How do human brains vary?

The newly launched Center for Human Brain Variation seeks to understand biological diversity in the brain.

The Center for Human Brain Variation

PIs: Evan Macosko & Steven McCarroll

Significant contributors: Kiku Ichihara, Charles Vanderburg, Curtis Mello, Marina Hogan, Katelyn Flowers, Melissa Goldman, Khalid Shakir, Karol Balderrama, Nafiseh Yavari, Naeem Nadaf, Liv Spina, Nicole Rockweiler, James Nemesh, Alec Wysoker, Matthew Shabet, Stephen Fleming, Sabrin Mohamednur, Alex Werley, Fei Chen, Elise Robinson & Mehrtash Babadi

ABSTRACT

The mission of the Center for Human Brain Variation is to address an unmet need in cell census research: to understand the cell-type-specific mechanisms and tissue-level biological principles that generate inter-individual variation in brain biology. To fully understand the brain's function and vulnerabilities, we must know and be instructed by its biological diversity across people. In this work, we will leverage new technologies in single-cell and spatial genomics, including many developed in our labs, to construct an atlas of human brain cell variation. Our Center is committed to assembling a project team with diverse perspectives, while fostering an inclusive environment where all team members flourish.

brain.broadinstitute.org

brain@broadinstitute.org

@BroadBrainCtr

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MOTIVATION

An inventory of the human brain's cellular components and their associated molecular repertoires – a cell atlas – will provide a powerfully enabling platform for translational neuroscience. Our atlas will simultaneously inform our understandings of:

- The common, shared cellular features that make all of our brains work
- The ways in which these features vary and co-vary across individuals
- The relationship of this biological variation to genes, alleles and biological function
- The tissue-based mechanisms of genetic risk for neurodevelopmental and neuropsychiatric disorders

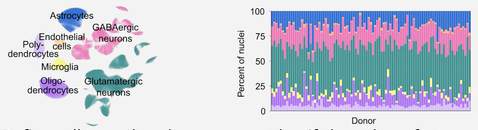
RESEARCH GOALS

1. Construct an atlas of human brain cell variation

	Group	Donors	Brain regions	Samples
Samples	Postnatal development 10 – 25 years	64 neurotypical	50 Associated with neurological & psychiatric disorders	3.1k
	Adulthood 25+ years	200 neurotypical		10k

Assays: snRNA-seq (90M nuclei) + Multiome ATAC + GEX (20M nuclei) + Slide-tags[1] (6M cells) = 116M cells

2. Characterize human brain biological variation



Define cell type abundance and spatial distribution; transcriptome; DNA accessibility

Identify how these features vary and co-vary across individuals

3. Use variation to reveal and understand biological function

How does genetic variation shape the biology of cell types, brain tissue and brain vulnerability?

DATA GENERATION

Scalable and rigorous data generation is critical. Our laboratory approach (**Figure 1**) had the best performance in a comparison of BRAIN Initiative Cell Census Network (BICCN) protocols[2]. These results have dispelled our initial concerns that peri- or post-mortem circumstances might obscure biologically meaningful relationships.

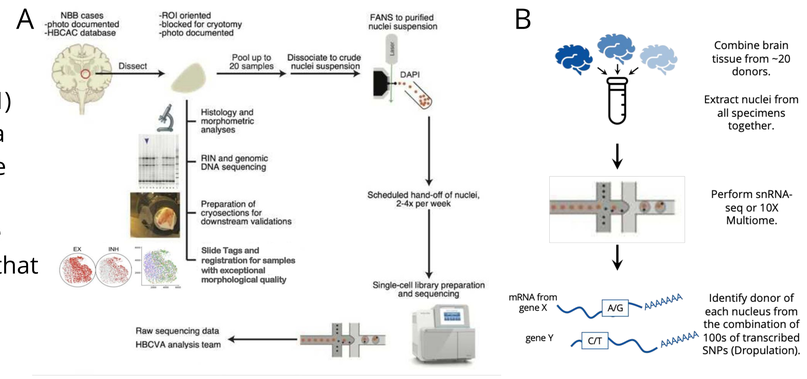


Figure 1: (A) Data generation workflow. (B) Detailed overview of donor villages.

DATA ANALYSIS

The computational infrastructure, algorithms, and statistical frameworks for data analysis and interpretation are summarized in **Figure 2**. Workflows are compatible with other BICAN sites.

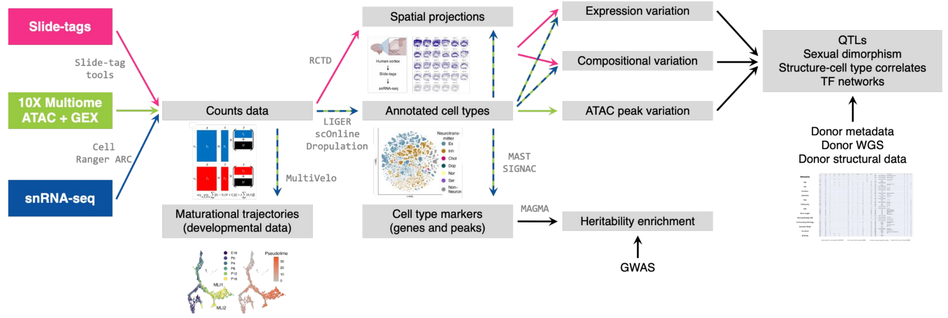


Figure 2: Data analysis and interpretation workflow.

OUTCOMES

By the end of the 5 year project, we will:

Provide an essential variation-focused **data resource** for cellular, molecular, genetic and translational neuroscience; improve interpretation for brain pathology studies.

Use the atlas data and analysis methods to **advance** psychiatric research.

Engage in outreach activities with a variety of organizations serving underrepresented groups.

Mentor at least 50 trainees, with the majority from underrepresented groups.

ACKNOWLEDGEMENTS

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REFERENCES

1. Russell, A. J. et al. Slide-tags: scalable, single-nucleus barcoding for multi-modal spatial genomics. bioRxiv (2023).
2. Bakken, T. E. et al. Comparative cellular analysis of motor cortex in human, marmoset and mouse. Nature 598, 111–119 (2021).