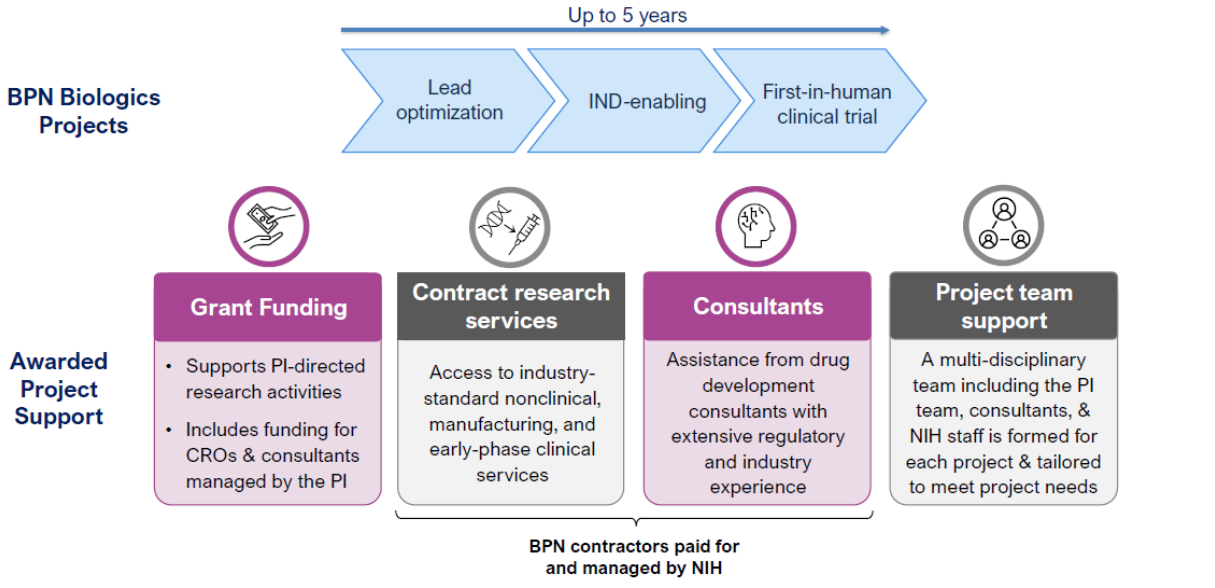
Objective: To accelerate the development of genome-editing therapeutic agents by facilitating IND-enabling studies, establishing pathways to regulatory approval, and disseminating successful strategies for initiating first in human clinical trials.

Phase 2 Initiatives:

1. Technologies and Assays for Therapeutic Genome Editing INDs (RFA-RM-22-014)
   - Developing technologies and assays for safety and efficacy studies (5 Projects)
2. IND-enabling Studies of Somatic Genome Editing Therapeutic Leads (RFA-RM-22-015)
   - Optimizing genome editing-based therapeutic leads to support advancement towards clinical trials (5 Projects)
3. Platform Clinical Trials for Somatic Genome Editing for Multiple Diseases (RFA-RM-22-016)
   - Supporting novel genome editing clinical trials for more than one disease (1 Project)
4. Somatic Cell Genome Editing Translational Coordination and Dissemination Center (RFA-RM-22-017) (1 Award)
5. IND-enabling Studies for Platform Clinical Trials of Genome Editors in Multiple Disease (RFA-RM-24-001) (2 Projects)

Program Duration: 5 years, FY23-27

Precision Molecular Circuit Therapies Appendix D:
Blueprint Biologics



In all cases: *The PI's institution retains rights to existing IP and is assigned rights to any new IP developed within the program*

Accelerating Human Neuroscience Appendices

Accelerating Human Neuroscience Appendix A: Cross-Cutting Themes from the Human Neuroscience Roadmap Concepts

Prior to the Fall 2024 BRAIN retreat, the Human Neuroscience concept teams group developed cross-cutting scientific areas that encapsulate the individual roadmap concepts, as well as ongoing human neuroscience in BRAIN. The cross-cutting areas were then refined with BRAIN-wide input at the retreat.

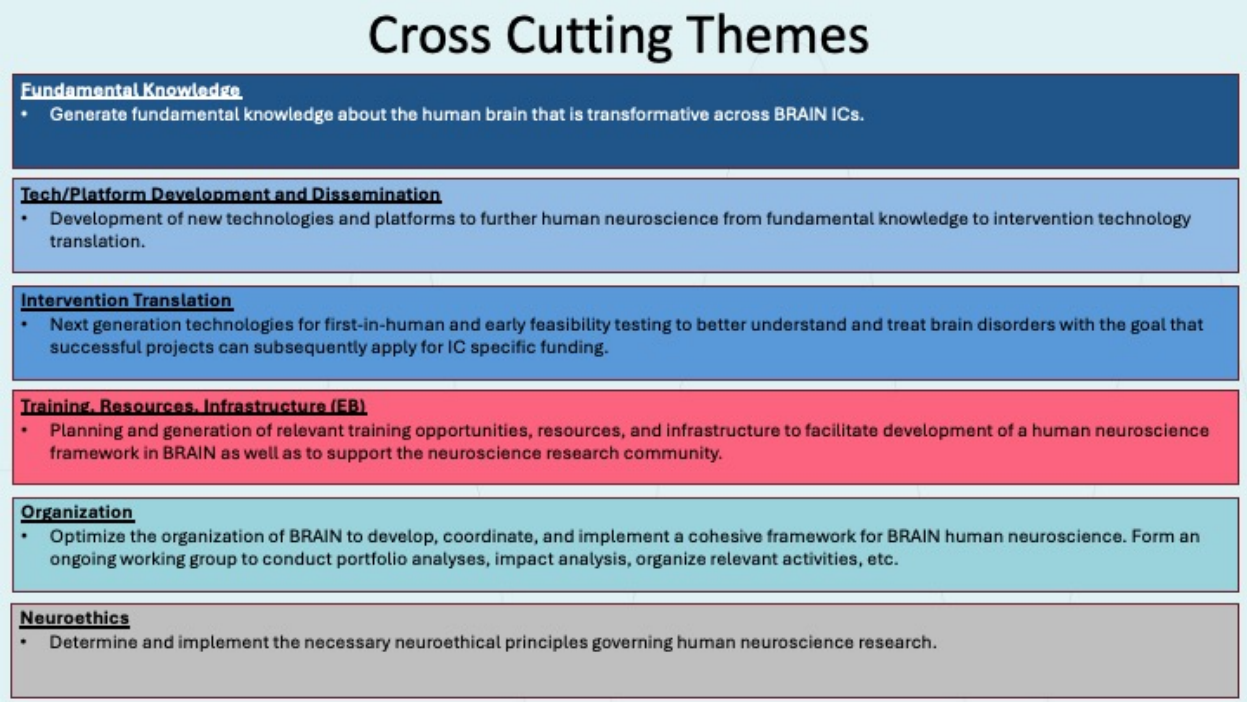


Figure 1: Cross-cutting scientific areas that encapsulate individual research roadmap concepts, as well as ongoing human neuroscience in BRAIN.

Accelerating Human Neuroscience Appendix B: Research Roadmap Retreat Feedback

BRAIN September 2024 Retreat: Human Neuroscience Innovation Domain Notes

Q1: What are the most critical scientific, technical, and operational challenges that need to be overcome for BRAIN to achieve transformative impact in this domain?

Items sorted by frequency, from most to least.

1. Translation across species and from animal models to human studies
2. Common Data Elements (CDEs), data standardization, and data sharing
3. Understanding underlying biological mechanisms
4. Possible ethical and social risks associated with human neuroscience research

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Items 5-10 were mentioned once.

5. Harmonization of results (e.g., EEG and MRI results)
6. Holistic view of human body in context of understanding brain function (e.g., multi-omics)
7. Coordination between invasive and non-invasive research
8. Tool development to study complex processes in humans
9. Implanted patient care infrastructure, such as translating and maintaining devices
10. Determining technical priorities from the community

Q2: What specific expertise, resources, and operational structures will be crucial for BRAIN's success in this ID?

- There is a strong need for collaboration and team science.
- Suggestion to form a large human research consortium.
- Centralized, online resource would support promotion of CDEs.

Q3: From the BRAIN scientific program team perspective, how might this Innovation Domain complement or build upon existing BRAIN programs across all Research Areas?

- Integrate and coordinate to make sure there is no overlap between the teams and what we fund.
- Researchers need expertise to move technologies to clinical use. Could provide matchmaking to help PIs get the expertise they need (e.g., the HEAL PURPOSE Network).
- Emphasis on creating a consortium to facilitate interactions, team science, and data standardization.
- Could have mini-retreats every year to keep BRAIN community informed.
- Human Neuroscience WG
    - Organize/coordinate RFAs, activities, and integration with OBD/BRAIN priorities.
    - Space for more 'translational' efforts
    - Need to consider how it relates to existing BRAIN scientific program teams
    - Is there a need for a Trans-NIH WG?
    - How to align and coordinate between separate NIHIC human neuroscience research priorities

Q4: What existing efforts or emerging advancements across the scientific ecosystem outside of BRAIN can this Innovation Domain complement or build upon? Specifically consider opportunities internal to NIH and external to NIH (e.g., other federal agencies, private foundations, industry, etc.)

- Leverage the NIH SBIR/STTR programs for tool development and validation
- Could invite people from other agencies to talk to us about their programs
- The Human Neuroscience WG could facilitate program connections within and outside NIH
- Could be an area to focus on regulatory science.
    - Contracts with tech companies, metrics and outcomes can be reported out by established test labs, MOUs with agencies including the FDA
    - Coordination with European regulators, test labs, industry

Q5: How would non-human animal research programs (not already mentioned) facilitate the scoping process and synergize with this Innovation Domain to inform understanding gaps in the translation of knowledge between animals and humans?

- Could ask investigators to define how their work in models advances human neuroscience
- Need more collaborations across multiple species and to generate data that allows for direct comparisons. Also, need to identify the necessary computational approaches.
    - Consortia are one way to facilitate these interactions.
- There is a lot to learn by integrating across scales and species models. This needs to be done in a systematic way.
- Need to promote interactions between animal and human researchers
- Reverse translational studies from human work to animals to discover mechanistic pathways. Need to target future animal studies to specific human-relevant tools and pathways.

Q6: Any suggestions on helpful next steps not included?

- Portfolio analysis
    - Which technologies have been developed? Is anyone using these technologies?
    - BRAIN has invested a lot in animal studies. What has been achieved and what can be improved upon?
- RFI
    - Ask research community about potential use cases for technology that has been developed, both in humans and animals.
- Align and coordinate the separate IC human neuro research priorities and identify gaps that BRAIN can fill.
- (Long-term) Human Neuroscience RFAs
    - High risk high reward projects

Accelerating Human Neuroscience Appendix C: Summary of Extended Working Group meeting

The meeting on March 17, 2025, focused on the long-term directions of the Human Neuroscience Innovation Domain, aligning with the agenda outlined in the "Human Neuroscience Innovation Domain Extended WG Agenda 3.17.docx. The primary objectives were to discuss current programs, identify needs for targeted portfolio analyses, discuss the formation of the Human Neuroscience Working Group and potential sub-groups basis of specific tasks/programmatic areas, and establish a timeline for future activities.

Key Discussion Points:

1. **Current Program Overview**:
    - Brief updates were provided on existing BRAIN programs, including ROH/eROH, BBQS, CONNECTS, Transformative Brain Non-invasive Imaging Technology Development, Next Generation Devices, and Blueprint MedTech. These programs are central to understanding human brain function and developing new technologies.
2. **Metrics of Success**:
    - The group deliberated on appropriate metrics to evaluate the success of current and future programs. This included considering transformative progress opportunities and aligning these with BRAIN's unique mission.
    - Programmatic analyses will address the following questions with the understanding that each program is unique and may have additional metrics of relevance:
        1. What technologies/modalities and indications have been funded by BRAIN in the human neuroscience space?
        2. Have there been quantifiable outcomes from funded research? (e.g., projects moving forward with IC funding, adoption of technologies, FDA approvals, industry adoption or interest?)
        3. What BRAIN funded studies have enabled IC-specific science/applications?
        4. What are the ICs funding portfolios in the space of each of the programs under analysis? What are unique versus overlapping areas? (Basic topic mapping)
3. **Challenges Identified**:

- A significant challenge discussed was the limited manpower and time constraints. The need for efficient resource allocation and prioritization of tasks was emphasized.
- Difficulty of identifying research gaps when "gaps are things we don't know". The goal will be to focus on strategic roadblocks that government/NIH/BRAIN are best poised to address rather than creating a comprehensive list of all research gaps in human neuroscience.
- Tradeoff between accessibility of technology vs pushing the boundaries. The more you push the more expensive and less accessible the technology will be. What does BRAIN want to do? Cutting edge vs. portability vs. accessibility and cost effectiveness.
- Challenge of planning amid organizational uncertainty.

4. **Strategic Planning and Sub-group Formation**:
   - Discussion centered on the formation of planning sub-groups to address specific objectives and streamline efforts. A detailed scope of work will be created for each sub-group to identify priorities and guide their activities.

5. **Leadership Engagement and Resource Needs**:
   - Engaging leadership and gaining buy-in for proposed plans was a priority. The group discussed strategies for gathering feedback from leadership to ensure alignment with overall strategic direction of BRAIN.

6. **Action Items and Next Steps**:
   - The meeting concluded with action items, including preparing a summary of the discussion, developing core elements of the plan, and scheduling follow-up meetings. Establishing clear milestones and timelines was deemed crucial for tracking progress and making necessary adjustments.

   - **Next steps:** i) three sub-groups will be formed around the scientific objectives in the scoping plan, ii) core evaluation data elements will be agreed on (see above), iii) each sub-group will conduct analyses relevant to their scientific areas/programs, iv) the full group will assess the totality of the analyses as whole to inform understanding of scientific gaps, v) the possibility of rapid turn-around "mini-workshops" to assess these gaps will be discussed and/or planned, vi) new programs and/or re-envisioned existing programs will be proposed that most strategically address gaps.

Overall, the meeting was collaborative, with a focus on strategic planning, addressing challenges, and ensuring alignment with organizational goals to enhance the effectiveness of the Human Neuroscience Innovation Domain.

BRAIN NeuroAI Appendices

NeuroAI Appendix A:

Advances and Challenges in NeuroAI Data Integration

Current Data Landscape

Neuroscience data collection has expanded dramatically in recent years, with recording technologies approaching petabyte-scale daily volumes across modalities including spikes, local field potentials, stereo-electroencephalography, functional magnetic resonance imaging, and electroencephalography. Major repositories like DANDI and OpenNeuro, along with datasets from the Allen Institute, International Brain Laboratory (IBL), and Human Connectome Project (HCP) represent significant advances in centralized data storage. Despite these heroic collection efforts distributed across hundreds of laboratories, current neural recording datasets still vastly under-sample brain activity –the entirety of spike recordings available in public repositories represents less than the number of spikes generated in the human brain each second.

Current BRAIN datasets face critical limitations for driving NeuroAI progress. Many are characterized as "low entropy" with insufficient labeling to understand multimodal embodied or agentic computations across spatial scales. The narrow slices of behavior typically captured focus primarily on controlled, reproducible tasks rather than naturalistic interactions. This can create significant challenges for developing computational models that generalize beyond specific experimental conditions. Existing datasets can effectively inform local learning mechanisms, neuromodulation effects, and architectural properties, but they struggle to capture the full complexity of brain computation in natural contexts.

Cross-Scale Integration Requirements

A central technical challenge in NeuroAI involves bridging multiple scales and modalities to create comprehensive neural models. Bio-centric atlases like cell type maps and connectomes (e.g., FlyWire) typically achieve better coverage than neural activity atlases, but critical bridges between scales remain underdeveloped. For example, translating connectomic data to simulated neural activity would require additional transcriptomic data for each neuron, receptor distribution information, and complete characterization of electrical activity.

At the November 12-13, 2024 BRAIN NeuroAI Workshop, participants identified several technical priorities for data integration in the next decade of neuroscience. These include developing comprehensive resources combining genetic background, cell atlases, transcriptomes, molecularly annotated connectomes, neural activity maps, and calibration datasets to stitch these modalities together. Such integration would parallel the transformative

effect of combined resources like Protein Data Bank (PDB) and UniProt in structural biology, which enabled the protein folding revolution. Integration requires standardized formats, cross-modal alignment techniques, and shared ontologies that can accurately map between different data types while preserving biological relevance.

NeuroAI Appendix B:

Technical Approaches to Neural Computation and Validation

Computational Modeling Approaches

NeuroAI research encompasses multiple computational approaches, each with distinct technical considerations. Large-scale AI models like foundation models offer powerful capabilities for identifying patterns in complex neural data but often trade interpretability for prediction accuracy. As Konrad Körding noted, AI has proven "surprisingly effective at describing high-dimensional, heterogeneous neural data," but these models "often lack interpretable structure," raising questions about their value as frameworks for understanding rather than prediction.

Alternative approaches emphasize mechanistic understanding through biophysically detailed models that incorporate specific neural mechanisms like dendritic computation, neuromodulation, and glia-neuron interactions. These models prioritize biological plausibility over performance metrics, implementing multi-timescale dynamics that better reflect brain operation – electrical signals on millisecond scales, astrocytic chemical signals on 10-20 second scales, and slower cytoskeletal rhythms on minute timescales. Workshop participants emphasized that the ideal approach likely involves a diversity of modeling strategies, from biophysically detailed to more abstract computational models, with appropriate frameworks for translating between these different levels of description.

Validation Frameworks and Benchmarks

A fundamental technical challenge in NeuroAI involves validating computational models against biological systems. Current approaches often rely on neural regression scores, where linear mapping between artificial neural networks and brain activity serves as a primary evaluation metric. However, as a recent position paper argues, "maximizing neural regression scores may not identify good models of the brain" (Schaeffer et al., 2024) particularly for highly overparameterized regimes with far more units than stimuli. This creates unintuitive and complex relationships between scores and how well an artificial neural network actually matches brain function.

More robust validation requires closed-loop experimental paradigms where computational predictions drive new experiments that test model capabilities. Examples include "inception

loops" that find maximizing stimuli for visual neurons and holographic optogenetics approaches that can nudge neural activity in targeted patterns. These heroic experiments provide glimpses of what comprehensive validation might involve but remain technically challenging and resource-intensive. Workshop discussions and other community inputs have identified several priorities for improved validation frameworks, including increased stimulus diversity, targeted experiments designed to differentiate between models, and combined metrics (such as Representational Similarity Analysis, Dynamical System Analysis, and Centered Kernel Alignment) that capture different aspects of neural-computational alignment.

NeuroAI Appendix C:

Neuromorphic Computing and Hardware Implementation

Energy Efficiency and Design Principles

Neuromorphic computing represents a paradigm shift from traditional von Neumann architectures, drawing inspiration from biological neural systems to create hardware that integrates processing and memory within artificial neurons and synapses. The core advantages stem from brain-inspired operational characteristics: highly parallel computation, collocated processing and memory, event-driven operation, and inherent stochasticity. These features enable neuromorphic systems to achieve orders of magnitude improvements in energy efficiency for certain workloads – current AI systems running on GPUs consume megawatts of power to accomplish tasks that the human brain performs with approximately 15-20 watts.

At the November 12-13, 2024 BRAIN NeuroAI Workshop, discussions emphasized that the field lacks fundamental understanding of which aspects of biology are critical to energy efficiency, representing a major gap in current knowledge. Mixed-signal neuromorphic circuits operating in the sub-threshold regime have demonstrated remarkable capabilities in biomedical applications, achieving complex signal processing tasks while consuming only microwatts of power. These implementations provide insights into both biological computation and artificial system design, particularly for applications requiring closed-loop operation, adaptability, and mobile deployment. A dedicated effort to bridge theory to hardware implementation was identified as a critical technical need, with particular focus on principles of dendritic computation, diverse plasticity mechanisms, and multi-scale learning.

Implementation Challenges and Opportunities

Neuromorphic computing faces significant technical challenges in practical implementation. Manufacturing limitations include high costs for logic-process implementation, limited accessible fabrication platforms, and lack of standardized testing methods for novel components like memristor arrays. Workshop participants at the October 2024 Neuromorphic Principles for Biomedicine and Health (NPBH) workshop highlighted the "chicken and egg"

problem facing hardware engineers and developers – they need validation data to justify investment in novel architectures, but gathering this data requires investment in custom fabrication and test evaluation of the devices themselves. This has led to incremental improvement of existing technologies rather than exploration of truly innovative designs which may have transformative potential.

Technical integration challenges persist across multiple levels, from connecting neuromorphic components with conventional systems to combining different sensing modalities in multimodal interfaces. The regulatory pathway presents additional complexity, particularly for adaptive systems that learn and change over time, raising questions about how to quantify adaptation benefits and establish appropriate safety frameworks. Workshop participants emphasized the need for shared design resources and validation frameworks to accelerate innovation, including improved design tools for asynchronous circuits and standardized interfaces between hardware and "wetware" (such as biological systems for biocomputing or biohybrid designs). The gap between design tool ecosystems available for traditional digital signal processing versus neuromorphic computing was identified as a significant barrier to adoption and innovation.