International Consortium for Primate Brain Mapping
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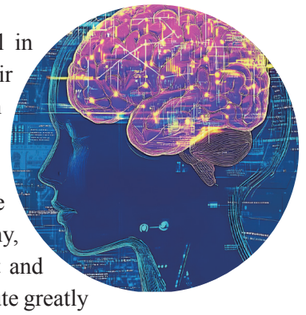
Synopsis

Despite over a century of research, our understanding of the structure and function of the primate brain remains in a nascent stage. Mapping the mesoscopic (i.e. cellular and circuit-level) structure of the primate brain is critical for understanding the mechanisms underlying human brain functions and brain diseases. The mission of the International Consortium for Primate Brain Mapping (ICPBM) is to establish an international network for communication and collaboration in primate brain research. Its main goal is to unravel the cellular and neural circuit basis of primate brain functions and pathogenic mechanisms underlying brain diseases. This will be achieved by identifying all cell types (neurons and glial cells) in the brain of non-human primates (NHPs) and humans as well as characterizing their spatiotemporal distribution and connectivity across the whole brain. To facilitate the implementation of ICPBM's programs and projects, we will establish a central core research facility and data centers around the globe. This consortium is distinctive as an international research alliance dedicated to the mapping of primate brains at the cellular resolution.

Background

Understanding the brain structure and function at cellular and neural circuit level is critical for unraveling the neural basis of cognition, affective and social behaviors, and brain diseases. Mesoscopic brain mapping that resolves the diverse cell types and their spatiotemporal organization and connectivity will provides a foundational framework for linking molecular mechanisms with circuit-level architecture and function. This knowledge is indispensable for developing targeted therapies for brain disorders, which collectively affect over 1 billion people worldwide and cost the global economy trillions of dollars annually[1]. Brain disorders, including neurodegenerative diseases such as dementia and movement disorders, and neurodevelopmental disorders such as schizophrenia and autism spectrum disorders, remain poorly understood at the molecular, cellular and circuit level. Underscoring an urgent need for mesoscale mapping that links our understanding at these three levels.

Over the past decade, large-scale initiatives on brain mapping have led to unprecedented progress in neuroscience. The development of single-cell and spatial multi-omics technologies facilitated the construction of mesoscopic cell atlases for *Drosophila*, zebrafish, and mouse brains[2-4]. Using both light and electron microscopy methods, mesoscopic connectomes (i.e., comprehensive maps of neuronal connections among different types of neurons within and across all brain areas) have also been obtained for *Drosophila* and zebrafish brains. Given the rapid progress in this area, completion of the mesoscopic mapping of the mouse brain within the next five years could be expected. These pioneering efforts are revolutionizing our understanding of neural circuits governing sensory processing, motor control, instinctive behaviors, and cognition in these animals. Notably, mapping of glial cells (e.g., astrocytes[5], oligodendrocytes[6] and microglia[7]) remains largely absent from these early maps, in spite of their critical roles in shaping and maintaining neuronal connectivity. Nevertheless, previous efforts of mesoscopic brain mapping have demonstrated the feasibility and advantages of large-scale mapping efforts and have established methodologies and paradigms for data acquisition, analysis, and open-access sharing, laying the groundwork for more difficult tasks of mapping the primate brain.

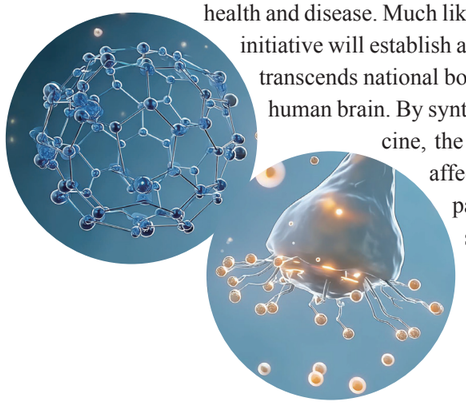


While model organisms like mice and *Drosophila* have been instrumental in fundamental discoveries, their evolutionary divergence from humans limits their utility in studying higher-order human brain functions and dysfunctions. Brain functions such as reasoning, complex decision making, empathy, sociality, self-awareness, and language—hallmarks of human intelligence—rely on highly complex neural circuits associated with the greatly expanded neocortex that are either absent or rudimentary in rodents and invertebrates. The genetics, anatomy, physiology and development of non-human primates (NHPs) such as marmoset and macaque monkeys resemble those of humans, thus findings in NHPs could contribute greatly to our understanding of human brain functions and diseases. Moreover, it is feasible to perform experimental manipulations in NHPs that are practically impossible or considered unethical in humans, such as testing invasive recording systems, targeted circuit manipulations via genetic and physical means, and longitudinal developmental studies. Furthermore, based on comparative knowledge of cell types and their connectivity between human and NHPs, pre-clinical studies on NHP models of brain disease symptoms will likely facilitate the understanding of brain disease pathogenesis and the development of novel pharmaceutical and physical neuromodulation therapies. Finally, since human brains are far more complex than those of NHPs, comparative studies between the two can identify molecular, cellular and circuit-level mechanisms unique to humans, offering insights into evolution of human-specific higher cognitive functions and brain disorders.

Mesoscopic mapping of primate brains[8-11], however, poses numerous technical challenges. For example, the human brain contains approximately ~86 billion neurons, interconnected by trillions of synapses, with cell-type diversity and network complexity far exceeding commonly used model organisms such as zebrafish and rodents. Primate-unique traits that are particularly specialized in humans, such as expanded associative cortices and protracted brain development, provide the substrates for developing advanced cognitive capability, but also vulnerability to neurodevelopmental and degenerative conditions. The molecular and circuit-level underpinnings of neural processing in primate-specific associative cortices remain poorly characterized. Successful mapping the NHP and human brains requires technological breakthroughs that overcome obstacles such as post-mortem tissue degradation, the large scale of brain tissues, and the scarcity of cell type-specific labeling methods. It will also demand high-throughput infrastructure for large-scale data collection and integration as well as AI-assisted analytical frameworks for processing multimodal datasets. Additionally, the heterogeneity of human and NHP samples analyzed worldwide—spanning genetic, developmental, and environmental variability—calls for extensive communication and consensus among researchers for the experimental designs as well as the collection, analysis and interpretation of data. Such global alignment ensures that findings are reproducible, comparable across studies, and could be integrated into a coherent framework. Open data sharing, standardized protocols, and agreement on best practices would reduce the duplication of efforts, enhance statistical power via data pooling, and accelerate the translation of results into clinical applications.

Identification of cell types and mapping their connectivity in human and NHP brains are ongoing in many laboratories worldwide. There is an urgent need for a coordinated global effort that unites technological innovation, cross-disciplinary collaboration, and ethical governance, to more efficiently acquire the cell type and connectome maps, particularly for human brains under various disease conditions. In order to cope with the size and structural complexity of the primate brain, further technological innovation needs to be focused on optimizing tools for NHP and human brains, such as large field-of-view spatial multi-omic techniques, cell type-specific labeling methods, high-throughput imaging technologies, and unique neuro-informatics solutions, The application of these advanced technologies will inevitably generate multi-modal datasets of unprecedented coverage and resolution, which necessitates international coordination in harmonizing tools for data collection, annotation, and open-access sharing, as well as in fostering reproducibility and accelerating discovery. Ethical imperatives, such as anonymizing human data and minimizing the NHP use, are also vital. The NHP brains offers the unique opportunity to study large, living, healthy brains without the intrusion of disease-related or post-mortem changes.

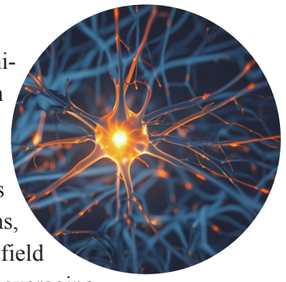
Within the coming decade, ICPBM aims to deliver complete mesoscopic atlases of primate brains of various species, elucidating the diversity, spatiotemporal organization, and connectivity of brain cells in health and disease. Much like the Human Genome Project that transformed life sciences, this initiative will establish a new framework for global neuroscience, in which collaboration transcends national borders for the common interest of unraveling the mysteries of the human brain. By synthesizing interdisciplinary insights and integrating clinical medicine, the consortium will redefine our approach to brain disorders that affect over 1 billion people worldwide, while establishing a new paradigm for international scientific governance in ethically sensitive research domains.



Overall Goals and Specific Aims

The ICPBM seeks to establish a coalition of research institutions and laboratories driven by a shared vision and common research goals towards a global, open, and innovative collaborative network. The Consortium will identify specific challenges and explore solutions in various areas of mesoscopic brain mapping, through coordinated international efforts in technical development and brain mapping. To achieve this, ICPBM will establish international exchange programs and collaborative projects, secure governmental and private funding, promote consensus in the standards of techniques, data collection, analysis and interpretation, and establishing guidelines and mechanisms for efficient global sharing of data and samples across teams or countries. Three specific aims are described in the following.

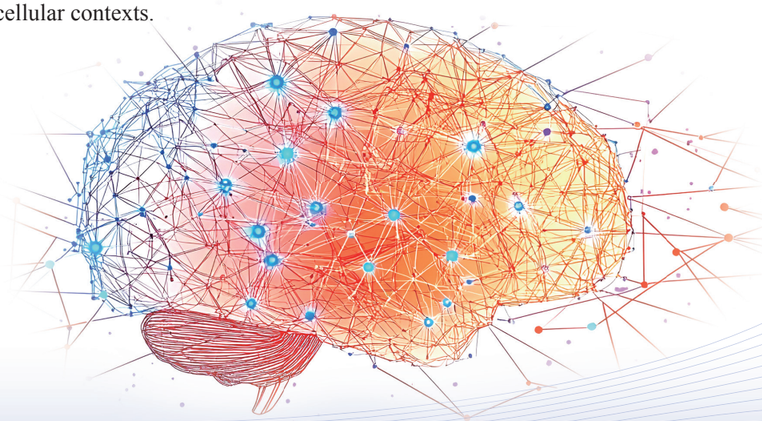
Aim 1.Mapping all cell types in human and NHP brains

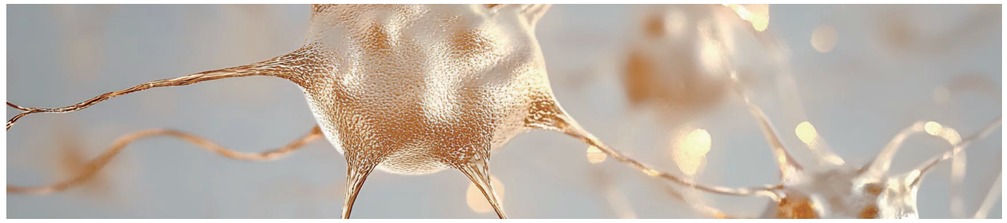


The ICPBM aims to serve as a unified platform for formulating a consensual definition of neuronal and non-neuronal cell types that integrates multimodal information across evolution, development, health and disease states. It will also serve to coordinate human and NHP brain studies via consensual standard operating procedures (SOPs) for annotation, sample processing, and data acquisition. To address challenges posed by the large size and post-mortem degradation of human brains, ICPBM will sponsor projects to develop new technologies that enable large-field multi-omic characterization of thick brain tissues at subcellular resolution. Leveraging single-cell and spatial multi-omic work (spanning genomic, epigenomic, transcriptomic, and proteomic modalities), ICPBM will systematically profile cell types in the central nervous system of multiple primate species while correlating molecular signatures with physiological, morphological (dendritic/axonal), and subcellular features (synapses, organelles). These efforts will build upon the brain regional and cellular maps generated by earlier human and non-human primate atlases[12-16].

Spatial transcriptome-based cell-type mapping will allow refinement of traditional brain parcellation schemes while uncovering dynamic cell interaction networks throughout evolution and development, as well as during aging and disease progression. By investigating age-related deterioration and pathological (mal)adaptation of specific cell types and the neural networks they support, ICPBM will use a system approach to identify novel biomarkers and therapeutic targets for neurological disorders such as aging-related dementias. Comparative analysis of cell types across primate species, including lemurs, marmosets, macaques, and humans, will provide new insights into the molecular and cellular mechanisms underlying the emergence of primate- and human-unique cognitive functions and selective human vulnerability for psychiatric and neurological disorders. Characterization of local milieu of various cell types, their unique molecular signatures, morphologies and connectivity will form the basis for full multi-omics data integration.

The resulting cell atlases will act as a unique multi-modal platform for cross-species structural and functional modeling, facilitating targeted drug development for brain disorders such as autism and schizophrenia that currently lack evolutionary relevant animal models. Together, ICPBM aims to redefine our understanding of primate brain organization while establishing a framework for precision neurotherapeutics grounded in evolutionary and cellular contexts.





Aim 2. Mapping brain-wide connectomes of primate brains

High-precision whole-brain mesoscale connectomes serve as a critical pathway to comprehensively elucidate brain functions and, in doing so, considerably advance our understanding of the human brain and our ability to protect and simulate it. Currently, mapping whole-brain neural networks has been universally recognized by the life science community as one of the pivotal frontier challenges of this century. The interest of neuroscience community in understanding the neural circuit basis of brain functions is evidenced by major international efforts such as U.S. BRAIN Initiative, EU's Human Brain Project and EBRAIN Project, Japan's Brain/MIND Project, Korea Brain Initiative, China Brain Project, Big Brain Project, and International Consortium for Brain Mapping. In collaboration with members of these existing national and international brain projects, the ICPBM aims to map the cell type-specific whole-brain mesoscale input-output connectomes in primates (including marmosets, macaques and humans), systematically elucidating the organizational principles of primate neural network architecture. To achieve this goal, ICPBM will undertake the following three tasks.

The first task is to develop multimodal parcellation atlases for primate brains. We will integrate primate whole-brain spatial transcriptomic maps with multimodal data (including histology and macroscopic brain imaging) to delineate boundaries of cortical and subcortical regions, thereby constructing a high-resolution 3D standardized brain region template, featuring a layer-annotated cortical surface and a comprehensive parcellation atlases for primate brains. A key principle in defining cortical areas is the 'FACT' framework, which integrates information on Function, Architecture, Connectivity, and Topography[17]. This approach will help to confirm and refine parcellation derived from decades of rigorous region- or system-based primate brain studies and single subject-based atlases.

The second task is to map the brain-wide connectome in NHPs, including healthy and diseased NHP brains: (i) Map whole-brain input connectomes using traditional retrograde tracers together with newly developed virus-based approaches for NHPs; (ii) map brain-wide projectomes with single-axon resolution across defined cell types in various brain regions, using high-resolution microscopy methods including fMOST (fluorescence Micro-Optical Sectioning Tomography) and ViSOR (Volumetric Imaging with Synchronized on-the-fly-scan and Readout). Generating comprehensive brain-wide connectivity maps in healthy and diseased NHPs will reveal how various cell types in distinct brain regions interact to support various brain functions, facilitate cross-species comparisons and integration with functional/behavioral data, and provide insights into brain development, evolution, and disorders characterized by network-level dysfunctions.

The third task is to map the brain-wide connectome in healthy and diseased human brains. We will establish sparse neuronal labeling protocols and wide-field high-speed scanning platforms that are optimized for post-mortem human brain specimens, enabling the systematic mapping of human whole-brain mesoscale connectomes. Recent breakthroughs in synchrotron X-ray sources and detection technologies will enable X-ray microtomography to achieve sub-micrometer resolution, making it uniquely suitable for comprehensive mesoscopic-level imaging of large brain samples, especially human specimens. For regions requiring even higher resolution, X-ray nano-tomography offers isotropic imaging at the tens-of-nanometer scale. Together, these novel imaging techniques, applied to the same specimens using the same imaging contrast, together with spatial omics technologies at single-cell resolution, could provide a scalable framework for bridging whole-brain architecture with fine-scale neuronal details.

Aim 3. Mapping brain-wide synaptic interactome and synaptic diversity in NHPs and humans

Cognitive abilities arise from complex synaptic connectivity in neuronal networks. Disruptions of synapses are linked to major human neurological and psychiatric disorders[18-20]. While mapping the brain's connectome offers important insights, it does not reveal dynamic formation and function of active neural assemblies that drive behaviors. This is due to the additional complexity introduced by the functional diversity of neurons and their synapses[21-23].

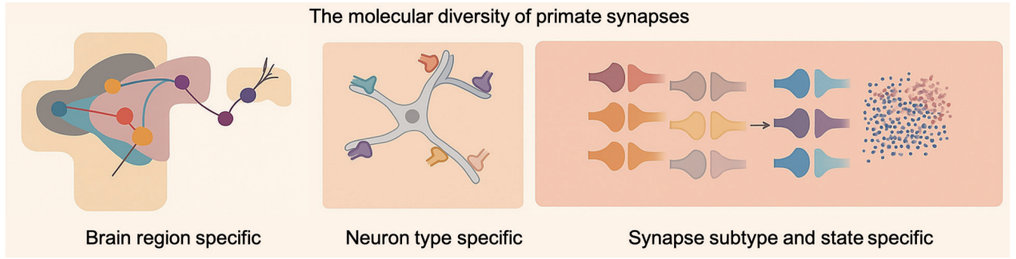


Figure 1. The molecular diversity of primate synapses may exist in a brain region-specific, cell type-specific, and synapse subtype- and state-specific manner, giving rise to many functionally diverse synapses that enable higher cognitive functions in primates

Direct functional studies of human synapses are limited by lack of access to live, healthy brain tissue. Therefore, a promising strategy is to identify molecular and functional synaptic fingerprints in NHPs and compare them with those found in brain biopsy samples of human patients and post-mortem human brain samples. We will use these techniques to study brain synapses in defined neural circuits, achieving mapping in four major directions: **(i) Synapse proteomic atlas:** Combining cell type-specific and synapse type-specific labeling, we will perform synaptosome proteomics to map region- and cell type-specific synaptic protein compositions[24] in NHP and human brains, enabling cross-species comparisons and uncovering novel therapeutic targets for psychiatric diseases. **(ii) 3D ultrastructure of neurons and synapses in NHP and post-mortem human brains:** Using advanced electron microscopy[25-27], we seek to elucidate the synaptic and neuronal architecture of the primate brain, including human brains, at the ultrastructural level. This approach seeks to uncover structural features underlying human brain functions and vulnerabilities to neurological diseases**. (iii) Mapping synapse types in NHP and human brains:** We aim to develop viral tools for high-throughput mapping of synapse types in NHP brains as well as biomarkers for identifying synapse types in human brains. **(iv) Functional diversity of primate glutamatergic synapses:** Combining electrophysiology and *in situ* molecular characterization via super-resolution microscopy (e.g. STED, Stimulated Emission Depletion) and expansion microscopy[28,29], we seek to define the molecular profile of distinct synapse subtypes by identifying pre- and postsynaptic cell types, axon/dendrite-localized transcriptomes, vesicle components, and AMPA/NMDA receptor contents in the brain of NHPs and brain tissue biopsy samples from normal and diseased human subjects.

In summary, ICPBM aims to unite mapping of all cell types, their whole-brain connectomes, and synaptic interactomes across humans and multiple NHP species in one coordinated global effort. It combines cutting-edge technologies—from multi-omic profiling to high-speed volumetric imaging, and ultrastructural electron microscopy—with standardized methodologies, open-science infrastructure, and harmonized ethical frameworks. This integrative, consensus-driven approach ensures reproducibility, enables large-scale data sharing, and links evolutionary insights to precision neurotherapeutic development, setting a new benchmark for collaborative transnational brain research.

Development of Brain Mapping Technologies

1） New technologies for brain-wide cell atlases

The integration of single-cell and spatial multi-omics technologies have significantly advanced our understanding of primate brain organization at molecular and cellular levels. However, previous efforts have primarily focused on single modalities such as transcriptomics, limiting a comprehensive understanding of brain functions. There are now emerging spatial multi-omics platforms such as Stereo-CITE that employs antibody-derived tag (ADT)-labeled antibodies combined with polyT-based mRNA capture through spatial barcoding. These innovative approaches also enable high-resolution mapping of the localization and interaction of proteins and transcripts as well as post-translational modifications and could yield detailed multi-omic information with subcellular resolution in intact brain tissues and provide critical insights into diversity of cellular functions, neurodevelopmental processes, and the molecular pathology of brain disorders.

A complementary technological advancement involves the application of spatial transcriptomics to formalin-fixed paraffin-embedded (FFPE) samples. Despite the well-documented challenges of RNA degradation in FFPE specimens, the implementation of random probe-based RNA capture strategies and the development of large probe sets for imaging-based technologies has enabled successful transcriptome profiling while maintaining compatibility with standard hematoxylin-eosin staining protocols. Other emerging technologies, such as the Stereo-seq_V2, Visium-HD, Xenium, MERSCOPE platform and the NanoString platform, exemplify this progress, facilitating cost-effective, species-agnostic analysis of both coding and non-coding RNAs, as well as host-microbe interactions.

The field of multi-omics has been further revolutionized by long-read sequencing (LRS) technologies, including PacBio HiFi, Oxford Nanopore, and Cyclone-SEQ platforms. These systems offer distinct advantages: (i) comprehensive transcript isoform characterization, enabling detailed study of neuronal diversity through alternative splicing patterns and fusion transcripts, (ii) detection of structural genomic variations that may influence neurodevelopment and disease susceptibility, and (iii) direct profiling of epigenetic modifications (e.g., 5mC, m6A) critical for understanding neurobiological regulation. The integration of spatial omics with LRS represents a particularly promising direction. Such multimodal approaches could resolve spatially restricted transcript isoforms and allele-specific expression patterns, correlate epigenetic modifications with cellular localization, and bridge molecular diversity with tissue architecture.

Collectively, these technological advances provide unprecedented opportunities for primate brain research. By enabling simultaneous investigation of protein-RNA dynamics in preserved tissues and spatial epigenomic profiling, they offer novel opportunities to study brain development, evolution, and pathology. This convergence of molecular details with spatial context promises to accelerate both fundamental neuroscience discoveries and their translation into clinical applications.

2） New technologies for brain-wide mesoscopic mapping of connectomes

To reveal the connectomes of primate brains, new imaging and labeling techniques need to be developed. To facilitate precise connectome mapping, robust and versatile labeling strategies are essential. Emerging technologies leverage cell type-selective genetic labeling driven by cis-regulatory elements (enhancers and promoters specific to identified neuronal marker genes). Such genetically encoded markers need to be adapted to fluorescence microscopy, electron microscopy, and X-ray micro/nano-tomography. Most importantly, these markers must enable both anterograde tracing, for visualizing the full extent of brain-wide projections of individual axons and retrograde tracing, for identifying neurons that send projections to specific neurons. The development and validation of these molecular tools will significantly enhance the accuracy and functional relevance of results obtained from traditional bulk-labeling connectomic analysis. Currently, researchers mainly use replication-defective viral vectors to express transgenes in NHPs. The efficacy may be limited by the antibodies in the NHP serum, the diffusion of viral particles, the species- and brain region-specific properties. Thus, optimization is required to achieve cell-type specific, sparse and bright fluorescence labeling.

Due to the large volume of NHP brains (e.g. a macaque brain is about 200 times larger than that of a mouse), imaging of the whole brain of a single NHP with the spatial resolution that enable identification of fine dendritic/axonal arbors currently requires 2 months of imaging time. Thus, a much more efficient optical microscopic imaging approach must be developed to accelerate data acquisition, without compromising the image resolution and quality. Additionally, the cytoarchitecture of the brain should also be acquired during the imaging procedure to ensure that the mesoscopic connection data could be precisely localized for the normalization of different samples. Finally, the generated data size of mesoscopic images will be in the order of the petabyte for each whole-brain sample, which poses significant challenges for the storage, processing, and sharing of data. Thus, new technologies in image acquisition and data processing are critical for achieving the cell type-specific mesoscopic connectome of NHP brains.

Recent advancements in brain imaging, particularly synchrotron-based X-ray microtomography, have dramatically enhanced our capabilities in detailed brain mapping. By employing large numerical aperture (NA) visible-light objective lenses in combination with high pixel-count complementary metal-oxide-semiconductor (CMOS) detectors, current imaging systems could simultaneously achieve large fields of view, exceptional spatial resolution, and fast data acquisition. This integrated imaging approach allows sub-micrometer-scale 3D reconstructions of large brain specimens from NHPs and humans, thereby capturing neuronal structures across extensive regions without compromises on detail or speed. However, efficient cell type-specific labeling suitable for X-ray microtomography remains to be developed.

3）New technologies for mapping primate synaptic interactomes

To investigate the molecular composition of synapses in the primate brain, a suite of advanced techniques is essential, including high-resolution imaging methods such as cryogenic electron tomography[30], volume electron and light microscopy[25,31], super-resolution microscopy[28], automated multiplexed immunofluorescence labeling for high-throughput molecular-resolution imaging[32,33], and single-synapse mass spectrometry. This endeavor will also require bioinformatic platforms for cross-species and multi-omics data analyses[34,35,] high-throughput 3D reconstruction tools for volumetric light and electron micrographs, and AI-assisted data processing and visualization.

Among these methods, a critical technique for studying post-mortem primate brain tissue is high-resolution, multiplexed, post-embedding immunolocalization[36]. In this method, chemically fixed post-mortem brain tissue is dehydrated and embedded in epoxy resin, then cut into ultrathin sections (100–200 nm). These serial sections undergo chemical processing to achieve specific, high signal-to-noise immunolabeling of key presynaptic proteins (e.g., voltage-gated calcium channels, RIM, SNARE complex, synaptotagmins) and postsynaptic proteins (e.g., AMPA and NMDA receptor subunits). The labeled proteins are visualized using standard fluorescent methods and imaged with confocal or STED microscopy. Postsynaptic neurons are identified with cell type-specific molecular markers such as parvalbumin, calbindin, somatostatin, and specific potassium channel or receptor subunits.

Additionally, we need to develop viral labeling strategies that can track large numbers of synaptic connections among various primate neuron types identified in cell type mapping studies. These tracked synapses will be analyzed via electron microscopy and super-resolution microscopy. The goal is to identify conserved connectivity motifs in the human brain by comparing NHP and human data, generating insights into synaptic architecture, circuit organization, and the molecular basis of cognitive function in primates.

Analysis of Mapping Data

1）Data Integration

The ICPBM will generate vast, multi-scale datasets, from single-cell spatial transcriptomes to brain-wide mesoscopic connectomes. Integration of this diverse information represents a significant challenge. Our core integration strategy focuses on establishing robust 3D spatial frameworks, including Common Coordinate Frameworks (CCFs) for marmoset and macaque, and adapting human brain atlases. Unlike in current projects using mice, where efforts have been made to reduce sources of variability by using genetically similar mouse lines, the consortium will embrace the need to address individual variability as a key part of making the datasets useful for humans. We will rigorously address inter-individual variability, including the use of computational techniques that allow probabilistic mapping of structures to template brain coordinates, such as those already developed for the marmoset[37]. The use of parcellation-free mapping (where the data themselves drive the assignment of a cell/synapse to a part of the brain) will also be instrumental for this aim.

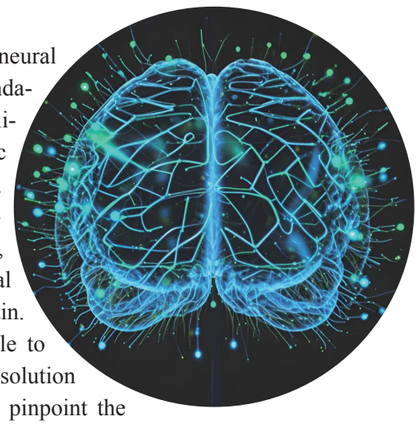
An accurate yet flexible spatial scaffold is essential for accurately co-registering diverse data types, including gene expression patterns, distributions of molecularly defined cell types, single-neuron projection patterns, synaptic organization, white matter tracts, and neuronal activity maps. Key to this scaffold is to develop robust, efficient algorithms for precise spatiotemporal alignment and standardization of heterogeneous brain atlas data. This includes tackling challenges in aligning data across varying modalities and scales (e.g., spatial transcriptomics, MRI, connectomes), which inherently possess different coordinates, resolutions, and deformations. High-precision 3D registration algorithms will focus on 3D reconstruction of spatial transcriptomics and its precise alignment with mesoscopic and macroscopic connectome maps within a standard 3D brain atlas space, considering tissue deformation, multi-resolution fusion, and cross-individual/species strategies. Given inherent individual brain differences, we will establish a pipeline to accurately map standard space information back to individual brain space, preserving original data and supporting research on inter-individual variability.

Complementing spatial alignment, we will develop and deploy advanced computational methods for joint multi-modal analysis. Sophisticated statistical learning, deep learning, and network analysis techniques will correlate distinct data layers, such as linking regional gene expression or cell composition to structural/functional connectivity. These methods will move beyond simple correlations to achieve deep feature fusion of local cellular and molecular information with global network characteristics, revealing cross-scale organizational principles. This includes developing algorithms for deep feature fusion of multi-scale, multi-modal brain atlas data to uncover associations such as between gene expression and connectivity patterns.

Foundational to this effort are rigorous data standardization, including common metadata schemas and interoperable formats, and the creation of shared databases and open platforms equipped with tools for collaborative query, visualization, and analysis. This integrated, multi-omic approach aims to foster discoveries and build comprehensive computational models of the primate brain. This will involve optimizing key technologies for precise alignment and deep feature fusion of high-resolution spatial transcriptomic data with multi-scale brain connectome data. Utilizing these technologies, primate whole-brain 3D multi-modal atlases will be constructed, integrating single-cell resolution spatial transcriptomics, and connectome data, incorporating multi-dimensional information such as cell types, gene expression, and connectivity patterns.

2）AI tools for data analysis

The endeavor of mesoscopic mapping of primate brains involves managing an immense volume of complex data, including single-cell omics, spatial omics, microscopic images, functional MRI etc. These datasets are characterized by their high dimensionality, multi-scale and multi-modality nature, with intricate temporal and spatial relationships. Additionally, they often present challenges such as noise, batch effects, and missing data elements. Traditional data analysis methods frequently fall short in effectively handling these complexities. However, recent advances in artificial intelligence (AI) technologies offer transformative capabilities for data analysis in neuroscience.



AI technologies such as self-supervised deep learning, graph neural networks, multi-modality alignment, and emerging large language foundation and CLIP models are particularly promising. These tools can facilitate several critical data analysis tasks that are essential for mesoscopic mapping. **Firstly,** AI tools can integrate different modalities of omics, imaging, and functional data, providing a holistic view of brain structure and function. **Secondly,** AI can assist in cell-type annotations, which involves identifying hundreds of brain cell types. This is crucial for understanding the diverse cellular landscape of the primate brain. Building on these foundations, we can develop an AI-driven module to integrate population-scale human genetics data with high-resolution spatial-omics data, producing 3D maps at single-cell resolution that pinpoint the specific spots in the brain where disease-associated genetic variants exert their effects[38]. **Thirdly,** AI also provides tools for constructing spatial and functional interactions and connectivity between neurons and glial cells across brain regions. This has already been attempted in small datasets of human developmental tissues integrating deep learning and spatial statistics in health and disease to map cellular organization and needs to be scaled further on larger datasets[39]. Such AI tools can integrate interactive annotation, proofreading, and automated neuron tracing, significantly reducing manual labeling effort. For example, interactive segmentation methods based on SAM[40] could provide flexible neuron annotation capabilities. **Fourthly,** AI excels at identifying important markers, patterns, and structures within large datasets, which is essential for uncovering new insights into brain organization. AI can also enhance data preprocessing by reducing batch effects, noise, and missing data, thereby improving data visualization. **Fifthly,** the automation and acceleration of data processing pipelines through AI tools are also beneficial for large-scale mesoscopic mapping, significantly reducing the time and effort required for analysis.

Advanced microscopic imaging platforms—such as rapid light-sheet fluorescence microscopy and synchrotron X-ray tomography—enable whole-brain circuit mapping at the mesoscopic level, while serial block-face electron microscopy and FIB/SEM provide synaptic-resolution maps of specific regions, such as the human cerebral cortex and hippocampus. However, these neuroimaging techniques routinely generate multi-teravoxel datasets whose raw volume reaches tens of petabytes, imposing unprecedented burdens on data transmission, long-term storage, and downstream analytics. To address these challenges, we need to develop a lightweight AI compression toolkit designed for neuronal volumetric image compression. Such model usually leverages an end-to-end, learnable 3D deep-learning network to perform volumetric data compression, effectively capturing spatially distributed morphological features while preserving detailed neuronal structures. When processing large-scale whole-brain optical microscopy data, the AI-driven compression model can efficiently handle batch processing of 3D input data in parallel and is compatible with images of various modalities and resolutions.

Furthermore, AI-driven generative modeling can aid in hypothesis generation and testing, allowing researchers to simulate various scenarios and predict outcomes based on existing data. This capability not only enhances our understanding of primate brain structures but also opens new avenues for exploring brain disorders and potential therapeutic interventions. All data modalities will be integrated to develop AI-Virtual models capable of simulating neural circuit organization principles underlying primate cognition, predicting disease etiology, and prioritizing therapeutic targets. By leveraging AI methods, researchers may gain new insights into the complex architecture of primate brains, paving the way for advances in neuroscience and related fields.

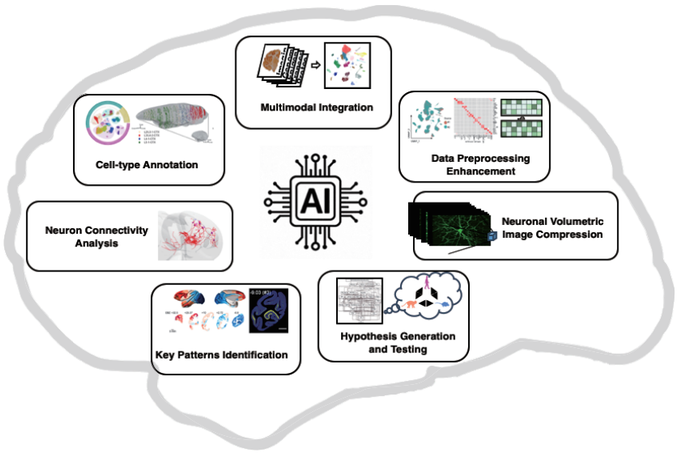


Figure 2. AI tools for mesoscopic mapping of primate brains

Infrastructure of ICPBM

The ICPBM proposes a cutting-edge Big Science Infrastructure to tackle the complex task of constructing mesoscale brain atlases for NHPs and humans through international collaboration. This initiative addresses the unprecedented challenges of cross-scale, multi-modal, high-throughput data acquisition and analysis, from single-cell multi-omics to whole-brain connectomics that require participation of neuroscientists around the globe with diverse expertise and research interests but a common goal of understanding the primate brain. To this aim, the ICPBM will establish a Central Hub and globally distributed International Hubs to facilitate the coordinated efforts in technological development, as well as in data acquisition, analysis, interpretation, and sharing. Through efficient and productive operation of these hubs, we hope to achieve the goal of ICPBM in achieving comprehensive understanding of the structure and function of primate brains and neural basis of brain disorders.

1) Central Hub

The ICPBM's Central Hub (likely to be located in Shanghai) will provide a collaborative platform for standardized data acquisition, integration, cross-species and multi-scale interoperability, as well as protocols that meet bioethics and safety regulations. It will serve for the interaction, integration, and dissemination of technologies, resources, and data in order to facilitate international collaborations in primate brain mapping.

(a) Sample resources: The Central Hub will provides high-quality, well-documented, ethically sound sources of NHP and human brain samples via autopsy programs with detailed provenance, with ensured sample integrity and adaptability for cutting-edge mapping studies. The resources will be available for studies performed by consortium members at the Central Hub or distributed to International Hubs whenever permissible under national regulations for international transfers of biological samples.

(b) High-resolution whole-brain imaging facilities: The Central Hub will establish efficient, multi-channel, submicron-level whole-brain imaging facilities across diverse modalities that are capable of capturing mesoscopic molecular and cellular details. These facilities will be available to consortium members for individual or collaborative projects at the Central Hub. The Central Hub will assist the International Hubs to establish these facilities if needed.

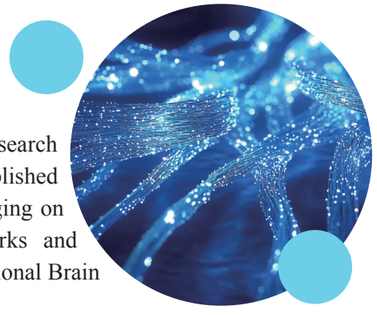
(c) High-throughput data acquisition and initial processing: The Central Hub will supports high-throughput raw data acquisition and initial analysis, high-speed transmission, and access to world-class HPC for initial processing and quality control. These raw data may be processed at the Central Hub or transferred to International Hubs for further analysis by ICPBM members.

(d) Unified computation and system interpretability: The Central Hub will harmonizes diverse computational environments and ensures interoperability using strategies like CBRAIN[41]. This includes developing common data models, APIs, and shared metadata standards to enable unified analytical workflows across a federated HPC ecosystem of ICPBM. This will help to streamline data integration from heterogeneous sources.

(e) Sustainable user support and collaboration ecosystem: The Central Hub will organize dedicated teams to operate and maintain data platforms, continuously refine them based on user feedback, provide collaborative annotation/analysis infrastructure, and offer regular training for facility users. For example, the Data Coordination Team will be guided by core principles of technical standardization, global consensus in bioethics, and open access collaboration. Through these measures, a safe, efficient, and inclusive data hub will be constructed to promote the transformation of primate brain science from fragmented research efforts into a cohesive global collaborative program.

(f) Standardized workflows and training: The Central Hub will develop and validate standardized, automated workflows for brain atlas mapping and offers comprehensive training of researchers from ICPBM member laboratories as well as a wider brain mapping research community.

(g) Global research support and collaboration: The Central Hub will facilitate international cooperation and development of joint research programs in primate brain mapping and organize international fund-raising activity for collaborative projects. The Central Hub will integrate premier domestic resources and actively collaborate with leading global research institutions and consortia.



2) International Hubs

Globally distributed international Hubs will be based on existing research institutions and consortia in various countries as well as newly established centers by ICPBM members in their respective institutions, leveraging on the experience and mechanisms developed by existing networks and platforms such as LORIS[42,43], the Big Brain Project, and the International Brain Mapping Project.

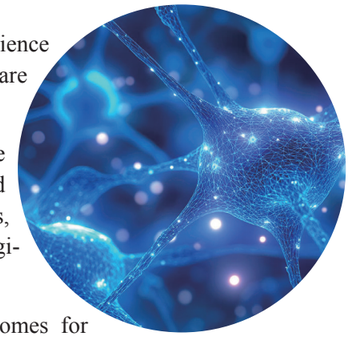
(a) Data acquisition, governance and compliance: International Hubs will perform primate brain mapping based on ongoing programs in respective institutions and networks, participate in new mapping initiatives of ICPBM in data acquisition and analysis as collaborative partners (either at the Central Hub or at respective Internation Hub), and ensure data management, storage, access, and sharing that comply with national and local regulations. The ICPBM will establish ethical and biosafety frameworks for compliant cross-border data sharing.

(b) Multimodal data integration and visualization: Via interaction and coordination with the Central Hub, International Hubs will establish their respective platforms for acquisition of brain mapping data, integration of multimodal data using AI-driven algorithms for inter-scale harmonization (at molecular, cellular, circuit levels), and interactive visualization for analyzing and accessing diverse mapping data. These platforms will allow analysis of both locally generated data and raw data collected in the Central Hub, using standardized ICPBM protocols.

(c) Distributed cloud infrastructure and connectivity: A distributed hybrid cloud infrastructure with edge nodes in key regions (Asia, Europe, America) will reduce data transmission latency and support resource-scarce areas via lightweight mirror sites. Data mirrors will ensure integrity and accessibility, and decentralized trust mechanisms will be developed for open resource sharing.

(d) Tiered data access and security: The platforms at the Central Hub and International Hubs will feature tiered data access with robust security. De-identified reference atlases will be public, while sensitive metadata and raw data will have advanced encryption and granular access control, building on technologies like the Canadian Open Neuroscience Platform[44-46]. In principle, brain mapping data acquired and analyzed by the consortium members through either individual or collaborative efforts will be open to access by the public after initial publication of the data.

Major Anticipated Achievements



The ICPBM is poised to deliver transformative advances in neuroscience through its ambitious research agenda. The following key achievements are anticipated:

(a) Construction of high-resolution, multi-omic cell atlases of primate brains by integrating single-cell and spatial transcriptomic, proteomic, and epigenetic profiles with morphological data from neurons and glial cells, enabling systematic characterization of cellular diversity in both physiological and pathological states.

(b) Mapping of cell type-specific brain-wide mesoscopic connectomes for primate brains, revealing connectivity principles underlying brain functions and dysfunctions.

(c) Mapping the 3-D synaptic architecture of primate brains that identifies molecular and functional synaptic fingerprints, unravels synaptic ultrastructure associated with brain function, aging, and brain disorders.

Together, these efforts will link molecular and cellular diversity to synaptic and neural circuit organization, providing a comprehensive framework for understanding structure and function of primate brains and disease mechanisms.

Major Challenges

Several critical challenges exist for accomplishing ICPBM's goal of mesoscopic mapping of primate brains, including technical, computational, ethical, and governance issues, that require innovative solutions and international collaboration. These include:

(a) Technical limitations in human brain mapping: While fluorescence-based connectomics is feasible in NHPs, human brain mapping requires non-invasive or post-mortem-compatible methods. Current techniques, such as immunohistochemistry, MRI and medical CT, lack the resolution or scalability for whole-brain single-cell tracing. Developing cell type-specific labeling for human tissues and improving imaging throughput remain highly challenging. The consortium will address this by research dedicated to establishing the precise cellular-level relationship between the gold standard represented by tracers and new non-invasive techniques, leveraging on the technologies and data collected for NHP brains.

(b) Large datasets and computational demands: Harmonizing protocols for sample preparation, data acquisition, and annotation across institutions is critical to avoid methodological discrepancies that hinder cross-study comparisons. Consortium-wide standard operating procedures (SOPs) must address this logistical challenge. Simultaneously, mesoscopic mapping generates petabytes to exabytes of structural/molecular data, necessitating advanced AI tools for data processing and analysis. Establishing scalable computing infrastructure and standardized analytical pipelines across international partners is essential to prevent data fragmentation.

(c) Ethical issues and data management infrastructure: The anticipated benefits of this primate brain mapping project is apparent to neuroscience community. There remain general ethical concerns involve managing sensitive human research data and the welfare of the animal subjects, specifically macaque and marmoset monkeys. Human data handling protocols need to be well established, safeguarding individual anonymity and addressing the complexities of genetic data sharing among international research partners whilst allowing open access to the research findings for consortium members. Animal research proposals will undergo independent ethical review by the competent authorities in various jurisdiction systems where research is carried out. There has been substantial convergence of welfare standards in recent years[47] and the ICPBR-established protocols will adhere to or exceed the highest standards in each country involved in the brain mapping projects. Exchange of animal tissue will comply with the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) and regulations of relevant countries. After thorough analysis, the consortium will curate the research data into an open-access repository, facilitating consultation and exploration by the broader scientific community, fostering transparency, and enabling future discoveries.

Overview and Outlook

Understanding the structure and function of the brain is the ultimate challenge for humans, given the complexity of the endeavor and its implications for understanding ourselves and our place in nature. The ICPBM will further integrate the outputs of multidisciplinary scientists to map the primate brains at the mesoscopic level, providing a new paradigm and database for future global brain science research. By combining the results of brain mapping of multiple species, we will be able to analyze the biological mechanisms underlying primate brain evolution and unravel the genetic and cellular basis of higher cognitive ability of humans. By comparing the cellular and mesoscopic connectivity maps of healthy and diseased brains across multiple pathologies, we will accurately identify pathogenesis-related neuronal and glial cell types and decipher pathological circuit mechanisms across the brain regions, provide targets for diagnosis and treatment of brain diseases and facilitate the development of pharmaceutical, physical, and behavioral intervention approaches. The primate whole-brain connectivity map will help to navigate for research and development of new brain-inspired machine learning algorithms and artificial neural network architecture, driving emergence of the next generation of sustainable AI technologies that align with societal needs.

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