

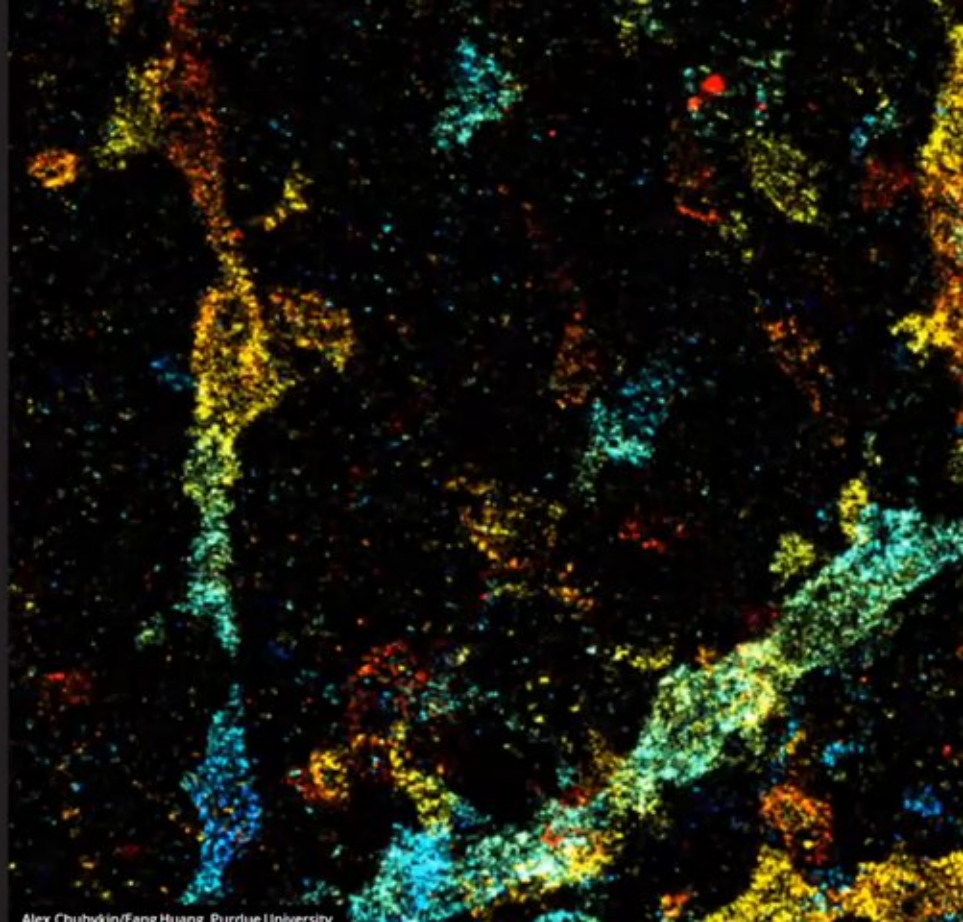
The BRAIN Initiative®

Cell Atlas Network *Workshop*

From Single-cell Genomics to
Brain Function and Disorders –
Data Integration and Annotation

January 16-18, 2024

11:30 am - 4:30 pm EST



Session 1. Brain Cell Atlases for Neuroscience in Health and Disorders

Keynote Presentation 1

Decoding the Regulatory Code of Brain Cell Diversity

Joseph Ecker, PhD – Salk Institute

Bing Ren, PhD – UCSD

Nelson Johansen, PhD – Allen Institute



National Institutes of Health
The BRAIN Initiative



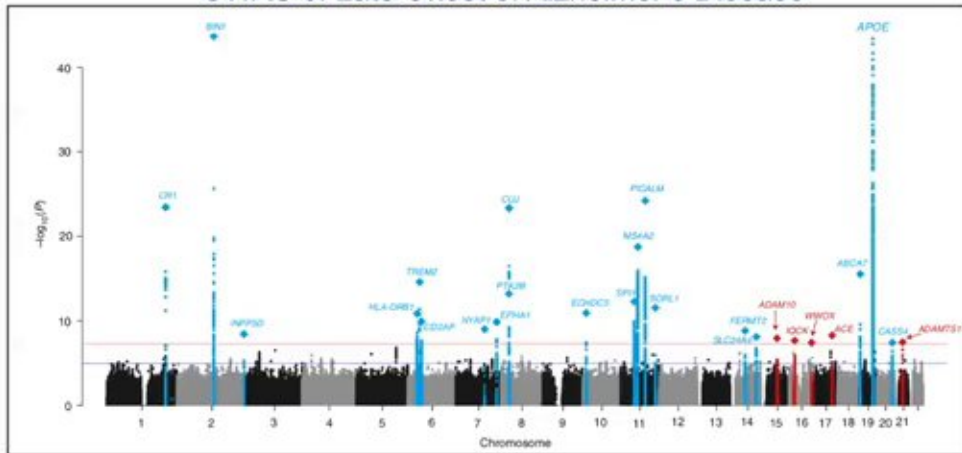
Image created by Dall-E

Decoding the Regulatory Code of Brain Cell Diversity

- Bing Ren (UC San Diego)
- Joseph Ecker (Salk Institute/HHMI)
- Nelson Johansen (Allen Institute)

A Key Knowledge Gap in the Study of Neurological Disorders

GWAS of Late Onset of Alzheimer's Disease



Kunkle BW et al. Nature Genetics 2019

Outline of presentation

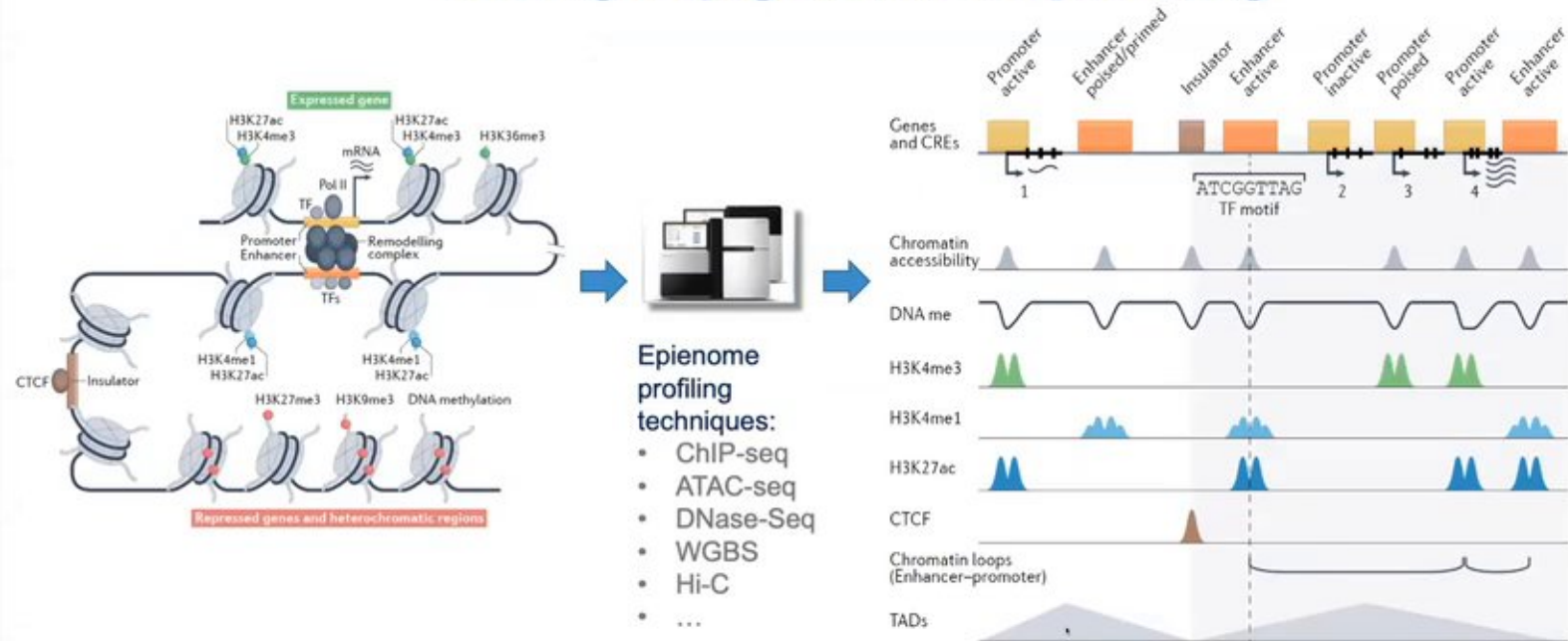
Introduction: strategies for gene regulatory code analysis in the brain cell types (Bing)

Mapping of cell-type specific regulatory programs in the mouse brain (Joe).

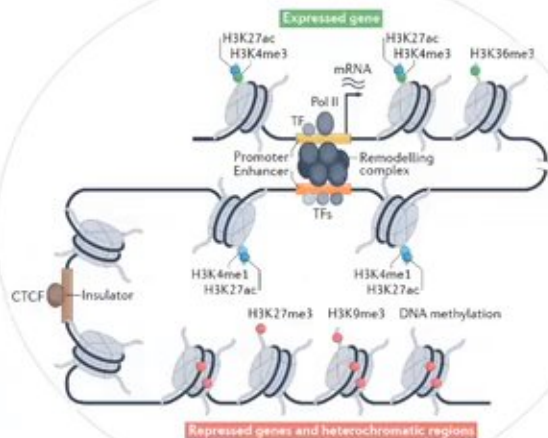
Mapping of cell-type specific regulatory programs in the human brain (Bing)

Enhancer challenge: predicting cell-type-specific enhancers from epigenome maps (Nelson)

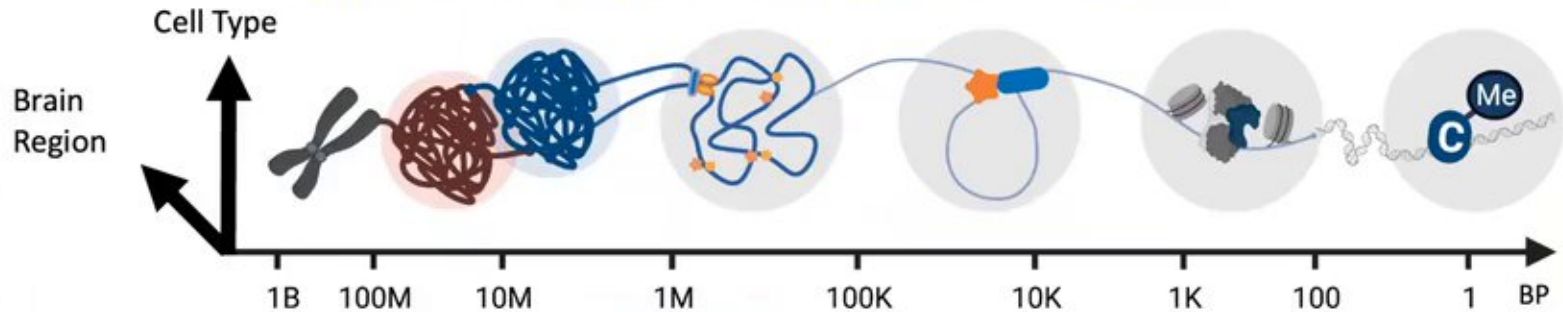
Finding and characterizing regulatory elements through epigenome sequencing



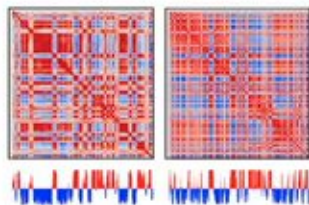
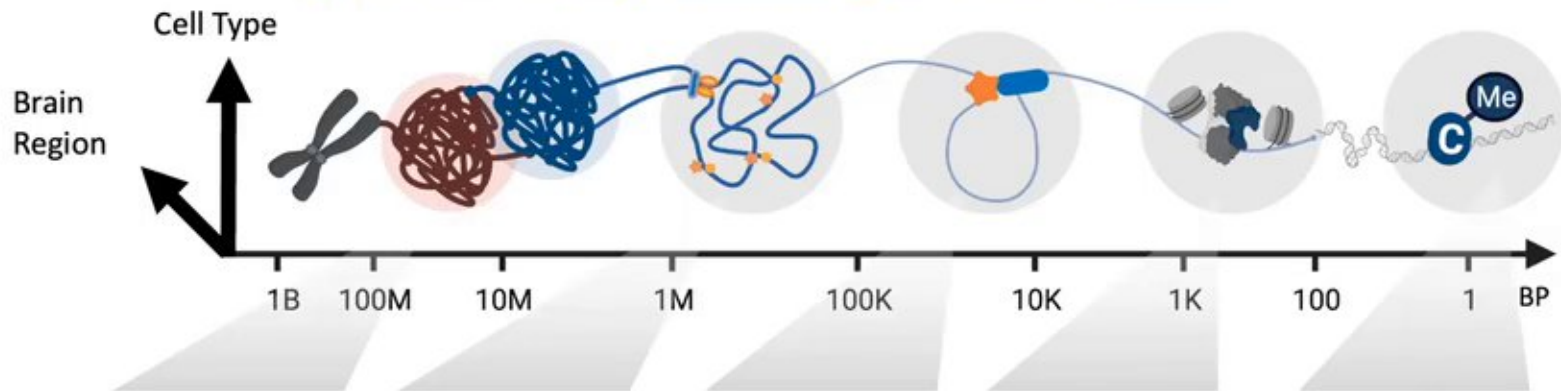
Single Cell Epigenomics



Epigenomic cell atlases enable investigation of cell-type diversity across genome scales



Epigenomic cell atlases enable investigation of cell-type diversity across genome scales



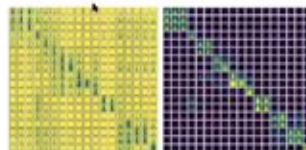
Genome
Compartment



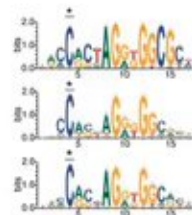
TAD Domain
& Boundary



DNA loop

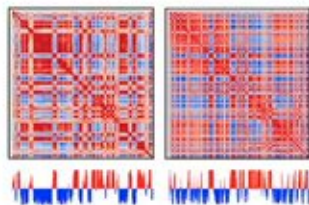
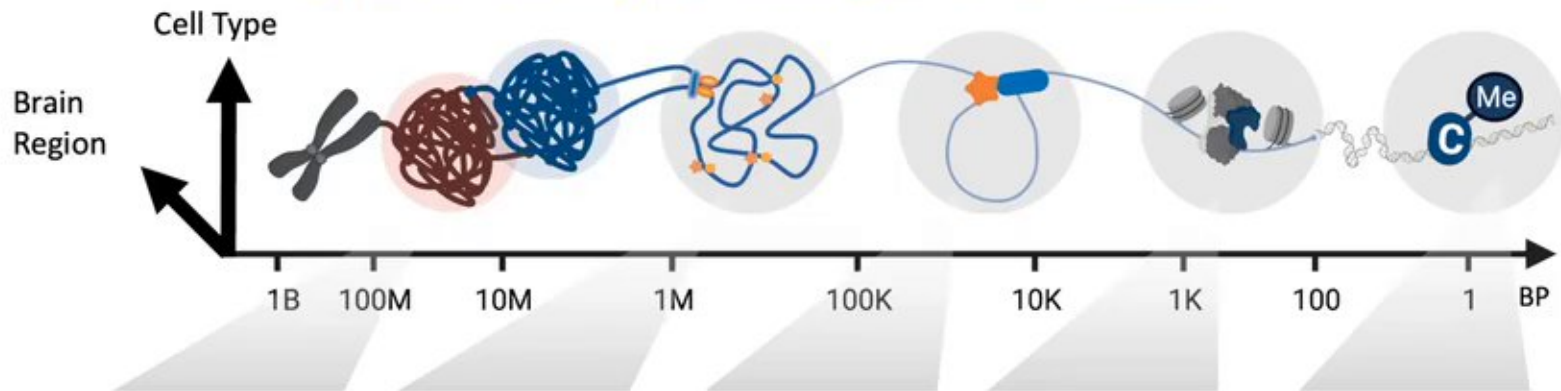


Reg. Elements
mCG & ATAC



Motif activity &
Single Base mC

Epigenomic cell atlases enable investigation of cell-type diversity across genome scales



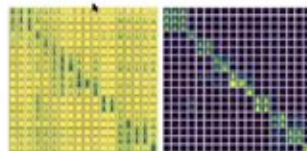
Genome
Compartment



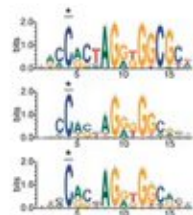
TAD Domain
& Boundary



DNA loop



Reg. Elements
mCG & ATAC



Motif activity &
Single Base mC

BRAIN MAPS

Heated debate

The factors that drive disagreement between climate models

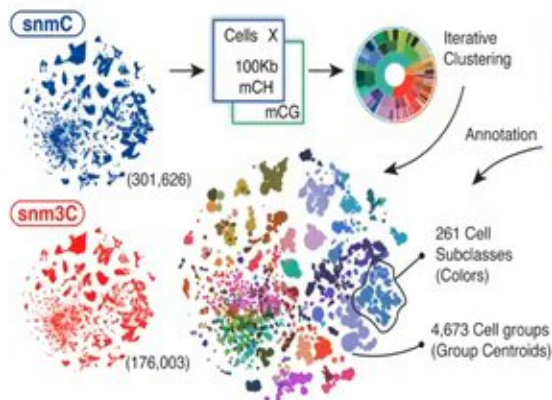
[illegible]

Zhu et al. Nature 2023

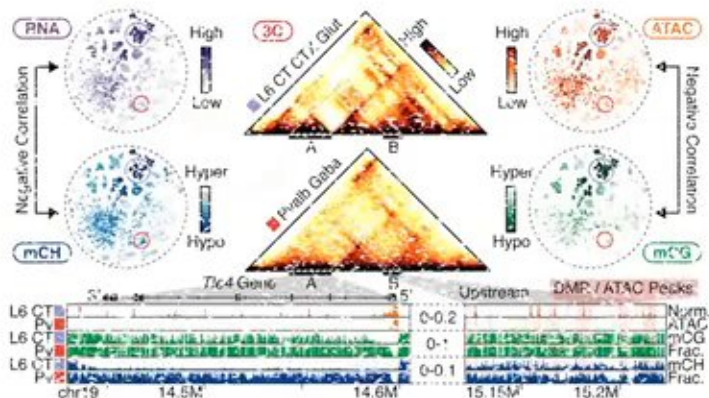
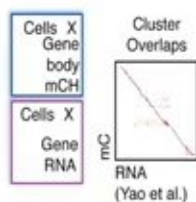
Single-cell DNA methylome and multi-omic atlases capture the cellular and genomic diversity in the whole mouse brain

Liu, Zhou et al. Nature 2023

Methylome-based Clustering

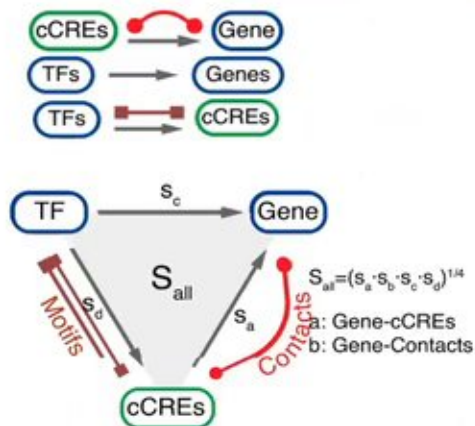


Cross-modality Integration

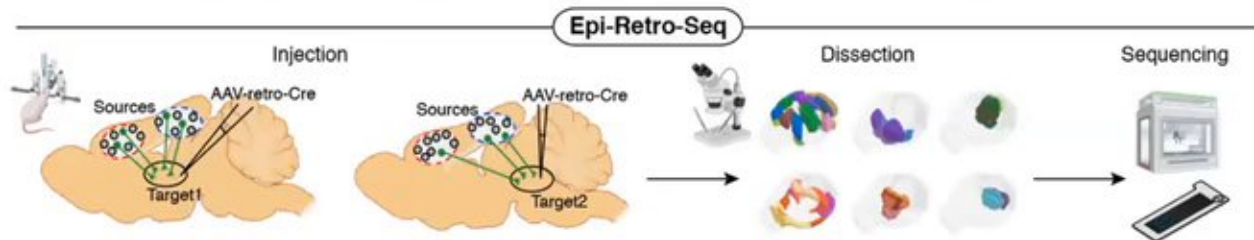


Chromatin conformation landscape of megabase-long genes,

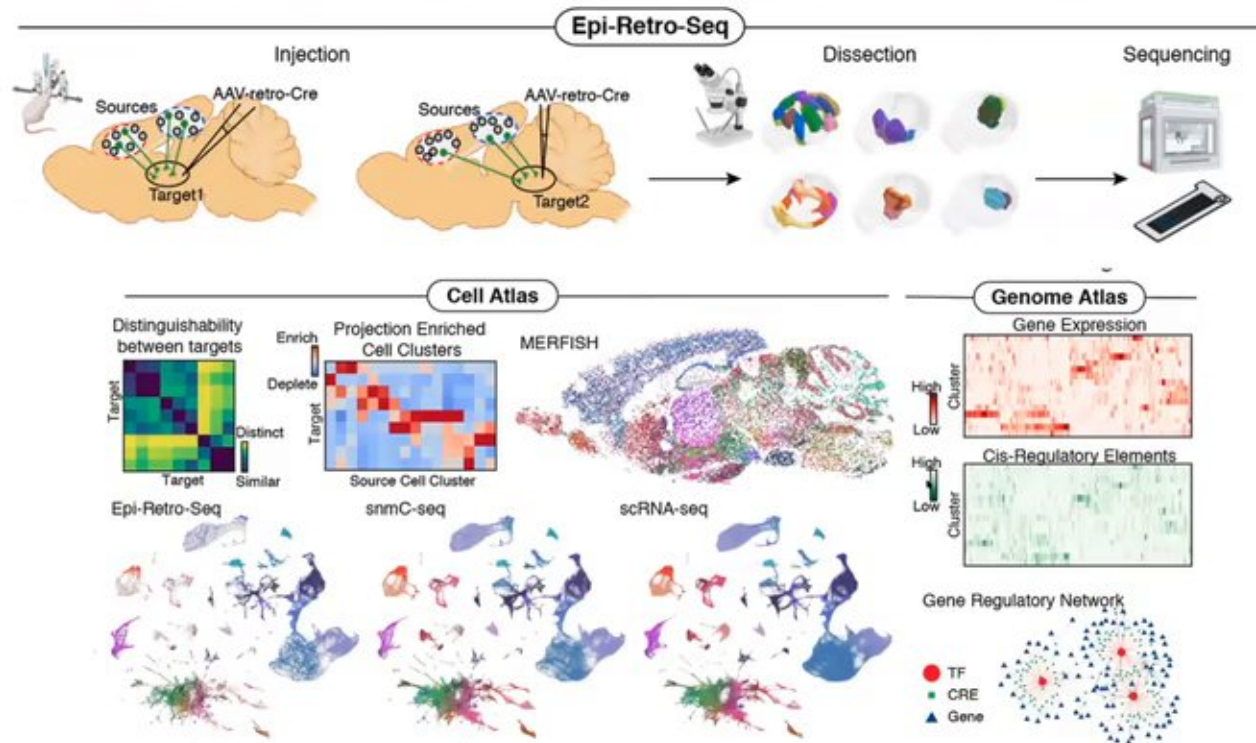
Brain cell type-specific gene regulatory networks



Epi-Retro-seq identifies neuron projection specific candidate cis-regulator elements



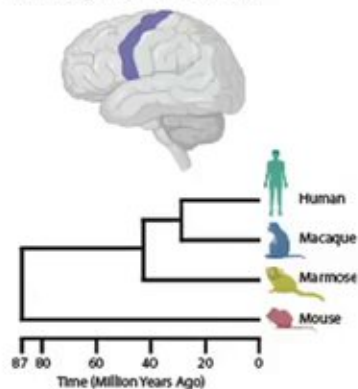
Epi-Retro-seq identifies neuron projection specific candidate cis-regulator elements



Cross-species evolutionary comparison of regulatory elements using single-cell multiomics

- Zemke, Armand et al. Nature 2023

Primary Motor Cortex



A naturalist goes to bat for
Mendel's legacy

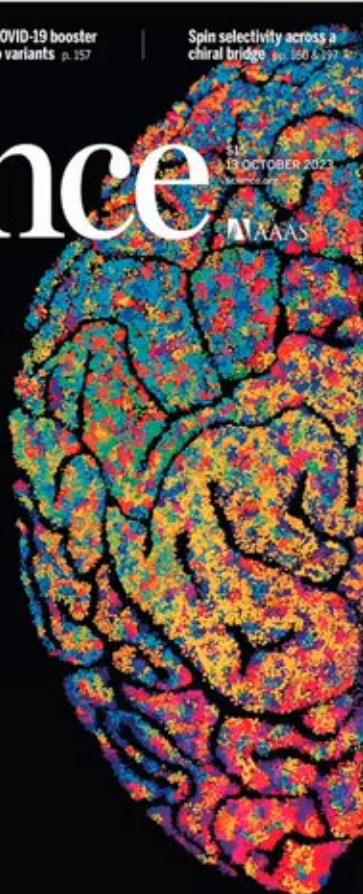
Adapting COVID-19 booster
vaccines to variants

Spin selectivity across a
chiral bridge

Science

SPECIAL ISSUE

BRAIN CELL CENSUS



Cell clustering

1.1 million cells
42 sub-classes
107 cell types

UMAP 2
UMAP 1

Interpret risk variants

---ACT G CGT---
---ACT C CGT---

DL models



Associations with neuropsychiatric disorders

LD score regression

19 GWAS traits and disorders



Characterization of 544k cCREs

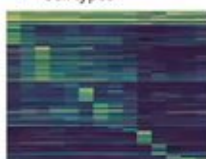
Novel cCREs



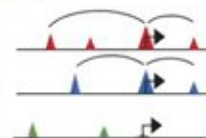
ENCODE known

Cell types

cCRE modules



Predict putative target genes

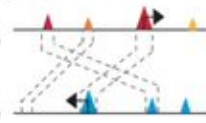


114k enhancers
13k target genes

Cross-species conservation

Human genome

Mouse genome



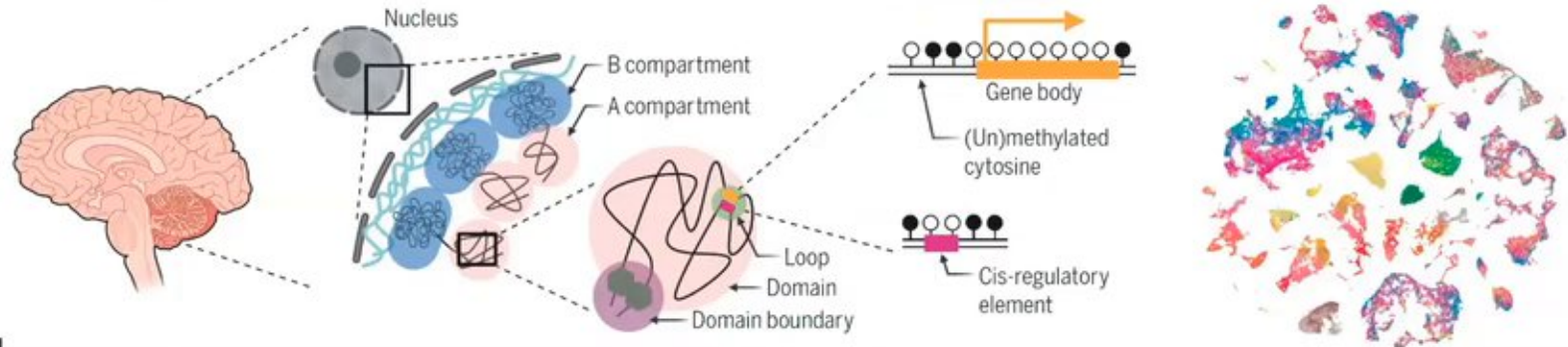
~ 1/3 of cCREs show conservation and accessibility in mouse

DNA methylation and chromatin conformation profiling in the human brain

3 brains, 46 regions

Single-cell DNA methylation and chromatin conformation profiling

Brain cell type identification



HiC

mCH

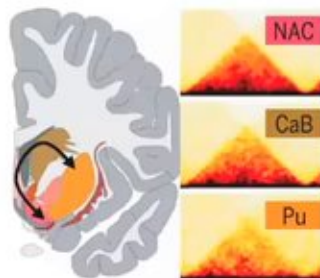
mCG

CRE

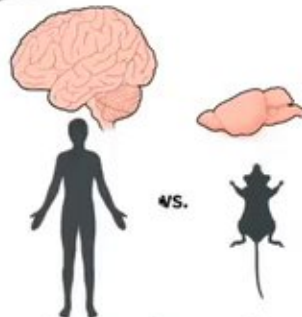
Gene

Loop

Cell type specific methylation and chromatin conformation



Regional heterogeneity

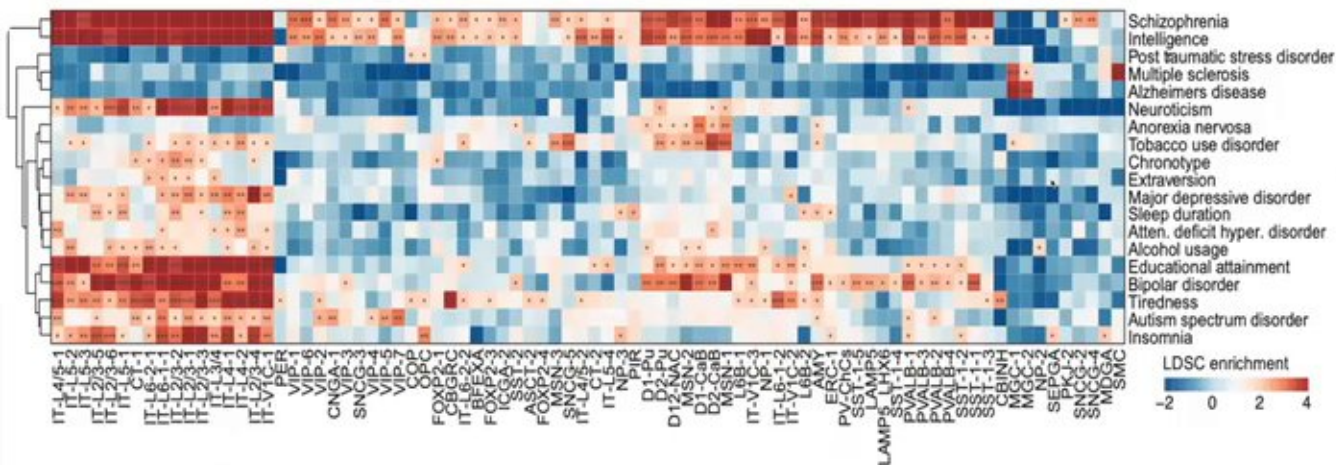


Cross-species comparison



Cell type barcodes

Brain eCRE atlas links neurological diseases to neuronal or glial cell types



Develop Deep-learning models to predict the influence of risk variants on gene regulation



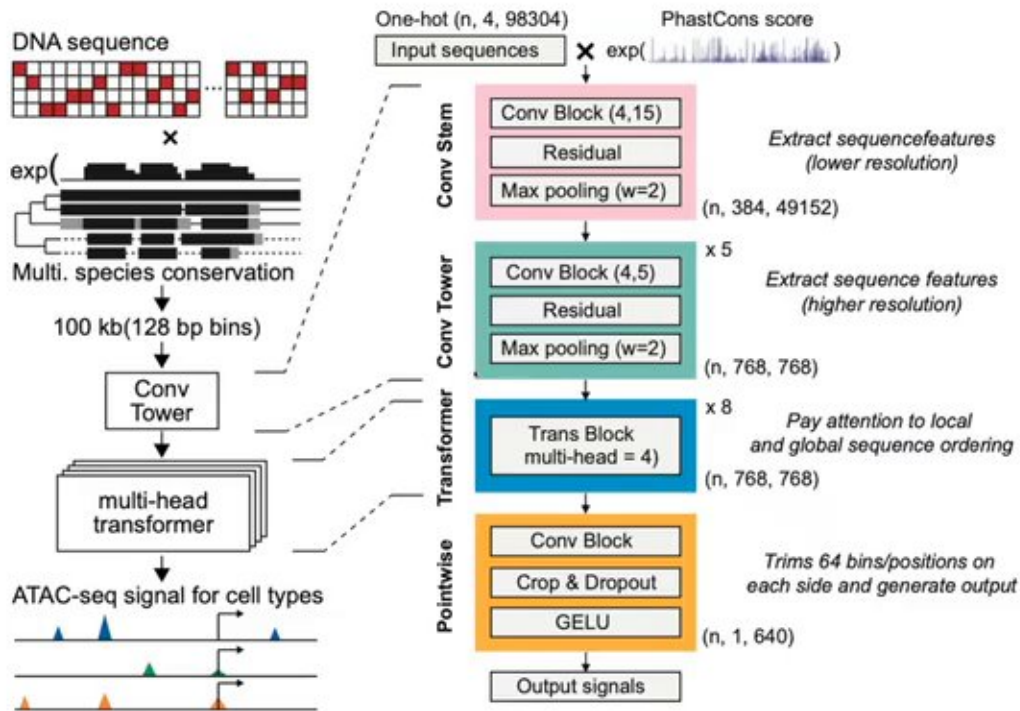
Yang Li, Ph.D.



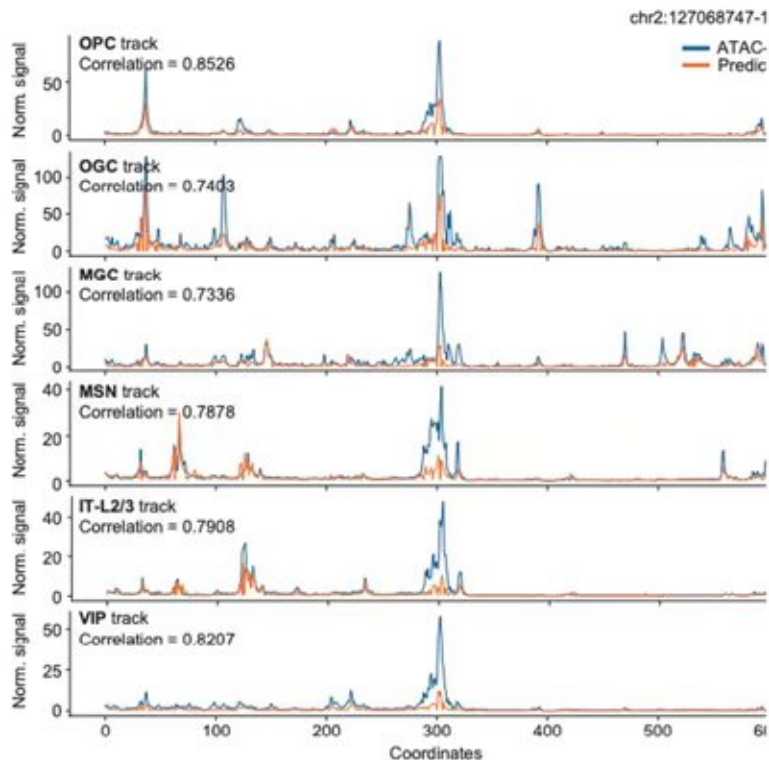
Zihan Wang
(PhD Candidate)



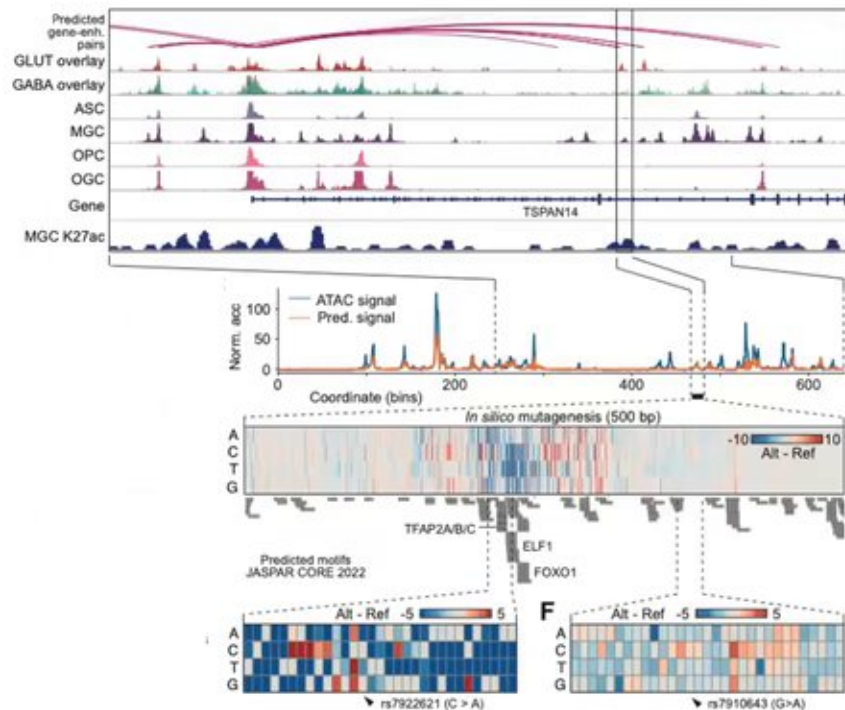
Jingbo Shang, Ph.D.
(UCSD)



Deep-learning model accurately predicts open chromatin in different brain cell types

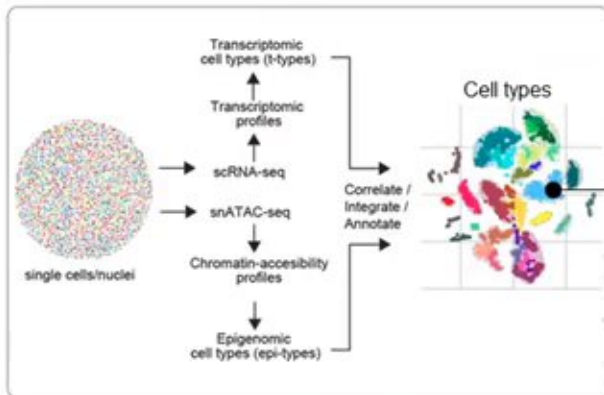


Deep-learning model predicts the effects of two non-coding AD risk variants

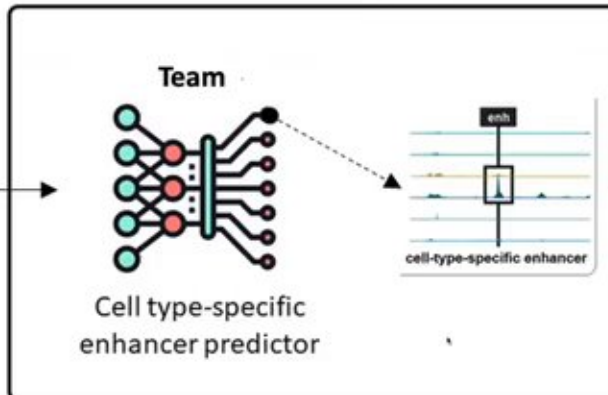


BICCN enhancer challenge: Predicting cell type-specific enhancers from epigenome

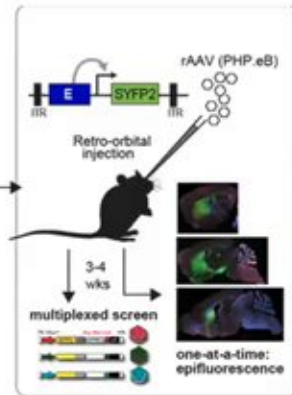
Multi-omic and multi-species single cell transcriptomics



BICCN Challenge: Machine learning models



Cell type-specific enhancer validation



Zemke et al. 2023, Li et al. 2023



Nelson Johansen



Bosiljka Tasic



Trygve Bakken



Ed Lein



Bing Ren



Joe Ecker

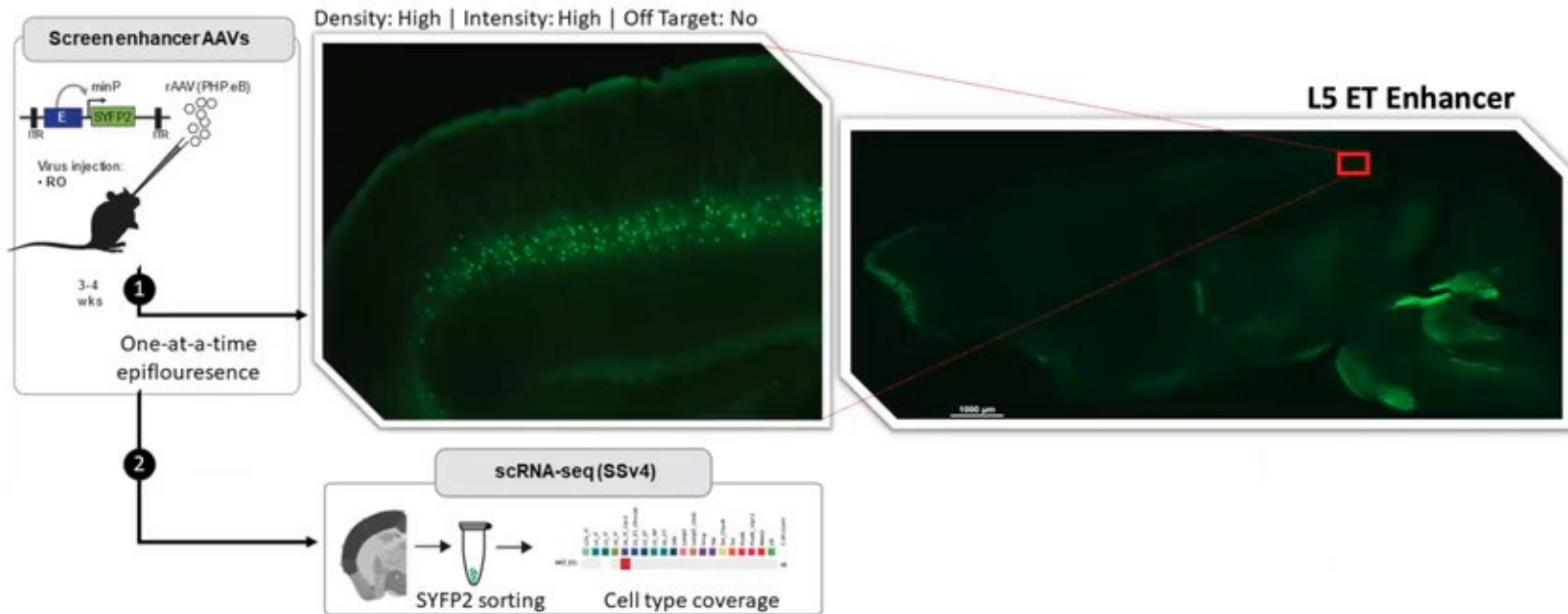


BICCN

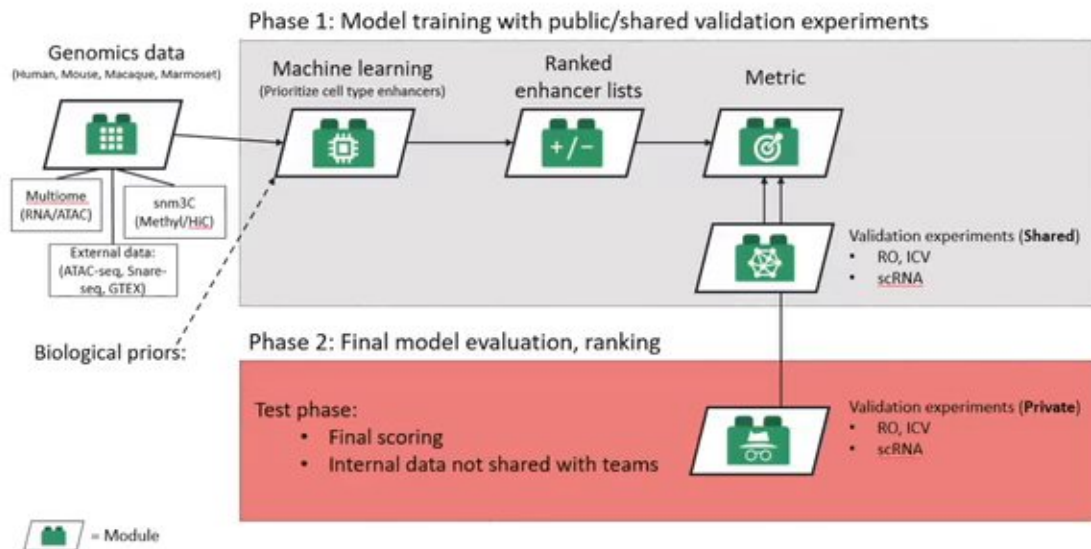


ALLEN
INSTITUTE

Screening enhancers enables validation of cell type targeting brain-wide



Challenge participants use machine learning to rank cell type-specific enhancers in M1



Leaderboard (12/11/2023)

Team	Score	Rank
Aerts_Lab (S_10_S_SP)	247.3445	1
Saroja_Lab	248.1175	2
Tanaka_Lab	256.75055	3
Zhang_lab (cselect)	291.9752	4
Gillis_Lab (lohia_r4)	304.8978	5
Greenleaf_Lab	307.7887	6

Leaderboard (11/20/23)

Team	Score	Rank
Saroja_Lab	248.1175	1
Aerts_Lab (aertslab_rank_seqlets_scplus)	254.78095	2
Zhang_lab	296.01155	3
Greenleaf_Lab	307.7887	4
Tanaka_Lab	309.3647	5
Gillis_Lab (lohia_final_highintense75)	309.8393	6

Challenge participants utilized diverse approaches providing insights into effective enhancer prediction

Team	Score	Rank
Stein Aert's lab	247.3445	1
PeakRankeR (AIBS)	248.1175	2
Tanaka lab	256.75055	3
Zhang lab	291.9752	4
Jesse Gillis lab	304.8978	5
ArchR	307.7887	6

Sequence deep learning models: DNA seq. predicts ATAC-seq.
Priors:

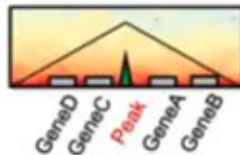
- Function enhancers contain motif diversity
- Motif-ATAC-RNA regulatory network inference

Meta-analysis: Multiple **models** and **species** used to inform on cell type-specificity of enhancer.

Characteristics of enhancer accessibility (no-ML):

- Specificity of ATAC-seq signal
- Magnitude of ATAC-seq signal
- Proximity of enhancer to known marker genes.

Prioritize enhancers with cell type-specific genes in Hi-C loop



Focus on orthologous genes



Differential expression,
chromatin, and methylation



LIRover
BEDtool
Biomart

Summary

Strategies for gene regulatory code analysis in the brain cell types

Mapping of cell-type specific regulatory programs in the mouse brain

Mapping of cell-type specific regulatory programs in the human brain

Enhancer challenge: predicting cell-type-specific enhancers from epigenome maps

THANK YOU

Human Cell Types
IVSCC
Tissue Procurement
& Processing
Histology
Imaging
FACS
Molecular Biology
Genomics
Bioinformatics
Program

management
Legal
OSR
Research Funding
Many external
collaborators



Ren Lab, UCSD

Yang Li (WashU)
Songpeng Zu
Kangli Wang
Ehtan Armand
Sainath Mamde
Lei Chang
Yang Xie
Zhaoning Wang
Bin Li
Rongxin Fang (Harvard)
Chenxu Zhu (NYGC)
Kai Zhang (Westlake)
Samantha Kuan
Maria Luisa Amaral
Yuelai Wang
Andre Chu
Jie Xu
Seoyeon Lee

Mukamel Lab, UCSD

Fangming Xie
Ethan Armand

Jinbo Shang Lab, UCSD

Zihan Wang

UCSD Center for Epigenomics

Sebastian Preissl
(Freiburg)
Nathan Zemke
Allen Wang
David Gorkin (Emory)
Quan Zhu
Justin Buchanan
Michael Miller
Xiaomeng Hou
Olivier Poirion, Ph.D.
Sarah Espinoza
Lin Lin
Qian Yang
Keyi Dong
Hannah Indralingam

Ecker Lab, Salk

Hanqing Liu
Jingtian Zhou
Zhuzhu Zhang
Qiurui Zeng
May Wu
Yan Pang
Bang-an Wang
Wei Tian
Wubin Ding
Anna Bartlett
Cesar Barragan
Peter Berube
Rosa Castanon
Joe Nery
Jordan Altshul
Mia Kenworthy
Huaming Chen
Wenliang Wang
Angeline Rivkin
Andrew Aldridge
Chongyuan Lu (UCLA)
Michael Nunn

Callaway Lab, Salk

Minh Vu
Paula Miyazaki
Alexis Franklin
Elora Williams
Cheng Ta Lee
Angelo Salinda
Will Nunez Lagos
Naomi Claffey

Behrens Lab, Salk

Jacinta Lucero
Julia Osteen
Nora Emerson
Nicholas D. Johnson
Antonio Pinto-Duarte
Jonathan A. Rink

Sten Linnarsson Lab, Kirolinska

Kimberly Siletti

Ting Wang I Lab, WashU

Daofeng Li
Xiaoyu Zhuo
Vincent Xu

Allen Institute

Hongkui Zeng
Ed Lein
Zhizhen Yao
Trygve Bakken
Boaz Levi
Bosiljka Tasic
Jonathan Ting
Rebecca D. Hodge
Daniel Hirschstein
Nadiya Shapovalova
Tamara Casper
Anna Marie Yanny
Julie Nyhus
Nick Dee
Kimberly A. Smith
Naz Taskin

Dirk Keene Lab, UW

Steven McCarroll Lab

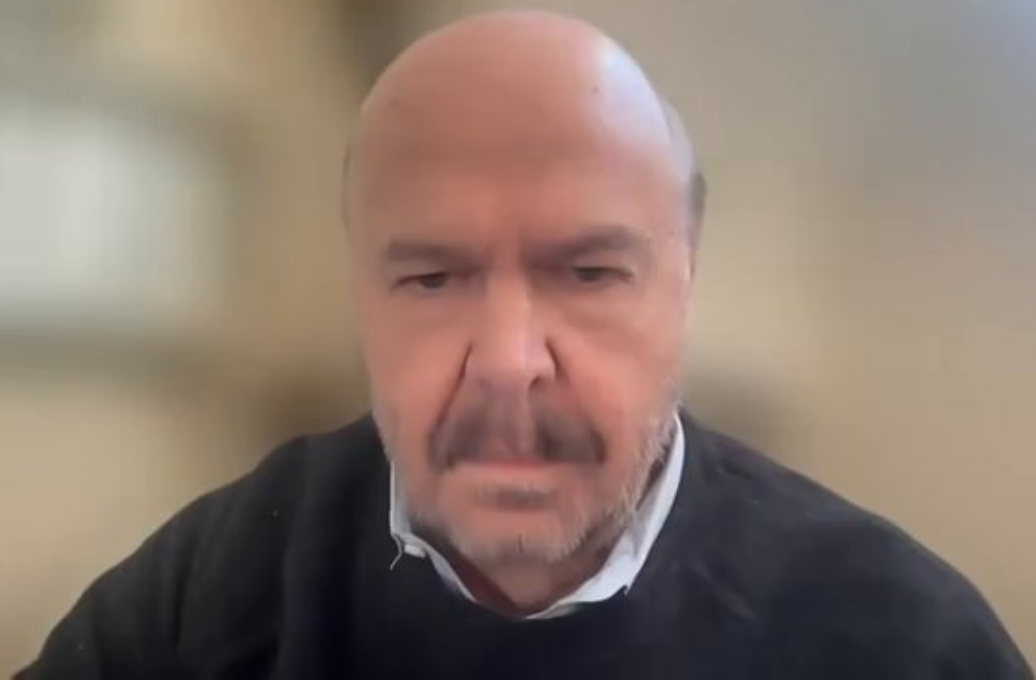
Fenna M. Krienen

Guoping Feng Lab

Qiangge Zhang



National Institute
of Mental Health



Panel 1: Brain Cell Atlases for Neuroscience Research

- **Moderators:** Fenna Krienen – Princeton Neuroscience Institute
Bosiljka Tasic – Allen Institute
- **Panelists:** Anton Arkhipov, Margarita Behrens, Jeremiah Cohen, Joseph Ecker, Guoping Feng, Rusty Gage, Ronna Hertzano, Josh Huang, Arnold Kriegstein, Kuo-Fen Lee, Chongyuan Luo, Tomasz Nowakowski, Bing Ren, Nenad Sestan, Douglas Shepherd, Michael A. Skinnider, Marta Sodan, Scott Sternson, Wenjin Jim Zheng, Larry Zipursky, Yimin Zou
- **Notetakers:** Rebecca Hodge, Alex Pollen, Daifeng Wang



National Institutes of Health
The BRAIN Initiative



Session 3 Panel 1: Brain Cell Atlases for Neuroscience Research

Day 3, January 18, 2024

Keynote Presentation: Decoding the regulatory code of brain cell diversity (Joe Ecker, *Salk*, Bing Ren, *UCSD*, and Nelson Johansen, *Allen Institute*)

Short Presentations

1. Michael Skinnider – Computational approaches to comparative brain cell atlases
2. Ronna Hertzano – NeMO Analytics – data visualization for health and disease
3. Bosiljka Tasic – Standards/metadata from BRAIN Armamentarium
4. Fenna Krienen – Enhancer-AAVs in primates
5. Jeremiah Cohen – Cell-type-specific structure-function links in the brain
6. Scott Sternson – CaRNA imaging platform
7. Marta Soden - Optogenetics and transcriptomics to map input-specific neuronal activation patterns

Panel Discussion: Anton Arkhipov, Marga Behrens, Jeremiah Cohen, Joe Ecker, Guoping Feng, Fred Gage, Ronna Hertzano, Josh Huang, Arnold Kriegstein, Kuo-Fen Lee, Chongyuan Luo, Tom Nowakowski, Bing Ren, Nenad Sestan, Douglas Shepherd, Mike Skinnider, Marta Soden, Scott Sternson, Wenjin Zheng, Larry Zipursky, Yimin Zou

Notetakers: Mike Hawrylycz, Rebecca Hodge, Alex Pollen, Daifeng Wang

Moderators: Bosiljka Tasic, Fenna Krienen



Computational approaches to comparative brain cell atlases

Jan 18, 2023 / Michael Skinnider



Context

The advent of comparative brain cell atlases

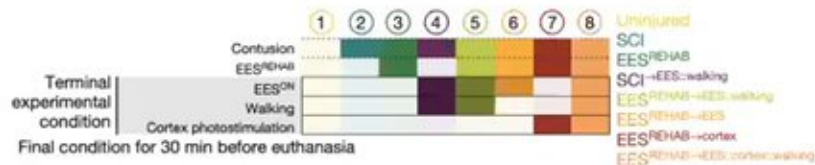
- Increases in the throughput of sc/snRNA-seq, scATAC-seq, and spatial transcriptomics are now enabling **comparative brain cell atlases**

Context

The advent of comparative brain cell atlases

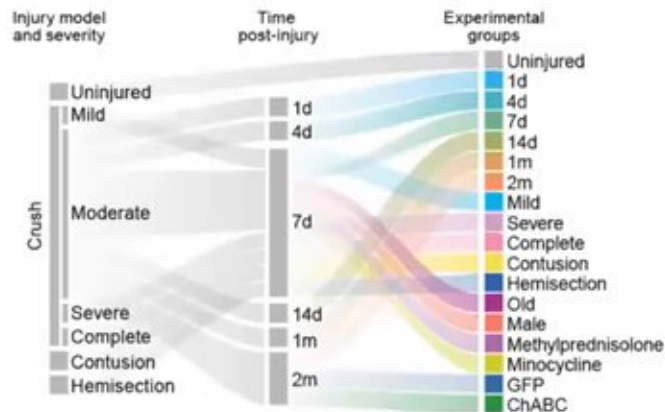
- ▶ e.g., in spinal cord injury

Lumbar spinal cord after neurostimulation
(snRNA-seq from **eight experimental conditions**)



Kathe*, Skinnider*, Hutson* et al., *Nature* 2022

Lesion site across timepoints, severities, models and treatments
(snRNA-seq from **18 experimental conditions**)



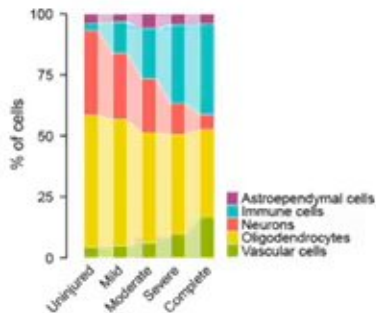
Skinnider*, Gautier* et al., *bioRxiv* 2023

Context

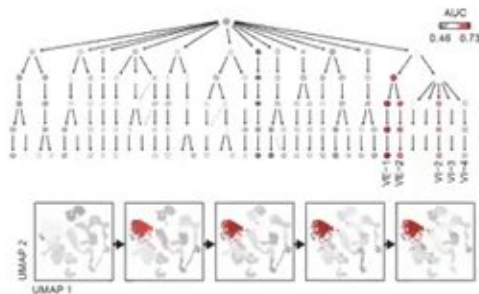
New biological questions require new computational tools

- Comparative atlases present new biological questions compared to single-condition atlases:

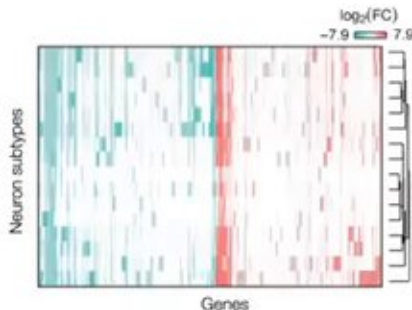
Do cell type proportions change with a given perturbation?



What cell types are most strongly affected by a given perturbation?



What genes are differentially expressed within and across cell types?

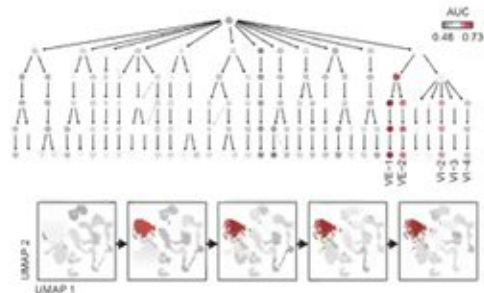


Augur

Identification of perturbation-responsive cell types

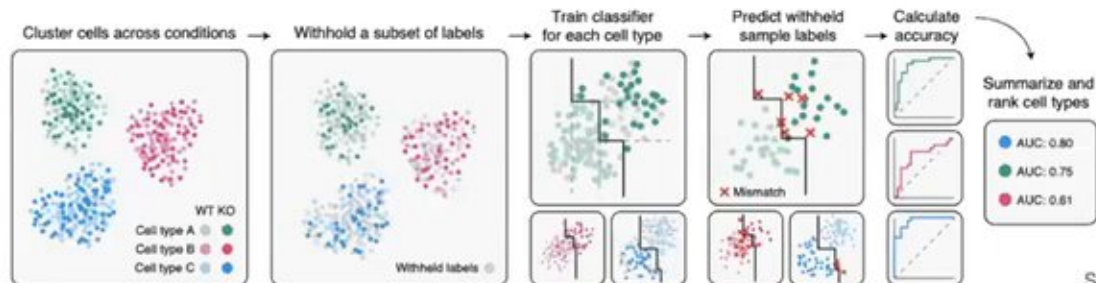
- Can we identify **subtypes of neurons that undergo a transcriptional response to stimulus?**

What cell types are most affected by a given perturbation?

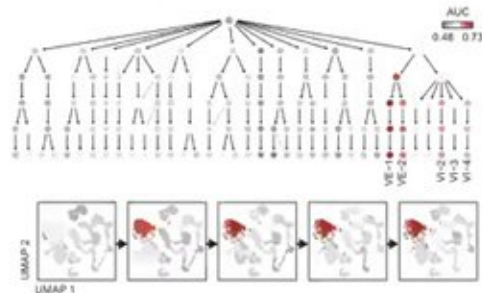


Identification of perturbation-responsive cell types

- Can we identify **subtypes of neurons that undergo a transcriptional response to stimulus?**
- Supervised classification approach: predict experimental condition from gene expression in cross-validation
 - Easy** when neurons of the same subtype are transcriptionally distinct across two conditions; **hard** when neurons are transcriptionally similar/identical



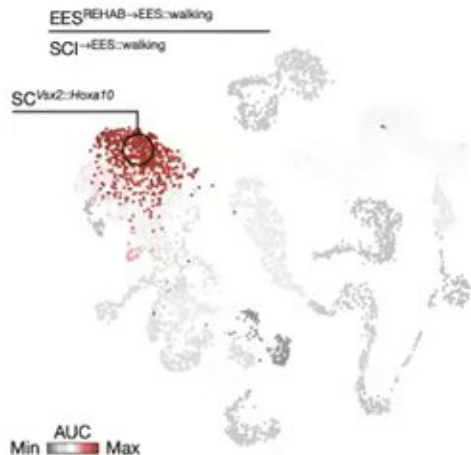
What cell types are most affected by a given perturbation?



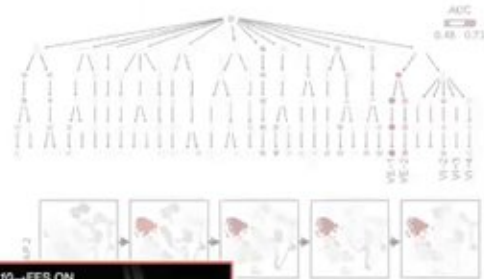
Augur

Identification of perturbation-responsive cell types

- Augur identified a neuron subtype that enables the recovery of walking after paralysis



What cell types are most affected by a given perturbation?

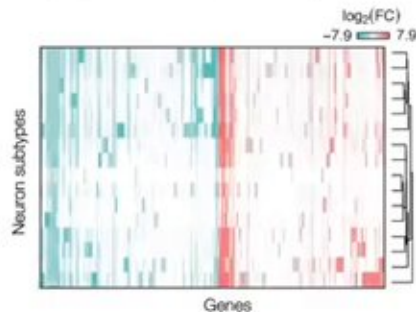


Libra

Differential expression for multi-sample single-cell data

- What **transcriptional programs** enable neuron subtype-specific contributions to neurological recovery?

What genes are differentially expressed within and across cell types?

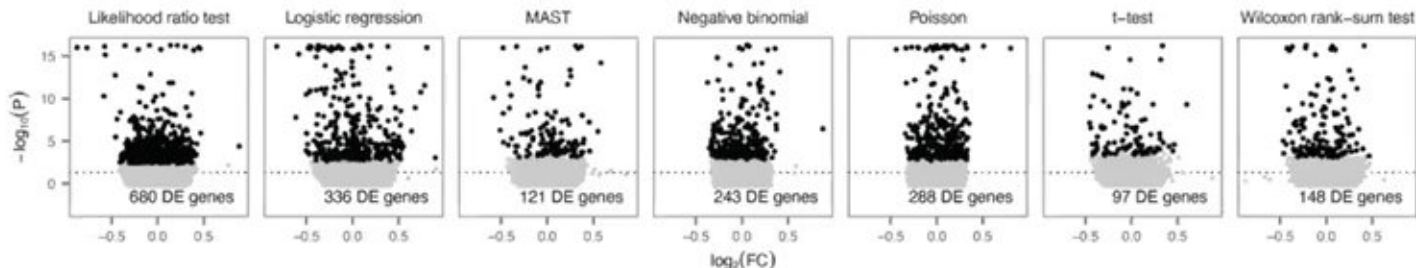
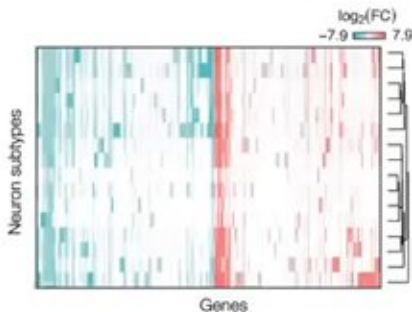


Libra

Differential expression for multi-sample single-cell data

- Widely used single-cell DE methods, e.g., Wilcoxon rank-sum test, produce **hundreds of false discoveries**

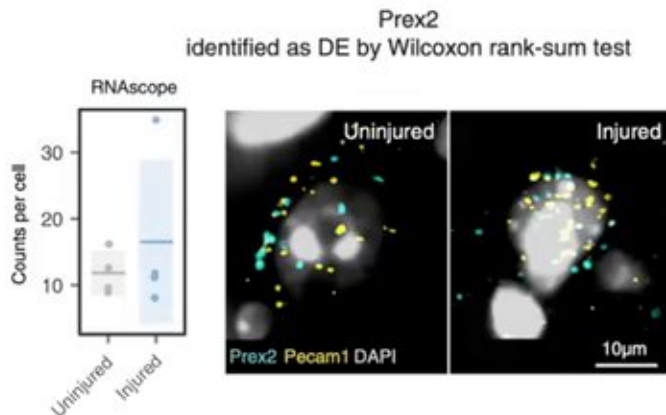
What genes are differentially expressed within and across cell types?



Libra

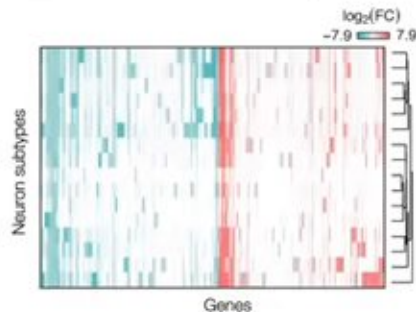
Differential expression for multi-sample single-cell data

- Confirmed through simulations, reanalysis of published datasets, prospective RNAScope



- Corrected by 'pseudobulk' methods, mixed models

What genes are differentially expressed within and across cell types?



Conclusions

- ▶ Comparative brain cell atlases present new biological questions
- ▶ Comparative brain cell atlases can contribute to neural circuit mapping
- ▶ Appropriate computational methods can decode shared and cell-type-specific perturbation responses

Thanks:



Grégoire Courtine



Claudia Kathe



Jordan Squair

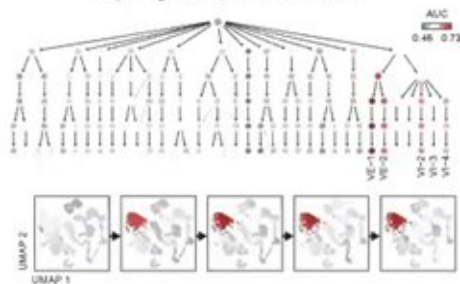


Mark Anderson



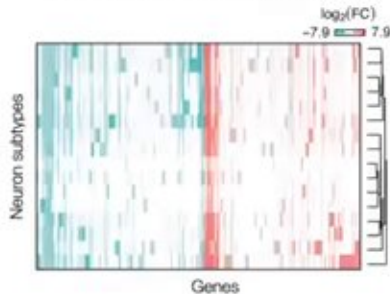
Matthieu Gautier

What cell types are most affected by a given perturbation?



Augur (github.com/neurorestore/Augur)

What genes are differentially expressed within and across cell types?



Libra (github.com/neurorestore/Libra)



Adobe Acrobat - NeMO Analytics Health & Disease single self meeting set 1 - Last Modified: Wednesday at 4:17 PM -

File Home Insert Design Transitions Animations Slide Show Record Review View Help Acrobat

Find Replace Select Create PDF and Share Link Create PDF and Share via Outlook Create PDF and Share via Outlook Delete Designer

Clipboard Styles

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NeMO

NeMO

Analytics

Data visualization for health and disease

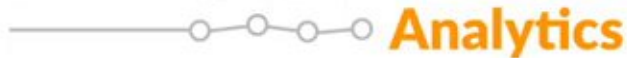
Nemoanalytics.org

Ronna Hertzano, MD PhD
Chief, Neurotology Branch
Chief, Section on Omics and Translational Science of Hearing
National Institutes on Deafness and Other Communication Disorders
National Institutes of Health

Click to add notes

Slide 1 of 10 Accessibility: Protected

NeMO



Data visualization for health and disease

Nemoanalytics.org

Ronna Hertzano, MD PhD

Chief, Neurotology Branch

Chief, Section on Omics and Translational Science of Hearing

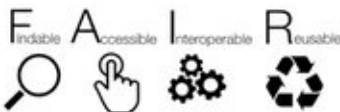
National Institutes on Deafness and Other Communication Disorders

National Institutes of Health

Goal: Increase the reuse and accessibility of multi-omic data and maximize the utility of hard-to-acquire datasets



Current NeMO Analytics datasets: 1,082



Human Genetics (2022) 141:319–322
https://doi.org/10.1007/s00439-022-02445-w

PERSPECTIVE

Advancing discovery in hearing research via biologist-friendly access to multi-omic data

gEAR: Gene Expression Analysis Resource portal for community-driven, multi-omic data exploration

To the Editor — Biologists are important stakeholders in genomic data, both as data generators and as users of genomic data resources. Tools to efficiently visualize and analyze multi-omic data are increasingly important to ensure accessibility and usability of genomic data for all biologists. We developed the gEAR portal (<https://www.gearportal.org>) to enable these functionalities (Fig. 1). The development of visualization tools for multi-omic biological data has not kept pace with the generation of transcriptomic and epigenomic data. Researchers allow users to deposit large datasets, but do little in the way of analysis. Therefore, the user must download the raw data and perform analyses locally, which is both time-consuming and out of the reach

of many biologists. While some web-based resources are now available to facilitate multi-omic data analysis, these resources are typically designed for specific domains, do not enable viewing data spatially overlaid onto a broad set of anatomical structures, and do not allow interrogation of multiple datasets at one time.

The gEAR portal provides a single platform for data deposition, display, analysis and interrogation, with a focus on allowing users to contextualize the site and their own data displays. The gEAR portal supports uploaded datasets for a range of organisms, including human, mouse, rat, zebrafish, chicken and macaw. Multiple datasets can be displayed side-by-side within a display profile, showing not only a

user's own data in a visual form of choice, but also allowing the user to select from hundreds of previously uploaded public datasets to display alongside their own for cross-experimental validation and discovery. Integration of the gEAR tool allows epigenetic modifications to be viewed in the context of gene expression. The portal is also designed to display a gene's species-specific annotation and links out to information on other systems such as the UCSC Genome Browser, CLDN, Ensembl, GENCODE and a variety of domain-specific resources. Further features available via drop-down menus include links to the raw data in the Gene Expression Omnibus (GEO), the associated publications, a tool to compare gene expression across conditions, a tool to

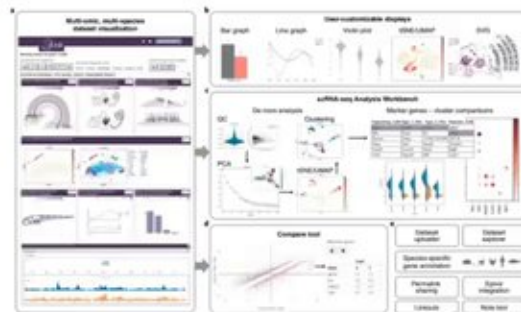
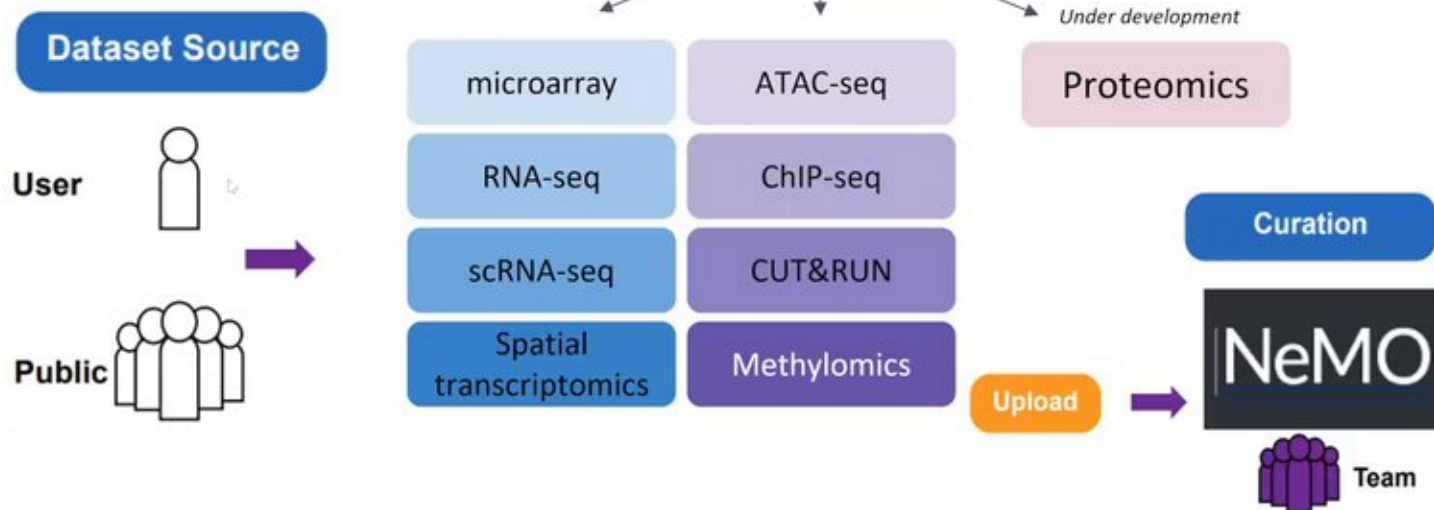


Fig. 1 **gEAR overview.** **a** gEAR result page example. **b** Users can select from a variety of custom displays. **c** The gEAR new Analysis Workflow offers de novo analysis of a dataset, or, for datasets uploaded with expression metadata, analysis can start from marker gene identification and cluster comparison. **d** The Compare tool identifies differentially expressed genes to generate gene cards. **e** Additional features.

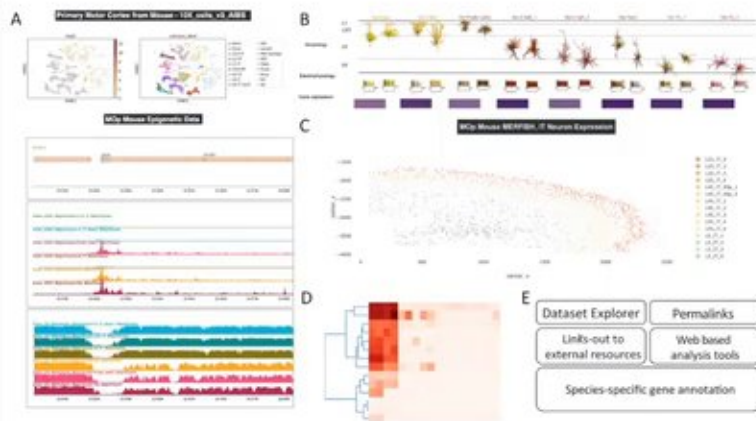
NATURE METHODS | VOL. 19 | AUGUST 2022 | 842–846 | www.nature.com/naturemethods

NeMO Analytics

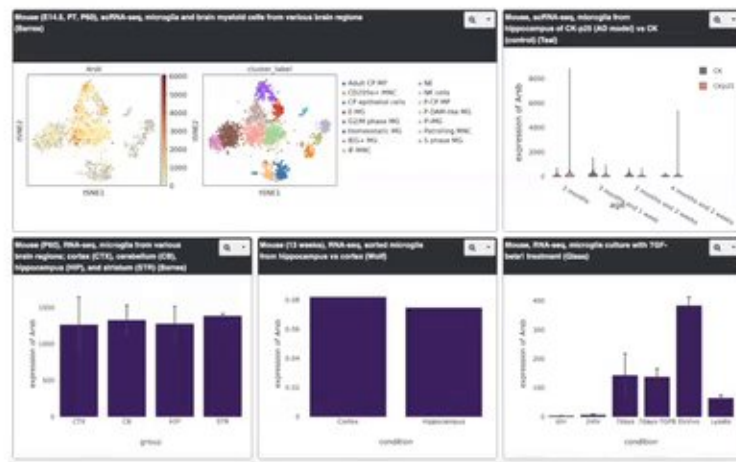
'One-Stop-Shop' to access & analyze multi-omic data



Dataset highlights: BICCN motor cortex



Dataset highlights: Alzheimer's disease



DOI: 10.1002/wt.015486

BASIC SCIENCE AND PATHOGENESIS

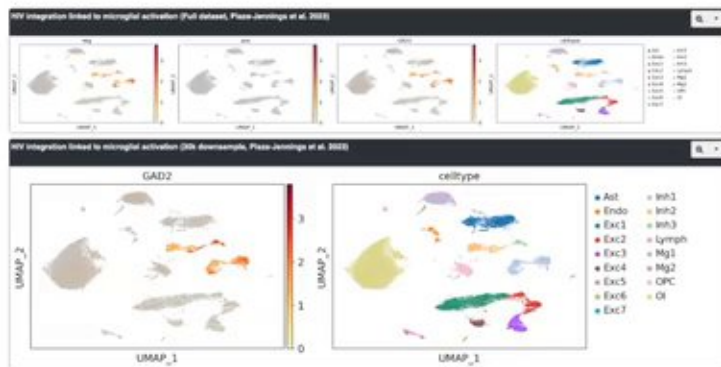
POSTER PRESENTATION

Alzheimer's & Dementia
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

NeMO-AD, a new neuroscience multi-omic visualization and analysis platform for Alzheimer's disease research

Dataset highlights: SCORCH consortium

Single Cell Opioid Responses in the Context of HIV



Molecular Cell

Article

HIV integration in the human brain is linked to microglial activation and 3D genome remodeling

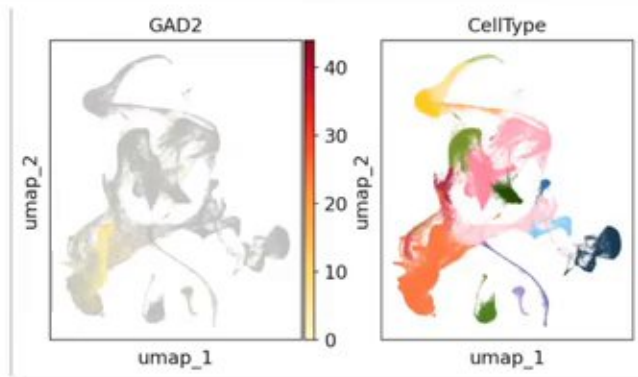
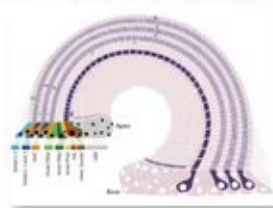
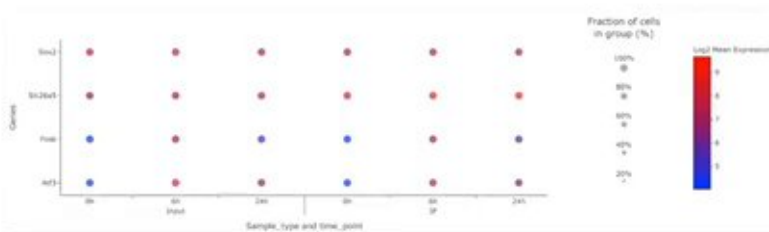
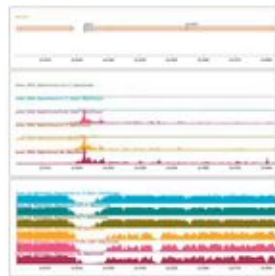
SCORCH

Dataset highlights:

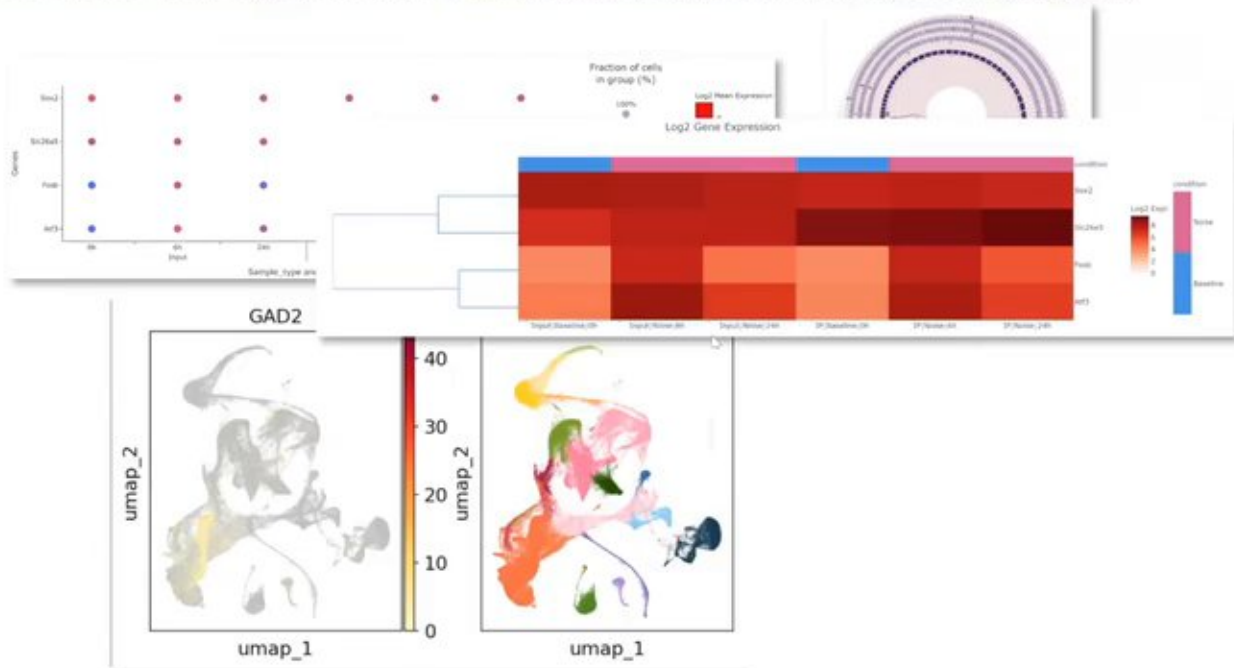
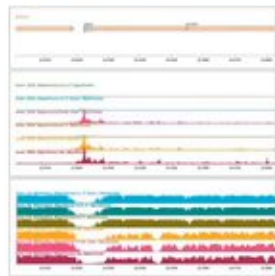
Your own data & any other dataset/s in NeMO Analytics

- Any dataset on the site can be *displayed side-by-side*
- Upload of data is free (and can remain private)
- Interactive link-outs from manuscripts/figures
- Customizable displays, ability to import, save, and export gene collections and more...

Dataset Curation (single, multiple gene displays, epigenetic tracks, vector graphics)



Dataset Curation (single, multiple gene displays, epigenetic tracks, vector graphics)



Analysis tools

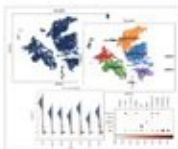


Tools and utilities:



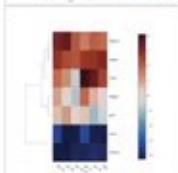
Comparison tool

Compare expression between two groups within a dataset



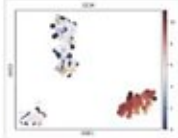
Single-cell workbench

Annotate cells, find clusters, and other visualizations (Replicates Scanpy pipeline in a GUI), analyze your own data or reanalyze an existing dataset



Create multigene displays

Create multigene displays including: heatmaps, volcano plots, quadrat plots etc.

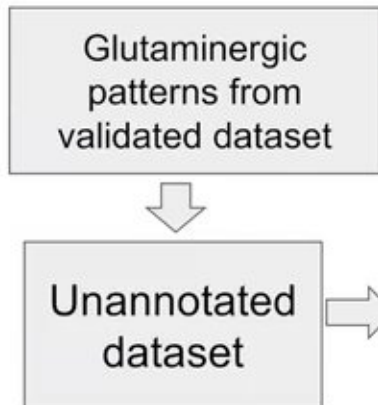
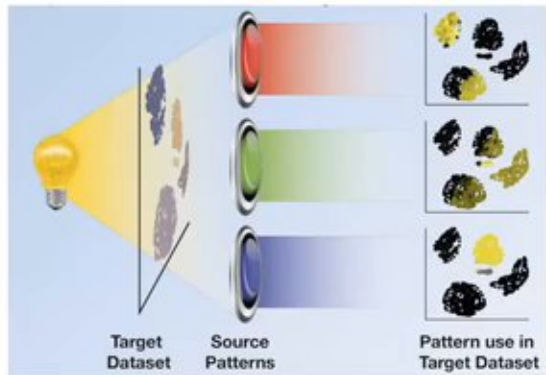


Transfer learning of datasets

Apply patterns or features learned from one dataset to another

NEW: ProjectR & Transfer learning

Infer cell types and patterns between datasets using a point and click interface



Select Pattern Source

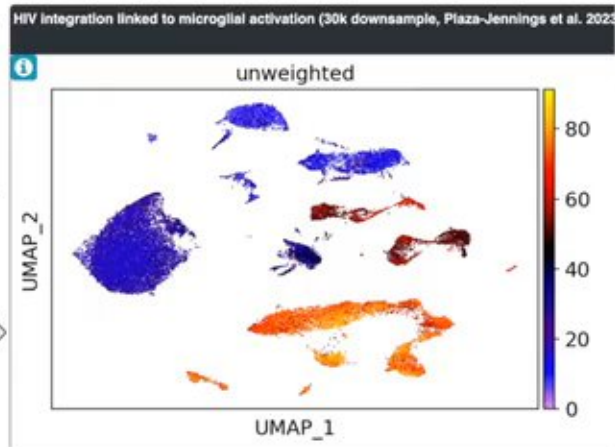
MetaMarkers_GlutamatergicTop10...

Select Algorithm

- ☒ Principal Component Analysis (PCA)
- ☐ Non-Negative Matrix factorization (NMF)
- ☐ Binary Gene Count

Select Display Mode

- ☒ Single-pattern display



The gEAR/NeMO Analytics Team



Joshua Orvis
Lead Engineer
Institute for Genome Sciences



Ronna Hertzano
MD PhD



Anup Mahurkar

Yang Song, PhD - informatics support, help desk, data upload

Daniel Lesperance – data curation and upload, help desk

Joe Receveur, PhD – outreach, user testing, data curation and upload

Ricky Shaun Adkins - user interface and analysis tools

Kevin Rose - user manual and more

Beatrice Milon, PhD – curation, user testing

Seth Ament, PhD - Informatics consultant

Carlo Colantuoni, PhD - Informatics consultant

Brian Herb, PhD - Informatics consultant

Hector Corrada-Bravo, PhD - Epiviz

Jayaram Kancherla - Epiviz













BRAIN Armamentarium Consortium Metadata schema

BICAN Workshop: Brain Cell Atlases for Neuroscience Research
January 18, 2024

Bosiljka Tasic, Ph.D.
Director, Molecular Genetics

Cell Type Definition (BICCN, BICAN) → Experimental Cell Type Access (**Armamentarium**)

Cell Type Definition (BICCN, BICAN) → Experimental Cell Type Access (Armamentarium)



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Tools and Technologies for Brain Cells and Circuits ▾

BRAIN Initiative Cell Census Network

BRAIN Initiative Cell Atlas Network

Armamentarium for Precision Brain Cell Access

BRAIN Initiative Connectivity Across Scales

Armamentarium for Precision Brain Cell Access

The Armamentarium for Precision Brain Cell Access is developing a collection of molecular genetic reagents to gain access to many different brain cell types. The expanded collection of Armamentarium tools will aid neuroscientists in studying circuits in laboratory animals and human tissue specimens. These technologies have the potential to transform neuroscience research by bringing the precision of molecular targeting to specific neural circuits that underlie behavior and network function.

With these reagents, molecular genetic probes can be addressed to specific cell types not only to map circuits but also to monitor and manipulate neural activity. The precise and reproducible access to these circuit components enables the functional relevance of cell types in behavior to be explored in detail. The cause-and-effect relationships of cell types defined by recent brain cell census efforts and behavior can be delineated using targeted probes. Electrode- and neuroimaging-based technologies have greatly informed the understanding of the brain. Cell type-specific targeted probes from the Armamentarium hold promise to drive

Program Officer

Douglas S. Kim, Ph.D.

National Institute of Mental Health (NIMH)

douglas.kim@nih.gov



Inspired by yesterday's sessions:

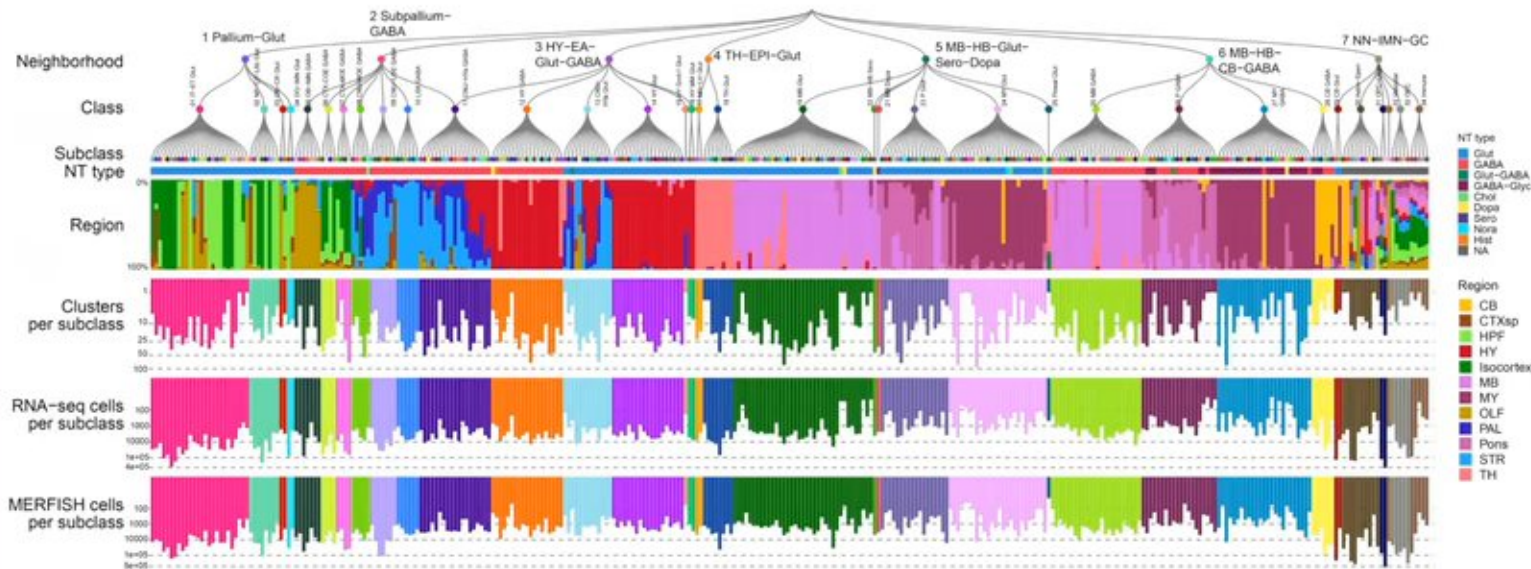
RESEARCHER + *Curator* (human vs. AI) →

COMMON METADATA + **DATA** (minimal vs. maximal; AI-friendly) →

FEATURES →

KNOWLEDGE

A High-resolution Cell Type Atlas of the Whole Mouse Brain



A taxonomy of **5,322** clusters, 1,201 supertypes, 338 subclasses, 34 classes (7 neighborhoods)

Neuronal: 5,205 clusters, 315 subclasses

Non-neuronal: 117 clusters, 23 subclasses

~7 million 10x cells profiled
~4 million passing stringent QC

Inspired by yesterday's sessions:

RESEARCHER + *Curator* (human vs. AI) →

COMMON METADATA + **DATA** (minimal vs. maximal; AI-friendly) →

FEATURES →

KNOWLEDGE

1_molecule ▾

2_delivery_vehicle ▾

3_subject ▾

4_procedure ▾

molecule type level 1	molecule type level 2	categories	consortium essential (Y/N)	consortium nice to have (Y/N)	single value (Y/N)	field type	unit	description
		information of interest for this molecule type	is this field required?	is this field not required, but important to have if available?	is this field restricted to one value?	expected entry type in this field	unit of measurement for this category	
DNA	enhancer	id	Y	NA	Y	free text	NA	unique identifier for this enhancer
		target_ROI_celltype	N	Y	N	controlled vocabulary	NA	brain or other organ region of interest and cell population the enhancer was designed to target (copy from Tables 12)
		originating_organization	Y	NA	N	controlled vocabulary	NA	organization where enhancer was discovered; one name per institution
		department_or_lab	Y	NA	N	controlled vocabulary	NA	department or lab where virus was created; one name per lab, can be the same as the PI
		principal_investigator	Y	NA	N	controlled vocabulary	NA	PI of the lab where enhancer was discovered; PI name standardized
		creator	Y	NA	N	controlled vocabulary	NA	individual(s) who called the enhancer peak; individual name standardized
		citation	N	Y	N	integer	NA	PMID of publication(s) where the enhancer was described/used
		mid	N	Y	Y	defined format	NA	research resource identifier for this enhancer
		sequence	N	Y	Y	free text	NA	enhancer sequence
		proximal_gene	N	Y	N	free text	NA	genes nearby this enhancer (putative target gene to the best of our knowledge)
		genome_build	N	Y	Y	controlled vocabulary	NA	genome reference build genome that the coordinates refer to
		genome_coordinates	N	Y	Y	defined format	NA	coordinates in the genome for this enhancer
	plasmid	id	Y	NA	Y	free text	NA	unique identifier for this plasmid
		target_ROI_celltype	N	Y	N	controlled vocabulary	NA	brain or other organ region of interest and cell population the plasmid was designed to target (copy from Tables 12)
		originating_organization	Y	NA	N	controlled vocabulary	NA	organization where plasmid was created; one name per institution
		department_or_lab	Y	NA	N	controlled vocabulary	NA	department or lab where virus was created; one name per lab, can be the same as the PI
		principal_investigator	Y	NA	N	controlled vocabulary	NA	PI of the lab where plasmid was created; PI name standardized
		creator	Y	NA	N	controlled vocabulary	NA	individual(s) who cloned/created the plasmid; individual name standardized
		citation	N	Y	N	integer	NA	PMID of publication(s) where the plasmid was described/used
		mid	N	Y	Y	defined format	NA	research resource identifier for this plasmid
		sequence	N	Y	Y	free text	NA	plasmid sequence
		full_name	Y	NA	Y	free text	NA	list of all components in the plasmid
		addgene_id	N	Y	Y	integer	NA	AddGene deposit identification number
	other							

1_molecule ▾

2_delivery_vehicle ▾

3_subject ▾

4_procedure ▾

molecule type level 1	molecule type level 2	categories	consortium essential (Y/N)	consortium nice to have (Y/N)	single value (Y/N)	field type	unit	description	
		Information of interest by this	is this field	is this field not required by a	is this field	is this field	unit of		
		delivery_vehicle type	categories	consortium essential (Y/N)	consortium nice to have (Y/N)	single value (Y/N)	field type	unit	description
DNA	enhancer								
						</			

1_molecule ▾

2_delivery_vehicle ▾

3_subject ▾

4_procedure ▾

molecule type level 1	molecule type level 2	categories	consortium essential (Y/N)	consortium nice to have (Y/N)	single value (Y/N)	field type	unit	description	
		information of interest for this	is this field	is this field not required for	is this field	of structure in this	unit of		
		delivery_vehicle type	categories	consortium essential (Y/N)	consortium nice to have (Y/N)	single value (Y/N)	field type	unit	description
DRNA	enhancer			NA	Y	free text	NA		unique identifier for this virus
	virus	subject type	categories	consortium essential (Y/N)	consortium nice to have (Y/N)	single value (Y/N)	field type	unit	description
		information of interest for this subject type	is this field required?	is this field not required, but important to have if available?	is this field restricted to one value?	expected entry type in this field	unit of measurement for this category		
		mouse	species	Y	NA	Y	controlled vocabulary	NA	species of animal used
			subject_id	Y	NA	Y	free text	NA	unique identifier of animal used
			background strain	Y	NA	N	controlled vocabulary	NA	dominant background strain(s) of animal used
			date of birth	Y	NA	Y	date	NA	date of birth of animal used
			genotype	Y	NA	Y	controlled vocabulary	NA	full genotype of animal used
			light cycle	Y	NA	Y	controlled vocabulary	NA	was animal housed using standard or reverse light cycle?
	plasmid	other	sex	Y	NA	Y	controlled vocabulary	NA	sex of animal used
			external source	N	Y	N	controlled vocabulary	NA	where this animal was procured
			transgene	N	Y	N	controlled vocabulary	NA	transgene(s) of transgenic animal used
			originating organization	Y	NA	N	controlled vocabulary	NA	organization where transgenic line was created; one name per institution
			department or lab	N	Y	N	controlled vocabulary	NA	department or lab where virus was created; one name per lab, can be the same as the PI
			principal investigator	N	Y	N	controlled vocabulary	NA	PI of lab where transgenic line was created; PI name standardized
			creator	N	Y	N	controlled vocabulary	NA	individual(s) who created the transgenic line; individual name standardized
		mid	repository	N	Y	N	controlled vocabulary	NA	repository where animal is available for public use
		sequence	repository_id	N	Y	N	integer	NA	unique identifier at repository for animal used
		addgene_id							
	other	rat	species	Y	NA	Y	controlled vocabulary	NA	species of animal used
			subject_id	Y	NA	Y	free text	NA	unique identifier of animal used
			background strain	Y	NA	N	controlled vocabulary	NA	dominant background strain(s) of animal used
			date of birth	Y	NA	Y	date	NA	date of birth of animal used
			genotype	Y	NA	Y	controlled vocabulary	NA	full genotype of animal used
			light cycle	Y	NA	Y	controlled vocabulary	NA	was animal housed using standard or reverse light cycle?
			sex	Y	NA	Y	controlled vocabulary	NA	sex of animal used
			external source	Y	NA	N	controlled vocabulary	NA	where this animal was procured
			transgene	N	Y	N	controlled vocabulary	NA	transgene(s) of transgenic animal used
			originating organization	Y	NA	N	controlled vocabulary	NA	organization where transgenic line was created; one name per institution
			department or lab	N	Y	N	controlled vocabulary	NA	department or lab where virus was created; one name per lab, can be the same as the PI
			principal investigator	N	Y	N	controlled vocabulary	NA	PI of lab where transgenic line was created; PI name standardized

Table 10: Mouse adult brain regions

Source: Allen Reference Atlas

<http://mouse.brain-map.org/static/atlas>

Select levels and names recommended to ease adoption

43 coarse regions

Table 11: Cell Major Divisions and Classes

Source: Yao et al. (2023) A high-resolution tra

<https://doi.org/10.1101/2023.03.06.531121>

4 divisions + 34 classes

mouse brain. bioRxiv

Description includes dominant neurotransmitter phenotype and location, but may include additional neurotransmitted phenotypes and locations.

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Source: Allen Reference Atlas

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mouse brain. bioRxiv

Table 10: Mouse adult brain regions

Source: Allen Reference Atlas

<http://mouse.brain-map.org/static/atlas>

Select levels and names recommended to ease adoption

Brain Region	Brain Region
ABR	Abducens brain
CA	Cerebrum
CTA	Cerebral cortex
CTG	Cerebral cortex
CTG1	Cerebral cortex
CTG2	Cerebral cortex
CTG3	Cerebral cortex
CTG4	Cerebral cortex
CTG5	Cerebral cortex
CTG6	Cerebral cortex
CTG7	Cerebral cortex
CTG8	Cerebral cortex
CTG9	Cerebral cortex
CTG10	Cerebral cortex
CTG11	Cerebral cortex
CTG12	Cerebral cortex
CTG13	Cerebral cortex
CTG14	Cerebral cortex
CTG15	Cerebral cortex
CTG16	Cerebral cortex
CTG17	Cerebral cortex
CTG18	Cerebral cortex
CTG19	Cerebral cortex
CTG20	Cerebral cortex
CTG21	Cerebral cortex
CTG22	Cerebral cortex
CTG23	Cerebral cortex
CTG24	Cerebral cortex
CTG25	Cerebral cortex
CTG26	Cerebral cortex
CTG27	Cerebral cortex
CTG28	Cerebral cortex
CTG29	Cerebral cortex
CTG30	Cerebral cortex
CTG31	Cerebral cortex
CTG32	Cerebral cortex
CTG33	Cerebral cortex
CTG34	Cerebral cortex
CTG35	Cerebral cortex
CTG36	Cerebral cortex
CTG37	Cerebral cortex
CTG38	Cerebral cortex
CTG39	Cerebral cortex
CTG40	Cerebral cortex
CTG41	Cerebral cortex
CTG42	Cerebral cortex
CTG43	Cerebral cortex
CTG44	Cerebral cortex
CTG45	Cerebral cortex
CTG46	Cerebral cortex
CTG47	Cerebral cortex
CTG48	Cerebral cortex
CTG49	Cerebral cortex
CTG50	Cerebral cortex
CTG51	Cerebral cortex
CTG52	Cerebral cortex
CTG53	Cerebral cortex
CTG54	Cerebral cortex
CTG55	Cerebral cortex
CTG56	Cerebral cortex
CTG57	Cerebral cortex
CTG58	Cerebral cortex
CTG59	Cerebral cortex
CTG60	Cerebral cortex
CTG61	Cerebral cortex
CTG62	Cerebral cortex
CTG63	Cerebral cortex
CTG64	Cerebral cortex
CTG65	Cerebral cortex
CTG66	Cerebral cortex
CTG67	Cerebral cortex
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CTG70	Cerebral cortex
CTG71	Cerebral cortex
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CTG77	Cerebral cortex
CTG78	Cerebral cortex
CTG79	Cerebral cortex
CTG80	Cerebral cortex
CTG81	Cerebral cortex
CTG82	Cerebral cortex
CTG83	Cerebral cortex
CTG84	Cerebral cortex
CTG85	Cerebral cortex
CTG86	Cerebral cortex
CTG87	Cerebral cortex
CTG88	Cerebral cortex
CTG89	Cerebral cortex
CTG90	Cerebral cortex
CTG91	Cerebral cortex
CTG92	Cerebral cortex
CTG93	Cerebral cortex
CTG94	Cerebral cortex
CTG95	Cerebral cortex
CTG96	Cerebral cortex
CTG97	Cerebral cortex
CTG98	Cerebral cortex
CTG99	Cerebral cortex
CTG100	Cerebral cortex

Table 11: Cell Major Divisions and Classes

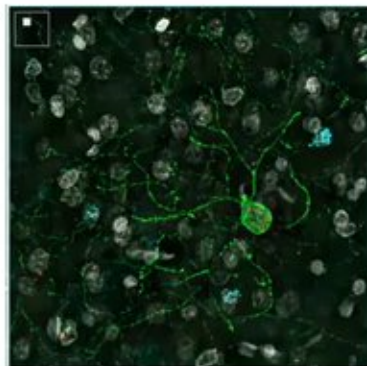
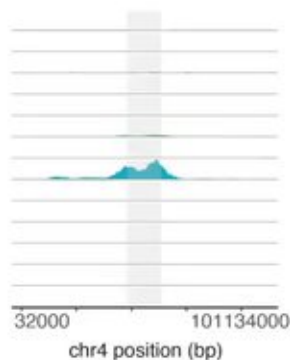
Source: Yao et al. (2023) A high-resolution transcriptomic and spatial atlas of cell types in the whole mouse brain. bioRxiv

<https://doi.org/10.1101/2023.03.06.531121>

Description includes dominant neurotransmitter phenotype and location, but may include additional neurotransmitter phenotypes and locations.

CMDR	Cell Major Divisions	Description
1	Neuron	Neurons
2	Neuron, Glut	Glutamatergic neurons
3	Neuron, GABA	GABAergic neurons
4	Non-Neuron	Non-neuronal cells
CCR	Cell Class	Description
1	PEP-Glut	Glutamatergic intralaminar and extralaminar neurons
2	MPCT-Glut	Glutamatergic near-projecting layer 5-6, corticothalamic layer 6, and layer 6b neurons
3	MPCT-GABA	Glutamatergic Cerebellar neurons
4	MPCT-Glut	Glutamatergic GABAergic cells and immature glutamatergic neurons
5	OB-IM-GABA	GABAergic olfactory bulb neurons potentially derived from LGI and the OB-derived immature neurons involved in adult neurogenesis
6	CTG-GABA	GABAergic neurons in cortex/pallidum derived from caudal ganglionic eminence (CGE)
7	CTG-MG-GABA	GABAergic neurons in cortex/pallidum derived from medial ganglionic eminence (MGE)
8	CTG-MG-GABA	GABAergic neurons in striatum/pallidum derived from medial ganglionic eminence (MGE)
9	CTG-LG-GABA	GABAergic neurons in striatum/pallidum derived from lateral ganglionic eminence (LGE)
10	CTG-GABA	GABAergic neurons in lateral septum (LSX) derived from embryonic septum
11	CTG-HV-GABA	GABAergic neurons in striatum/pallidum and anterior hypothalamus potentially derived from the embryonic preoptic area (POA)
12	CTG-GABA	GABAergic neurons from thalamic reticular nucleus (RT) and the ventral part of the lateral geniculate complex (LGC)
13	CTG-HV-Glut	Glutamatergic neurons located in hypothalamus, striatum-like amygdalar nuclei (AMV), and caudal pallidum regions of the cerebral nuclei (CNV) (extended amygdala)
14	CTG-GABA	Glutamatergic neurons located in hypothalamus
15	CTG-GABA	Glutamatergic GABAergic neuronal type in hypothalamus, developmentally derived from the embryonic olfactory epithelium
16	CTG-GABA	Glutamatergic neurons located in medial mammillary nucleus (MM) of hypothalamus
17	CTG-GABA	Glutamatergic neurons located in medial and lateral habenula (MH and LH)
18	TH-Glut	Glutamatergic neurons located in thalamus
19	MM-Glut	Glutamatergic neurons located in midbrain
20	MM-GABA	GABAergic neurons located in midbrain
21	MM-GABA	Dopaminergic neurons located in midbrain
22	MM-HV-Ser	Serotonergic neurons located in midbrain and hindbrain
23	P-Glut	Glutamatergic neurons located in pons
24	MM-Glut	Glutamatergic neurons located in medulla
25	PM-Glut	Glutamatergic neurons located in the dorsal part of the third ventricle and on top of superior colliculus (SC)
26	P-GABA	GABAergic neurons located in pons
27	PM-GABA	GABAergic neurons located in medulla
28	CB-GABA	GABAergic neurons located in cerebellum
29	CB-Glut	Glutamatergic neurons located in cerebellum
30	OB-Glut	Glutamatergic neurons from olfactory areas (OA), telencephalon, non-telencephalon, cerebellum, and Bergmann glia, as well as, ependymal cell types: astrocytes, ependymal cells, tanycytes, hypodermal cells, and choroid plexus (CHOR) cells
31	OPC-Oligo	Oligodendrocyte precursor cells and oligodendrocytes
32	OPC	Olfactory ensheathing cells
33	OPC	Arachnoid barrier cells (ABC), vascular leptomeningeal cells (VLMC), pericytes (Per), smooth muscle cells (SMC), and endothelial cells (End)
34	Immune	Microglia, border-associated macrophages (BAM), monocytes, dendritic cells (DC), and lymphoid cells, which contains B cells, T cells, NK cells and innate lymphoid cells (ILC)

Leveraging single cell atlases to generate cell type tools in nonhuman primates



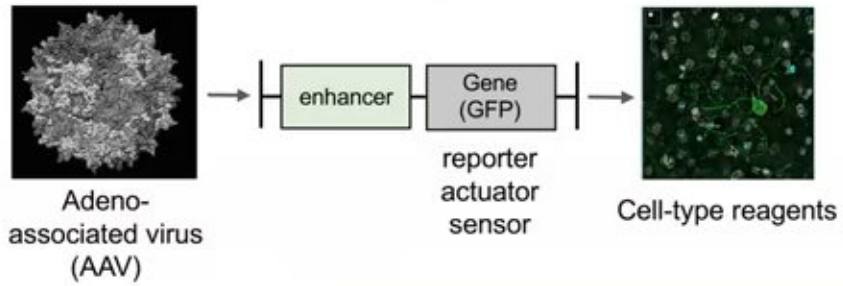
Fenna Krienen, Princeton University

BRAIN Cell Atlas Workshop
01-18-24

Addressing a need: tools to enable precision cell type access in primate models

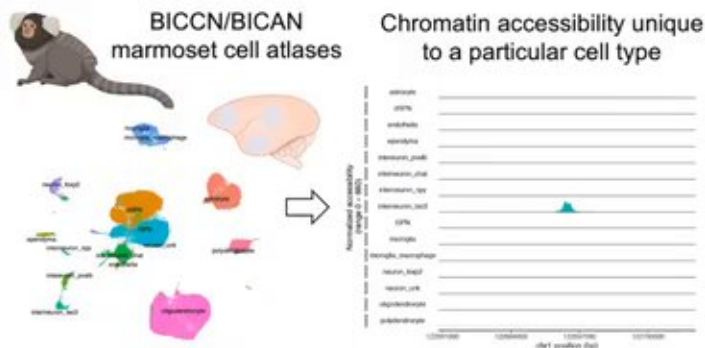


Addressing a need: tools to enable precision cell type access in primate models

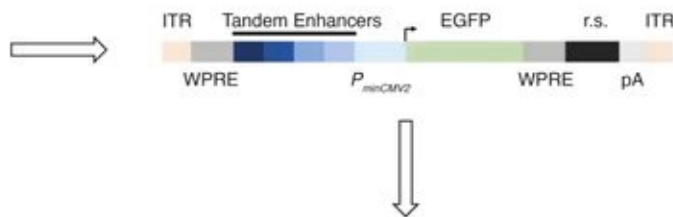
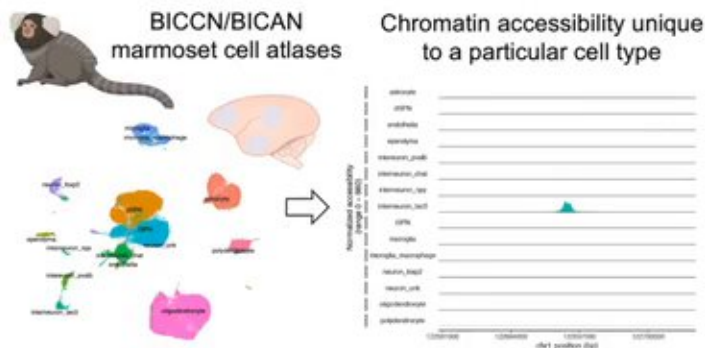


Dimidschstein et al. (2016) *Nat Neurosci*; Mich et al. (2021) *Cell Reports*; Graybuck et al (2021) *Neuron*; Vormstein-Schneider et al. (2020) *Nat Neurosci*; Krienen et al. (2023) *Sci Advances*

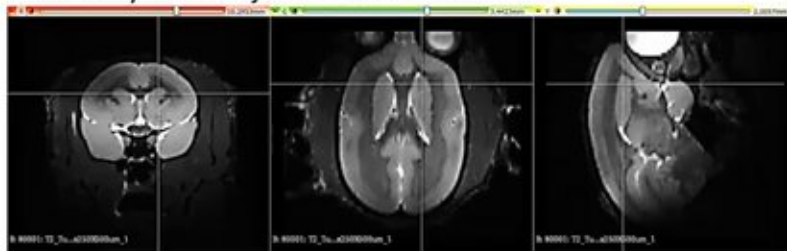
Leveraging single cell atlases to nominate cell type enhancers



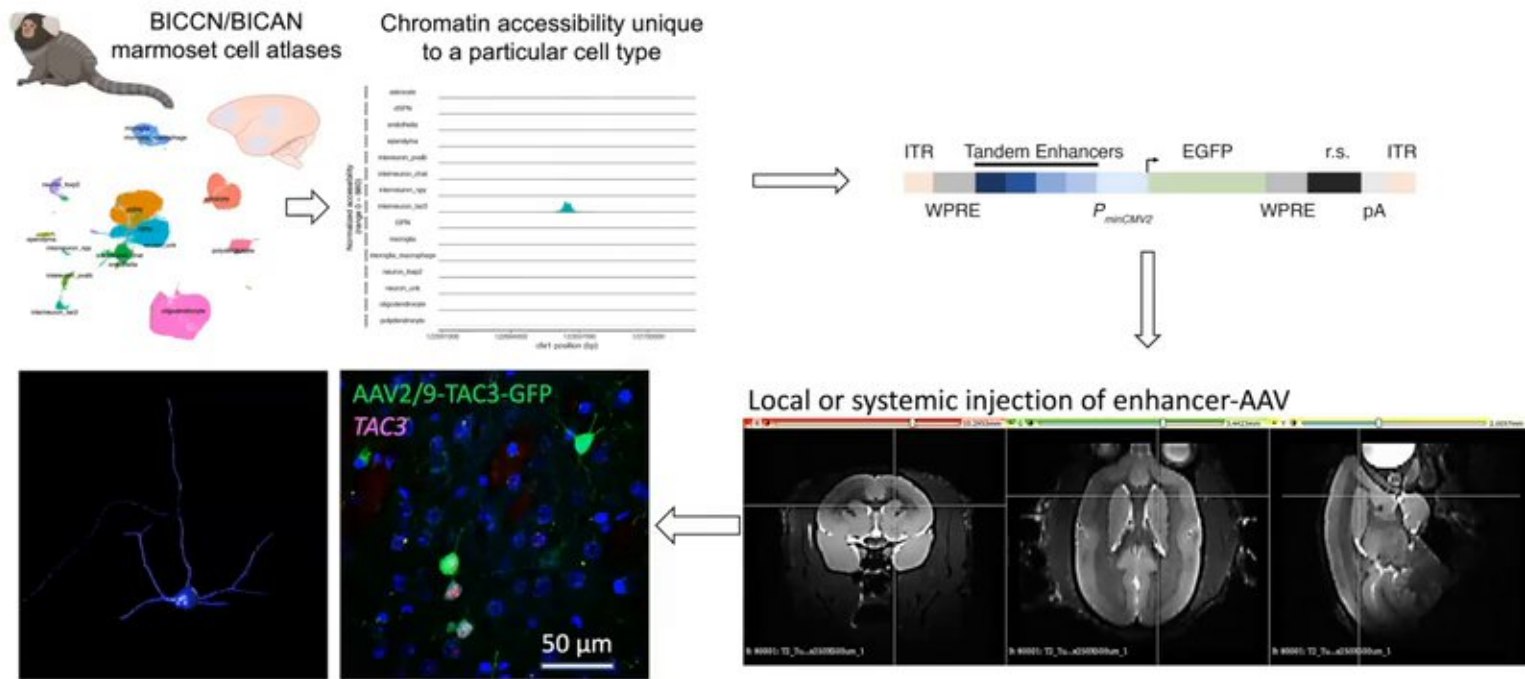
Leveraging single cell atlases to nominate cell type enhancers



Local or systemic injection of enhancer-AAV



Leveraging single cell atlases to nominate cell type enhancers



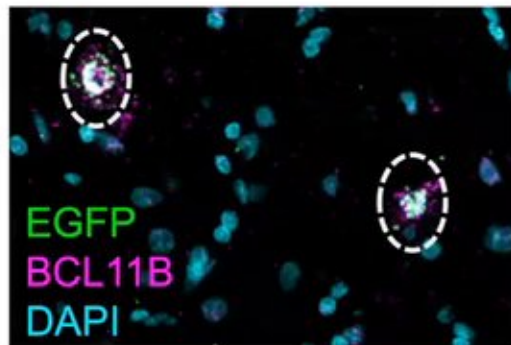
High-throughput development of AAV-enhancer constructs for NHP

How do we test and validate hundreds of enhancers in primates?

Cross-species conservation of cell type enhancer elements facilitates screening



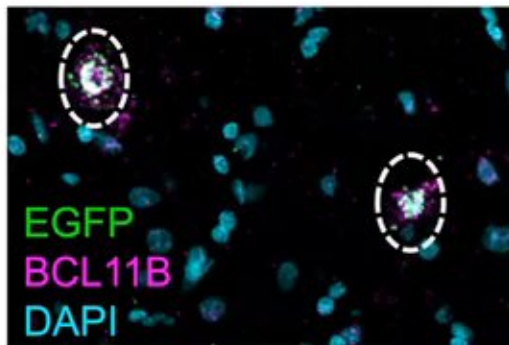
Pooled systemic injection
BI103 capsid, Ben Deverman



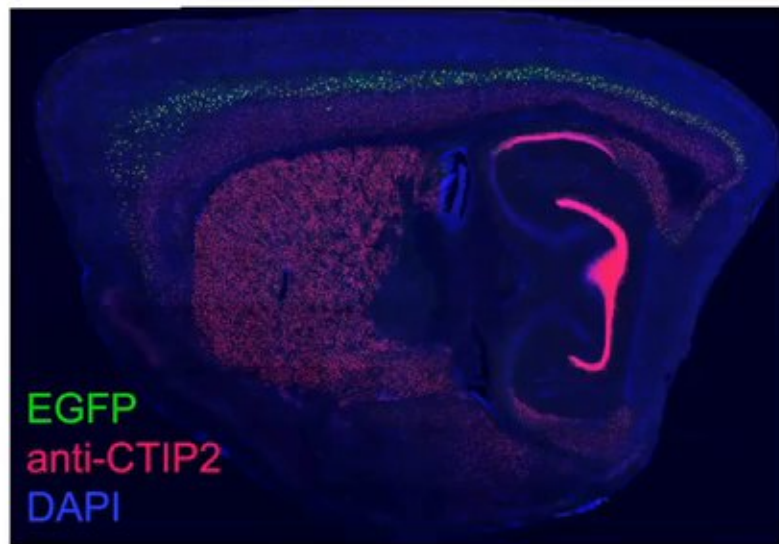
Cross-species conservation of cell type enhancer elements facilitates screening



Pooled systemic injection
BI103 capsid, Ben Deverman



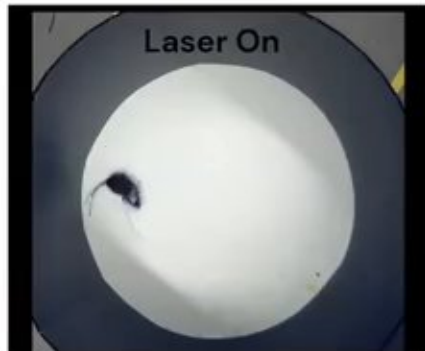
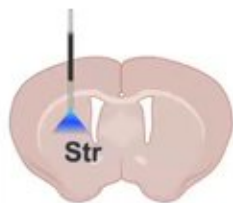
PhP.eB systemic injection



L5 *BCL11B*+ glutamatergic type enhancer
nominated in marmoset & conserved in mouse

Optogenetics

Drd2 enhancer
ChR2

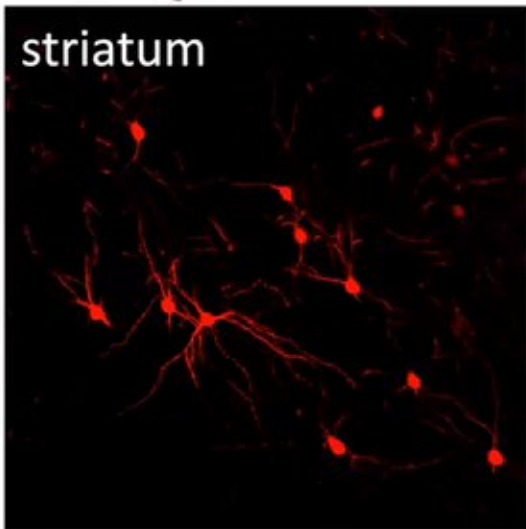


*Ipsilateral rotation upon stimulation of
unilateral indirect pathway*

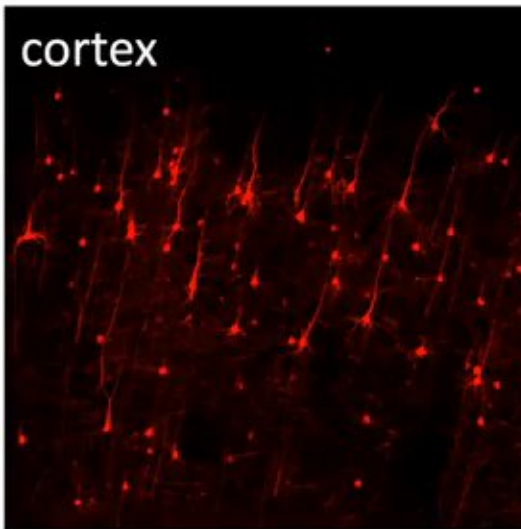
Towards cell type connectivity: enhancer-based rabies tracing



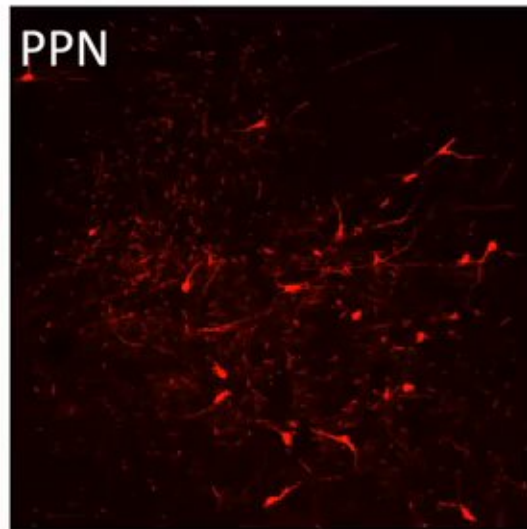
striatum



cortex



PPN



Summary

- Cell type specific enhancer-AAVs emerging as powerful tools for neuroscience
 - spatial/regional specificity
 - bypass Cre lines, advantageous for disease models, necessary for NHPs
- Many applications:
 - morphology & spatial distribution
 - calcium recording
 - opto/chemogenetics
 - connectivity
- Ongoing challenges:
 - delivery methods and AAV engineering for different species
 - ensuring robust expression while maintaining specificity
 - specificity/efficiency criteria depends on application

UG3MH126869
Guoping Feng (MIT)
Partha Mitra (CSHL)

Martin Wienisch (MIT)
Jitendra Sharma (MIT)

Ian Wickersham (MIT)
Ricardo del Rosario (Broad)

Steve McCarroll (HMS/Broad)
Ben Deverman (Broad)

NIH Program
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Jill Morris
Yong Yao

Feng Lab (MIT)
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Mandy Chen
Zheng Zhou
Kirsten Levandowski
Heather Zaniewski
Ryan Kast
Chenjie Shen
Yefei Chen
Ruoyang Chai
Eric Nyase
Andrew Harrahill
In-Hye Kang



Krienen Lab (Princeton)
Yongqi Wang
Siting He
Mike DeBerardine
Jessica Feliciano
Lakme Caceres
Reilly Nakamoto
Olivia Taylor
Sunny Mudhar







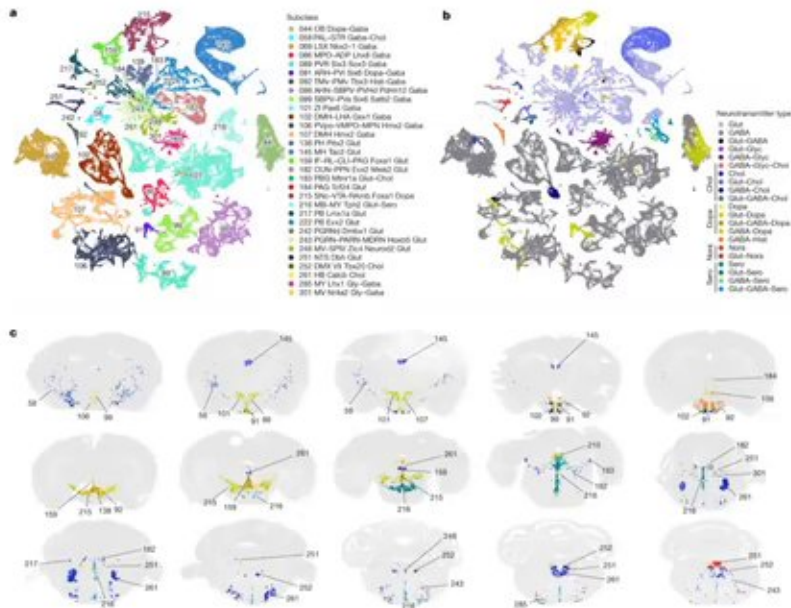


ALLEN INSTITUTE *for*
NEURAL DYNAMICS

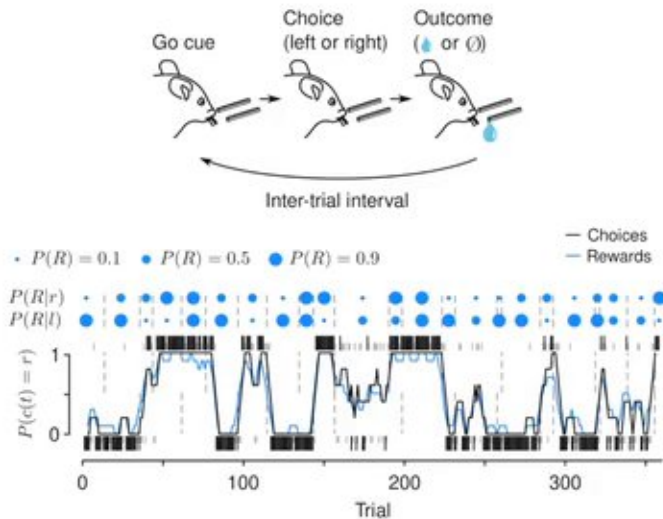
Cell-type-specific structure-function links in the brain

Jeremiah Y. Cohen

Neuromodulatory neurons in mice

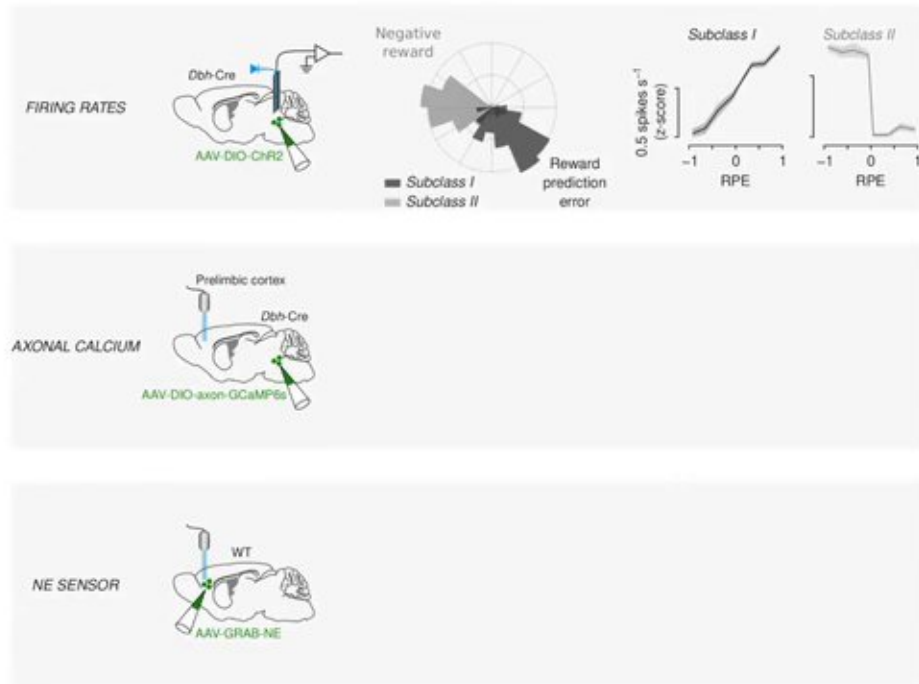


Yao Z et al., *Nature* 624: 317, 2023.

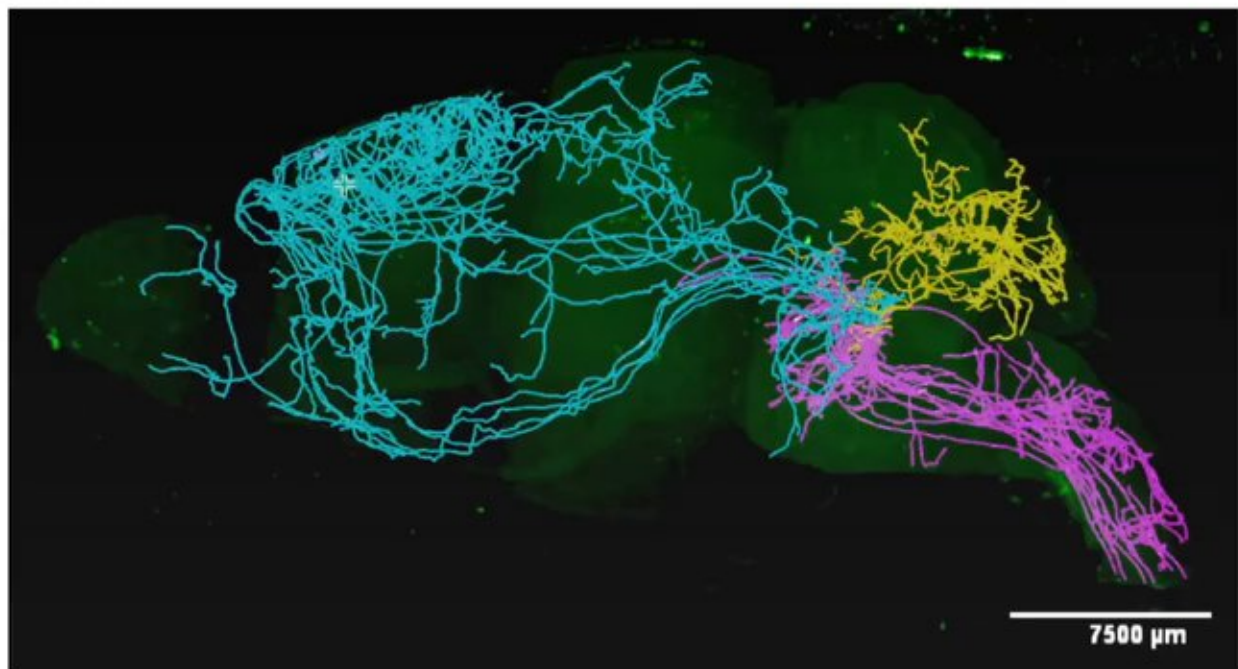


with Zhixiao (Sue) Su, Kenta Hagihara, Kanghoon Jung (Allen Institute for Neural Dynamics)



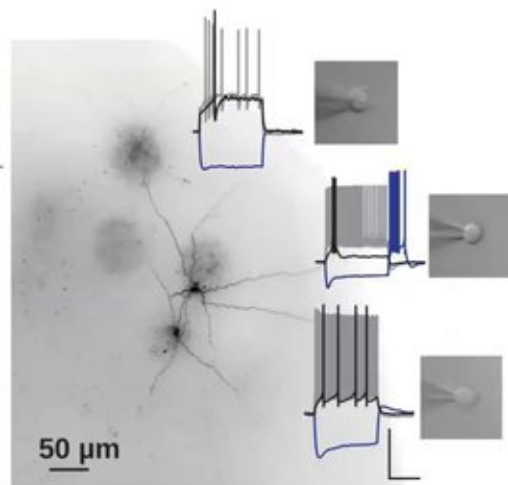
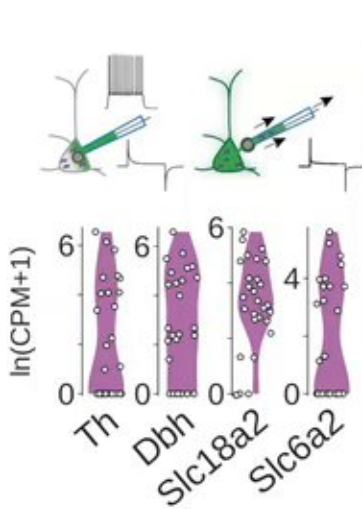
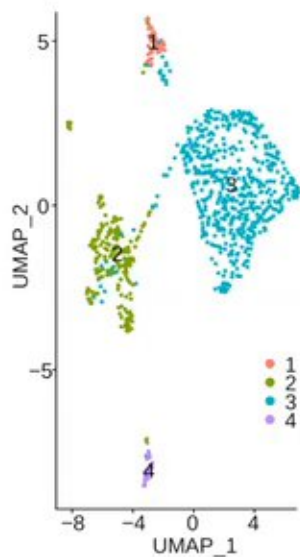


with Zhixiao (Sue) Su, Kenta Hagihara, Kanghoon Jung (Allen Institute for Neural Dynamics)

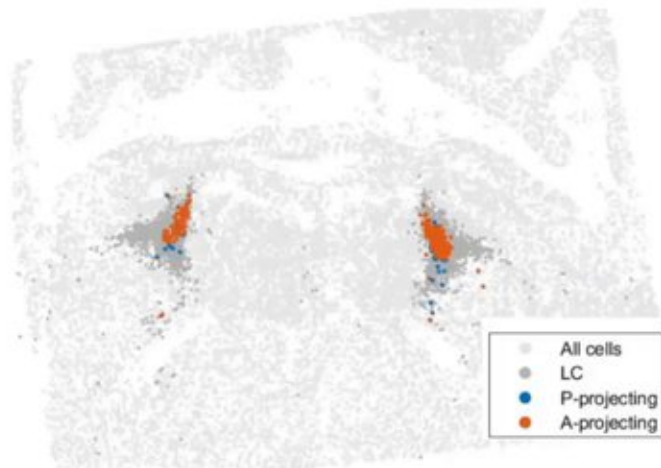


with Polina Kosillo, Peter Grotz, Adam Glaser, Jayaram Chandrashekar (Allen Institute for Neural Dynamics)

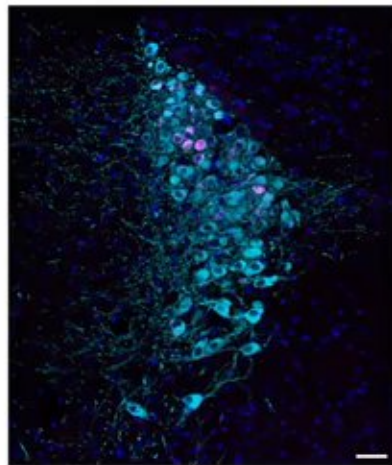
Locus coeruleus cluster identities



with Brian Lee (Allen Institute for Brain Science)



with Xiaoyin Chen (Allen Institute for Brain Science)



Kanghoon Jung



- What are the molecular (transcriptome, multiome) and anatomical (somatic morphology, projection targets) subtypes of NE and 5-HT neurons?
- What behavioral variables drive firing of NE and 5-HT neurons and release across brain targets?
- Structure and function link these key evolutionarily-conserved neuromodulatory systems
- Strong test of the transcriptomic type hypothesis

with

Jayaram Chandrashekar (Allen Institute for Neural Dynamics)

Brian Lee (Allen Institute for Brain Science)

Yoh Isogai (Allen Institute for Neural Dynamics)

Xiaoyin Chen (Allen Institute for Brain Science)

Polina Kosillo (Allen Institute for Neural Dynamics)

Boaz Levi (Allen Institute for Brain Science)

Bosiljka Tasic (Allen Institute for Brain Science)

Jonathan Ting (Allen Institute for Brain Science)



THANK YOU

We wish to thank the Allen Institute founder, Paul G. Allen, for his vision, encouragement, and support.

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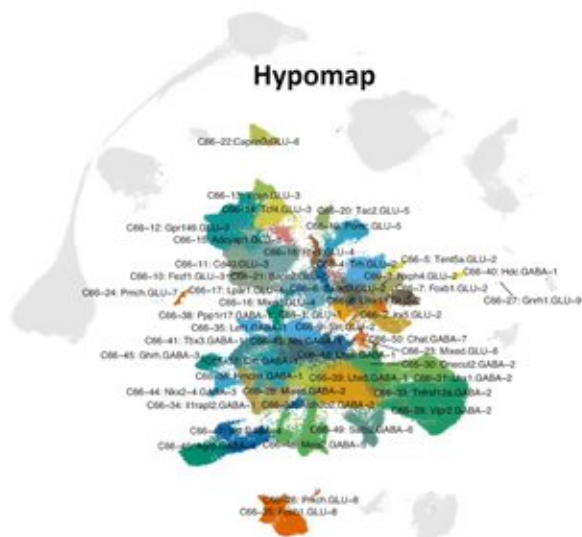




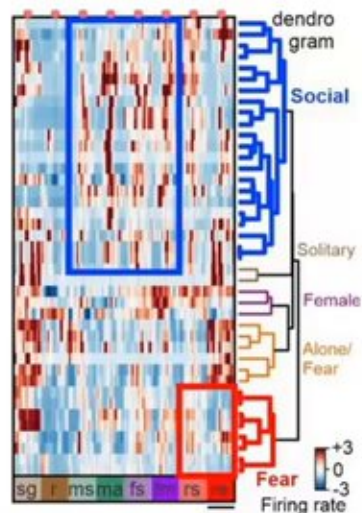


Molecular and functional neuron classification

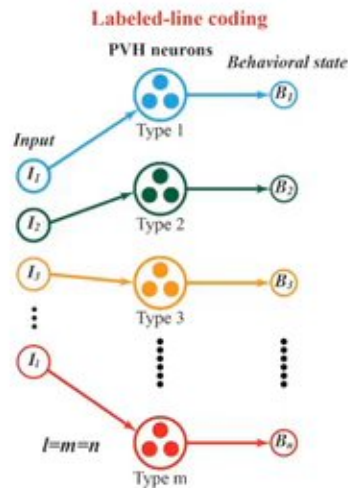
Molecular classification



Functional classification

Anderson, et al. *bioRxiv* (2023)

Behavioral state coding: 3 models

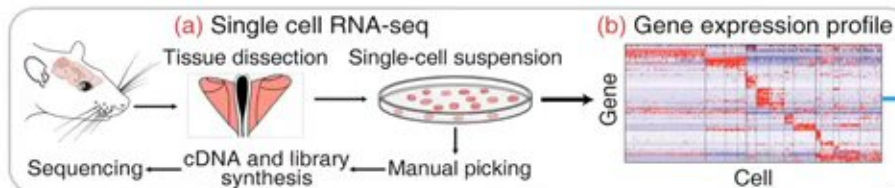


S. Xu, H. Yang, V. Menon, A.L. Lemire, L. Wang, F.E. Henry, S.C. Turaga, S.M. Sternson. Behavioral state coding by molecularly defined paraventricular hypothalamic cell type ensembles. *Science* (2020) 10.1126/science.abb249

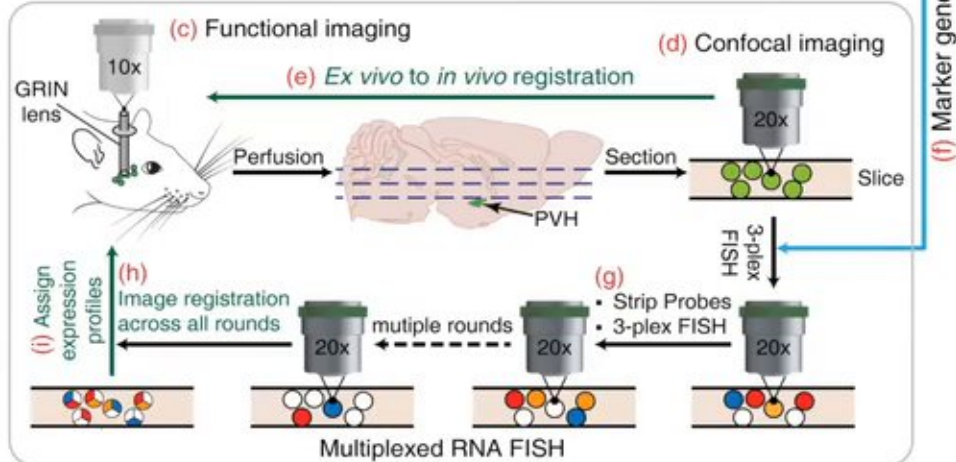
CaRNA Imaging: Dynamics of all molecularly defined cell types in a deep-brain structure, at the same time

CaRNA Imaging: Calcium and RNA Multiplexed Activity Imaging

Cell Type Classification

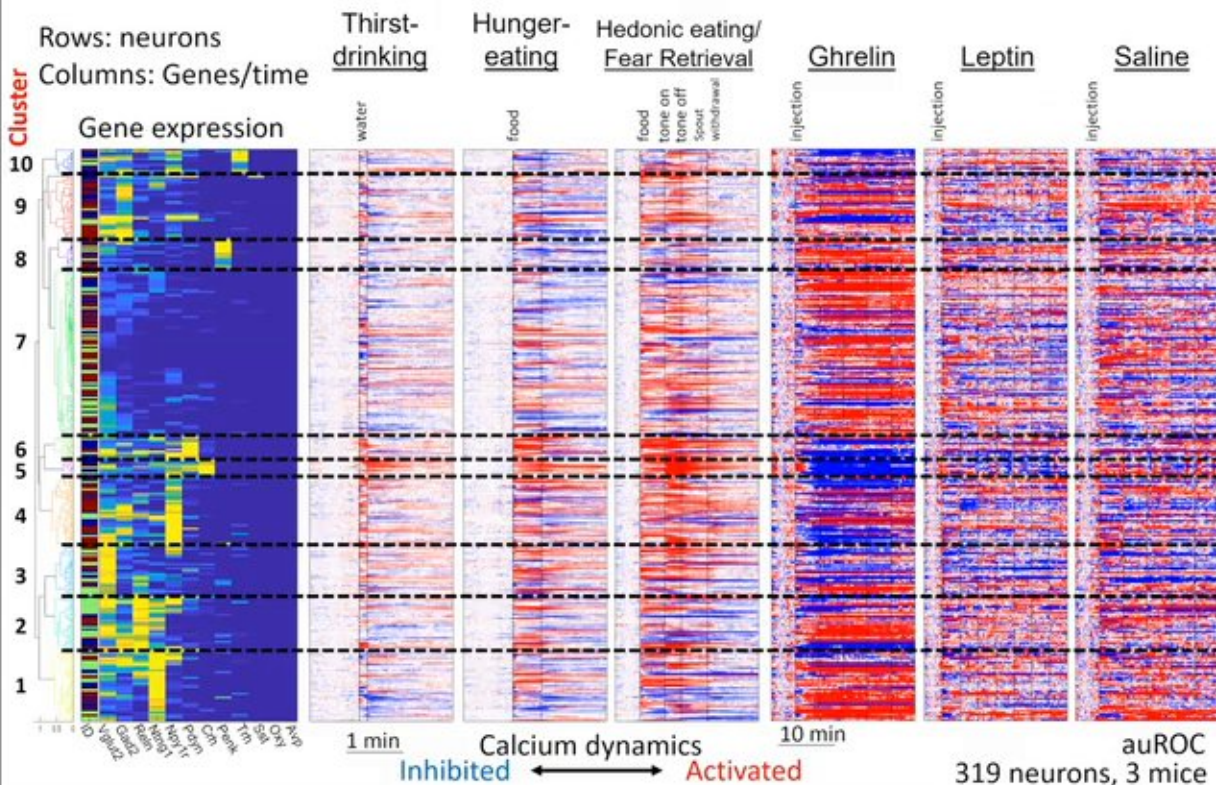


Functional Imaging

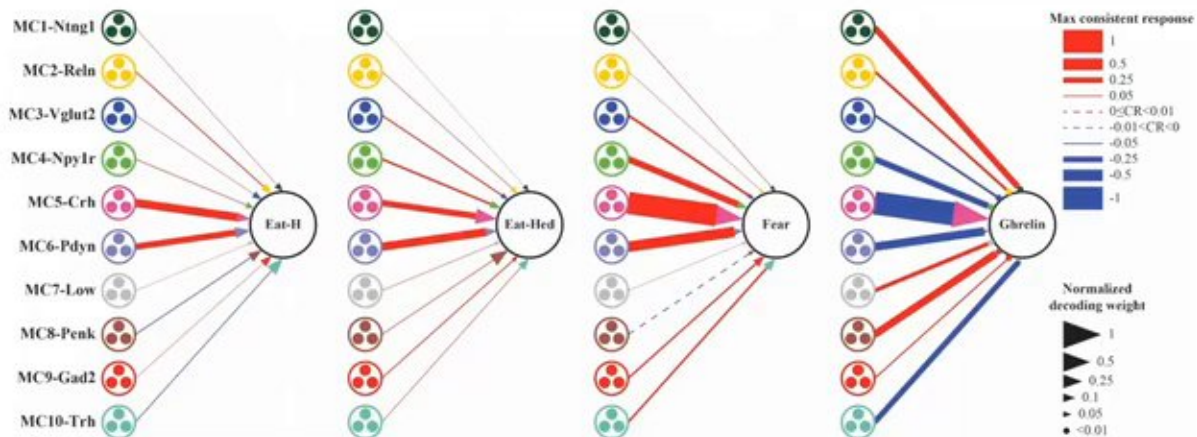


Post-hoc Cell Type Identification

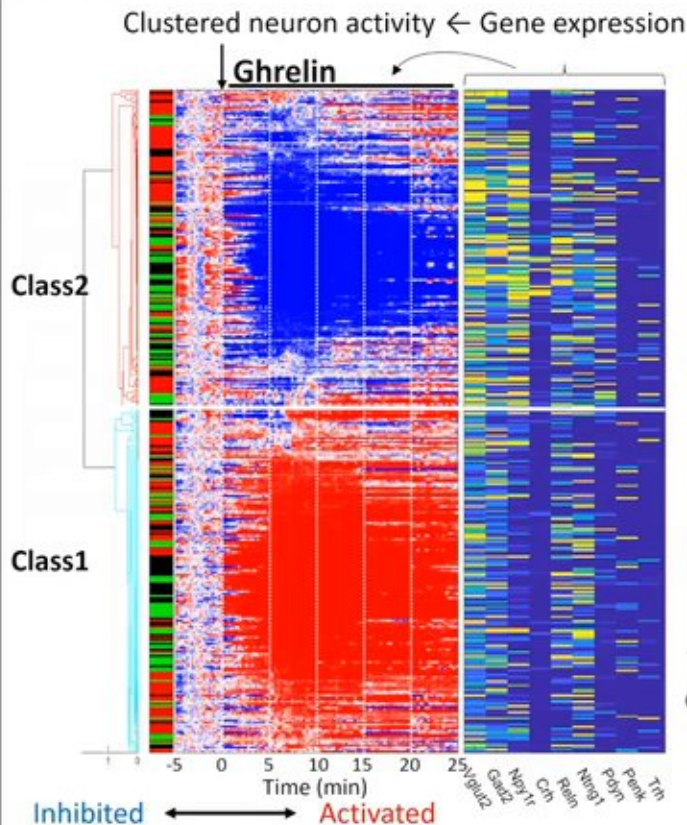
Gene expression clustering of PVH neurons and their responses under different behavior states



Molecularly defined response-decoding diagrams



Predict neuron response class w/ gene expression



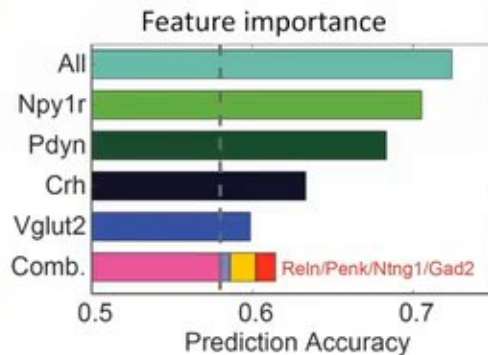
Fit quantitative predictive models

Gene expression level →
Functional response type

Features_{genes} $\xrightarrow{\text{Model}}$ Class_{1,2}

Logistic regression

Overall accuracy (CV): 72%



Molecularly defined systems neuroscience

- Deep-brain systems neuroscience w/ detailed molecular identity



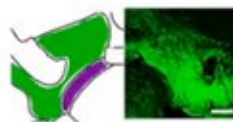
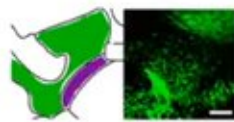
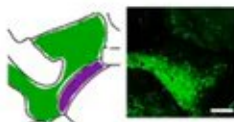


Combining optogenetics and transcriptomics to map input-specific neuronal activation patterns

Marta Soden
University of Washington

Harnessing transcriptomics to answer questions about circuit connectivity and neuronal excitability

Heterogeneity of axon innervation



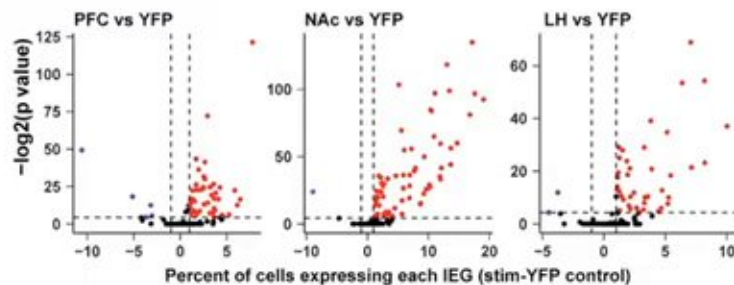
10	11	12	13	14
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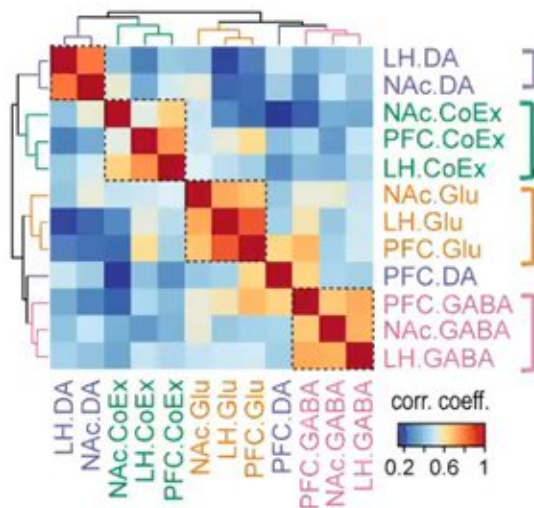
Types of analyses performed on opto-seq dataset

- Cluster analysis and identification of marker genes
- Analysis of IEGs to identify activated clusters
- Variability of IEG induction between cell types
- Correlations of ion channel genes with IEG expression
- Correlating fiber innervation with spatial activation patterns

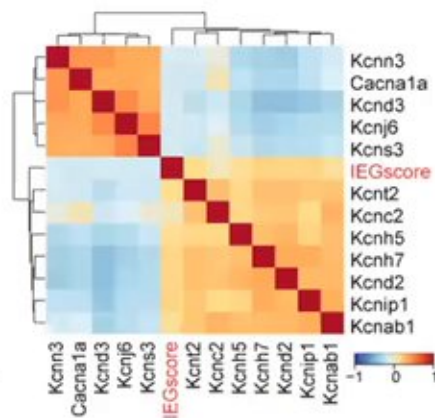
Analysis of stimulus-induced immediate early genes (IEGs)



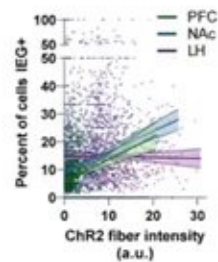
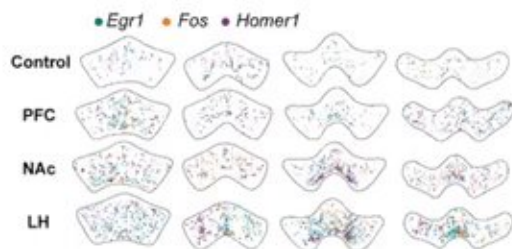
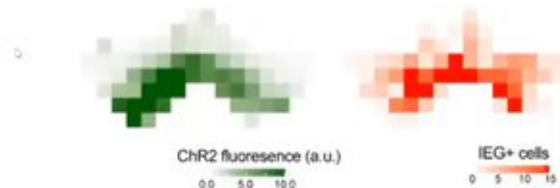
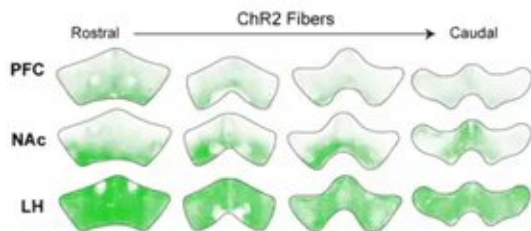
Variability of immediate early gene induction between cell types



Ion channel genes correlate with IEG activation



Quantification of IEG induction by multiplex *in situ*



Harnessing transcriptomics to answer questions about circuit connectivity and neuronal excitability

- Assess the net effect of stimulating specific inputs to better understand circuit function
- Identify activation of cell-type specific transcriptional programs
- Detect correlations between markers of activity (IEGs) and genes that determine excitability (ion channels) to identify new research targets

known

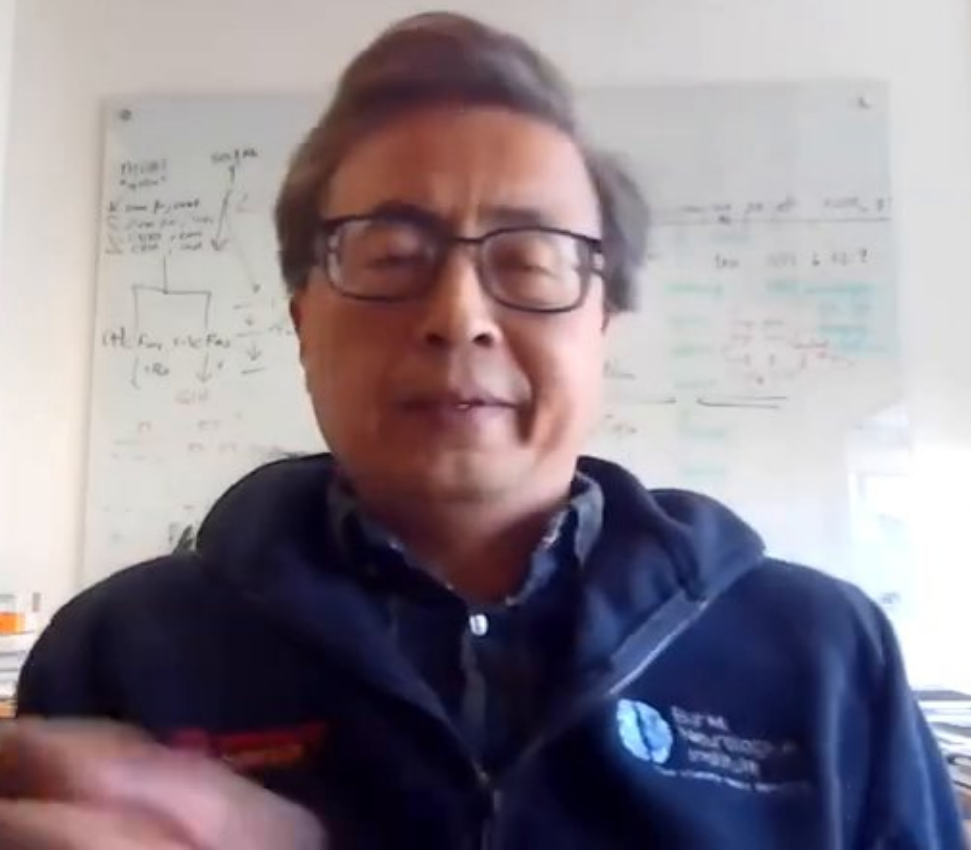




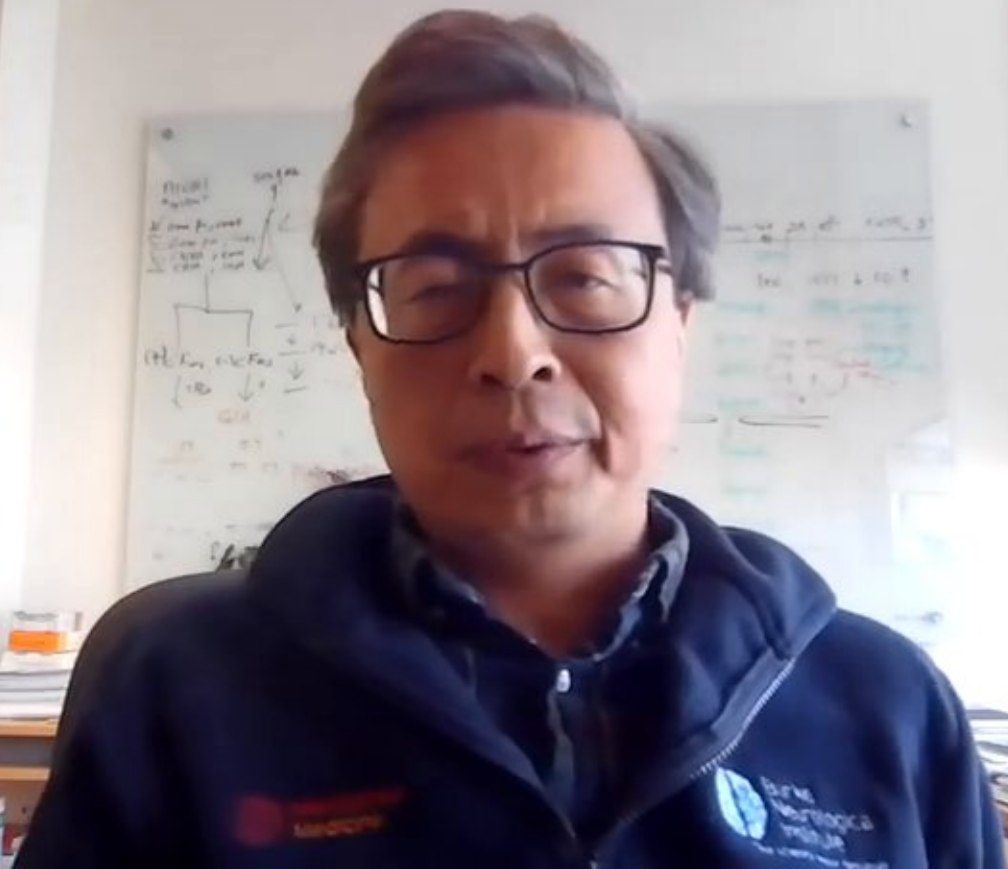


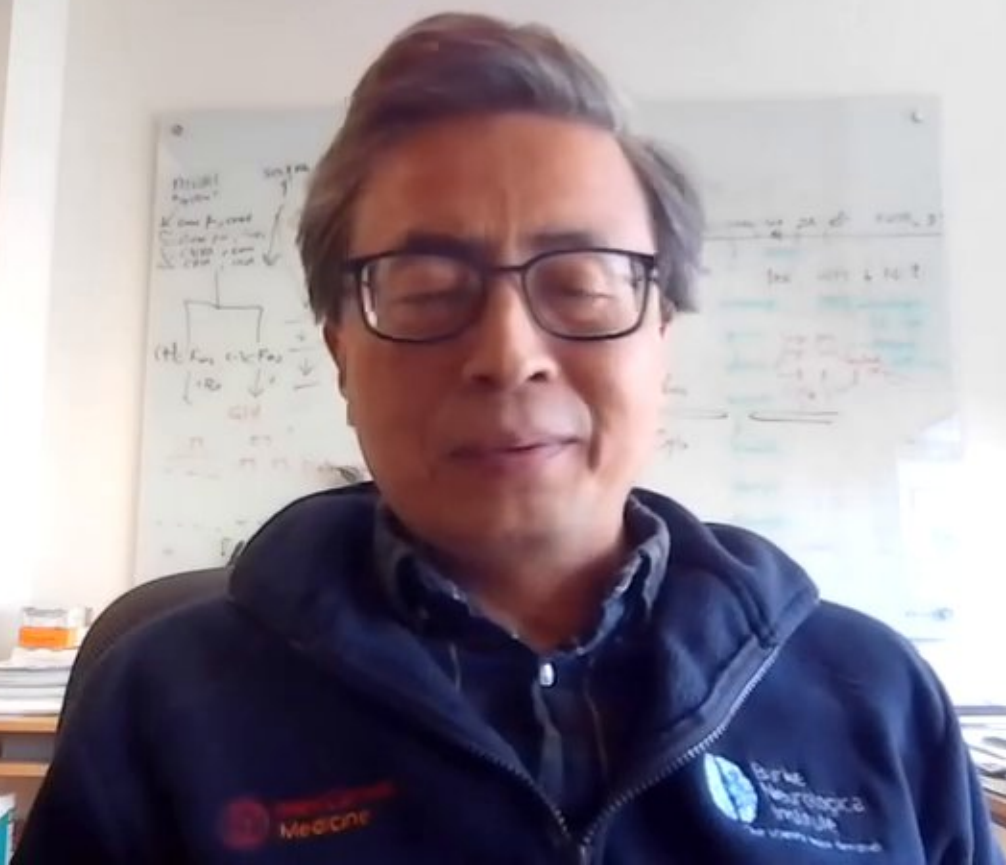


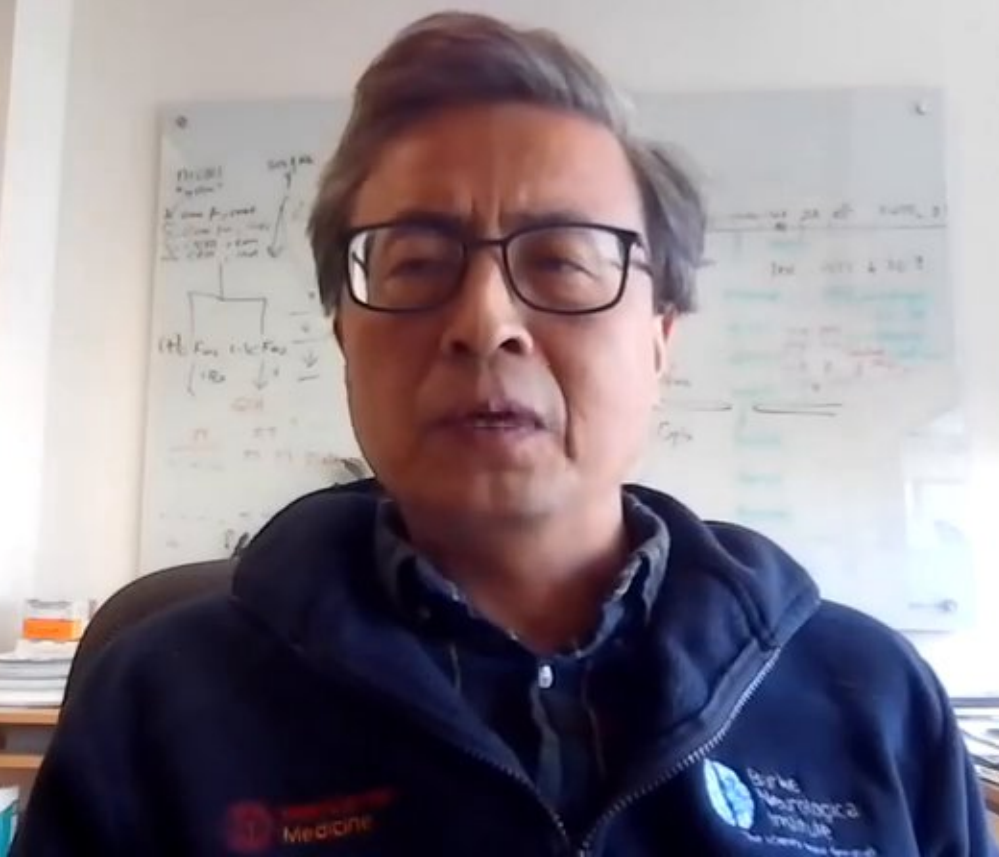
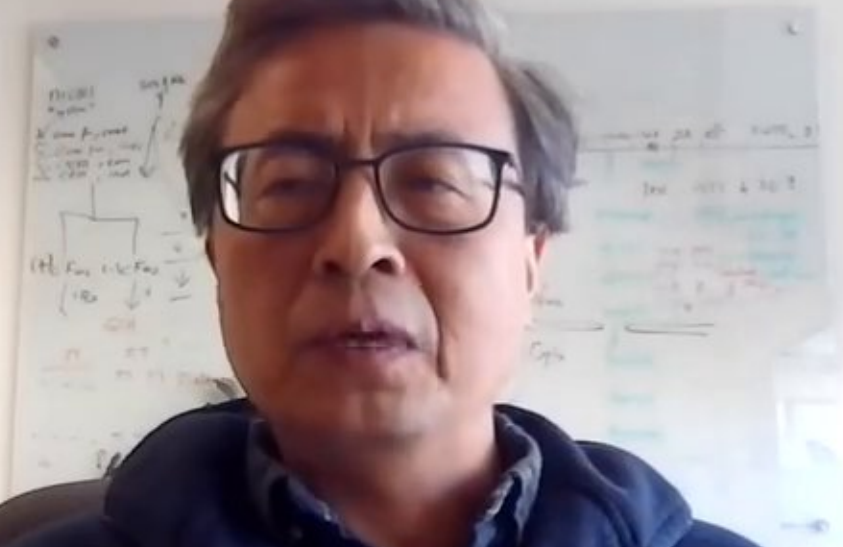


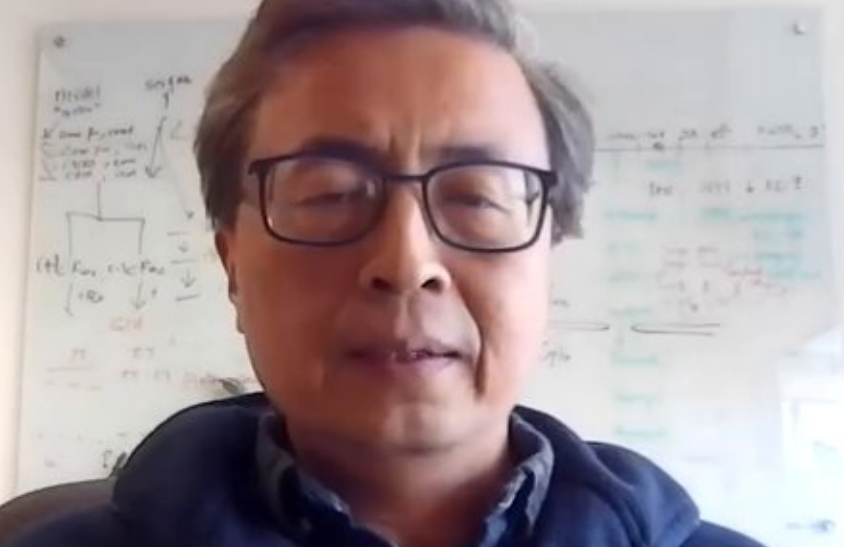


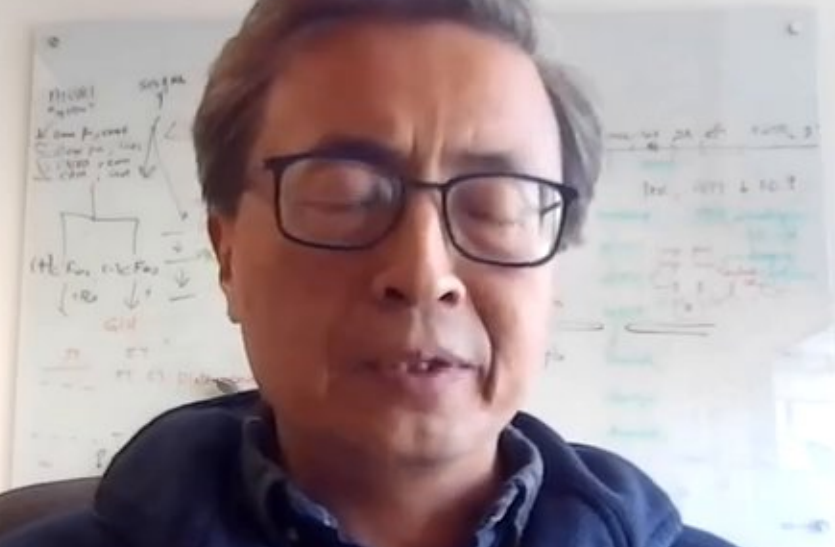
























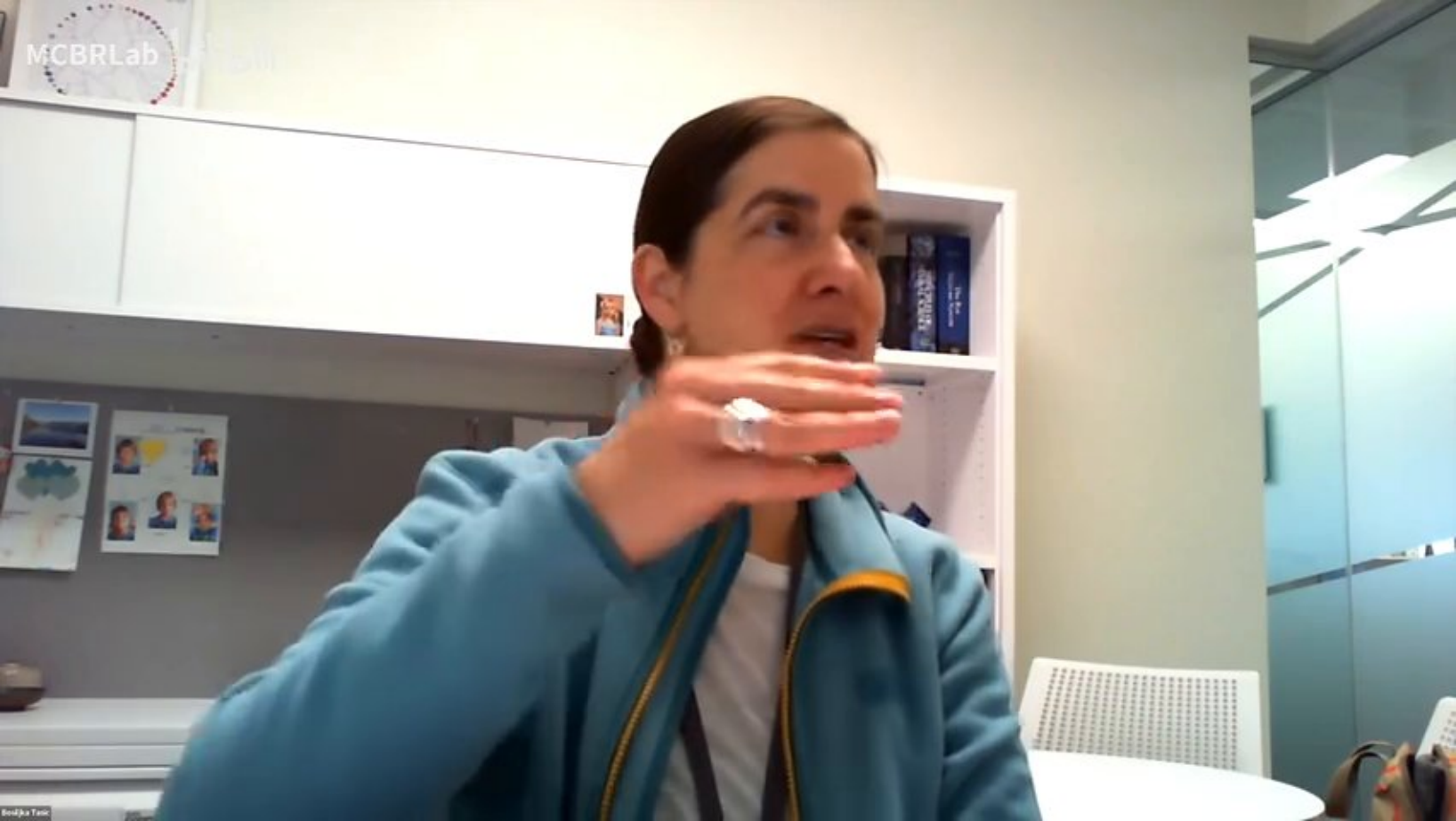












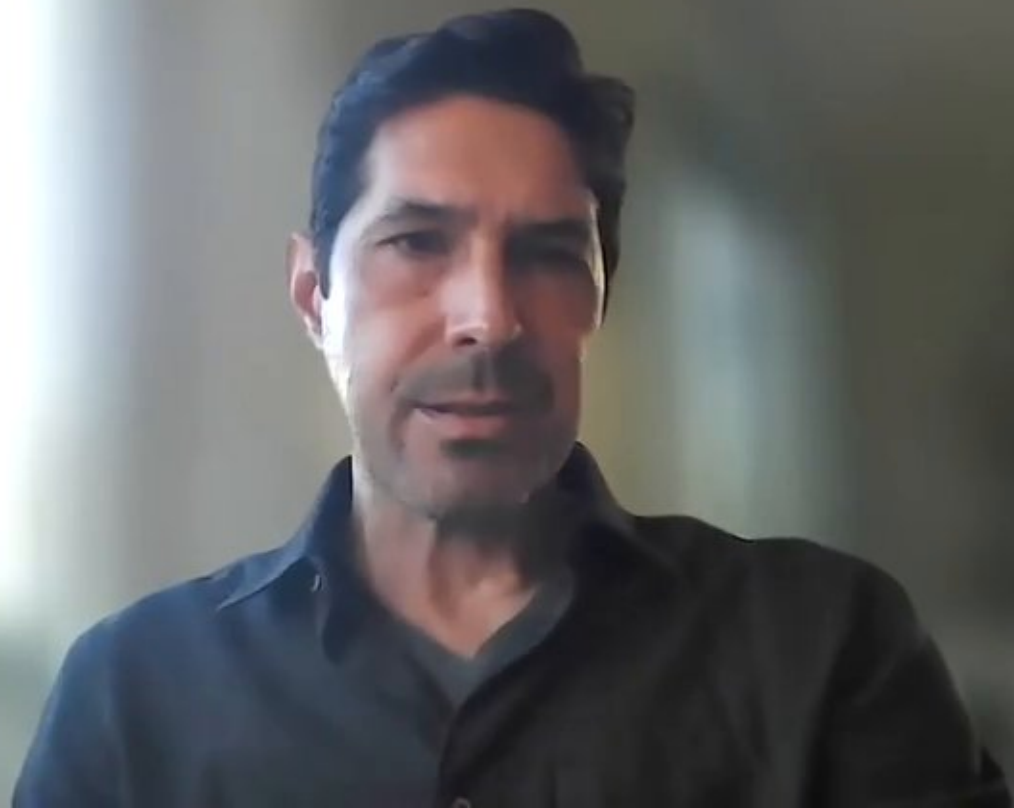


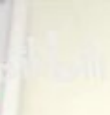






















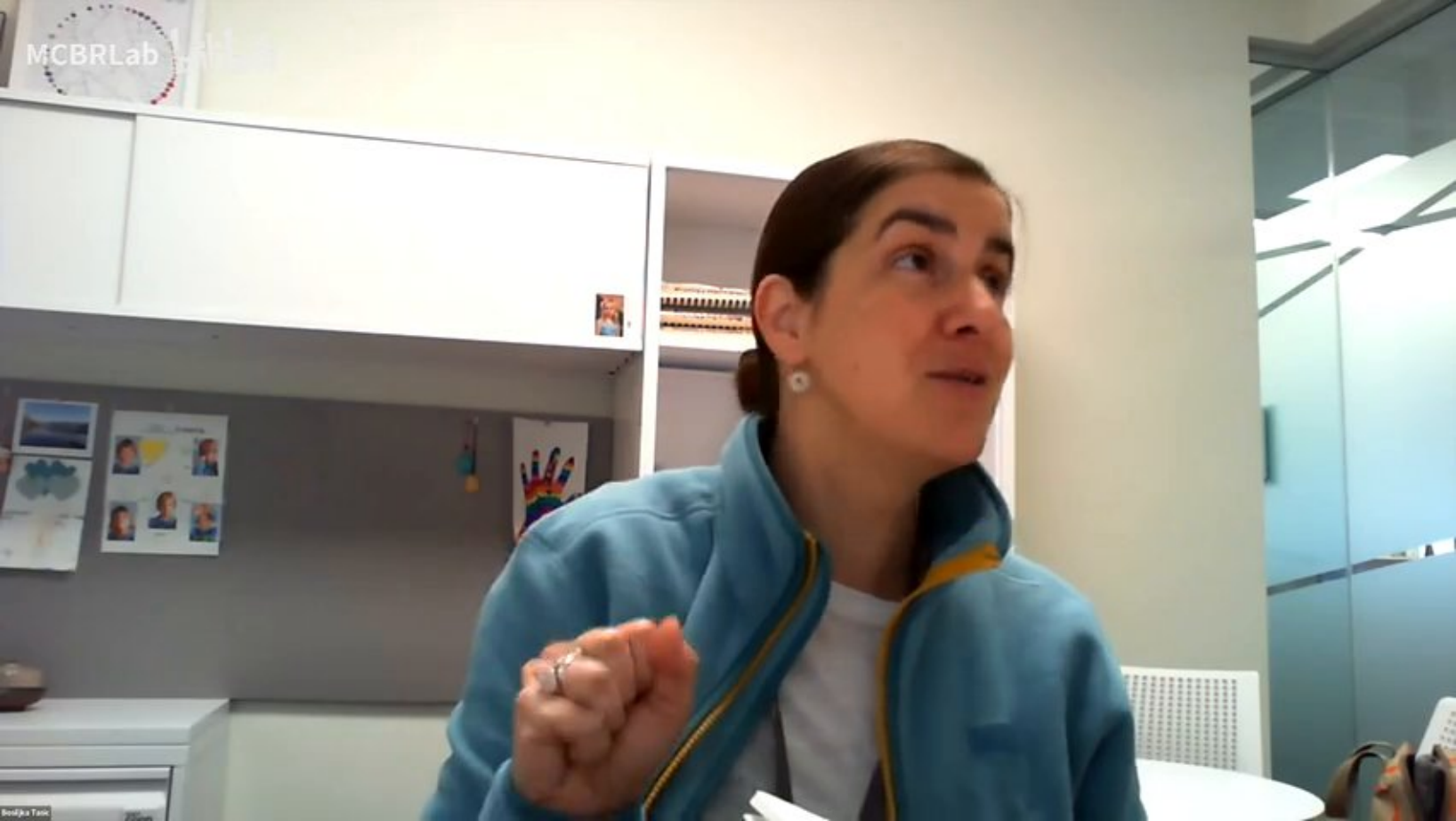






MCBRLab





















































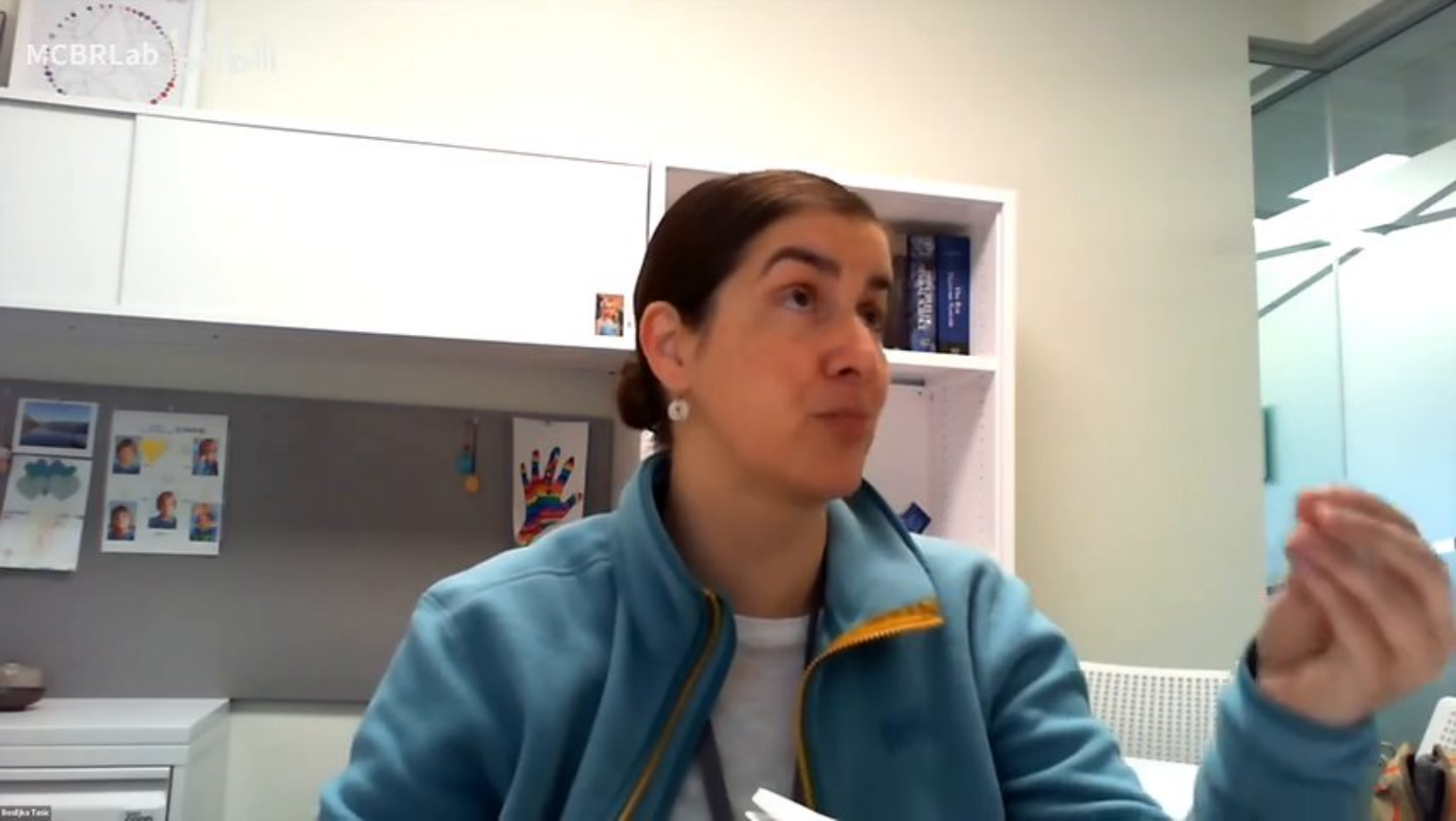
















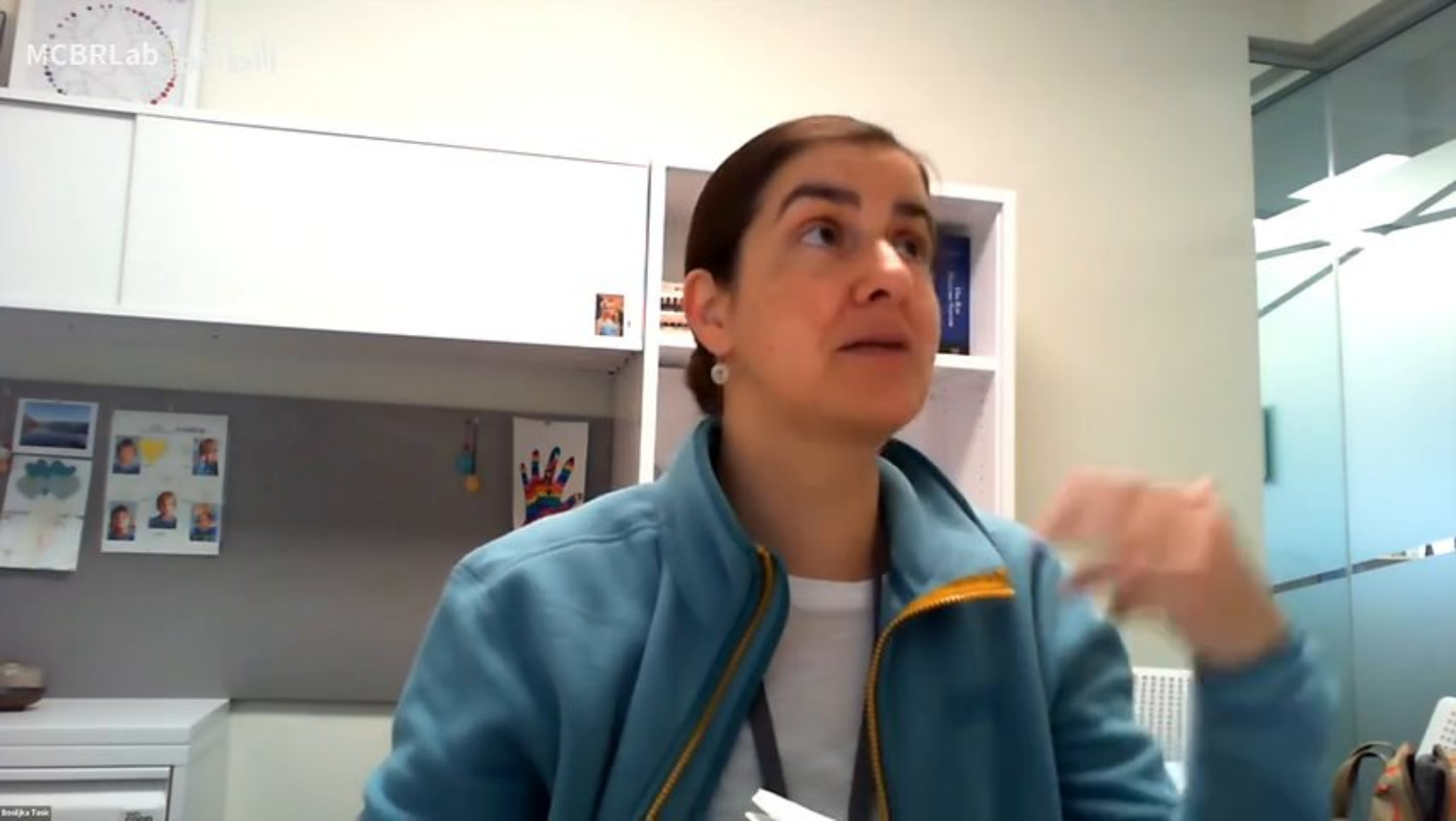














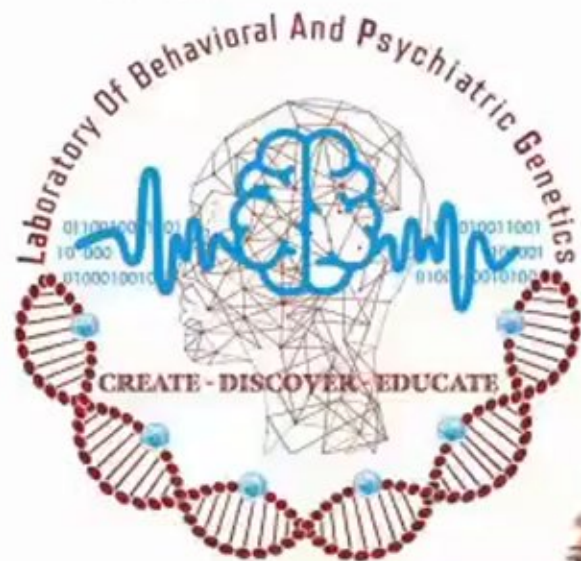












UPSTATE





UPSTATE











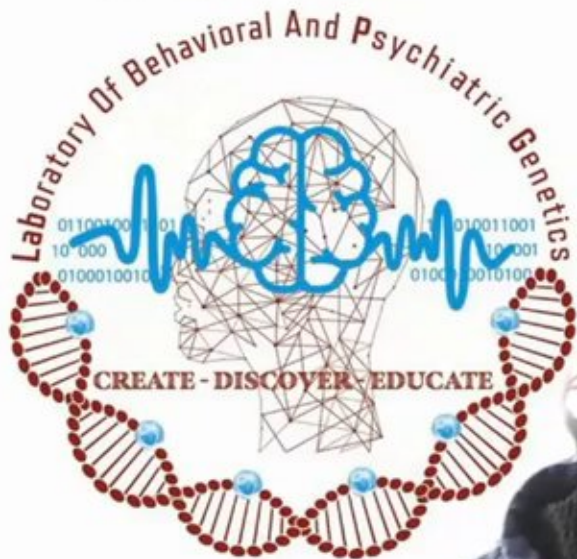






UPSTATE





UPSTATE





UPSTATE





























































VITAL CONNECTIONS

BRAIN CENSUS

DIVERSITY
UNMASKED



















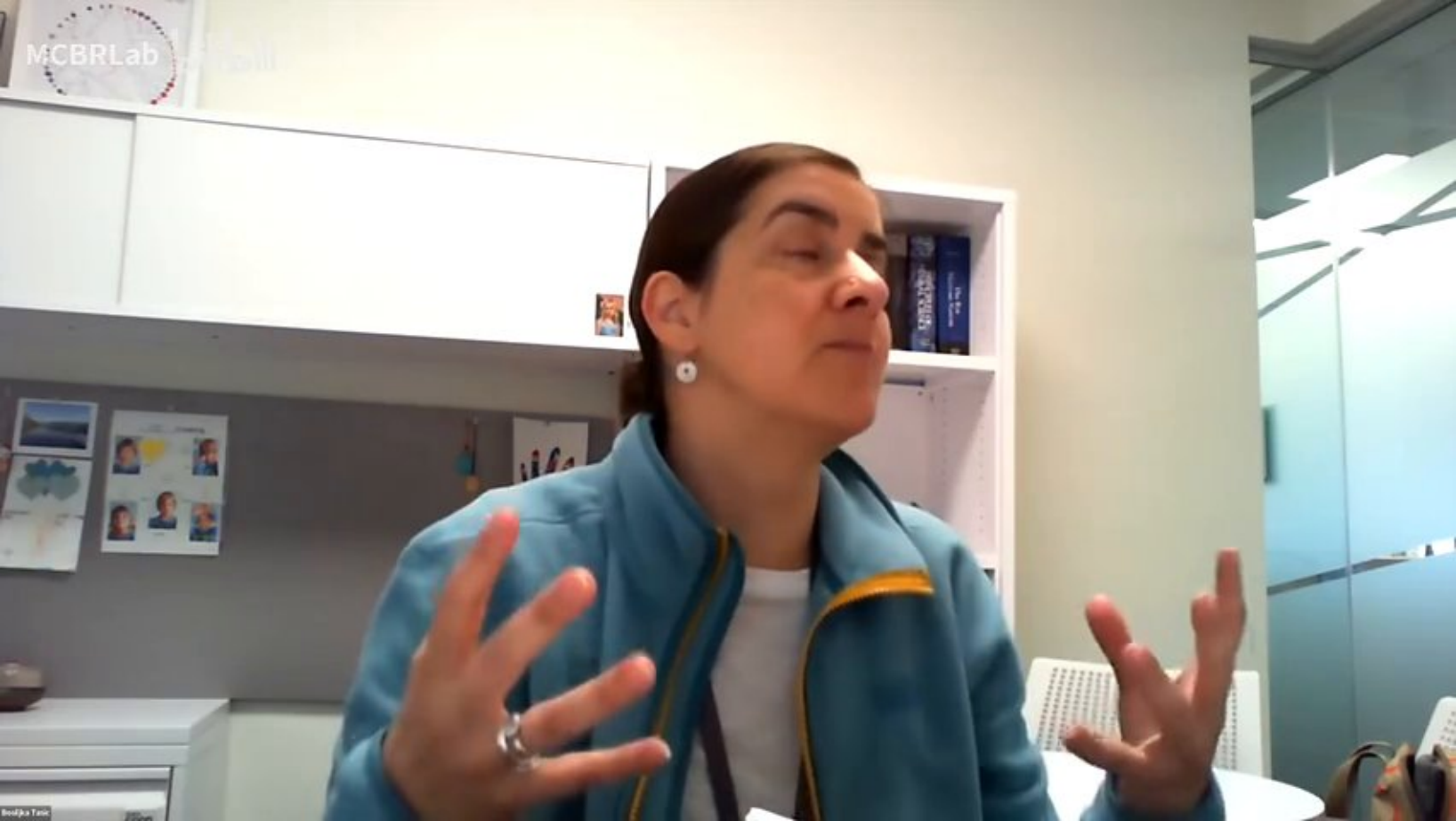








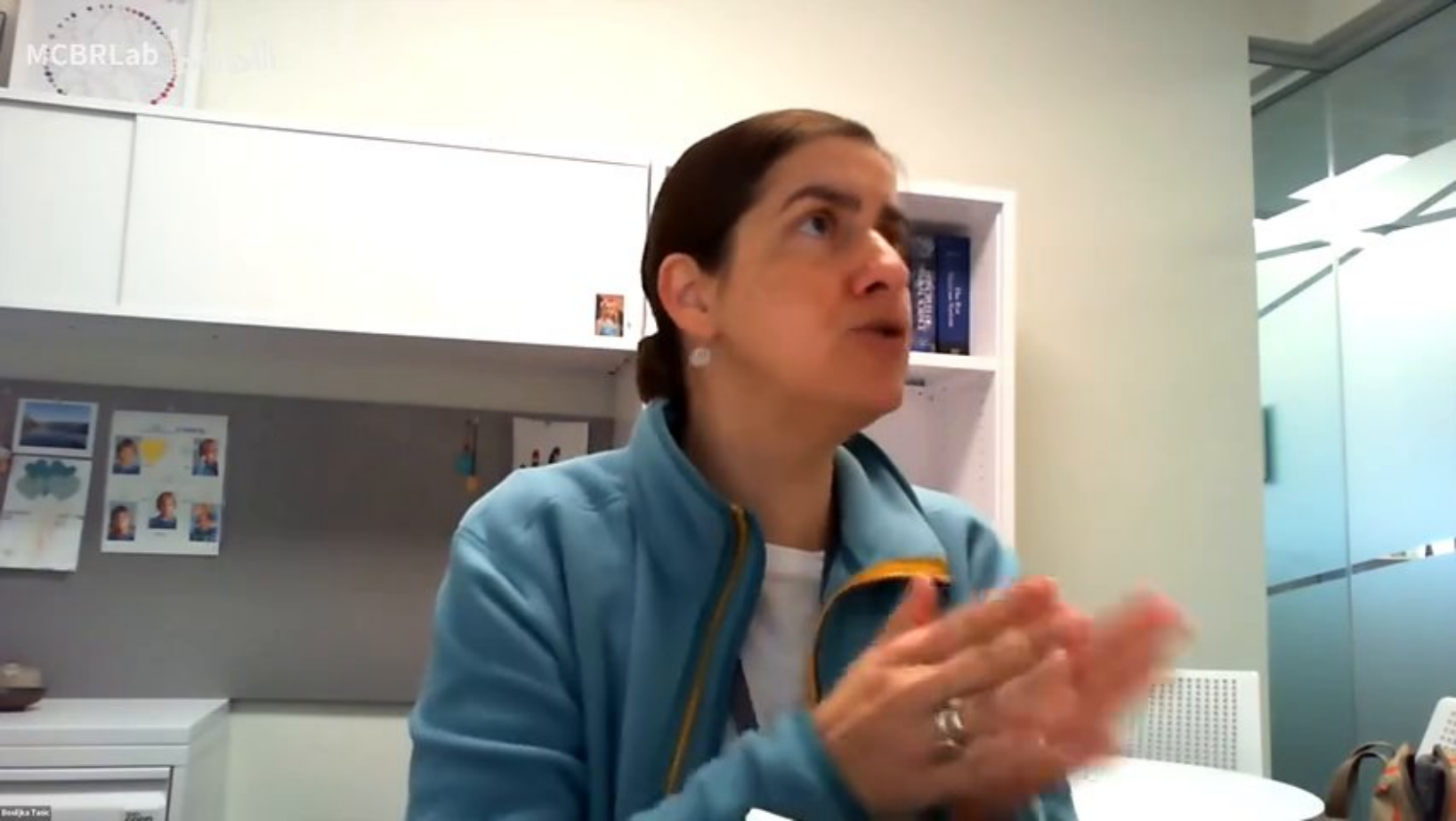




































































































































Keynote Presentation 2

Putting the human brain cell atlas to use: Insights into cellular vulnerabilities and disease trajectories from the Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD)

Ed Lein, PhD – Allen Institute



National Institutes of Health
The BRAIN Initiative





Putting the human brain cell atlas to use: Insights into cellular vulnerabilities and disease trajectories from the Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD)

Ed Lein, *Senior Investigator*

NIH BRAIN Initiative Workshop "From Single-cell Genomics to Brain Function and Disorders
- Data Integration and Annotation"

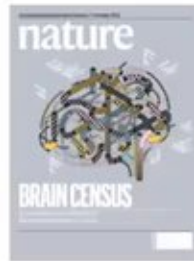
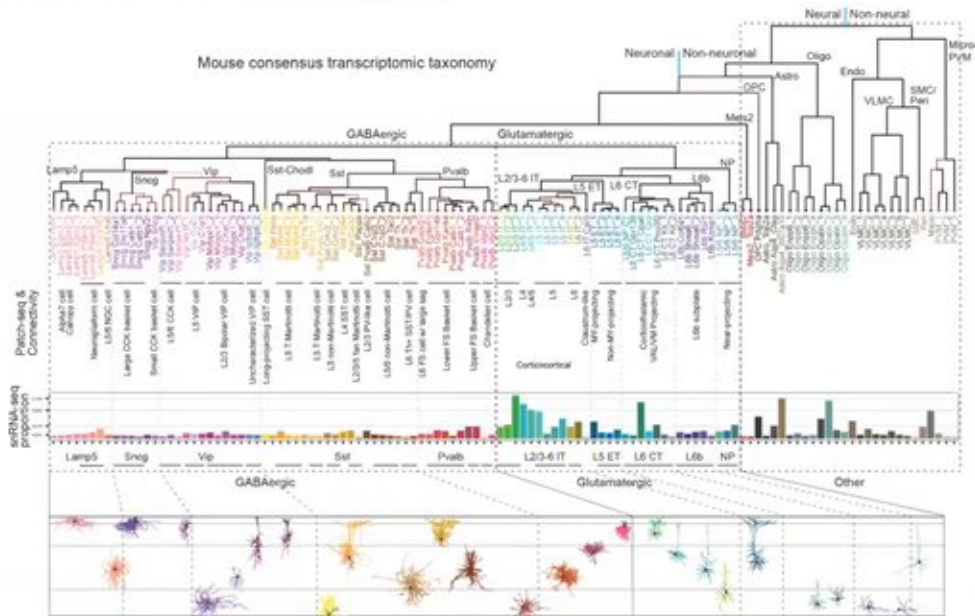
January 18, 2024

The brain cell atlas: A transcriptionally-based, highly annotated classification and census of cell types

Information content:

Cell types
Gene expression profiles
Epigenomic profiles
Proportions
Spatial organization
Cellular properties
anatomy
physiology
connectivity

Cross-species



The “pilot phase” of Human and NHP brain cell atlasing



Photo credit: Ivana Kapustová and Sten Linnarsson

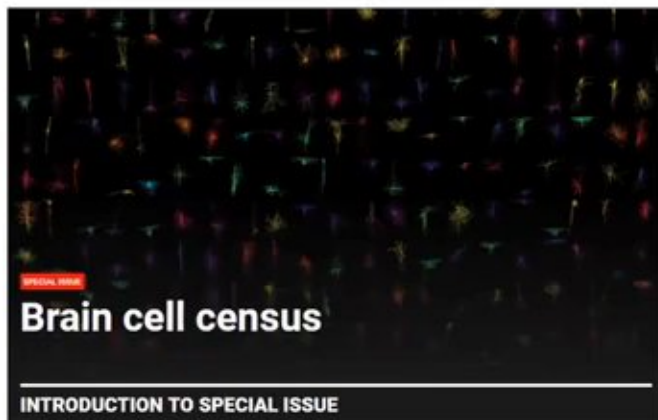


Photo Credit: Rachel Dalley, Sarah Walling-Bell and Brian Lee

Dedicated coordinated issues of Science and Science Advances highlighting BICCN work in human and NHP
21 papers total

Adult human single cell atlasing studies

Adult NHP single cell atlasing studies

Comparative single cell analyses

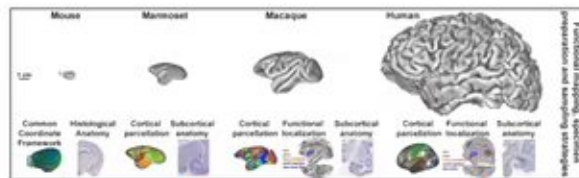
Human and NHP brain development single cell studies

Human neuronal cell type functional and anatomical analysis and modeling

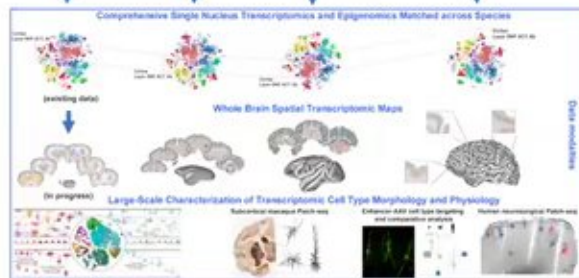
Human and Mammalian Brain Atlas (HMBA) project



fMRI

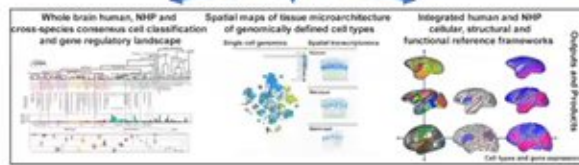


Single cell genomics



Spatial transcriptomics

Patch-seq



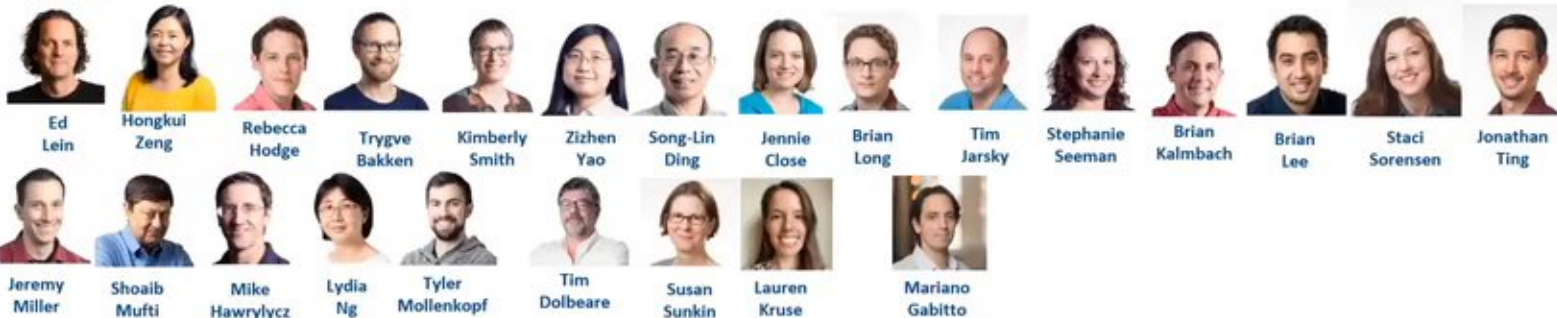
Products

Key driving concepts:

- Whole brain atlases
- Comparative human, NHP and mouse
- Multimodal
- Link function (fMRI) to cell types
- Individual variation
- Species conservation and divergence

BICAN: Human and Mammalian Brain Atlas (HMBA) Consortium

AIBS



UW



MGH



MIT



RU



WashU



INSERM



RIKEN



Princeton



ASU



UPenn



Karolinska



BCM



Tubingen



Szeged



Vrije



Leiden



EMBL



Annotating the reference classification quickly adds meaning and value to the community

Spatial tissue organization

Electrophysiology

Cellular anatomy

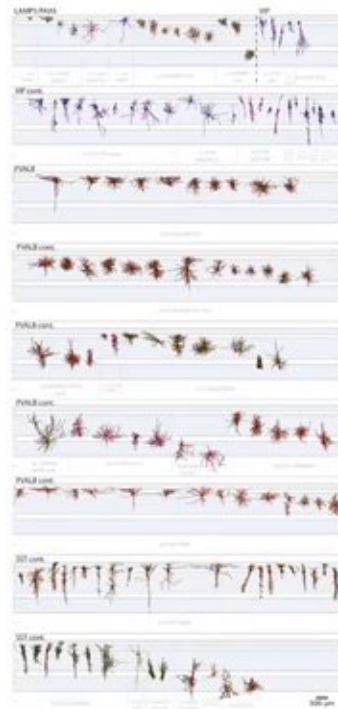
Developmental origins

Axonal projections

Synaptic targets

...

Identifying homologous cell types not only builds confidence in functional relevance of cell types, but also allows inference of properties in human based on phenotypes that cannot easily be measured (e.g. developmental origins, long-range connectivity)



Human
GABAergic
neuron
morphologies
using Patch-seq
on human
neurosurgically
resected tissues

Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD)



ALLEN INSTITUTE *for*
BRAIN SCIENCE



UNIVERSITY of
WASHINGTON



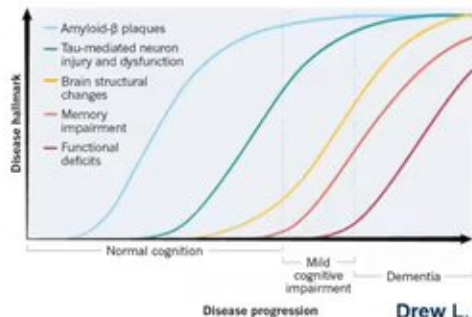
Alzheimer's Disease Research Center

Kaiser Permanente Washington
Health Research Institute



National Institute
on Aging

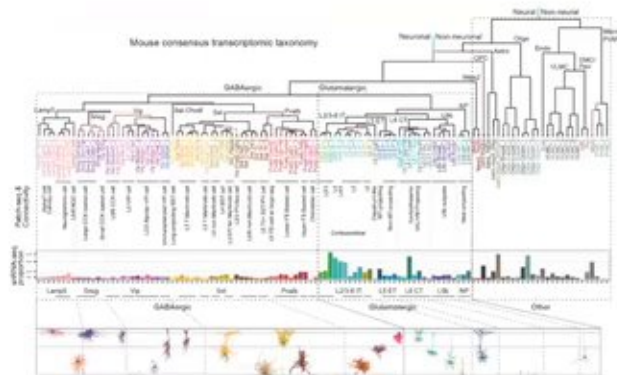
SEA-AD Approach and Aspiration: Put the BRAIN human cell atlas to work to understand cellular specificity and disease trajectories



Drew L. (2018) *Nature*

Comprehensive cellular analysis with cutting edge single cell genomics tools to better understand the cellular and molecular pathology of Alzheimer's disease

- Are some cell types selectively vulnerable or resistant?
- Can AD progression be defined as an abnormal aging trajectory?
- What molecular pathways are perturbed in which cell types?
- Can we identify new cellular and molecular targets for intervention?

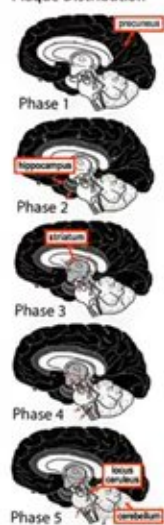


BICCN (2021) *Nature*

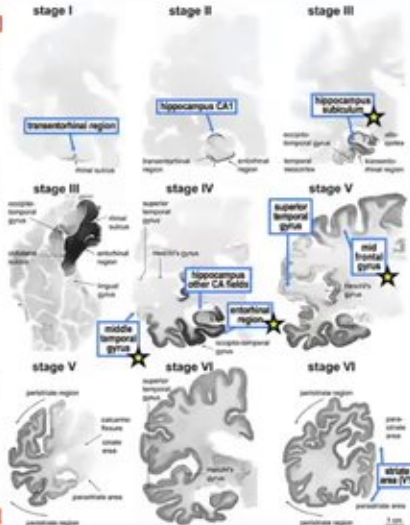
What, where and when?

Identifying cellular and molecular phenotypes of AD as a function of disease progression

A. Thal Phases: A β Plaque Distribution



B. Braak Stages: Neurofibrillary Tangle Distribution



Within-regions disease severity trajectories

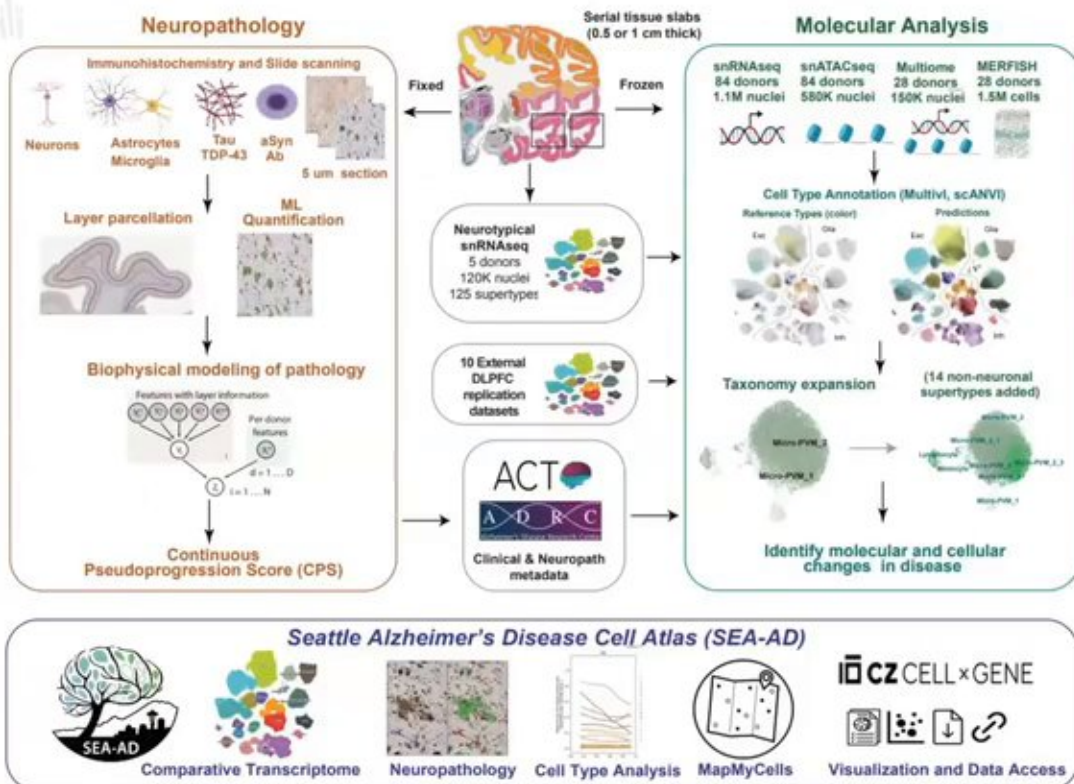


Middle Temporal Gyrus (MTG)
Frontal Cortex (BA9)

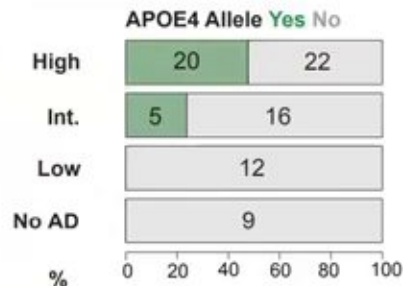
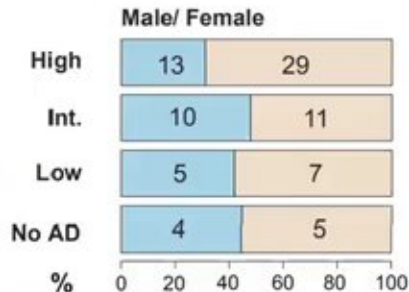
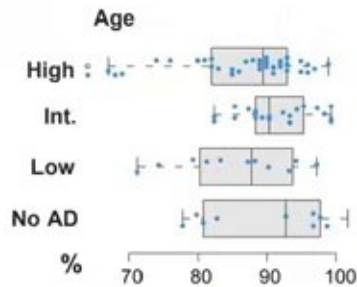
Within-individual disease progression trajectories



Entorhinal Cortex
Hippocampus
Primary visual cortex (V1)
Striatum
Additional regions



SEA-AD cohort: AD and AD/ADRD spectrum with optimized rapid autopsy brain preparation



Braak Staging

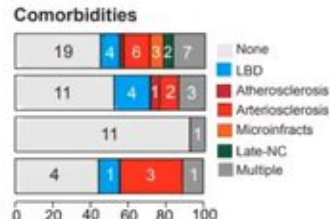
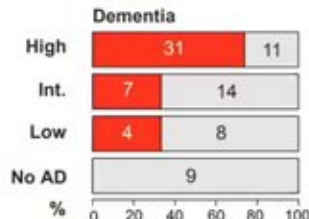
	0	I	II	III	IV	V	VI
High	0	0	0	0	29 (85)	13 (87)	
Int.	0	0	3 (50)	12 (52)	4 (12)	2 (13)	
Low	1 (50)	3 (75)	3 (50)	5 (22)	0	0	
Not AD	1 (50)	1 (25)	0	6 (26)	1 (3)	0	

Thal Staging

	0	1	2	3	4	5
High	0	0	0	0	21 (70)	21 (100)
Int.	0	0	2 (29)	11 (92)	8 (27)	0
Low	0	5 (100)	5 (71)	1 (8)	1 (3)	0
Not AD	9 (100)	0	0	0	0	0

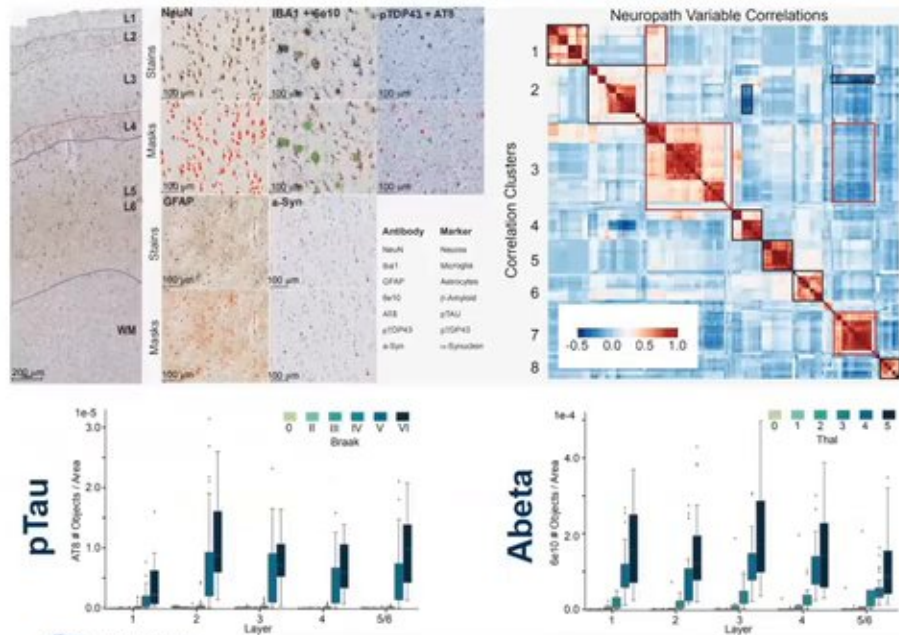
Cerad Score

	Absent	Sparse	Moderate	Frequent
High	0	0	16 (62)	26 (87)
Int.	1 (6)	7 (58)	10 (38)	3 (10)
Low	6 (38)	5 (42)	0	1 (3)
Not AD	9 (56)	0	0	0



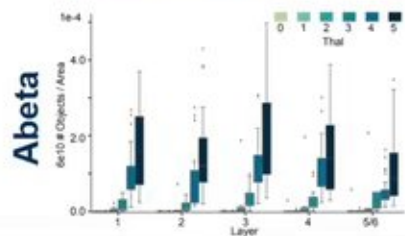
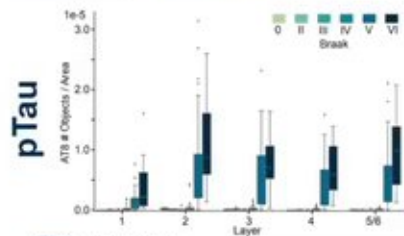
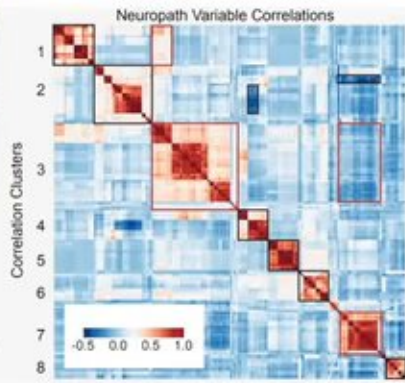
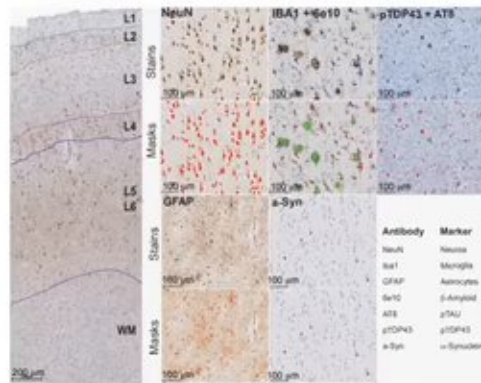
Capturing quantitative aggregate pathology burden in regions analyzed and using that information to model disease severity/progression

Quantitative neuropathology (QNP)

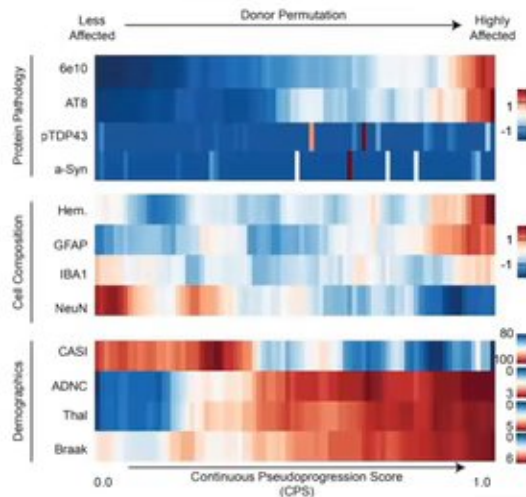


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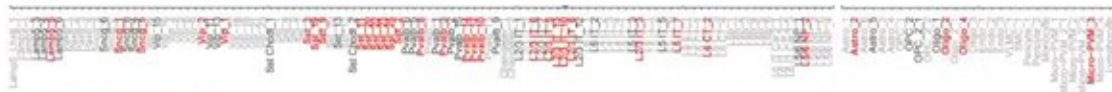
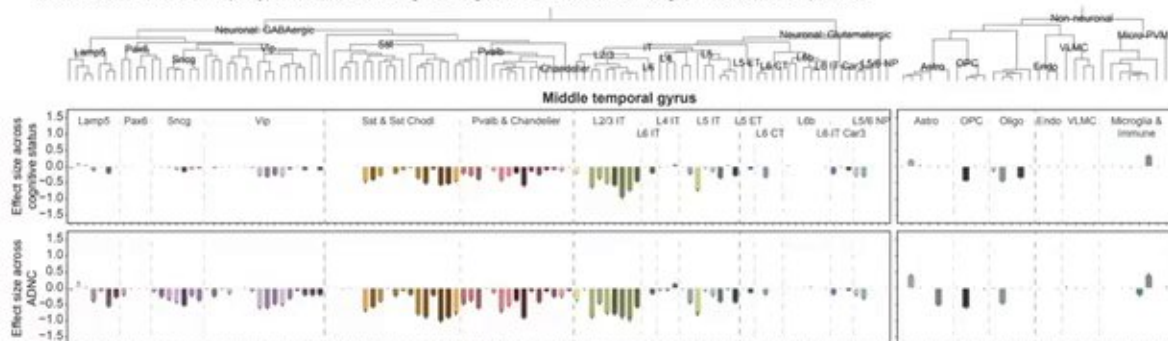


Continuous pseudo-progression score (CPS)



Abundance changes identify vulnerable and disease-associated cell types

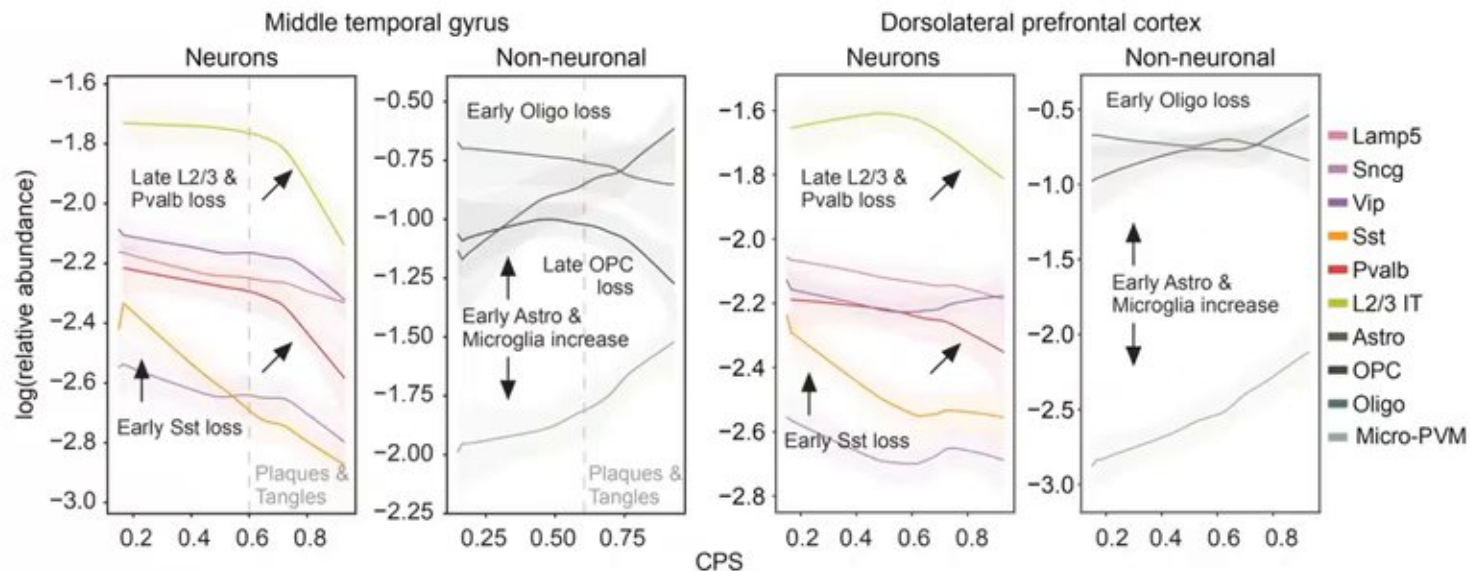
Coherent differences in supertype abundance changes along disease covariates in single nucleus transcriptomics



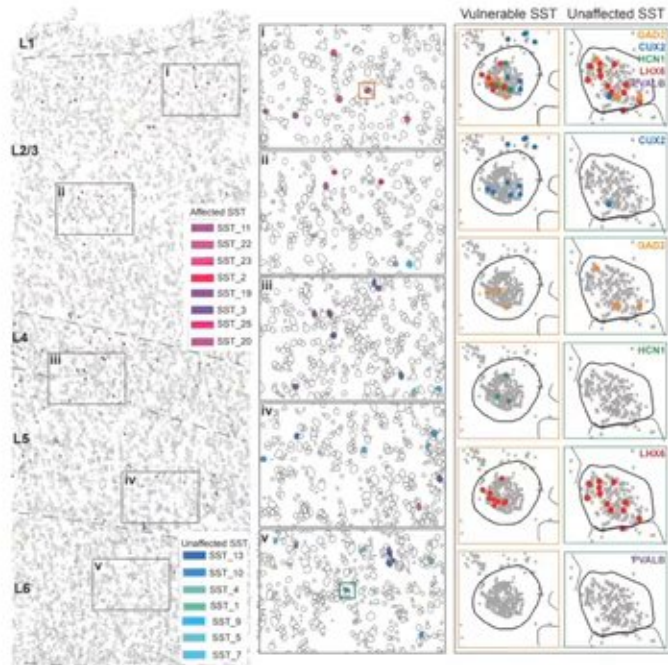
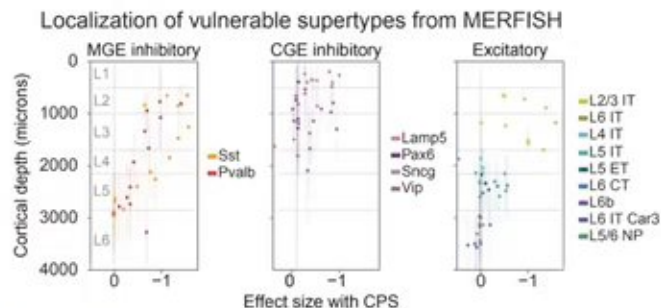
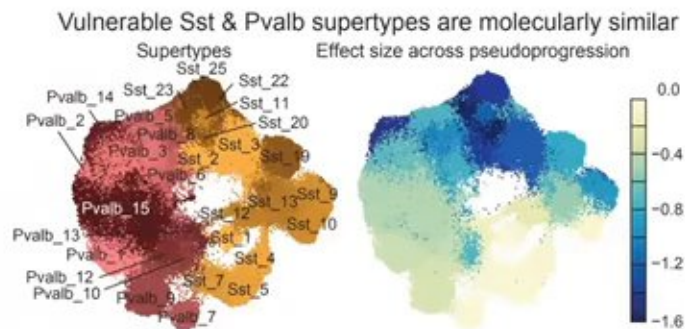
Significant in both regions (32/139)
Significant in one region (28/139)

Model: Supertype abundance ~ Cognitive Status | ADNC | CPS + Sex + Age + Race + 10x Method + APOE4 Status

Pseudotrajectory analysis predicts early and late cellular events

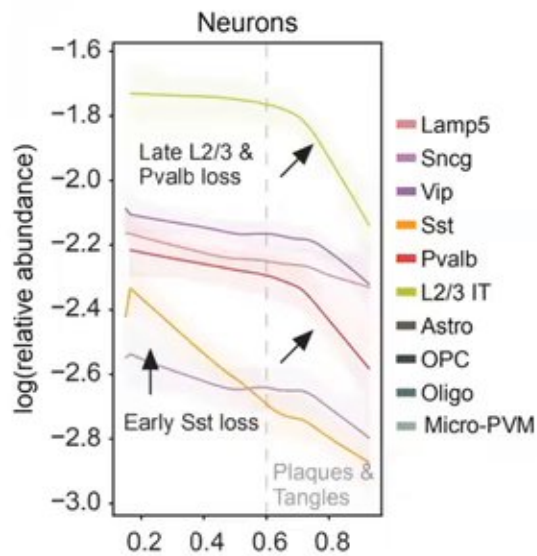


MERFISH demonstrates vulnerable Sst and other cell types are predominantly in upper cortical layers

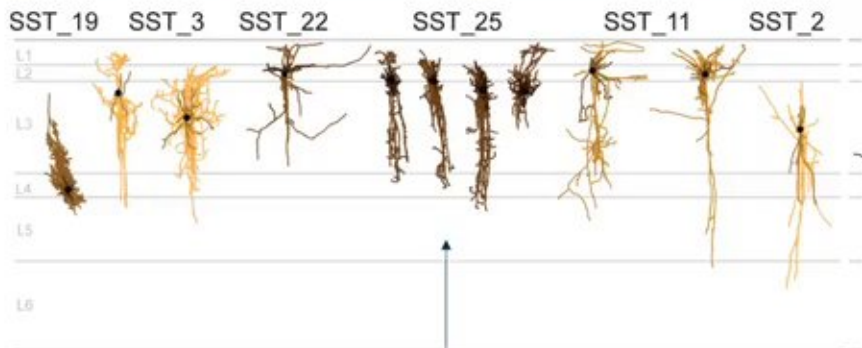


We can now begin to describe human disease-affected cell types at the highest granularity of cellular neuroscience:

Early vulnerable Sst supertypes are phenotypically diverse



Patch-seq analysis from non-AD neurosurgical resections



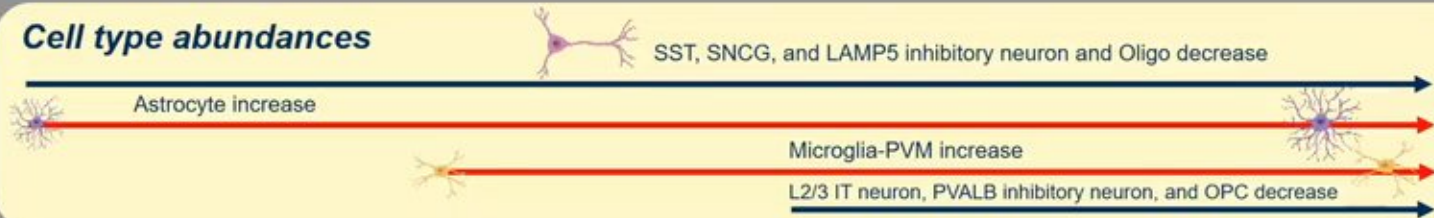
Lee*, Dalley* et al (2023) Science

Double bouquet cells

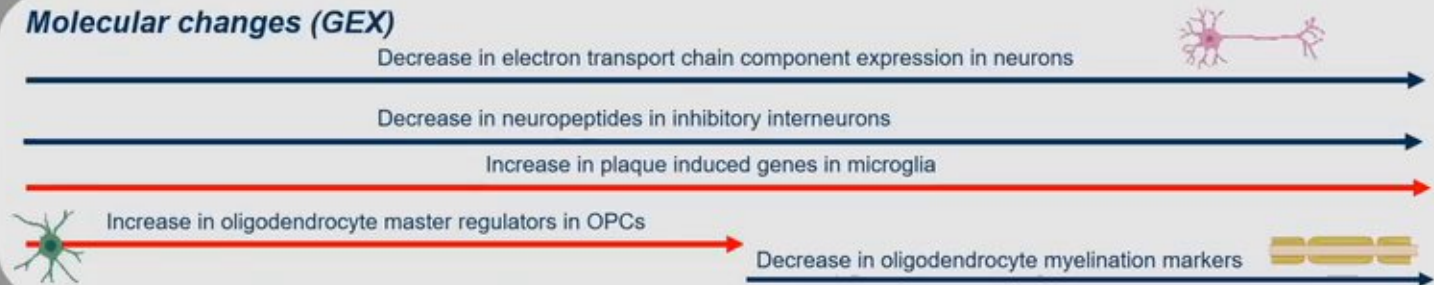
Quantitative Neuropath



Cell type abundances



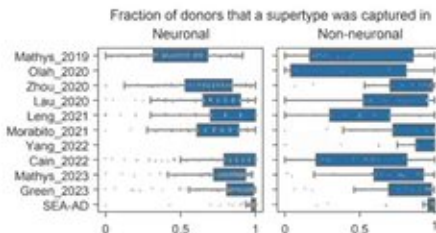
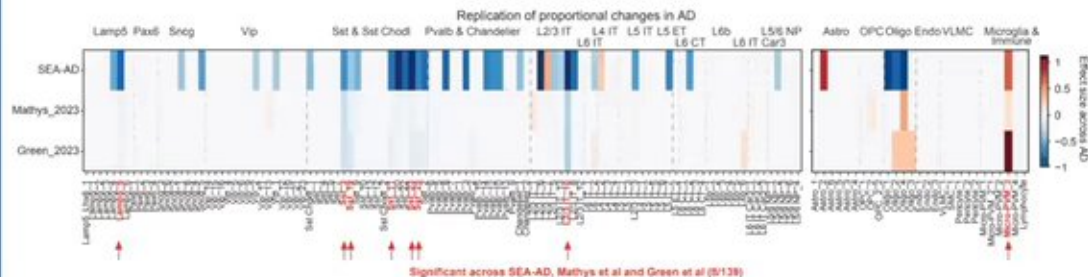
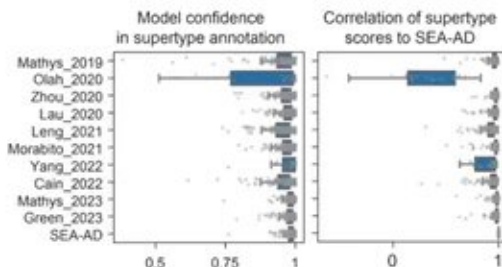
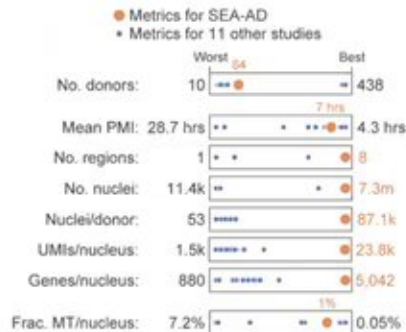
Molecular changes (GEX)



Expanding literature of single nucleus genomics AD studies

Paper	First author	Primary PI(s)	DOI	Brain Region(s)	Notes	Access to raw data
Mathys et al 2019	Mathys	Li-Huei Tsai, Manolis Kellis	10.1038/s41586-019-1195-2	DLPFC		AD Knowledge Portal
Grubman et al 2019	Grubman	Owen J. L. Rackham, Enrico Petretto, Jose M. Polo	10.1038/s41593-019-0539-4	MEC		GEO/SRA
Leng et al 2021	Leng	Lea T. Grinberg, Martin Kampmann	10.1038/s41593-020-00764-7	DLPFC, MEC		GEO/SRA
Lau et al 2020	Lau	Nancy Y. Ip	10.1073/pnas.2008762117	DLPFC		GEO/SRA
Olah et al 2020	Olah	Philip L. De Jager, Vilas Menon	10.1038/s41467-020-19737-2	DLPFC		AD Knowledge Portal
Zhou et al 2020	Zhou	Maxim N. Artyomov, Marco Colonna	10.1038/s41591-019-0695-9	DLPFC	Study includes Mouse and Human Data, Interested in Human Data Only	AD Knowledge Portal
Morabito et al 2021	Morabito	Vivek Swarup	10.1038/s41588-021-00894-z	DLPFC		GEO/SRA
Cain et al 2022	Cain	Naomi Habib, Philip L. De Jager, Vilas Menon	10.1101/2020.12.22.424084	DLPFC	Pre-print, not yet published	AD Knowledge Portal
Yang et al 2022	Yang	Andrew C. Yang, Tony Wyss-Coray	10.1038/s41586-021-04369-3	DLPFC, Hip		GEO/SRA
Green et al 2023	Green	Naomi Habib, Philip L. De Jager, Vilas Menon	10.1101/2023.03.07.531493	DLPFC	Pre-print, not yet published	AD Knowledge Portal
Sun et al 2023	Sun	Li-Huei Tsai, Manolis Kellis	10.1016/j.cell.2023.08.037	DLPFC, Hip, EC, AnG, Thal		AD Knowledge Portal
Mathys et al 2023	Mathys	Li-Huei Tsai, Manolis Kellis	10.1016/j.cell.2023.08.039	DLPFC		AD Knowledge Portal

Other datasets can now be integrated with the reference and used to cross-validate results



Open access data resources



Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD)

The Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD) consortium strives to gain a deep molecular and cellular understanding of the early pathogenesis of Alzheimer's disease. To accomplish this, we are leveraging advances in next-generation single-cell molecular profiling technologies developed through the BRAIN Initiative and at the Allen Institute for Brain Science. We are integrating single-cell profiling technologies with quantitative neuropathology and deep clinical phenotyping through collaboration with the University of Washington Alzheimer's Disease Research Center (ADRC) and Kaiser Permanente Washington Health Research Institute (KPWHRI), to create a multifaceted open data resource. We seek to understand the cellular and molecular changes that underlie Alzheimer's disease initiation and progressive cognitive decline, with the ultimate goal of identifying targets for therapeutic intervention.

Explore The Data



Cell Types

Cellular level transcriptomic data has the power to help uncover and understand cell type vulnerabilities in Alzheimer's and related diseases.

Two resources are provided to explore gene expression relationships in cell types of the middle temporal gyrus (MTG). For neurological reference brains and brains from the SEA-AD aged cohort that span the spectrum of Alzheimer's disease, the SEA-AD Transcriptomics Comparative Viewer enables side by side comparison of gene expression in matched cells for any gene, comparison with essential donor metadata, and quantification of expression differences. The Transcriptomics Explorer shows the set of MTG brain cell types from younger neurotypical donors, illustrating the gene expression basis for defining cell types in the SEA-AD aged donor cohort.

[Transcriptomics Comparative Viewer](#) →

[Transcriptomics Explorer \(Reference MTG\)](#) →

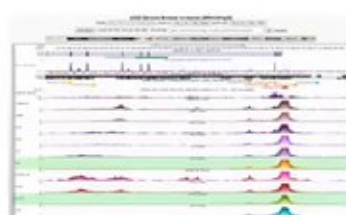
<https://portal.brain-map.org/explore/seattle-alzheimers-disease>

SEA-AD.org



Key elements

- Reference Transcriptome Explorer
- Transcriptomic cell type, gene expression viewer and gene x disease trajectory viewer
- Spatial Transcriptomics viewer
- Donor index
- Neuropathology image viewer
- Data availability through the Sage Bionetworks AD Knowledge Portal and AWS Open Data
- UCSC genome browser for ATAC-seq data
- CZI cell x gene
- **MapMyCells incorporating SEA-AD classification**



Acknowledgements



Many many other team members and collaborators!





Panel 2: Brain Cell Atlases in Brain Disorder Research

- **Moderators:** Keri Martinowich – Johns Hopkins University
Tomasz Nowakowski – UCSF
- **Panelists:** Seth Ament, Philip De Jager, Kiku Ichihara, Arnold Kriegstein, Ed Lein, Chunyu Liu, Dayne Mayfield, Steven McCarroll, Vilas Menon, Eran Mukamel, William Renthall, Panos Roussos, Douglas Shepherd, Michael A. Skinnider, Hongjun Song, Gustavo Turecki, Chuck Vanderburg, Hyejung Won, Yimin Zou
- **Notetakers:** Rebecca Hodge, Jeremy Miller, Alex Pollen, Daifeng Wang



National Institutes of Health
The BRAIN Initiative

Session 3 Panel 2: cell atlases in brain disorder research

- **Moderators:** Tom Nowakowski and Keri Martinowich
- **Goals - and challenges to their attainment**
 - Define a roadmap to use existing/proposed data to advance understanding of cellular vulnerabilities of risk/resilience & identify cellular targets for therapeutics
 - What are the inherent challenges to analyzing these data types across disease cohorts?
 - What can be done, practically, to conduct joint analysis & encourage data/resource sharing to mitigate challenges and attain the goals
- **Presentations**
 - Panos Roussos, "Single-cell gene expression analysis across multiple neuropsychiatric and neurodegenerative diseases"
 - Philip de Jager, "Cellular communities drive trajectories to Alzheimer's disease or alternative brain aging"
 - Chunyu Liu, "The impacts of precision and accuracy of scRNA-seq data on case-control comparisons"
 - Keri Martinowich, "Gene expression across spatial domains of the dorsolateral prefrontal cortex in neuropsychiatric disorders"
- **Panelists:** Seth Ament, Philip de Jager, Kiku Ichihara, Arnold Kriegstein, Ed Lein, Chunyu Liu, Dayne Mayfield, Steven McCarroll, Vilas Menon, Eran Mukamel, William Renthal, Michael Skinnider, Hongjun Song, Gustavo Turecki, Chuck Vanderburg, Hyejung Won, Yimin Zou
- **Notetakers:** Rebecca Hodge, Jeremy Miller, Alex Pollen, Daifeng Wang, Michael Hawrylycz











Single-cell gene expression analysis across multiple neuropsychiatric and neurodegenerative diseases

The BRAIN Initiative® Cell Atlas Workshop: From Single-Cell Genomics to Brain Function and Disorders—Data Integration and Annotation

Panos Roussos, M.D., Ph.D.

January 18th, 2024

Friedman Brain Institute
Department of Genetics and Genomic Sciences
Department of Psychiatry
James J. Peters VA Medical Center



Center for Disease
Neurogenetics



Icahn
School of
Medicine at
Mount
Sinai



Single-cell gene expression analysis across multiple neuropsychiatric and neurodegenerative diseases

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Icahn
School of
Medicine at
Mount
Sinai

PsychENCODE: Studying changes of gene expression and epigenome regulation across serious mental illness



National Institute
of Mental Health

Participating organizations include:

- Duke University
- Icahn School of Medicine at Mount Sinai
- Johns Hopkins University
- Lieber Institute for Brain Development
- Mayo Clinic
- National Institute of Mental Health
- Sage Bionetworks
- Stanford
- SUNY Downstate Medical University
- SUNY Upstate Medical University
- University of California Los Angeles
- University of California San Francisco
- University of Chicago
- University of Illinois
- University of Massachusetts Medical School
- University of North Carolina
- University of Southern California
- Yale University



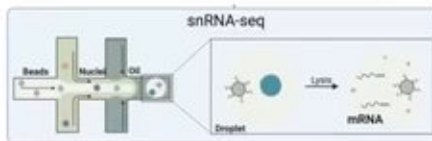
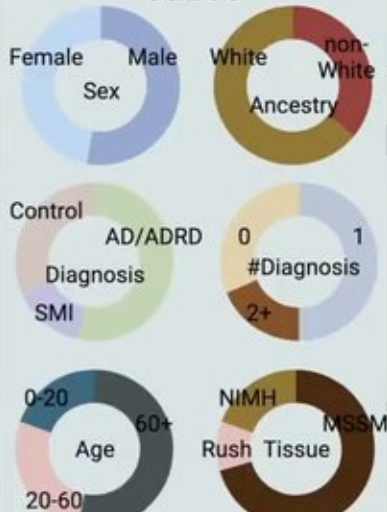


Center for Disease
Neurogenomics

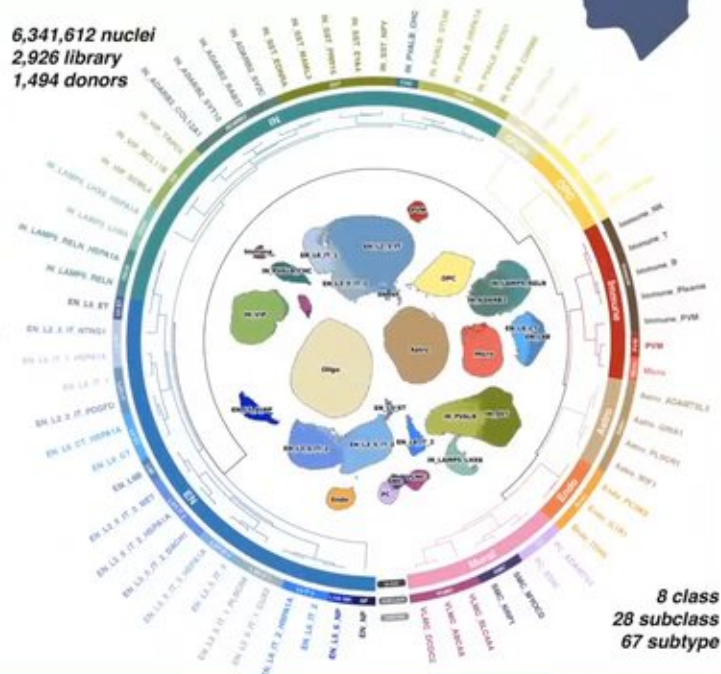
PsychAD: studying interindividual variation across disorders, aging and genetic architecture



1500 Autopsy cases



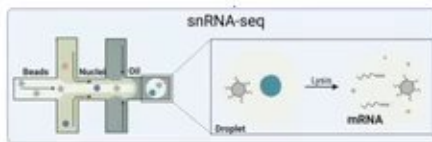
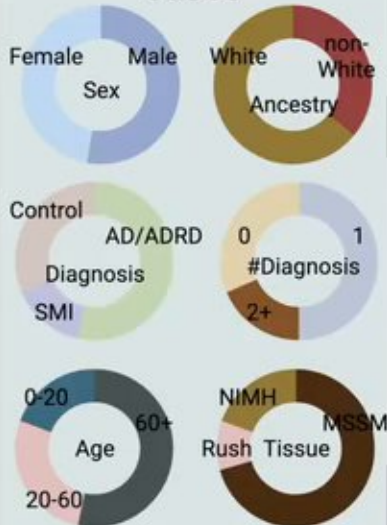
6,341,612 nuclei
2,926 library
1,494 donors



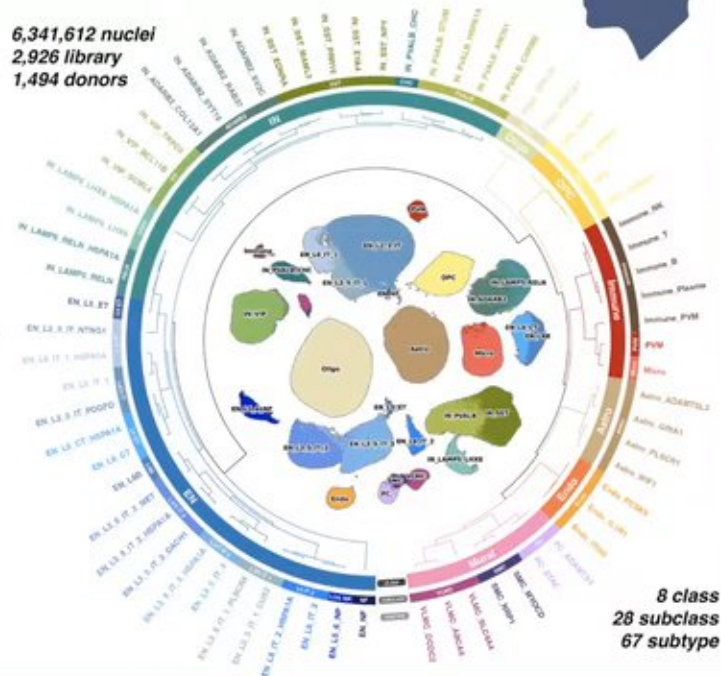
PsychAD: studying interindividual variation across disorders, aging and genetic architecture



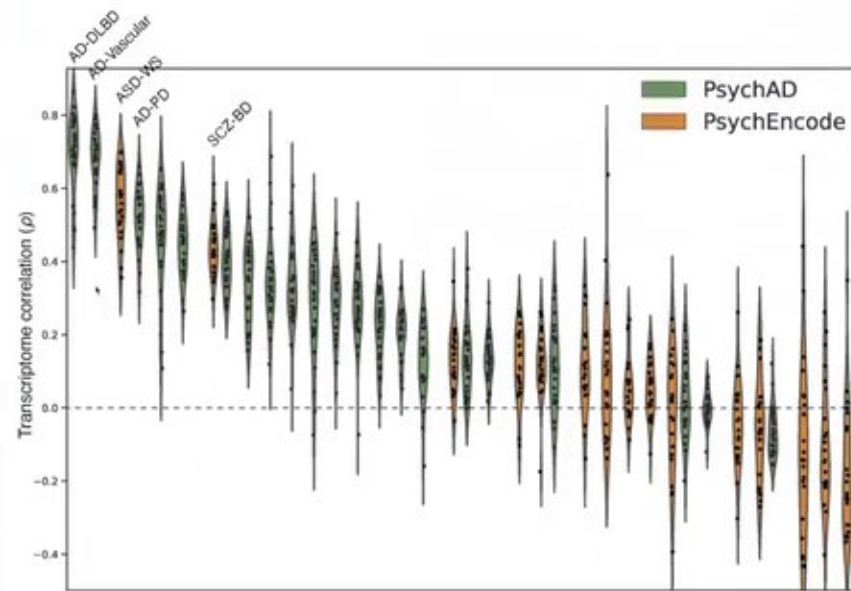
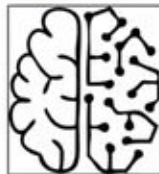
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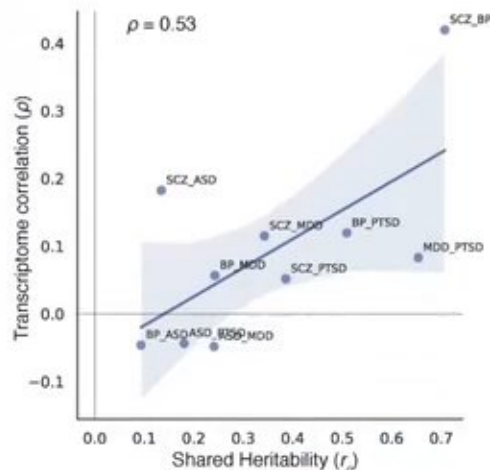
6,341,612 nuclei
2,926 library
1,494 donors



Creating a disease atlas by incorporating a cross-disorder design

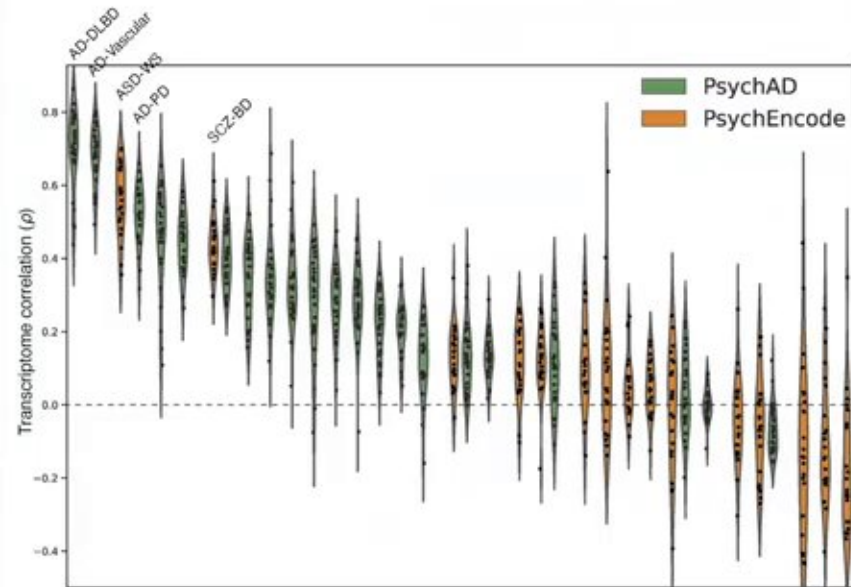
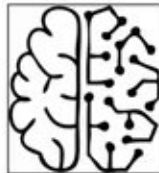


Transcriptome changes in specific cell types are shared

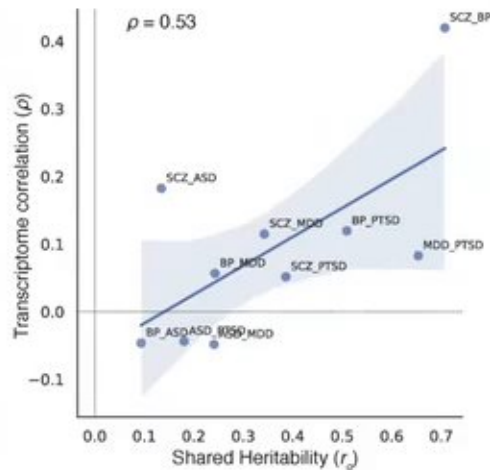


The degree of sharing of transcriptome changes is related to polygenic overlap

Creating a disease atlas by incorporating a cross-disorder design

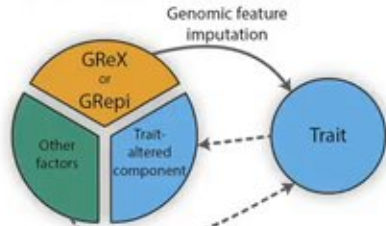


Transcriptome changes in specific cell types are shared among traits



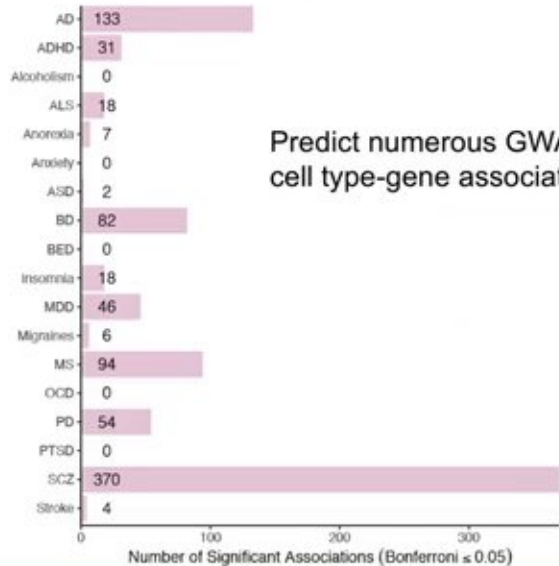
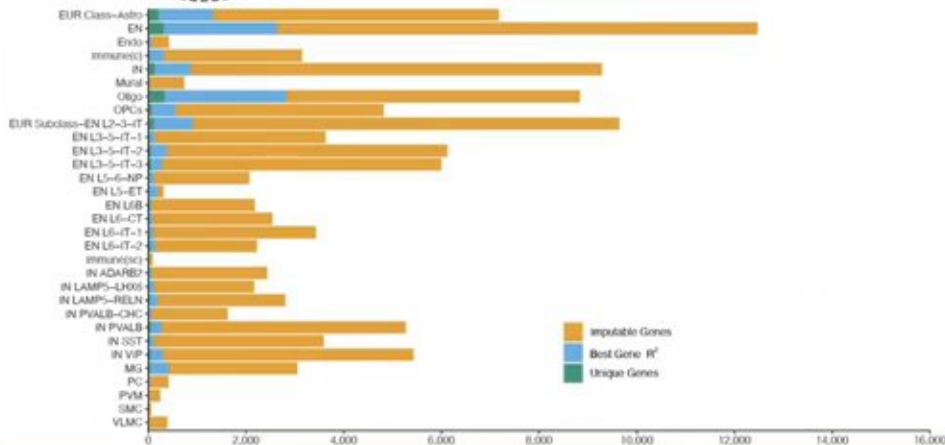
The degree of sharing of transcriptome changes is related to polygenic overlap across traits

Explaining the genetic architecture of neuropsychiatric traits at single cell resolution



confidently predict
23,486 unique
genes and 252,199
gene-cell
combinations

Predict numerous GWAS-
cell type-gene associations

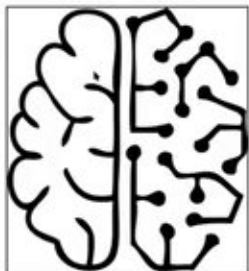


Annotating the BRAIN Initiative Cell Atlas with disease signatures

BRAIN Initiative Cell Atlas to provide an anatomical, cellular and functional lexicon of the human brain



Cross-disorder analysis to define shared and unique molecular changes across multiple traits within specific cell types



Population scale analysis to uncover shared and unique molecular traits at the single cell level underlying disease heritability



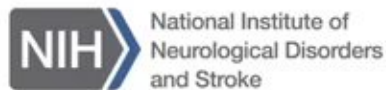
Acknowledgements



Accelerating Medicines
Partnership Program for
Alzheimer's Disease (AMP-AD)



PsychAD























Cellular communities drive trajectories to Alzheimer's disease or alternative brain aging

Philip L. De Jager, M.D. Ph.D.

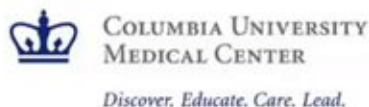
Weil-Granat Professor of Neurology

Director, Center for Translational & Computational Neuroimmunology

Chief, Division of Neuroimmunology

Grand Rounds

Northwestern University Feinberg School of Medicine



1 Cellular communities drive trajectories to Alzheimer's disease or alternative brain aging

Philip L. De Jager, M.D. Ph.D.
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Disclosures

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- Sponsored Research Agreement: Biogen, Merck-Serono
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- Funding from the Chan Zuckerberg Initiative
- Funding from the National MS Society
- Funding from the Lushby Foundation

Cohorts

NeuroGenetics Study
2010
• Genetic studies: GWAS and Mendelian Randomization
• Biobank UK

NeuroGenetics Study
2010
• Genetic studies: GWAS and Mendelian Randomization
• Biobank UK

- First in a series of international challenge studies: Genetic studies, GWAS, Mendelian Randomization, Biobank UK
- Genetic studies: GWAS and Mendelian Randomization
- Biobank UK
- Genetic studies: GWAS and Mendelian Randomization
- Biobank UK
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Single nucleus RNAseq of the aging neocortex: Phase 2



snRNAseq cortical data: Discovery & replication analysis



Cellular communities drive trajectories to Alzheimer's disease or alternative brain aging

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CTCN
THE CENTER FOR TRANSLATIONAL &
COMPUTATIONAL NEUROIMMUNOLOGY



COLUMBIA UNIVERSITY
MEDICAL CENTER

Discover. Educate. Care. Lead.

Cohorts

Religious Orders Study (ROS)

- Catholic priests, nuns and brothers
- Started in 1994

Memory and Aging Project (MAP)

- Older men and women in assisted living facilities in the Chicagoland area
- Started in 1997



- Free of dementia at enrollment
- Anatomical Gift Act, donate brains (spinal cords, select nerves and muscles at death)
- >3700 participants (>1500 ROS and >2200 MAP)
- Wide range of risk factors
- Up to 25 waves of annual cognitive function
- Annual serum, plasma, cryopreserved PBMC
- >900 with biennial imaging
- >750 cases of incident AD , >1200 incident MCI
- >1600 autopsies with half brain frozen
- >900 with post-mortem imaging

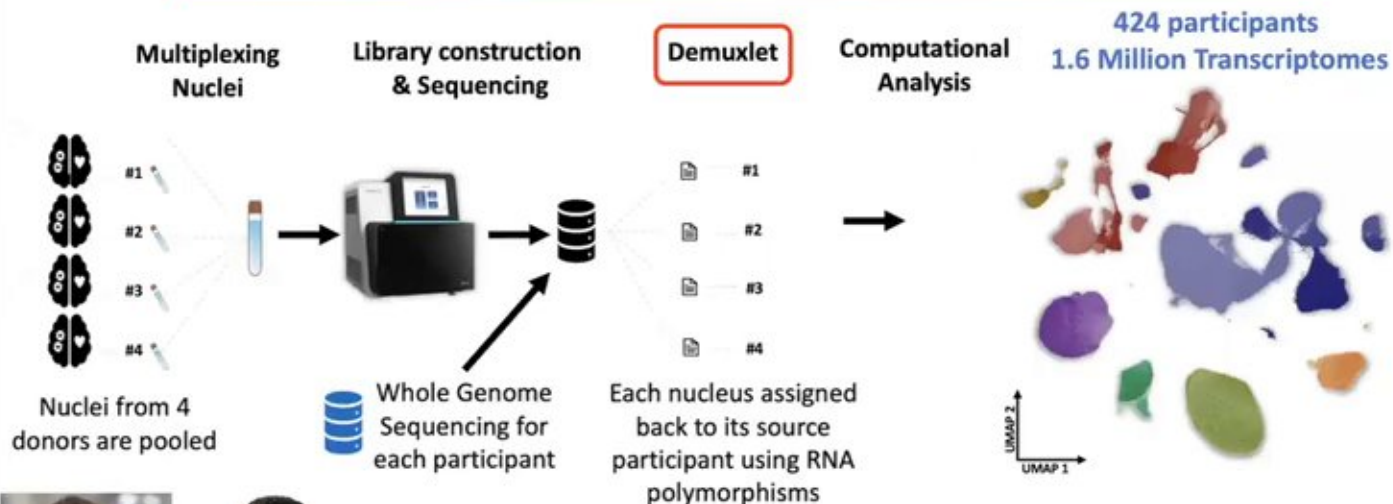


David Bennett



Julie Schneider

Single nucleus RNAseq of the aging neocortex: Phase 2



N. Habib



V. Menon



AD Knowledge Portal

Fujita et al *Nat Genet* (in press)
Green et al *BioRxiv* 2023

Astrocytes (n=228,925)
Oligodendrocytes (n=333,147)
OPCs (n=65,635)
Vascular Niche (n=18,499)

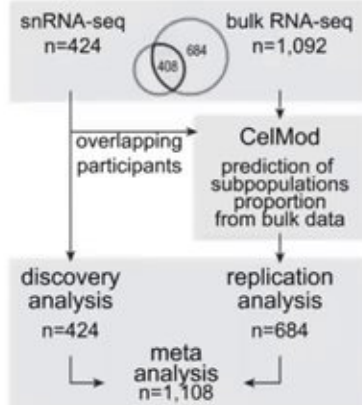
Inh. Neurons (n=257,929)
Exc. Neurons (n=685,336)
Microglia (n=83,729)
Immune (n=3,165)

snucRNAseq cortical data: Discovery & replication analyses

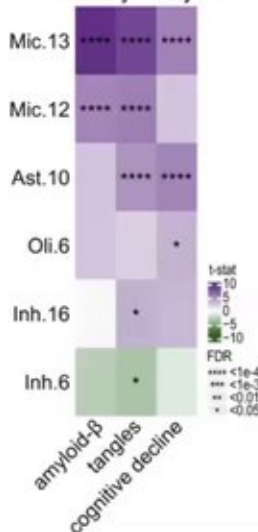
- Relate frequency of cell subtypes to pathologic and cognitive endpoints
- Discovery study (snucRNAseq) → Replication effort (Inferred frequencies from bulk RNAseq) → Meta-analysis

Total n for meta-analysis: 1,108 brains

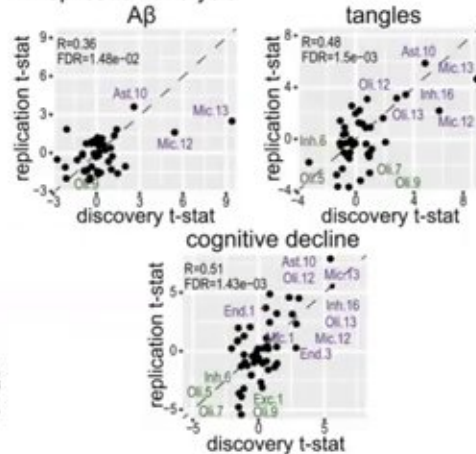
a Analysis overview



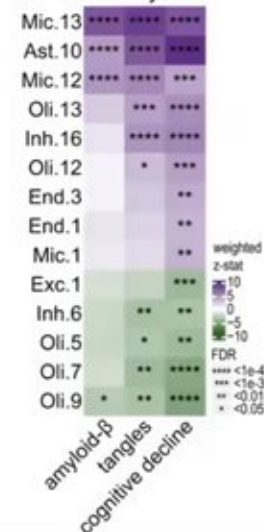
b Discovery analysis



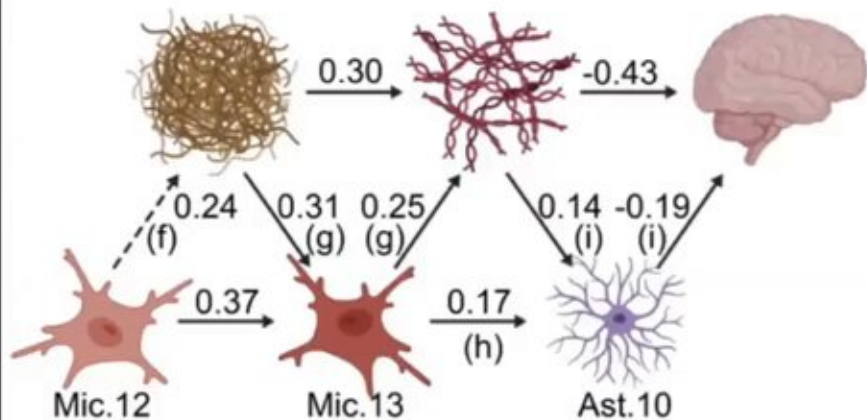
c Replication analysis



d Meta-analysis



Proposing a causal chain leading to cognitive decline



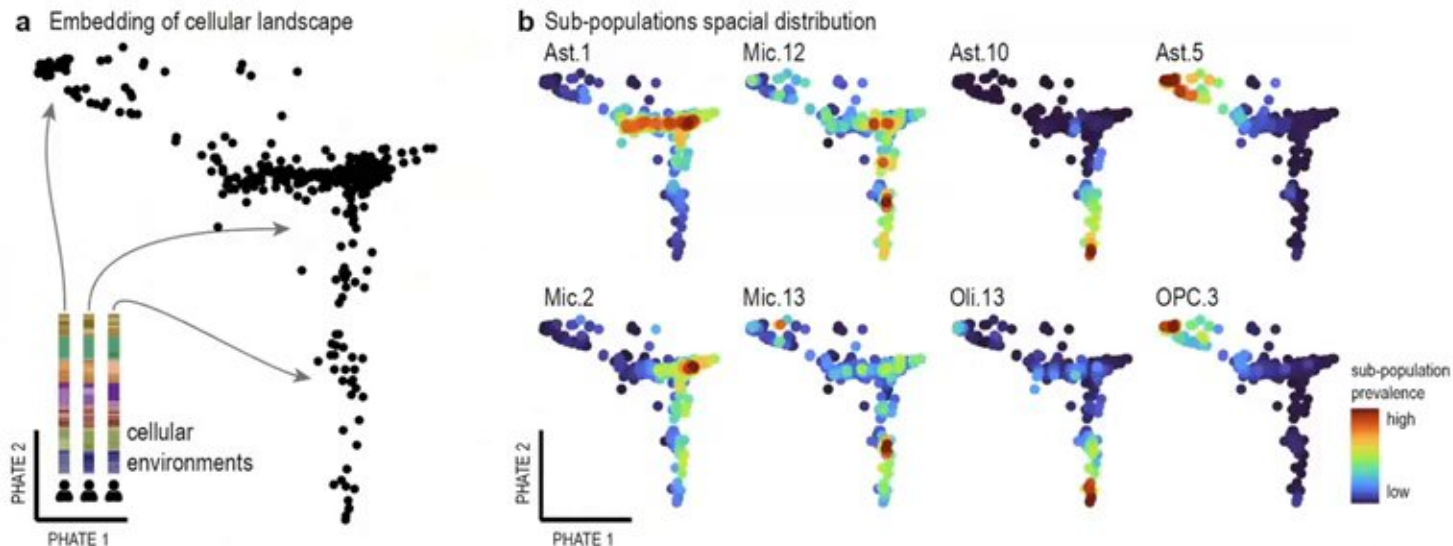
snRNA Nobs=400
 Chi-square p=0.31
 CFI=1.00, TLI=0.99,
 RMSEA=0.021
 (90% CI 0-0.071)

→ Replicated in CelMod
 --> Not replicated in CelMod

- Mediation modeling of cellular frequency & clinicopathologic outcomes
- Results integrated into a single model using structural equation modeling
- Different microglial subtypes influence amyloid and tau burden accumulation (Mic12 & Mic13)
- Astrocyte 10 (Ast10) mediates part of the effect of tau on cognitive decline

Identifying subtypes of participants based on cell subtypes

Each individual participant can be projected into a lower dimensional graph based on the frequency of their cell subtypes using the PHATE algorithm

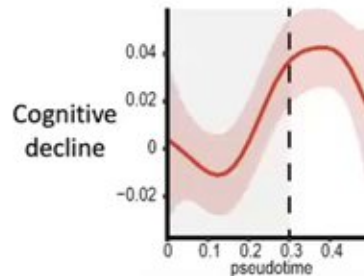
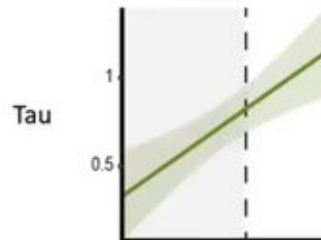
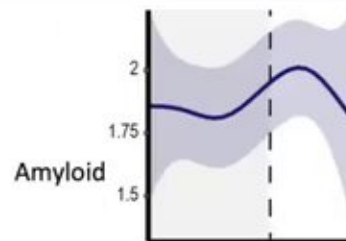
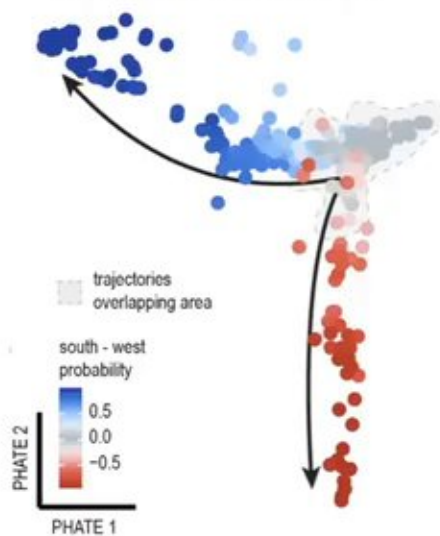




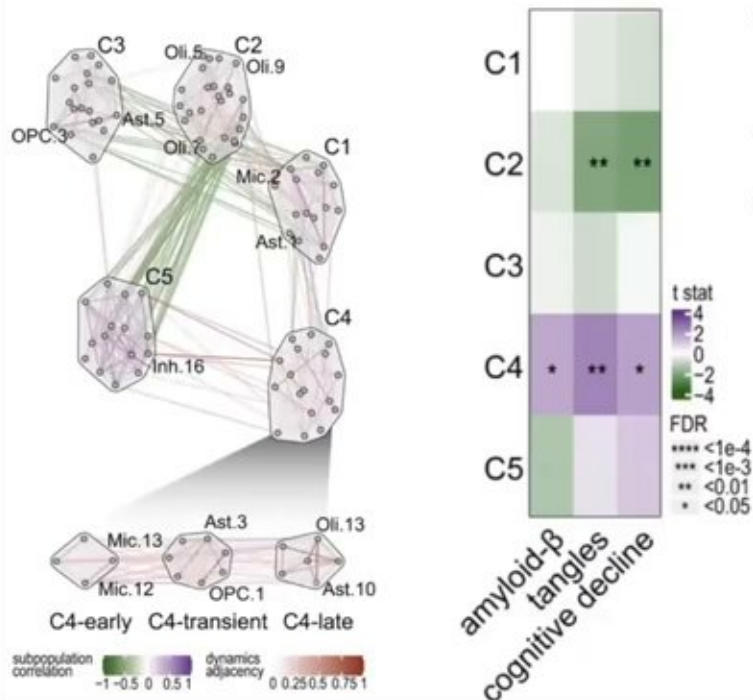
Two different trajectories of brain aging emerge, each with different characteristics



Trajectories in cellular landscape

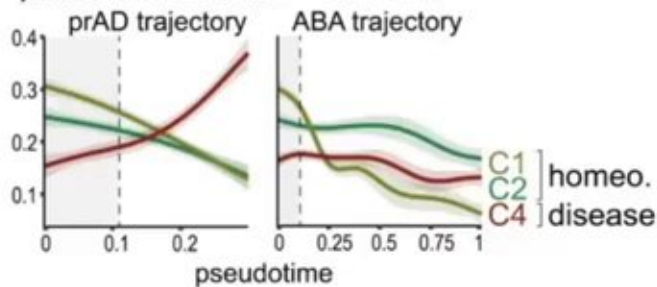


Defining cellular communities & relation to pathology



- Cellular communities are composed of correlated subtypes of different cell types (i.e. neurons, astrocytes, microglia,...)
- Pathologic community increases in frequency with advancing Alzheimer's disease
- Targetable unit is not a cell subtype but the pathologic community $\rightarrow$ identify key nodal subtypes within the community

prAD: homeostatic $\rightarrow$ disease



Large-scale snucRNAseq data from human neocortex uncovers new insights

- Replication of results is critical to provide a foundation for further work
- Proposed causal chain leading to Alzheimer
 - β amyloid $\rightarrow$ Microglia 13 $\rightarrow$ Tau $\rightarrow$ Astrocyte 10
- Heterogeneity of the older brain
 - 2 trajectories for brain aging with one being significantly enriched for poor cognitive outcomes (progression to AD)
- Cellular communities
 - Perturbed cellular communities not individual cells are the target in Alzheimer
- CASCADE project (U19 AG074862) launched: Large-scale spatial multi-omic profiling of the aging and Alzheimer brain



CASCADE



AD Knowledge Portal

Fujita *et al* Nat Genet in press
Green *et al* Biorxiv 2022

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Flow Cytometry SCI

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Mt Sinai Hospital

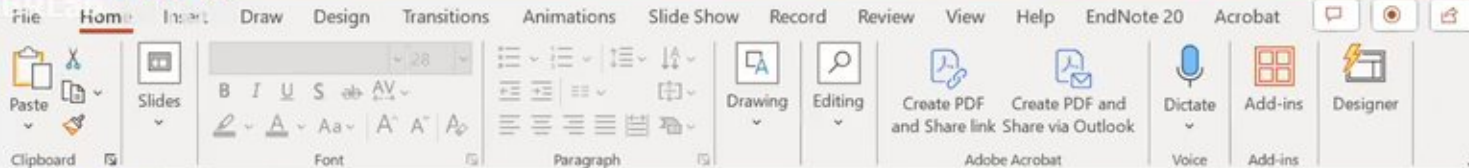
Alice Buonfiglioli, PhD

Lotje De Witte, PhD









The Impacts of Precision and Accuracy of Sc(sn)RNA-seq Data on Differential Expression Analyses

Chunyu Liu

Department of Psychiatry

SUNY Upstate Medical University

1/18/2024

BICCN workshop, Session 3 panel 2



Rujia Dai

0:00:04 || ↺

2:21 PM

The Impacts of Precision and Accuracy of Sc(sn)RNA-seq Data on Differential Expression Analyses

Chunyu Liu

Department of Psychiatry

SUNY Upstate Medical University

1/18/2024

BICCN workshop, Session 3 panel 2



Rujia Dai

Next slide

Driving question:
How can we improve
reproducibility through QC?

No Notes.

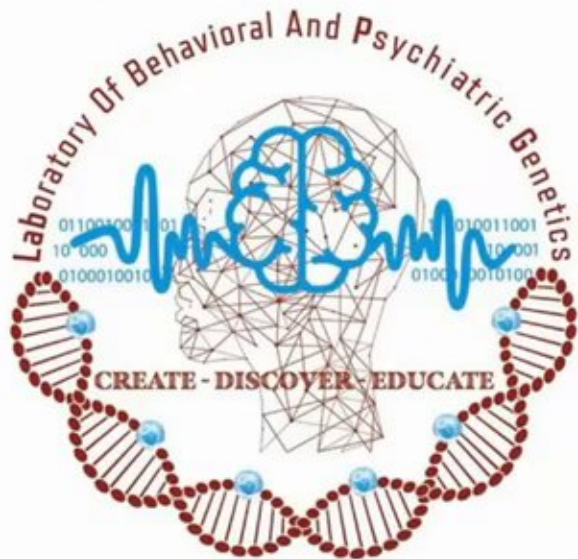


Slide 16 of 30



⌂ ⌂





UPSTATE



The Impacts of Precision and Accuracy of Sc(sn)RNA-seq Data on Differential Expression Analyses

Chunyu Liu

Department of Psychiatry

SUNY Upstate Medical University

1/18/2024

BICCN workshop, Session 3 panel 2

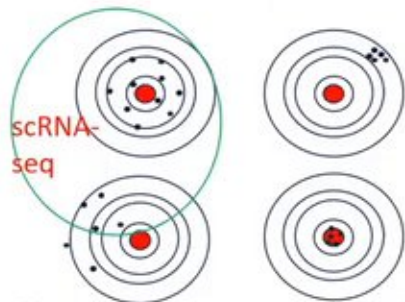


Rujia Dai

Driving question:
How can we improve
reproducibility through QC?

Review Summary of Session 1 Panel 2: Evaluation of Precision and Accuracy of ScRNA-seq Data

- **Low precision** and **poor accuracy** in scRNA-seq data when a small number of cells is sequenced.
- Pseudobulk with a large number of cells is needed to ensure a precise and accurate measure of gene expression.



Implication: *studies using a small number of cells will yield un-reproducible results with false positives and false negatives.*

Minor cell types will suffer the most.

Differential expression analysis

- Data:
 - Pseudo bulks from scRNAseq (for better precision)
 - Real bulks from pooled cells RNAseq (as ground truth for comparison)
- DEG compares LPS treated to untreated phagocytes from four species
- DEG method: edgeR LRT (likelihood ratio tests), $FDR < 0.05$
- Evaluation: comparing DEGs detected in sc and pooled cells for
 - Correlation of effect size of DEGs
 - Proportion of DEGs replicated.



LPS treated
phagocytes



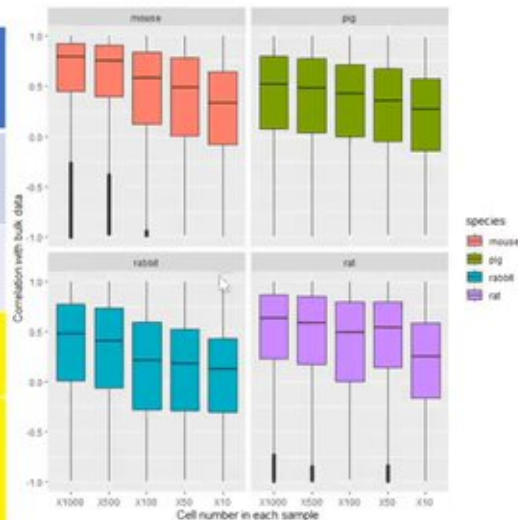
Untreated
phagocytes

Hagai et al. 2018. Nature.

Numbers of DEGs detected

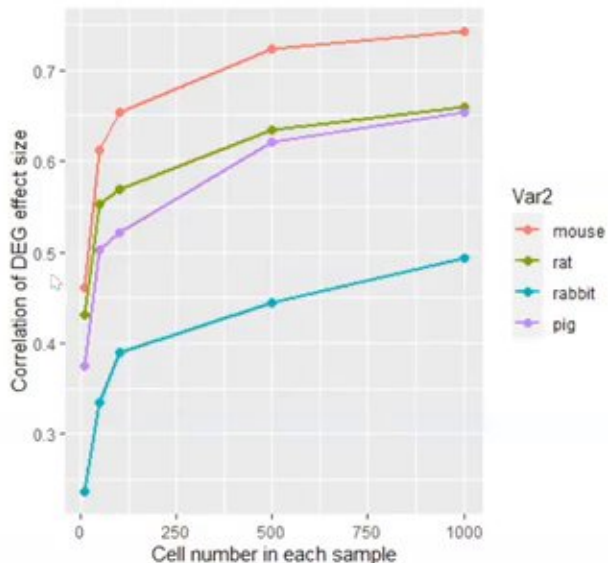
Same sample size a similar # of cells sequenced, but relatively poor accuracy for rabbit data with fewer DEGs detected and poor reproducibility.

	Mouse	Rat	Rabbit	Pig
Pseudobulks DEGs, using all single-cells	3455	2016	912	1395
Real bulks DEGs from pooled cells	3866	3511	114	2682
Proportion of replicated DEGs	73%	46%	76%	76%
Correlation of DEG effect size between sc and pooled cells	0.76	0.67	0.54	0.69

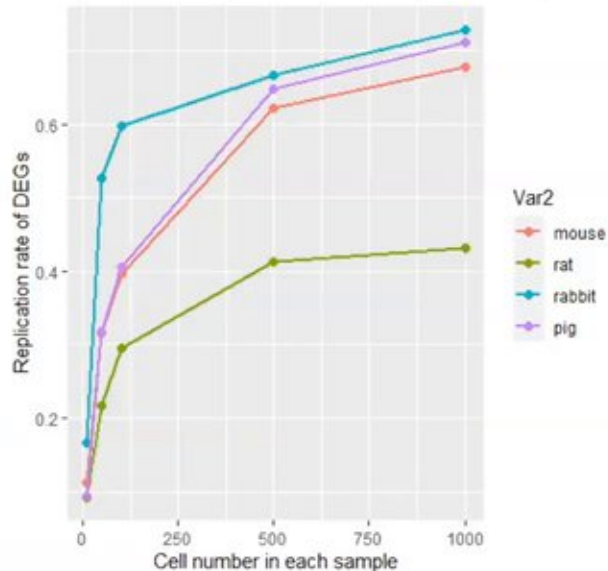


More DEGs detected with better reproducibility with more cells included.

Reproducibility of effect size (FC) of DEGs:



Proportion of replicated DEGs (FDR<0.05)



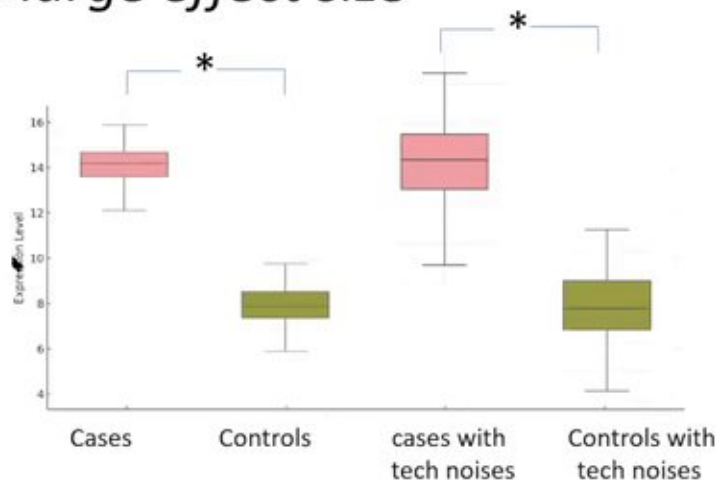
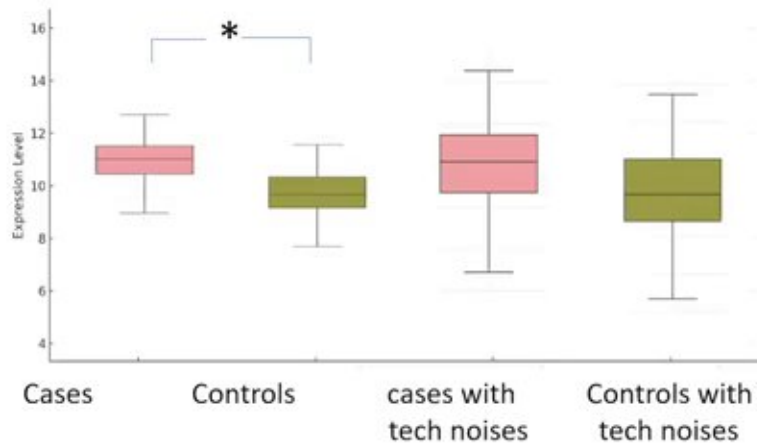
Mouse data were used

Why precision and accuracy are important for DEG analyses?

- **Precision affects power:** imprecise measures (noisy data) require much larger sample to achieve the same statistical power
- **Accuracy reflects true effect size** (group differences): inaccurate measures lead to false findings.
- Reproducibility

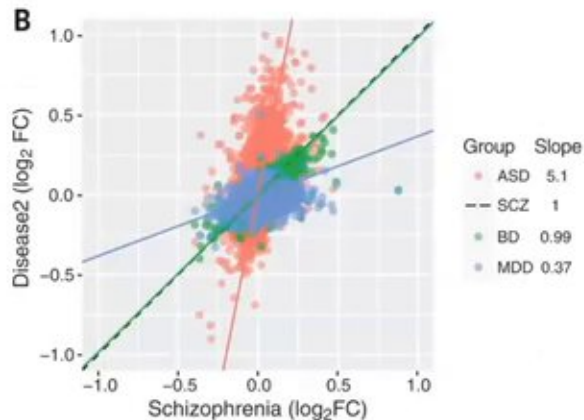
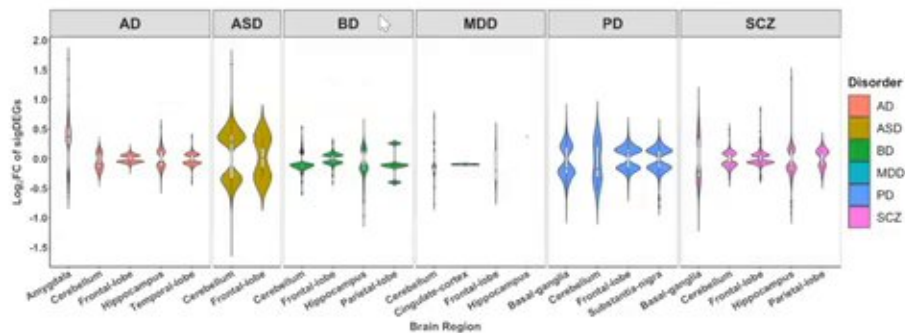
Technical noise can overwhelm small-effect signals but not large-effect signals, even with accurate measures

Small effect size vs large effect size



Most disease-control differences are small

Autism, schizophrenia, bipolar disorder, major depression, and others all have most brain DEGs with fold-change < 2.



Similar impacts expected for

- eQTL mapping (SNP-expression correlation)
- Cell classification (based on expression profile of marker genes)

Warning!

Expression quantification based on individual cells, or pools of a small number of cells per cell type, will likely yield many false findings, deemed unreproducible.



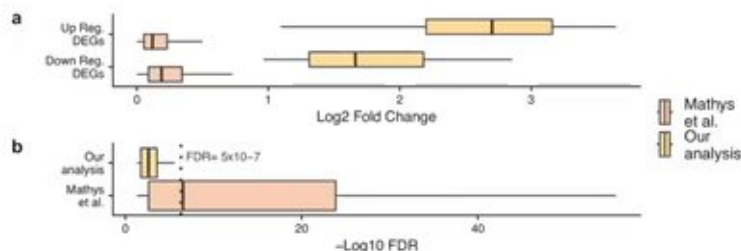
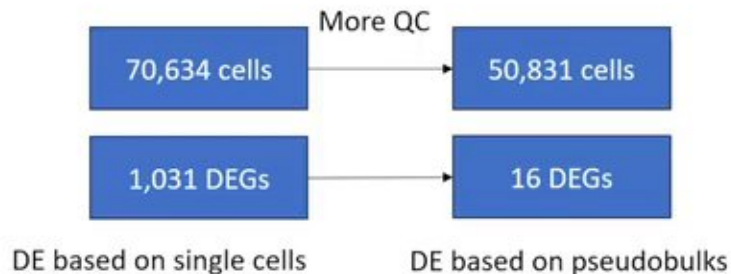
Avoiding false discoveries in single-cell RNA-seq by revisiting the first Alzheimer's disease dataset

Alan E Murphy , Nurun Fancy, Nathan Skene 

UK Dementia Research Institute at Imperial College London, United Kingdom; Department of Brain Sciences, Imperial College London, United Kingdom

Dec 4, 2023 · <https://doi.org/10.7554/eLife.90214.3>  

Modified QC procedures detected much fewer DEGs, but with larger effect sizes



QC: removal of empty droplets, nuclei with low read counts, and doublets

Take home message

We offer recommendations for analyses of existing data and future single-cell studies, aiming for reproducible findings:

- Incorporate CV into the scRNA-seq QC procedures
- Biological variation relative to technical noise determines the confidence of findings.
- Sequence more cells for the target cell types ($> 500?$), when sample size is limited.
- Better RNA quality is always preferred

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 - Sydney Wang
 - Xusheng Wang
 - Dalila pinto

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Gene expression across spatial domains of the dorsolateral prefrontal cortex in neuropsychiatric disorders

Keri Martinowich, PhD

Lead Investigator, Lieber Institute for Brain Development

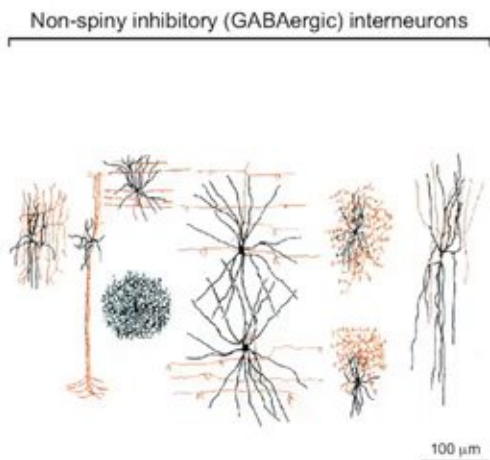
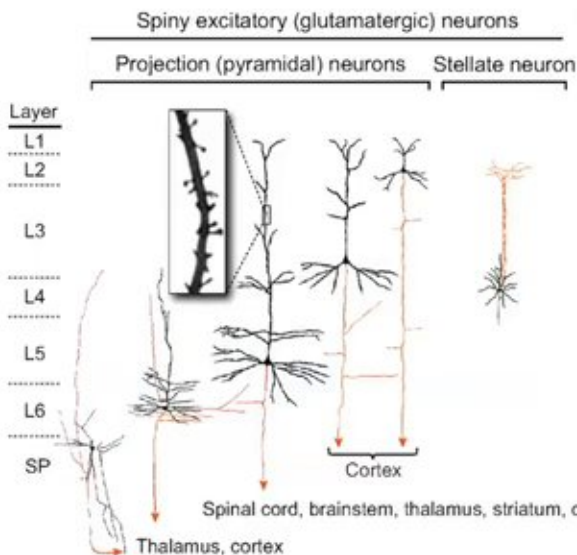
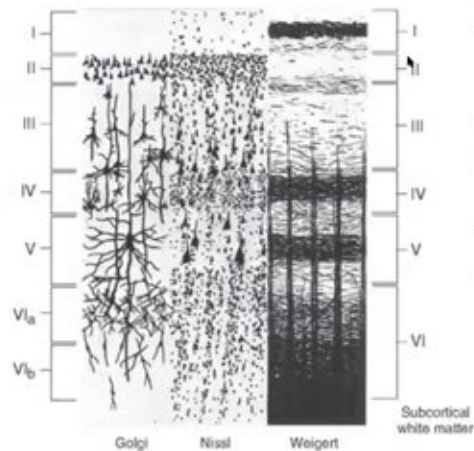
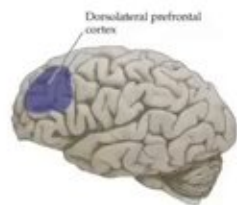
Professor, Johns Hopkins University, Departments of Psychiatry and Neuroscience

1/18/2024, Brain Initiative Cell Atlas Workshop
Session 3.2 – Cell Atlases in Brain Disorder Research



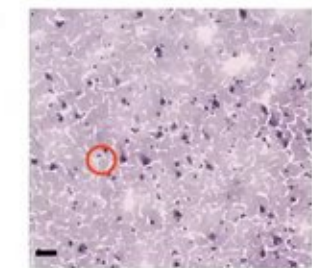
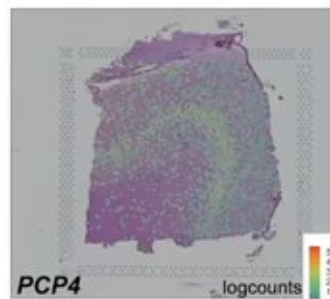
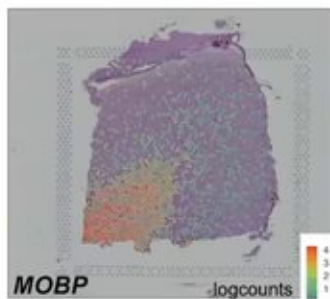
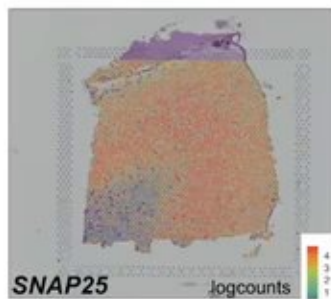
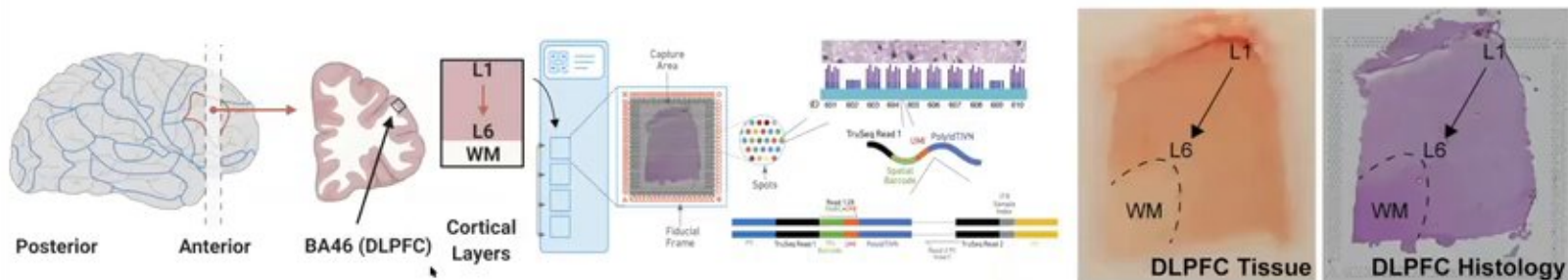
Kristen Maynard, Leo Collado-Torres, Stephanie Hicks, Stephanie Page

Spatial positioning influences cellular morphology, connectivity, and physiology



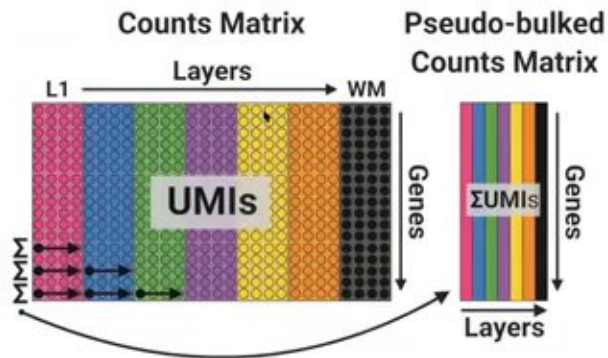
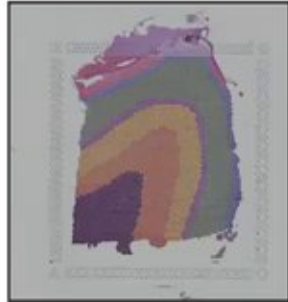
Kwan, *Development*, 2012

Visualizing gene expression in a histological context



50um/spot, ~3 cells/spot

Pseudo-bulking manually annotated spots generates layer-level molecular profiles

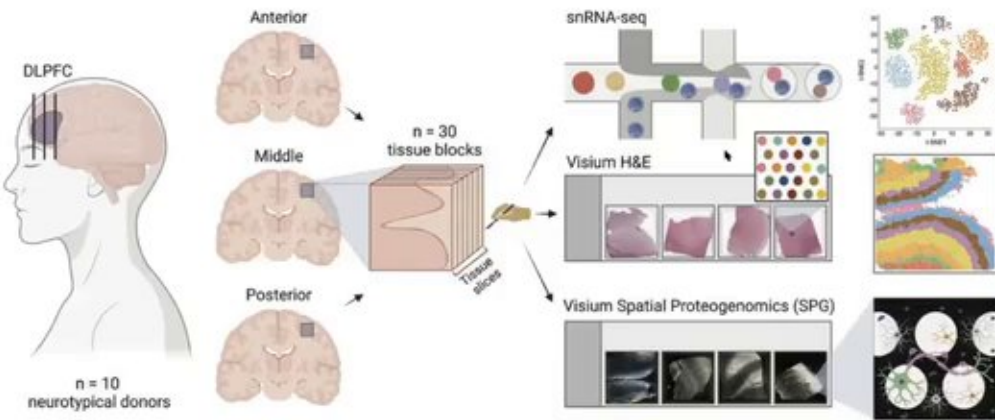


Group	FDR<0.05
Layer1	3033
Layer2	1562
Layer3	183
Layer4	740
Layer5	643
Layer6	379
WM	9124

Issues with scaling to accommodate case-control cohort studies

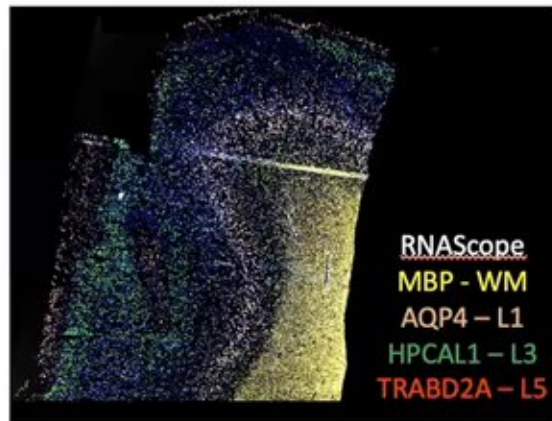
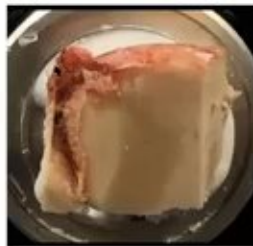
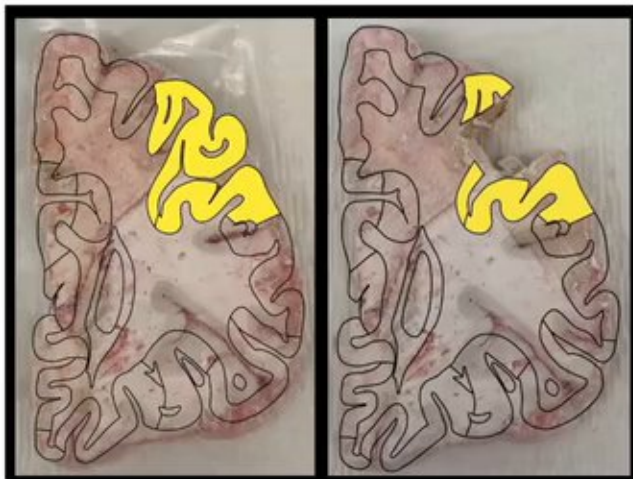
- Sampling confounds
 - Standardizing dissections
 - Neuroanatomical matching (laminae inclusion)
 - Spatial gradients across anterior-posterior axis
- Assessing methods for unsupervised spatial clustering
- Deconvolution of individual Visium spots

Preparation for large-scale, case/control studies

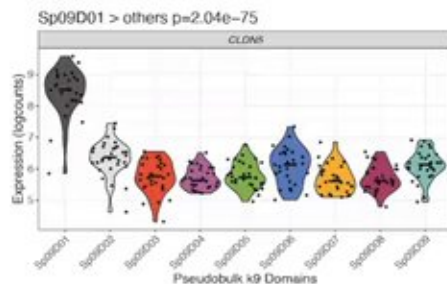
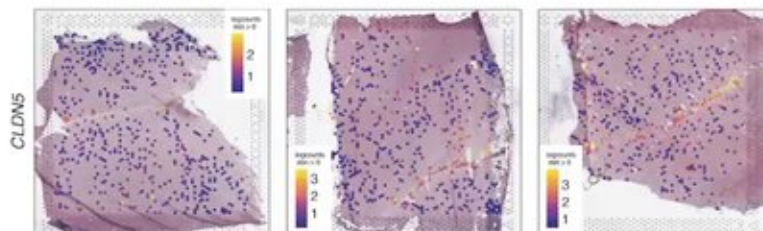
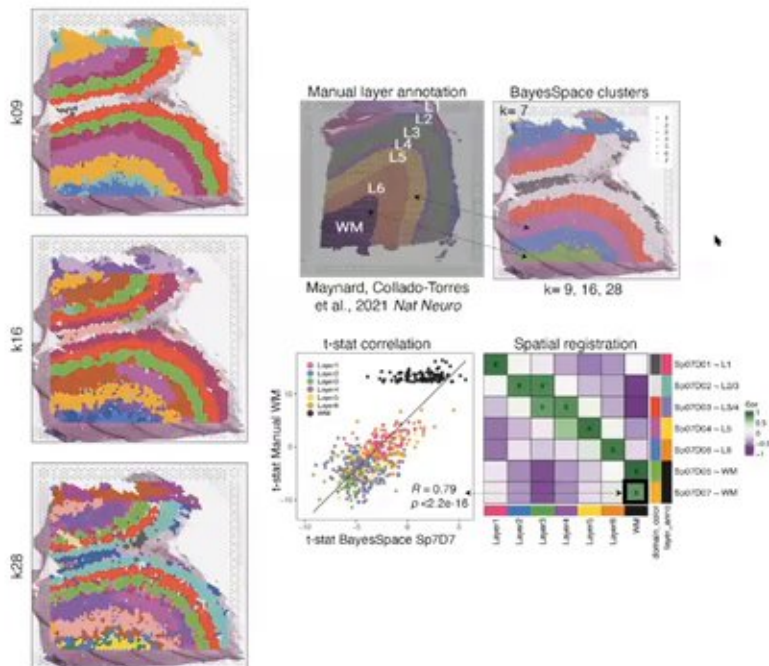


- Anatomical validations (smFISH)
- Compare unsupervised clustering algorithms to manual annotations
- Spatial registration with paired snRNA-seq
- Benchmark spot-level deconvolution with proteomic data for cell type markers
- Within-donor comparison over 3 anterior-posterior locations

Dissection optimization and anatomical validations

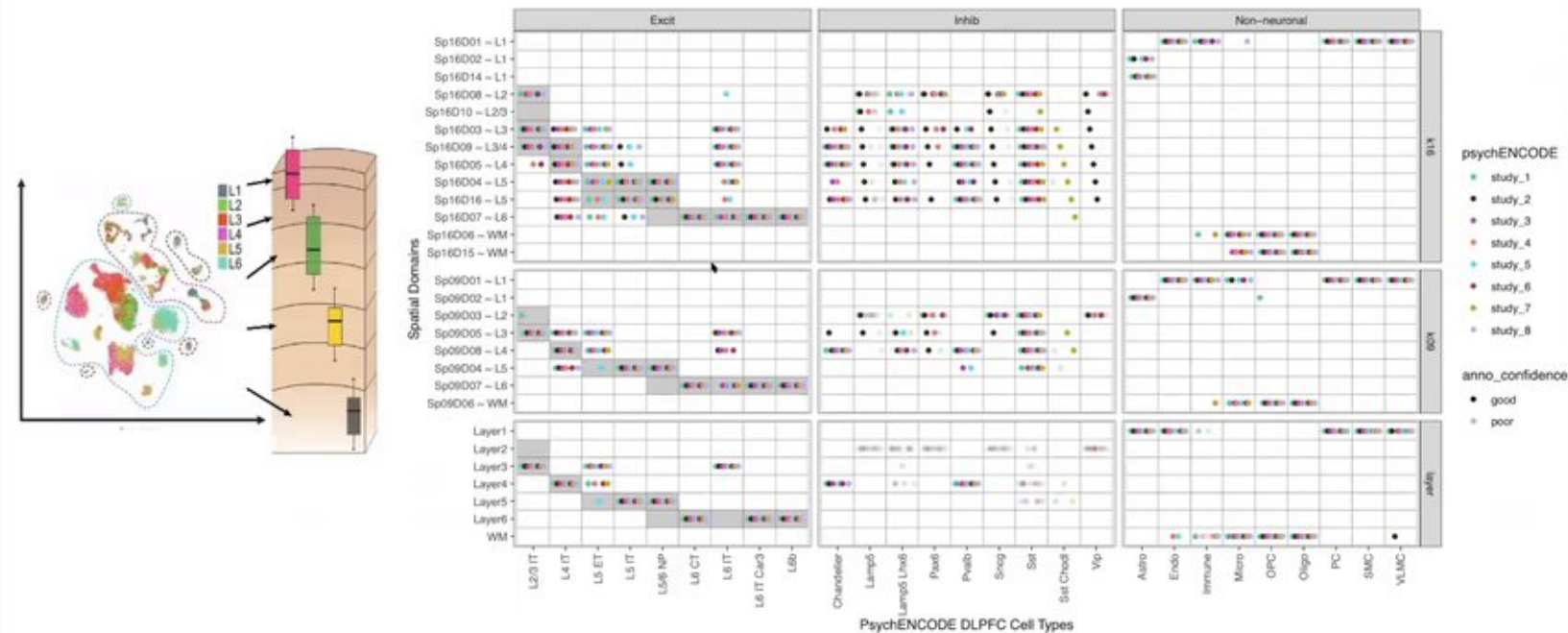


Unsupervised spatial clustering

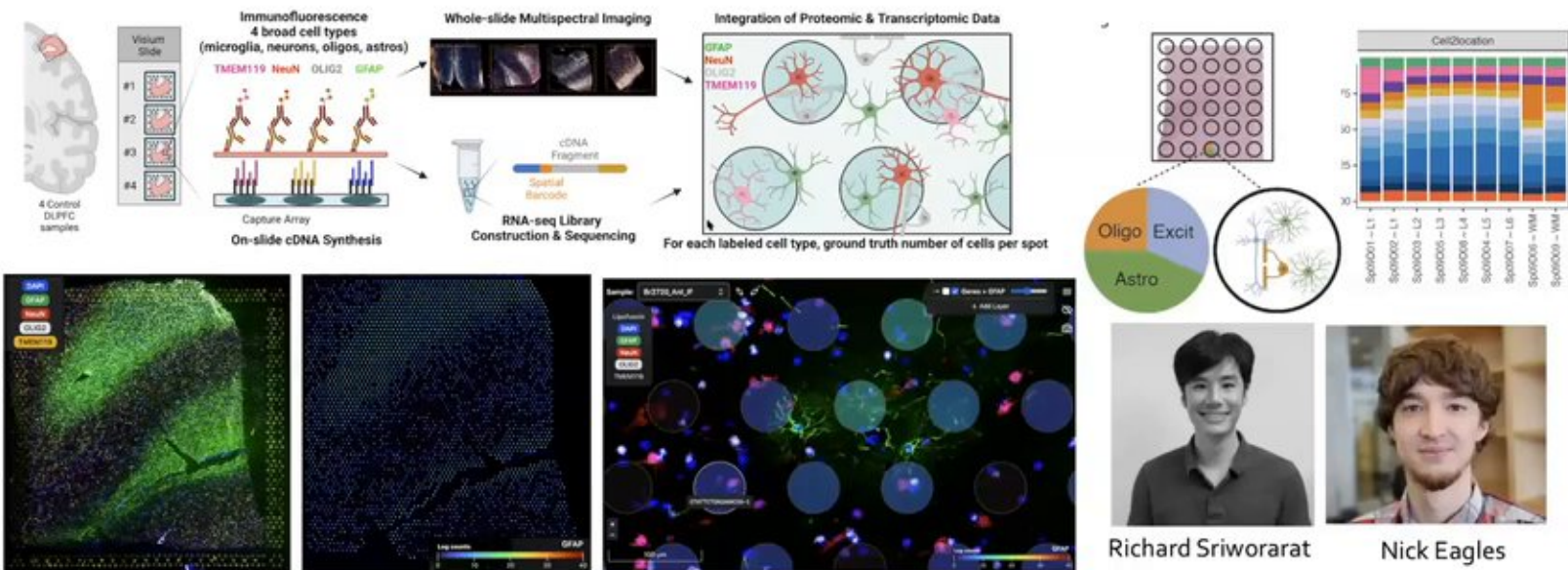


Louise Huuki

Spatial registration of snRNA-seq data



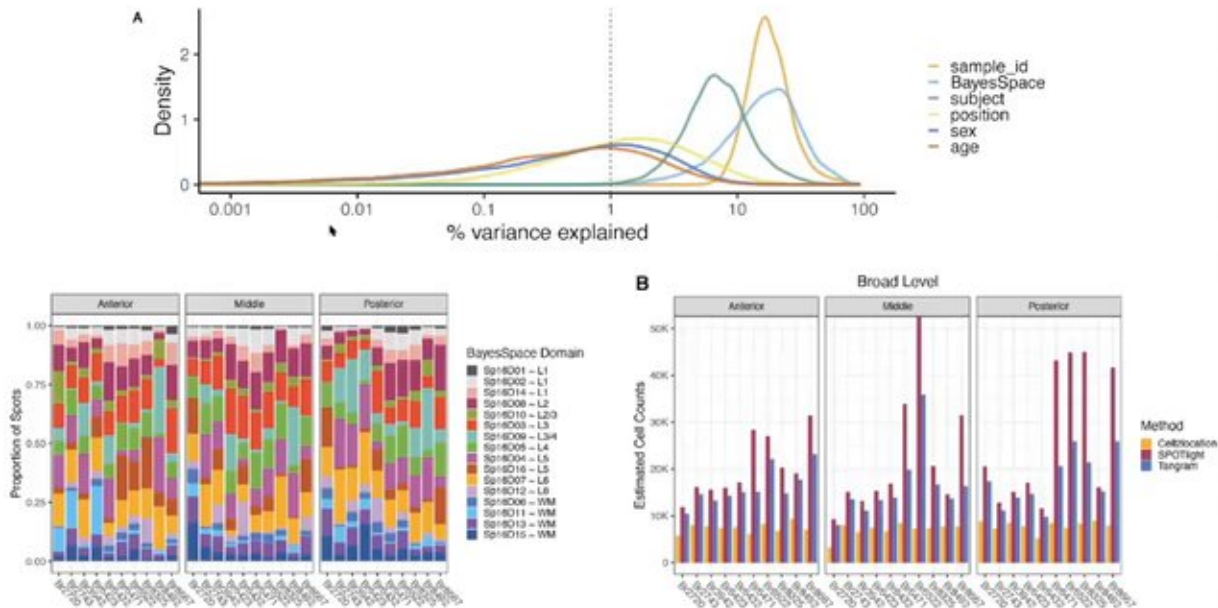
Benchmarking spot-level deconvolution with protein ground truth



Samui browser

Gene expression/cell counts over A-P axis of DLPFC

- 512 differentially expressed genes across A-P axis
- Differences across spatial domain and donor far outweigh variance from gradient over A-P axis
- No changes in cell counts/spot over A-P axis



Studies underway

- Dissection and anatomical validation of 240 DLPFC blocks
 - NTC, MDD, BPD, SCZ
- Data acquisition ongoing ,
- Additional benchmark studies (same n=10 well-characterized neurotypical control donors from DLPFC)
 - Hippocampus
 - Nucleus accumbens
 - Amygdala
 - Dorsal anterior cingulate cortex

Lieber Institute

Molecular Neuroanatomy

Kristen Maynard

Heena Divecha

Kelsey Montgomery

Ege Yalcinbas

Imaging Development

Stephanie Page

Uma Kaipa

Lina Oh

Lexy Papariello

Anthony Ramnauth

Madhavi Tippani

Data Science

Leo Collado-Torres

Nick Eagles

Louise Huuki

LIBD Brain Repository

Thomas Hyde

Joel Kleinman

James Tooke

Amy Deep

Neural Plasticity

Keri Martinowich

Suhaas Adiraju

Svitlana Bach

Yufeng Du

Sang-Ho Kwon

Jorge Miranda-

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Erik Nelson

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Michael Totty

Lukas Weber



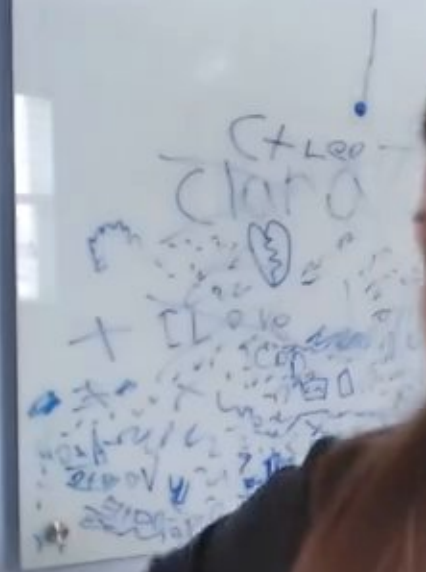
LIEBER INSTITUTE *for*
BRAIN DEVELOPMENT
MALTZ RESEARCH LABORATORIES













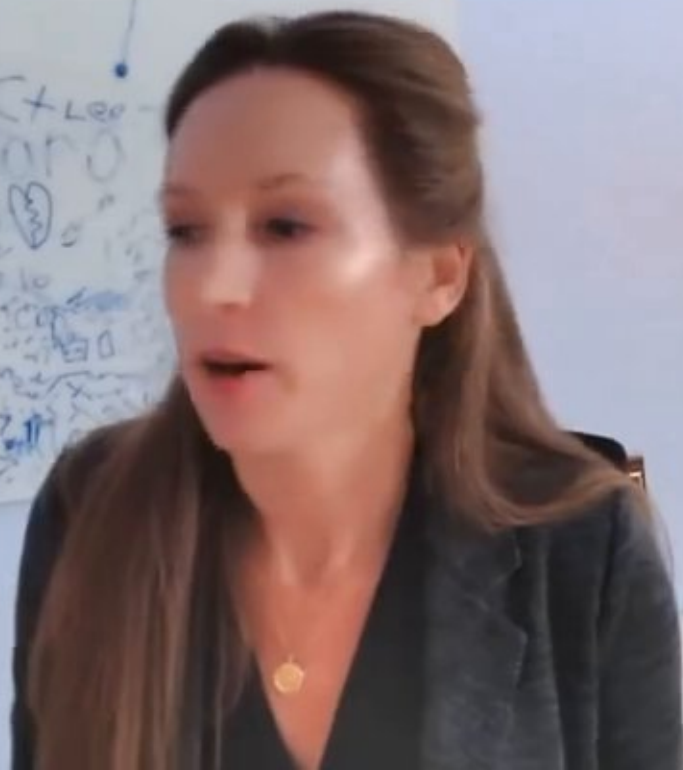


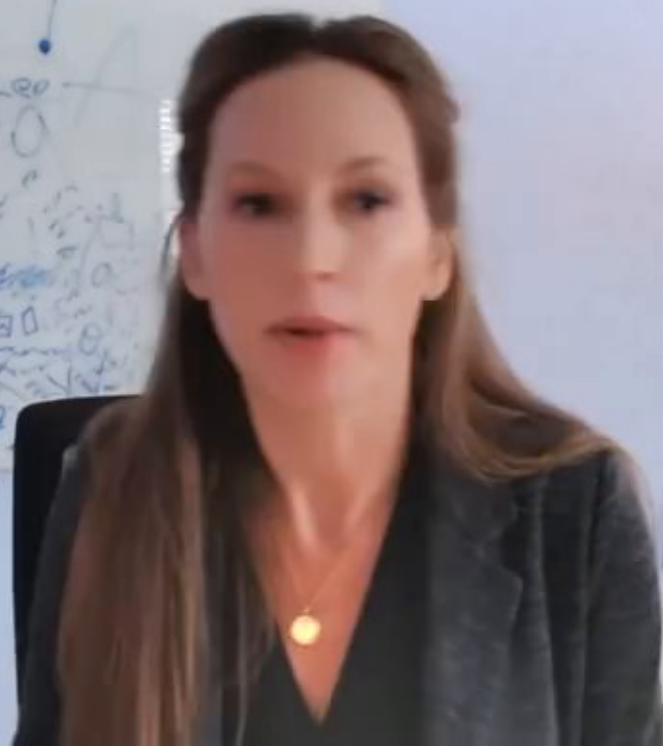
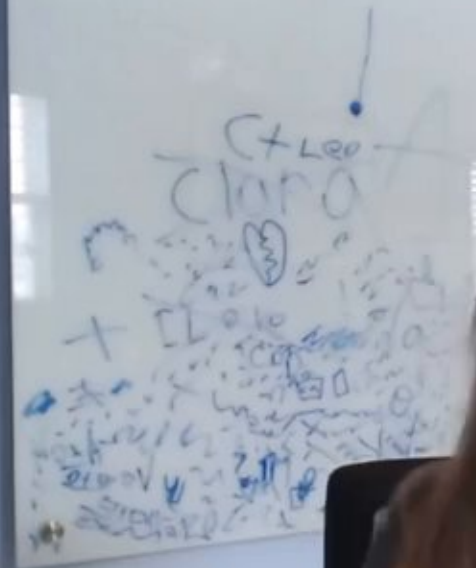








































































Fruit Tan Coy Table cell hypa
 Amy Li Li Irons mid. mid.
 mid. Li Li Tan P.P.
 mid. Li Li Amy
 mid. Coy

N. H. Ast to Δ up

Sing Tally X?
 All cell galls

Coy
 at mid. hypa
 only on

Philip De Jager



Tree	Tam	Cy	Table	cell
Aug	Li	Li	Tree	Miss
mid	Li	Li	Tam	P.P
middle	Li	Li	Aug	
mid			Cy	

11.12.2020
 Ast 20.8
 Sing T
 All



Trub	Tan	Cy	Talle
Ang	Li	Li	Scot
Li	Li	Li	Tan
Li	Li	Li	Ang
Li	Li	Li	Cy

Pl. 12



Ast 108

Sup T

At























Philip De Jager









Trub Tan Cy
 Am Li Li
 m Li Li
 m Li Li
 m Li Li



Sup T
 M













UPSTATE





UPSTATE



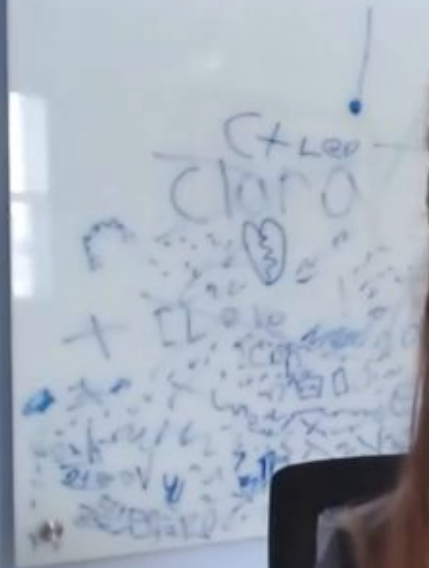


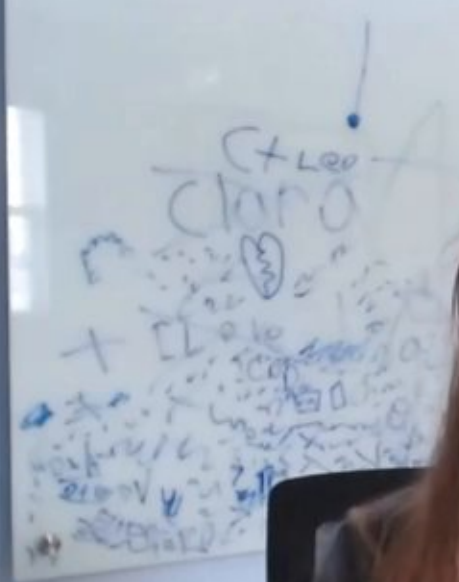


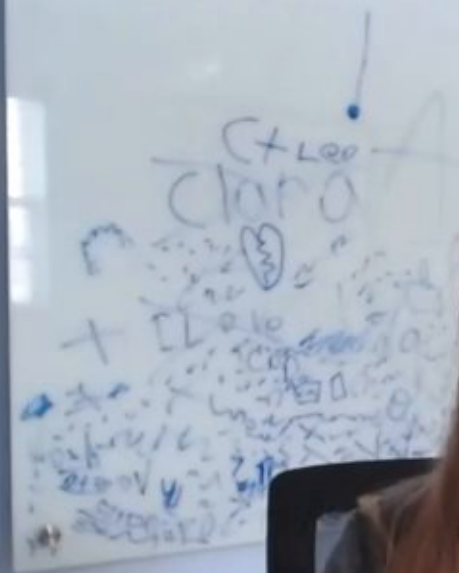


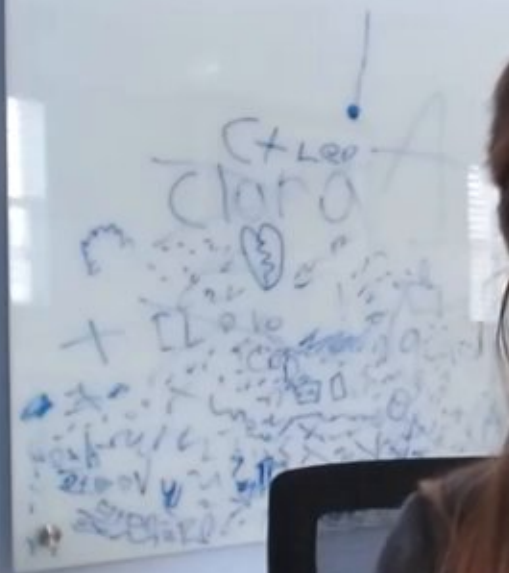


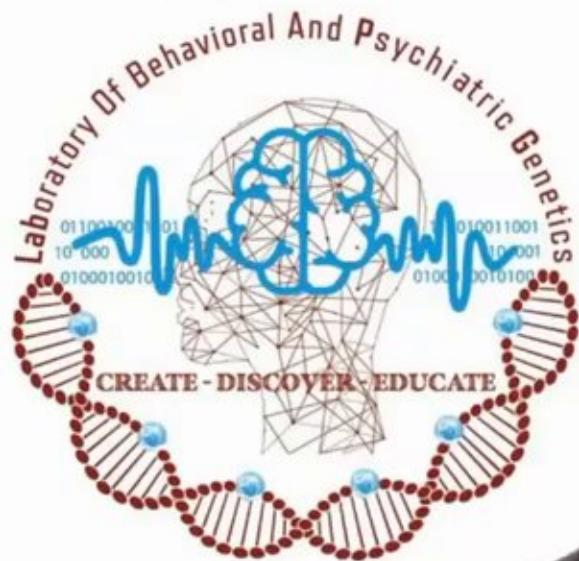












UPSTATE



Philip De Jager

Handwritten notes on a whiteboard:

Tree

Am	Tam	Cy
L _i	L _i	
L _i	L _i	
L _i	L _i	

Table

Jam	
Tam	
Am	
Cy	

Ast to C

Sing Tally X 2

All call n

all m

polymer

Tree	Tan	Cy	Table	Call	hug
Am					
am			Tom	Miss	Miss
am			Tan	P.P	
am			Am		
am			Cy		

PERMIT

Table	Meta
Iron	cell hyp
Tan	Mid mid
Ang	P.P
Cy	

Ast to Δ 47

245

Sup Tally X3
All call putty

Call me back
only on 9/1

Trunk
Arm
mid Li
mid Li
mid

Tan
Li
Li
Li
Li

Cy
Li
Li
Li
Li

Table
cell type
Mid point
P.P.

Tan
Tan
Arm
Cy

Main

Ast to Cy

D
M
K

Sing Tally X3
All call paths

Top
of mid
polyon r









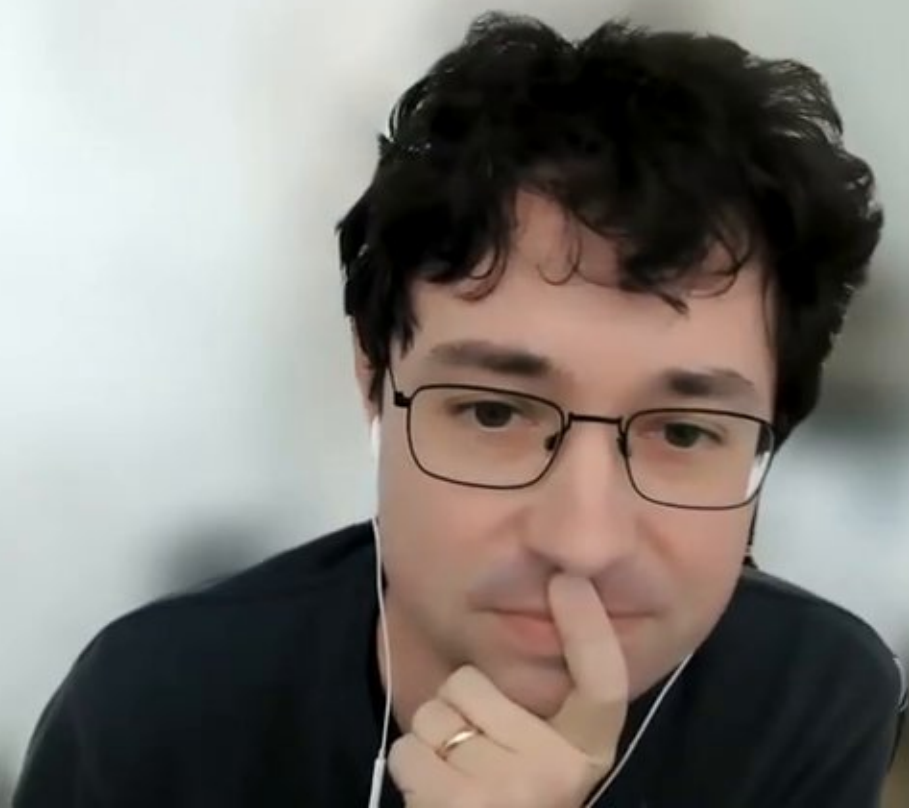


















































Fruit Tan Cy Table call
 Ang Li Li Smith Mill
 Li Li Li Tan P.P
 nile Li Li Ang
 nile Cy
 Mill
 Sup Telly X3
 All allphaps
 Cut
 all res. Eric Mill Kelly
 allphaps
 :

Tris Tan Cy Table
 Ang Li Li cell type
 on Li Li Li
 red Li Li
 red
 Nil
 L
 -
 -
 -
 D
 M
 K
 H
 Sup Tally X3
 All call types
 Cap
 all m. box Hill H
 only on 1

[illegible]

Trait

Tan	Cy
L ⁱ	L ⁱ
L ⁱ	L ⁱ
L ⁱ	L ⁱ

Molt

cell type	Hill rate
R ^p	

Astrodge

D	M	K	Hill
-	-	-	-
-	-	-	-
-	-	-	-

Sing Tally X3
All cell subtypes

Cell
all mol. Bce Hill Kelly
subtypes

















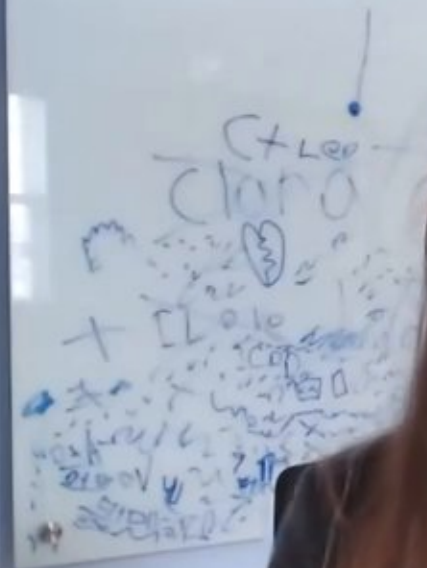






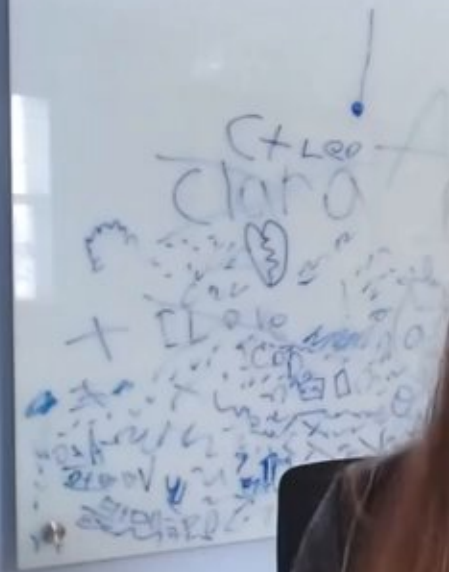


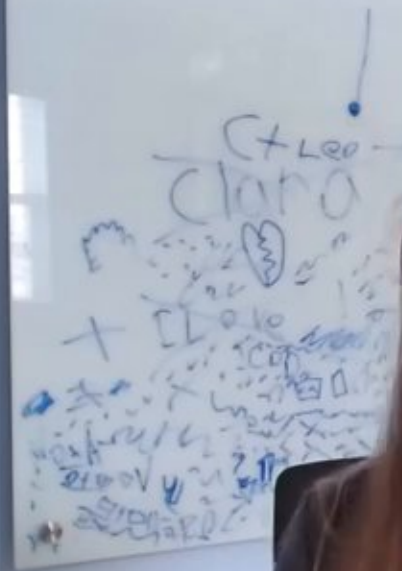


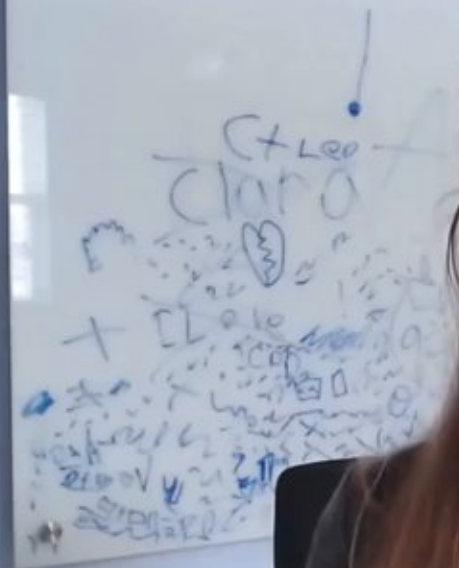


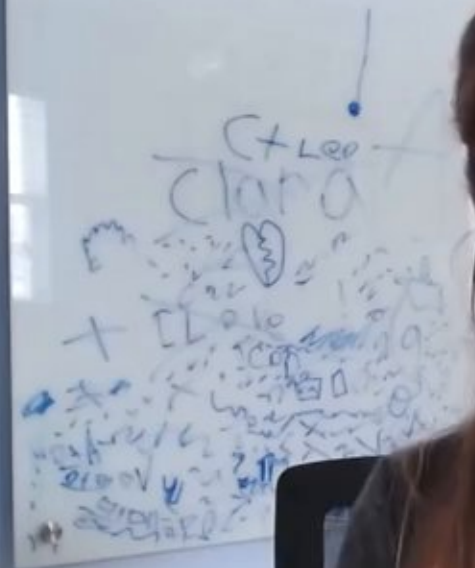


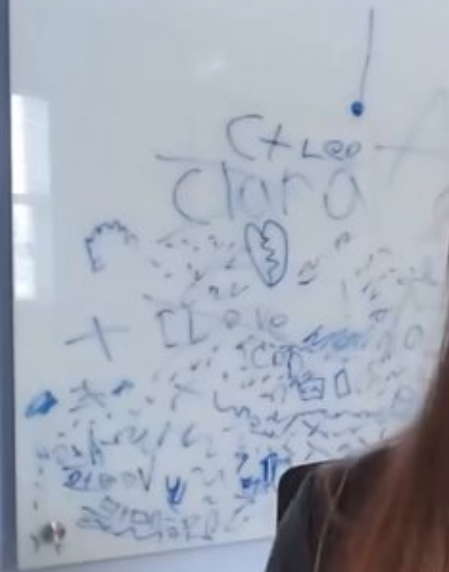


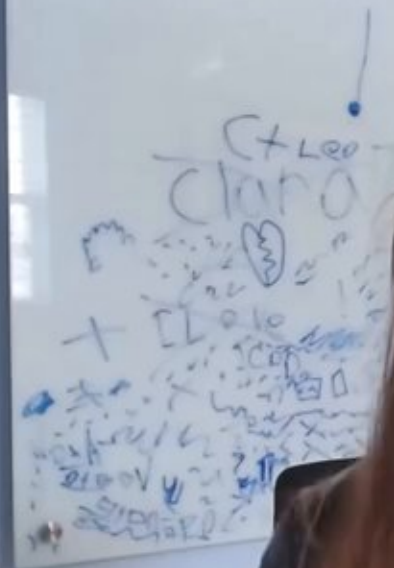


















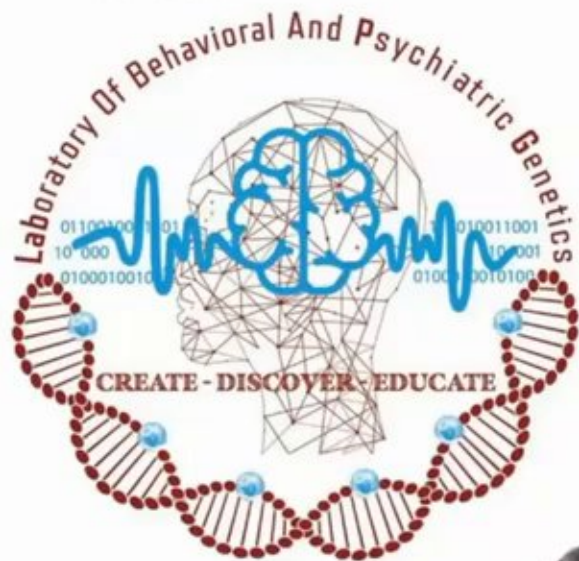












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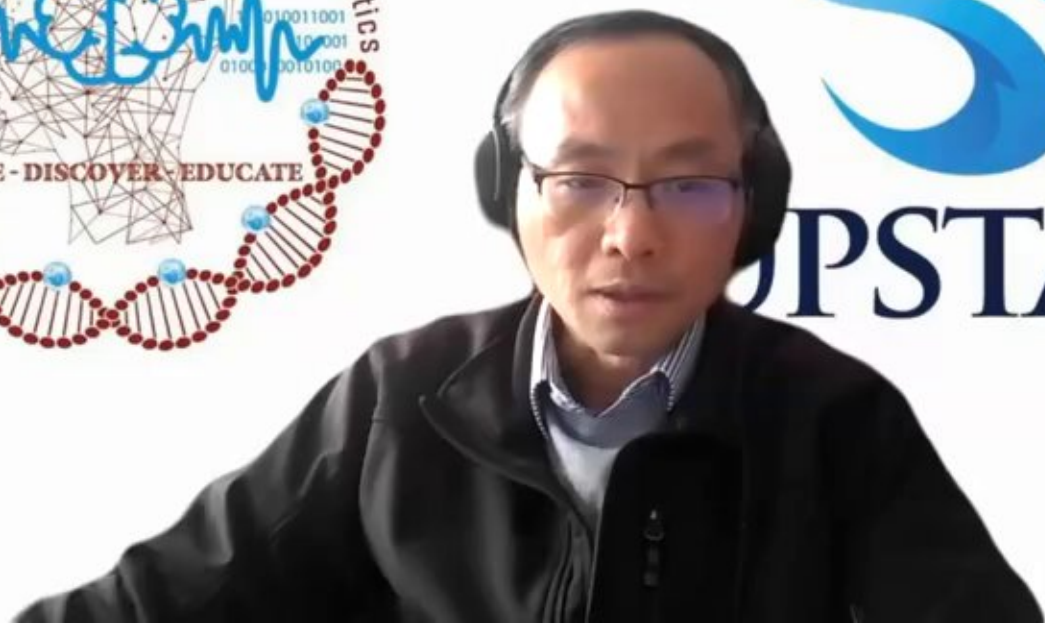


















Table Meta A

Test	Tan	Cy	call hypac
Am	Li	Li	mill/mill an
no Li	Li	Li	P.P
no Li	Li	Li	
no Li	Li	Li	
no Li	Li	Li	
no Li	Li	Li	

Table

Test	Tan	Cy
Am	Li	Li
no Li	Li	Li
no Li	Li	Li
no Li	Li	Li
no Li	Li	Li
no Li	Li	Li

Sup Telly X3
All call putty
Cap
all m. for M
mlyan 1

Asst to & up

D
M
K

Trunk
Arm
Leg

Torso
Leg
Leg

Chest
Leg
Leg

Table
Chest
Torso
Arm
Leg

Call
Head
P.P.

Sup Tally X3
All call tally

Cap
by no. box
dyan 9'

Fruct	Yam	Cy	Table	Flora
Am		Li		cell hypha
Li	Li		Iron	Mill / pink
Li	Li	Li	Yam	P.P
Li			Am	
Li			Cy	

11. 12. 13.

Sup Tally X3
At all points

all the time

Table	Plate
Iron	cell hyp
Tan	red
Gray	P.P
Cy	

Ast to Δ up

D
M
C

DIS

Table Meta Analysis

Trt	Tan	Cy	Trt	coll	hype
Am	Li	Li	Trt	coll	hype
Am	Li	Li	Trt	coll	hype
Am	Li	Li	Trt	coll	hype
Am	Li	Li	Trt	coll	hype
Am	Li	Li	Trt	coll	hype

Table Ast today

Trt	coll	hype
Am	Li	Li
Am	Li	Li
Am	Li	Li
Am	Li	Li
Am	Li	Li

Sup Telly X3
All callphgs

Cap
all m. for Mili
mlyan p

Table

	Male	Female
Tall	1	1
Medium	1	1
Short	1	1

Astrodice

Sing Tally X3
All all right

Cat
all male Sing Male K...
sing per 1



Fruit Tam Cyp
 Amy Li Li
 mid Li Li Li
 mid Li Li Li
 Ast Li Li

11:12



Table Mo
 cell by
 South Hill / mid
 Tam P.P.
 Amy
 Cyp

11:12

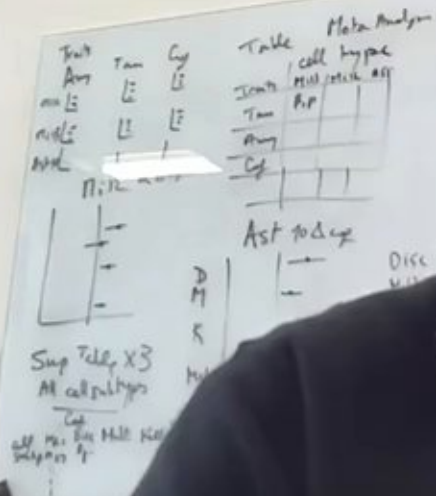
Ast to & up

D M

8

Sup Telly X3
 All cell types

Cyp
 cell has the Hb
 only on 1



Philip De Jager

Train Tan Cy Table cab
 Ang Li Li Jonty M.H. Co
 mid Li Li Tan P.P
 Ang Cy
 Mid M.H. Co
 L D
 M
 S
 Sup Tally X3
 At all railings
 Cab
 all railings
 M.H. Co

Philip De Jager



Tm	Tm	Cp	Table
Am	Li	Li	cell
Am	Li	Li	cell
Am	Li	Li	cell
Am	Li	Li	cell
Am	Li	Li	cell



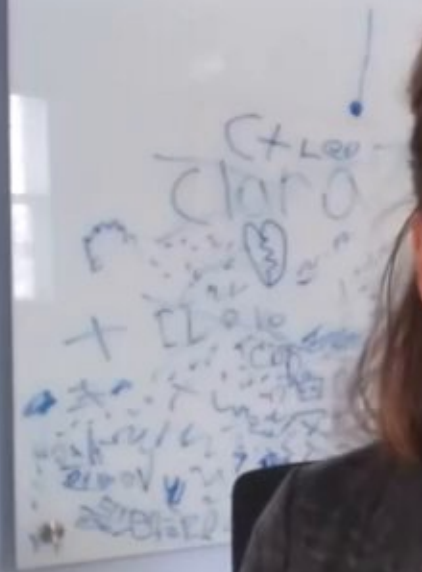
Ast to & up

D
M
K

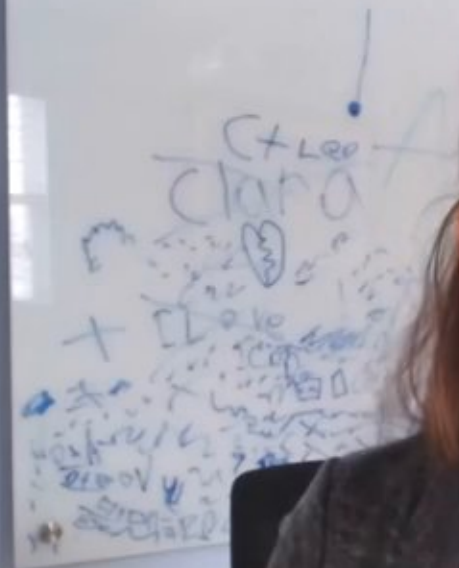
Sup Telly X3
At cell culture

cell no. 100 H
only 100 H

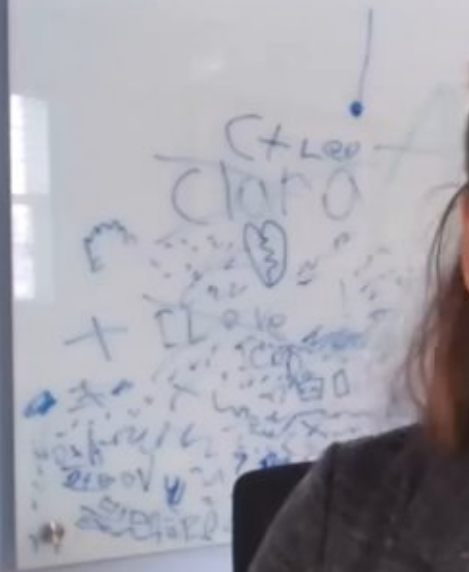








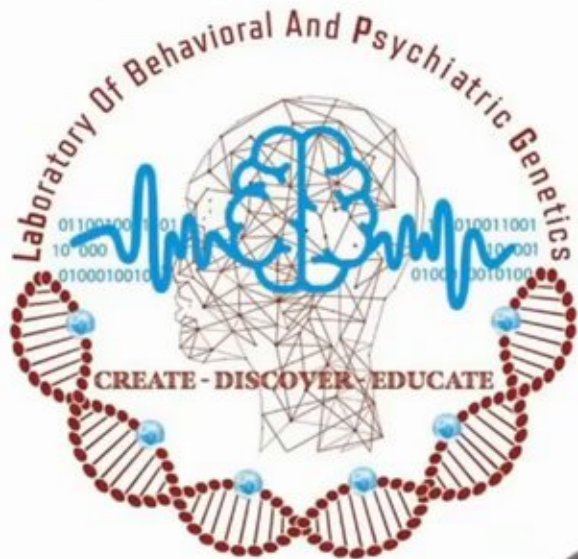












JPSTATE











































Plenary Session: Workshop Summary, Next Steps, and Roadmap

John Ngai, PhD - Director, The BRAIN Initiative, NIH
Ed Lein, PhD - Allen Institute





















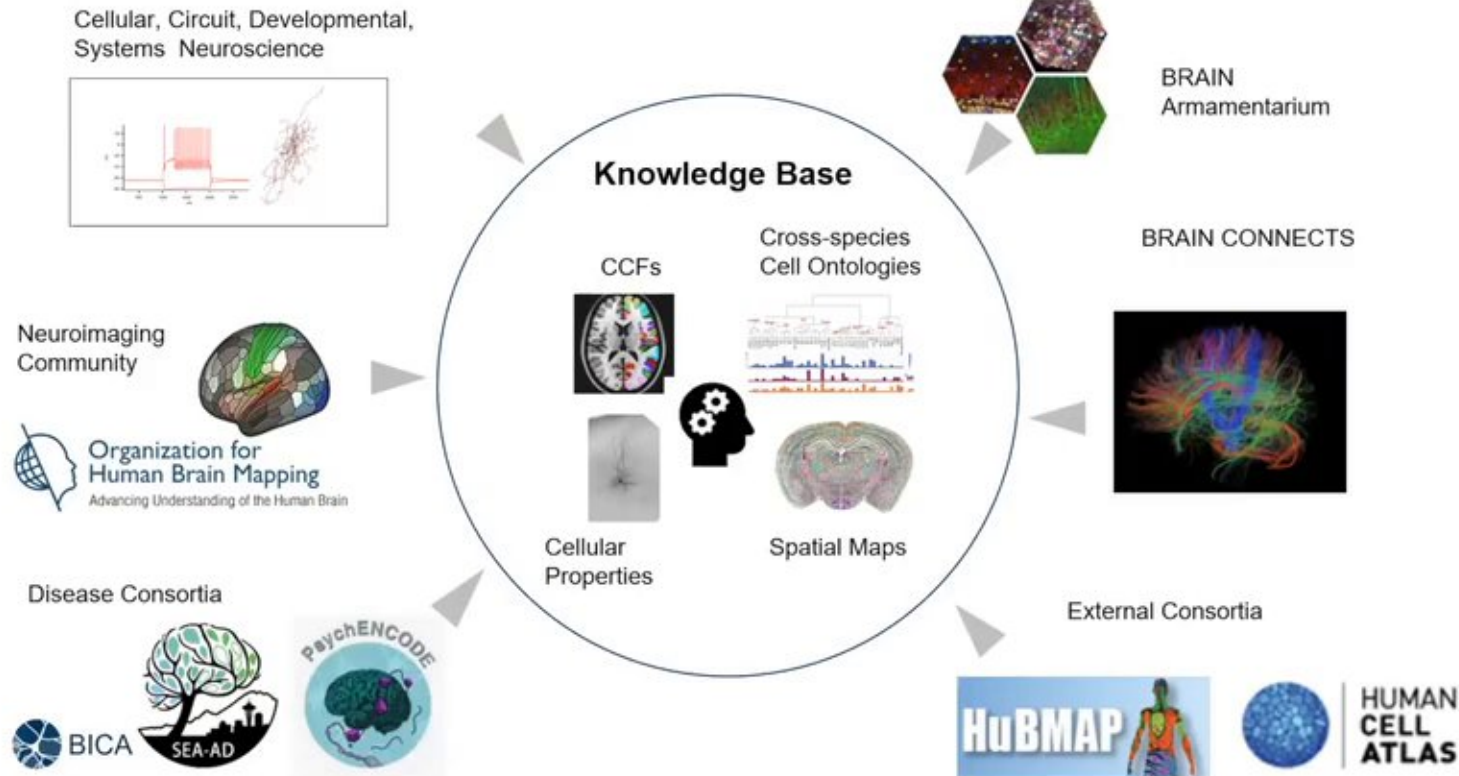
BICAN Joint Milestones and Sampling Plans

Ed Lein, *Senior Investigator*

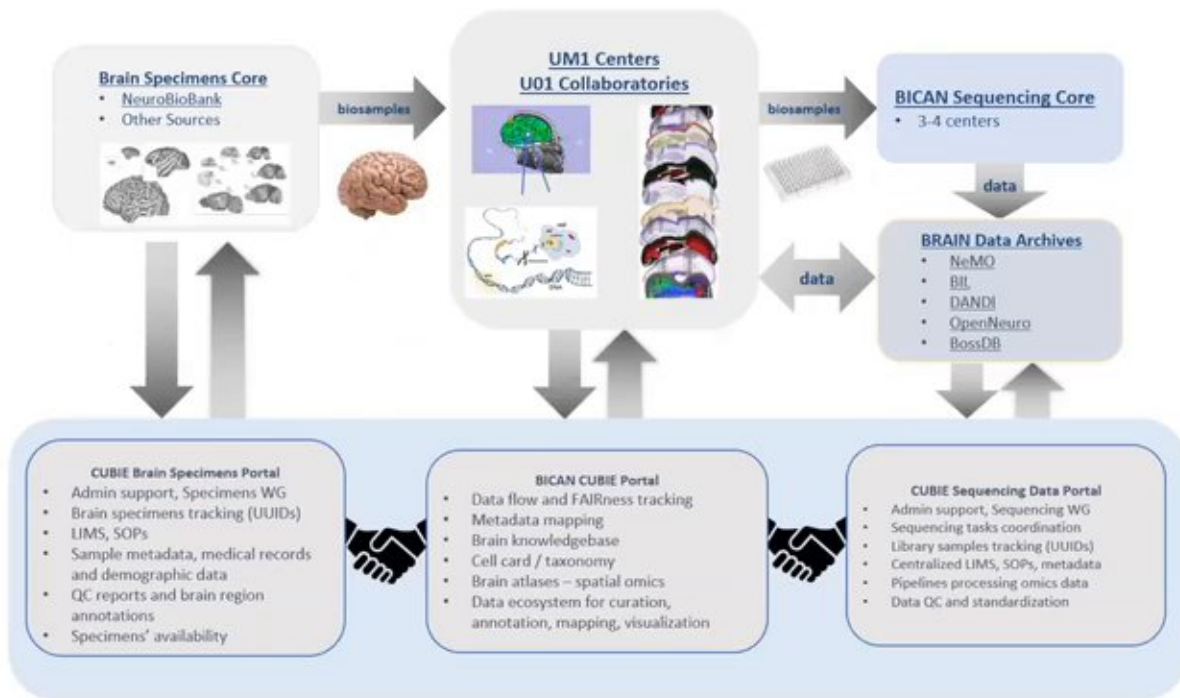
NIH BRAIN Initiative Workshop “From Single-cell Genomics to Brain Function and Disorders
- Data Integration and Annotation”

January 18, 2024

BICAN goal: Provide versioned brain standards and annotated data for the entire community



Centralized ecosystem in the BRAIN Initiative Cell Atlas Network (BICAN)

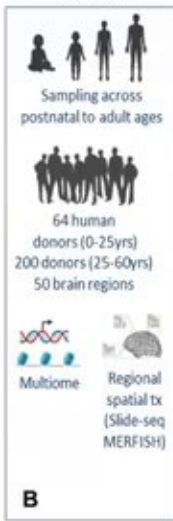


Multiple large-scale efforts contribute to these goals, necessitating a flexible ecosystem to incorporate these and future projects

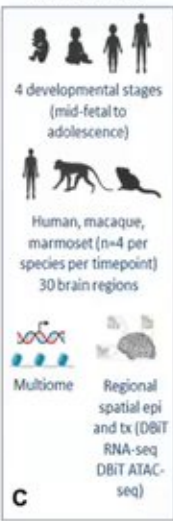
Center for Multi-omic Human Brain Cell Atlas



An atlas and understanding of human brain variation



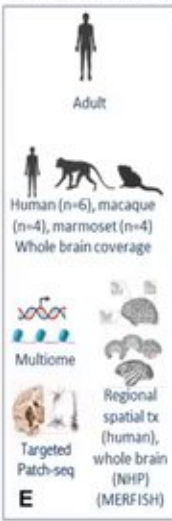
A multidisciplinary center for Developing human and NHP brain Cell Atlas



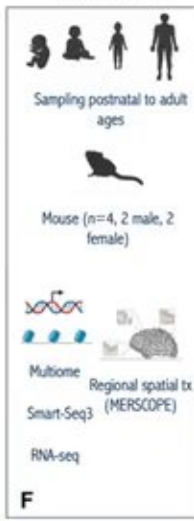
Spatiotemporal architectural cell atlas of developing human brains



Functionally guided adult whole brain cell atlas in human and non-human primate



Comprehensive single-cell atlas of the developing mouse brain



... + Additional Projects

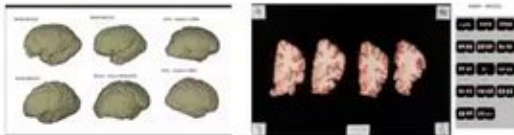
Brain preparation optimization and standardization across tissue banks



Dirk Keene
NBB program and directors
Eugenio Iglesias
Lydia Ng
Rebecca Hodge

NeuroBioBank and UC Irvine sites have been adopting new specifications on brain preparation, and testing sample quality across methods along with a subset of BICAN sites

- Thin slabbing (<5mm) for better precision from frozen slab dissection
- Slab freezing methods for good histological and RNA preservation
- Slab photodocumentation
- 3D surface imaging
- Vacuum sealing



Standardization of specimen metadata to be collected for all adult specimens

- Demographics
- General subject information
- Cause of death
- Toxicology
- Serology
- Neuropathology

Standardization of anatomical references for BICAN (and new atlas creation)

1) CCFS, templates and parcellations: Initial versions selected

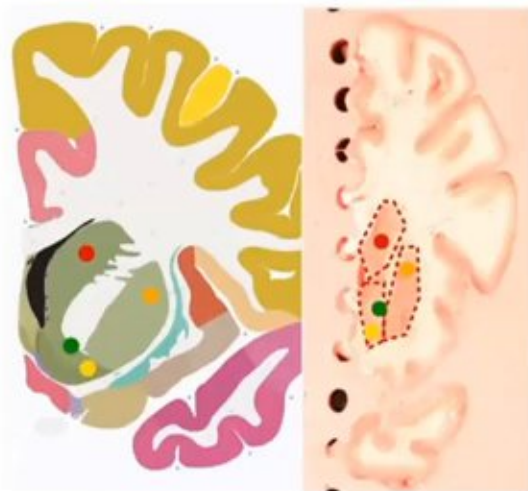


2) Anatomical structural ontologies: Unified cross species ontology in progress, keyed on Ding et al. adult human atlas



Specimen Portal to document anatomical sampling and assign system-wide identifiers

UTHealth Houston Specimen Portal Seq Library Portal



Current Request

Requested

Area	Local Name	Status	Pin	Action
☒	R-T480J48021	pin_requested	●	✎
☒	HQ2.30.001.CX.14.Cal.01	pin_requested	●	✎
☒	R-OP102017040	pin_requested	●	✎
☒	HQ2.30.001.CX.14.Pu.01	pin_requested	●	✎
☒	R-AC20C0C01030	pin_requested	●	✎
☒	HQ2.30.001.CX.14.NAC.01	pin_requested	●	✎

Dissected

Area	Local Name	Status	Action
☐	R-CD20B40208	submitted	✎
☐	HQ2.30.001.CX.14.NAC.01	submitted	✎
☐	R-AP1020170213	submitted	✎
☐	HQ2.30.001.CX.14.Pu.01	submitted	✎
☐	R-OP102017040	submitted	✎
☐	HQ2.30.001.CX.14.Cal.01	submitted	✎

☒ Requested ☐ Dissected

Annotations in current Atlas section

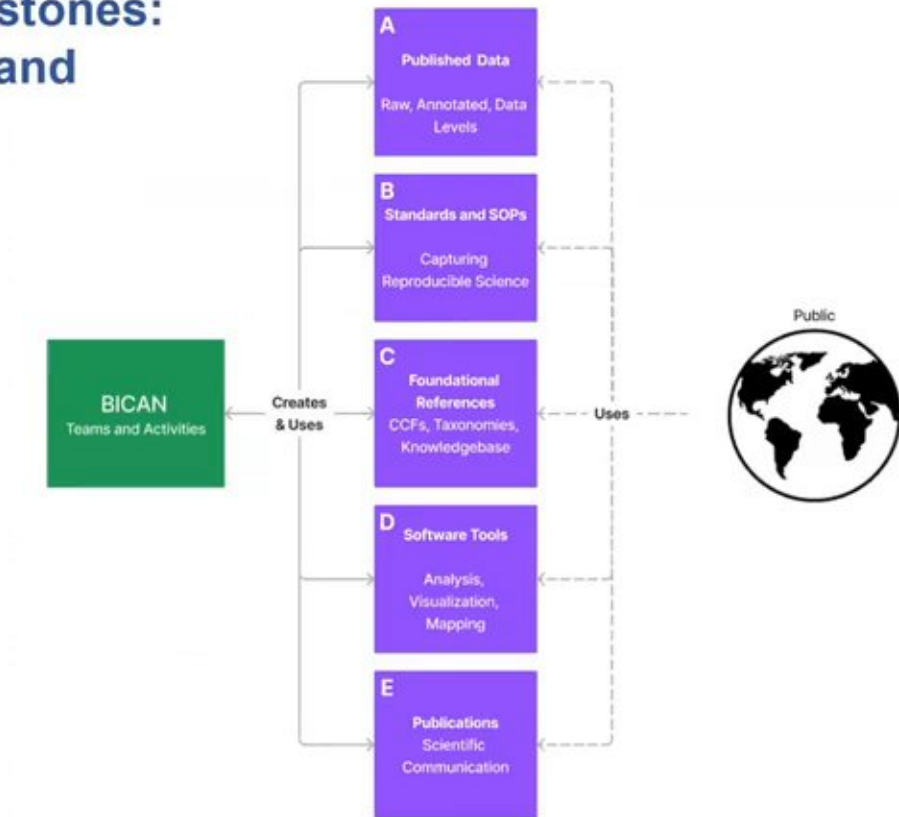
- R-H010P0002 [✎](#)
head of caudate (Cal)
- R-AC20F020106 [✎](#)
putamen (Pu)
- R-CD10200102 [✎](#)
shell of nucleus accumbens (NACs)
- R-PO10201011 [✎](#)
core of nucleus accumbens (NACc)

Consortium-wide joint milestones: Focus on BICAN Products and Outcomes as Deliverables

The BICAN consortium will produce 5 types of products and outcomes that collectively will be transformative for the field if done well

Outcome noted here conceptually encompasses both **Products** and the **Processes** to achieve them.

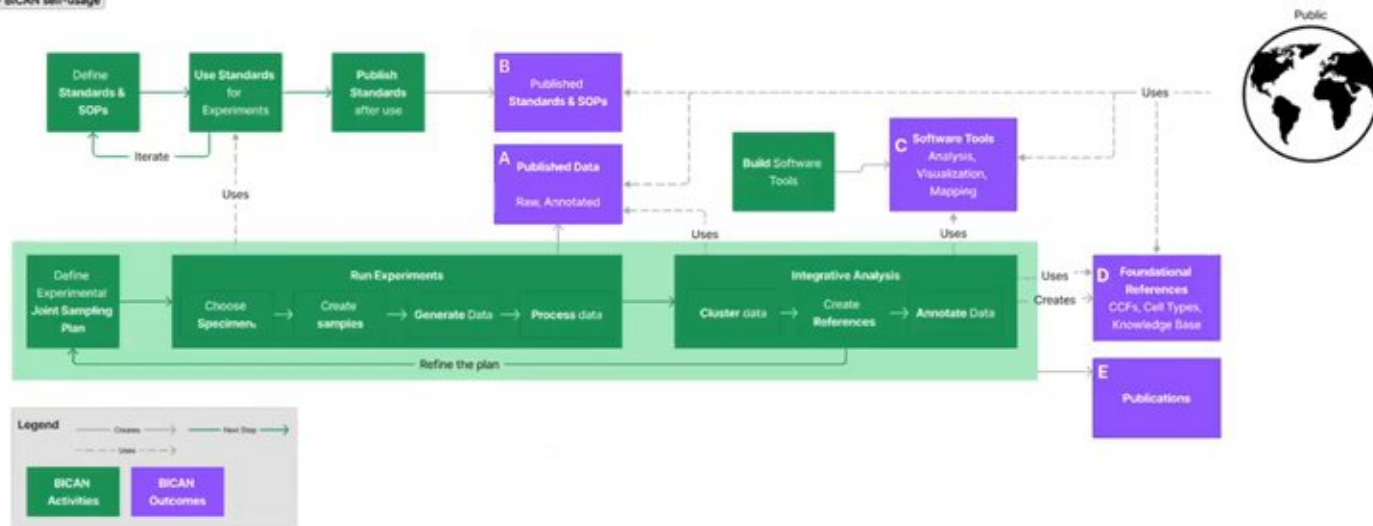
Milestones centered on achieving these goals.



BICAN Milestone Organization

Producing foundational resources

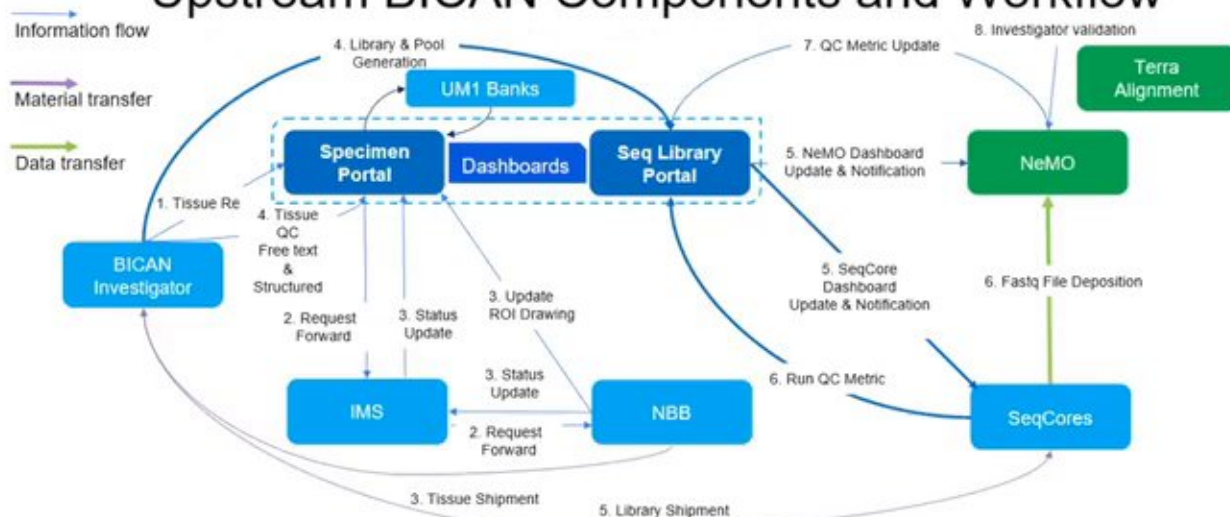
Detailed view - BICAN self-usage



A. Published Data

A.1 Design overall BICAN architecture and data workflows

Upstream BICAN Components and Workflow



1. Request tissue; 2. Forwarding request to banks; 3. Fulfilling request by banks; 4. Library preparation; 5. Library shipment & notification to SeqCore; 6. SeqCore tasks; 7. Fastq file ingestion and QC metric report; 8: Investigator validation of Fastq files

Dashboards in Specimen or Sequencing Portal: A. Investigator dashboard; B. IMS dashboard; C. NBB dashboard; D. SeqCore dashboard; E. NeMO dashboard; F. UM1 banks dashboard; G. NIH dashboard

Note: all dashboards will offer downloading in xls or other formats + API

GQ Zhang, 5/2023

GQ Zhang
Kim Smith

B. Specifications and Standards

Standards and SOPs required for the consortium to meet its goals.

- **B1:** Develop a **BICAN metadata data model** for joint consortia activities and infrastructure.
- **B2:** Define **tissue resource and laboratory protocols** for tissue specimen and sample metadata and SOPs
- **B3:** Establish **standards for library preparation**, and workflows for uniformly processing data.
- **B4:** Define **annotation standards for classifying data**, ontological and taxonomic cell types.
- **B5:** Develop **FAIR documentation and training materials** for BICAN scientists and external consortia and collaborators.

C. Foundational References

Complete, accurate and permanent resource references for neuroscience

C1: Generation of **cross-species cell type taxonomic classifications** in adult and development with versioning and maintenance and defined release dates.

C2: Development of a **CCF standards** for in adult and development in human, macaque, and marmoset brains.

C3: Formalization of **standard nomenclature and ontology** based on data driven cell types.

C4: Integration with knowledge base

C4: Open access and deployment of public standards with supporting documentation and tutorials for use.

D. Publications and Outreach

Presenting BICAN science to the community and public

- **D1:** Orchestrate **joint publications** on collaborative themes.
- **D2:** Following **FAIR principles** for data and resources.
- **D3:** Development of **publicization resources**.
- **D4:** Measuring **impact of consortium products**.
- **D5: Outreach activities** including PEDP activities, webinars, symposia, tutorials.

E. Software Tools

BICAN Federation of Tools for Visualization and Mining Data

Aims

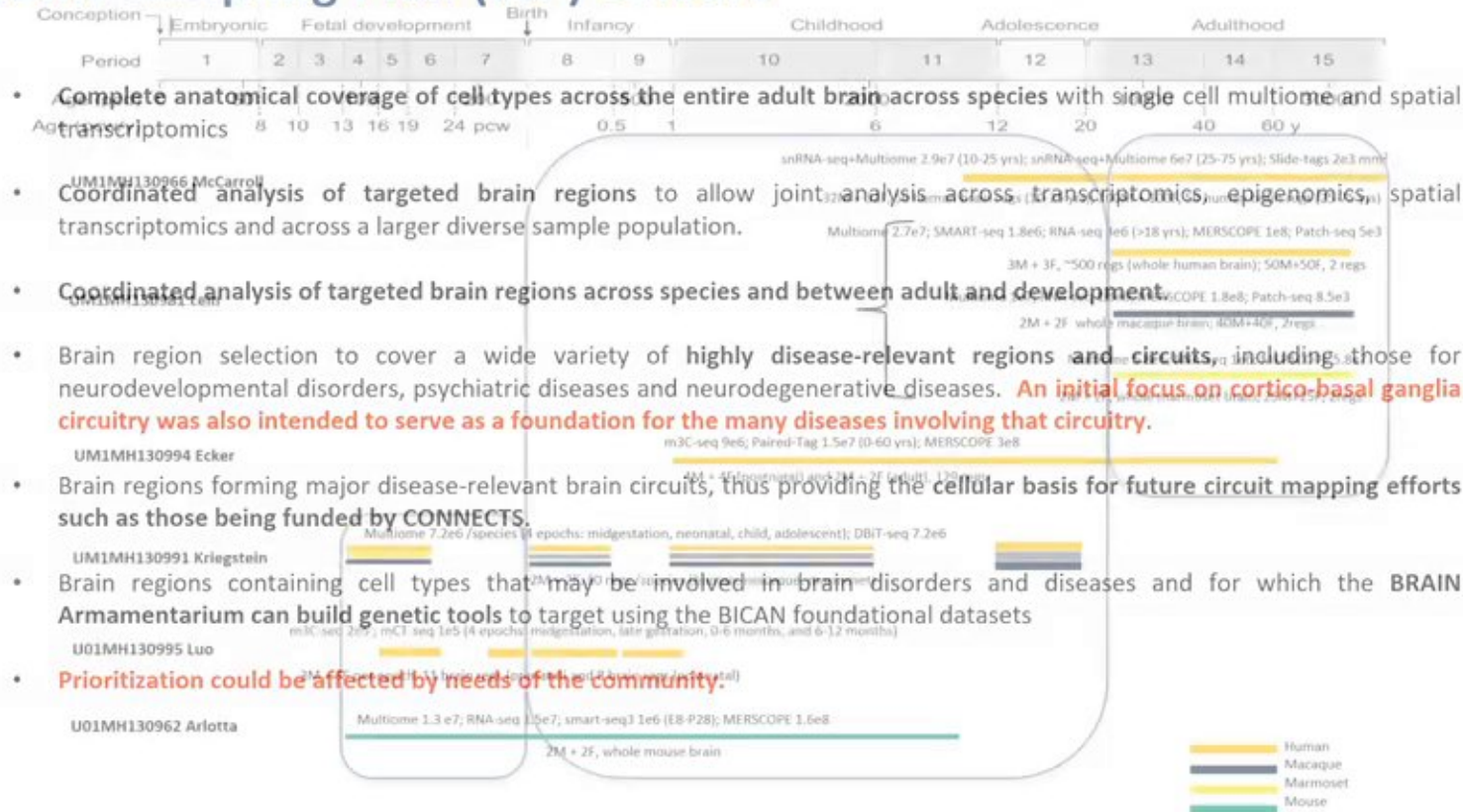
- **E1: Inventory and registry of tools** available and underdevelopment.
- **E2: Architectural description of BICAN Data Ecosystem** and contributing software.
- **E3: Development and release of contributing FAIR BICAN tools and software resources.**
- **E4: Specification and development of a BICAN knowledge base** and interacting components.
- **E5: Interfacing and sharing data and tools** with external consortia.

Joint Sampling Plan (JSP) Drivers

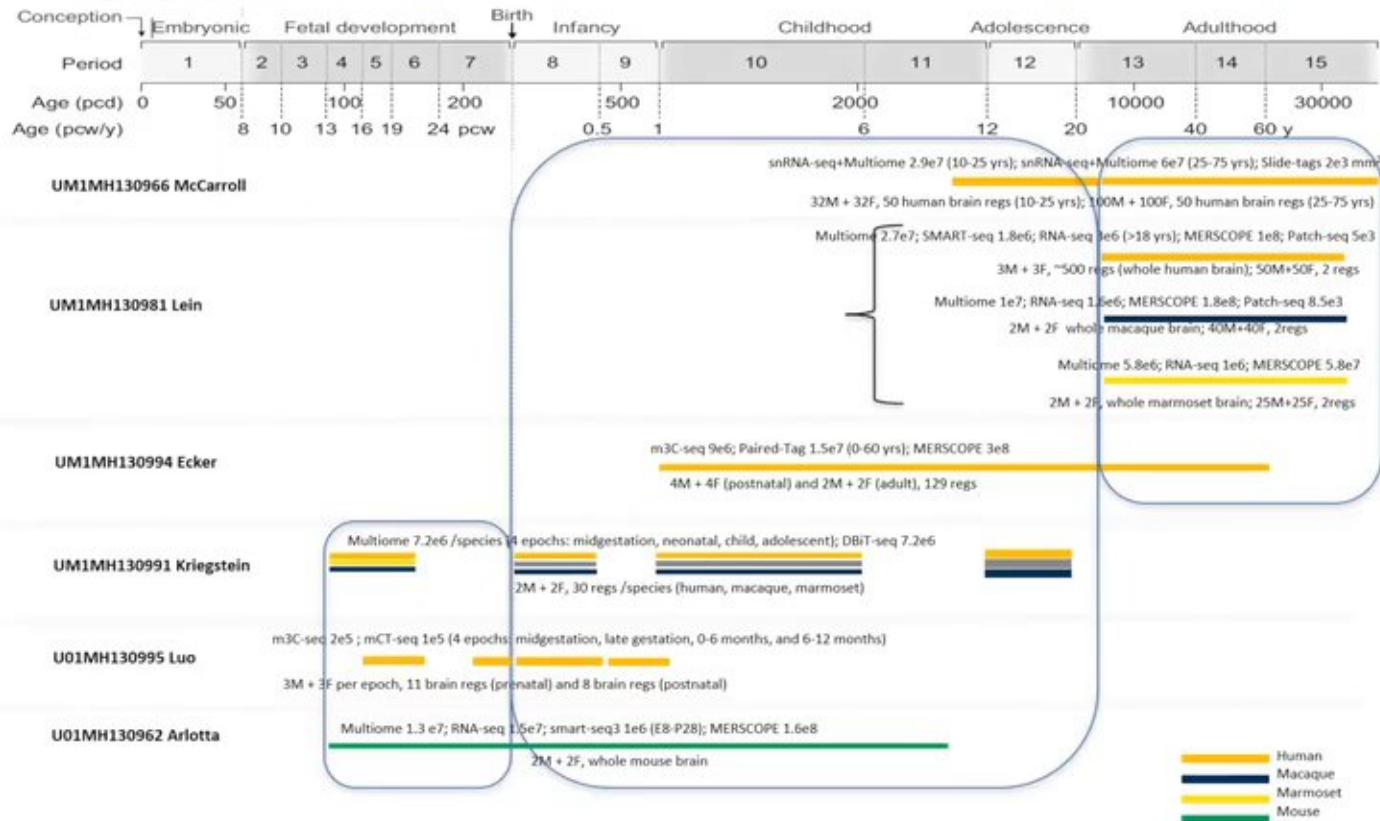
- **Complete anatomical coverage of cell types across the entire adult brain across species** with single cell multiome and spatial transcriptomics
- **Coordinated analysis of targeted brain regions** to allow joint analysis across transcriptomics, epigenomics, spatial transcriptomics and across a larger diverse sample population.
- **Coordinated analysis of targeted brain regions across species and between adult and development.**
- Brain region selection to cover a wide variety of **highly disease-relevant regions and circuits**, including those for neurodevelopmental disorders, psychiatric diseases and neurodegenerative diseases. **An initial focus on cortico-basal ganglia circuitry was also intended to serve as a foundation for the many diseases involving that circuitry.**
- Brain regions forming major disease-relevant brain circuits, thus providing the **cellular basis for future circuit mapping efforts such as those being funded by CONNECTS.**
- Brain regions containing cell types that may be involved in brain disorders and diseases and for which the **BRAIN Armamentarium can build genetic tools** to target using the BICAN foundational datasets
- **Prioritization could be affected by needs of the community.**

BICAN Joint Sampling Plan Development and Adult Coverage Across Projects

Joint Sampling Plan (JSP) Drivers

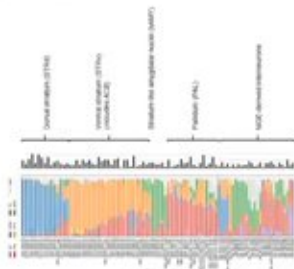


BICAN Joint Sampling Plan Development and Adult Coverage Across Projects



BICAN initial focus on cortico-basal ganglia circuitry: BICAN “mini-atlas”

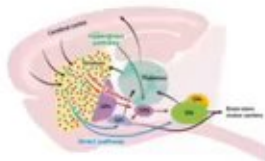
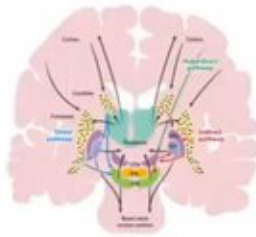
Transcriptomics /epigenomics



Patch-seq



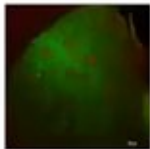
Spatial transcriptomics



Connectomics



Genetic tools



Basal ganglia dysfunction is implicated in a variety of brain disorders:

- Parkinson's disease
- Dystonia
- Huntington's disease
- Tourette's syndrome
- Addiction
- Autism spectrum disorder
- Obsessive compulsive disorder

Themes and joint analyses allowed by coordinated focus:

- Cellular diversity
- Species conservation and divergence
- Developmental cell type trajectories and mechanisms underlying species differences
- Regulatory mechanisms underlying cell type identity
- Molecular underpinnings of cell type phenotypes
- Cellular and molecular locus of disease
- Gene therapy applications

Additional benefits of this focus:

- Provides focus for joint analysis across BICAN
- Provides mechanism to try to replicate success of BICCN publication package on primary motor cortex
- Provides a manageable part of the brain to establish our atlasing efforts with single cell and spatial methods
- Provides a first phase to deal with tissue availability and inclusion/exclusion criteria

We want the community to use these references, and contribute to refining it rather than having redundant efforts in different consortia

Formal releases of the reference (and mechanism for versioning)

- Cell taxonomies within species and between species

Formal nomenclatures, with prior names as aliases

- Formal **data-driven** cell ontologies with nomenclature system that works across species

Tools to visualize the reference (e.g., UCSC genome browser)

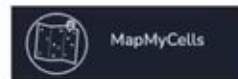
- Tools to visualize and mine the cell type references (e.g., ABC atlas, CellxGene, Catlas)

Tools to map against the reference (e.g., BLAST):

- Cell-BLAST-like tools for alignment and label transfer: MapMyCells

Knowledge bases to aggregate information like Gene Cards and others

- Cell Knowledge Explorer, Knowledge Base



BICAN Consortium



NIH Program staff



































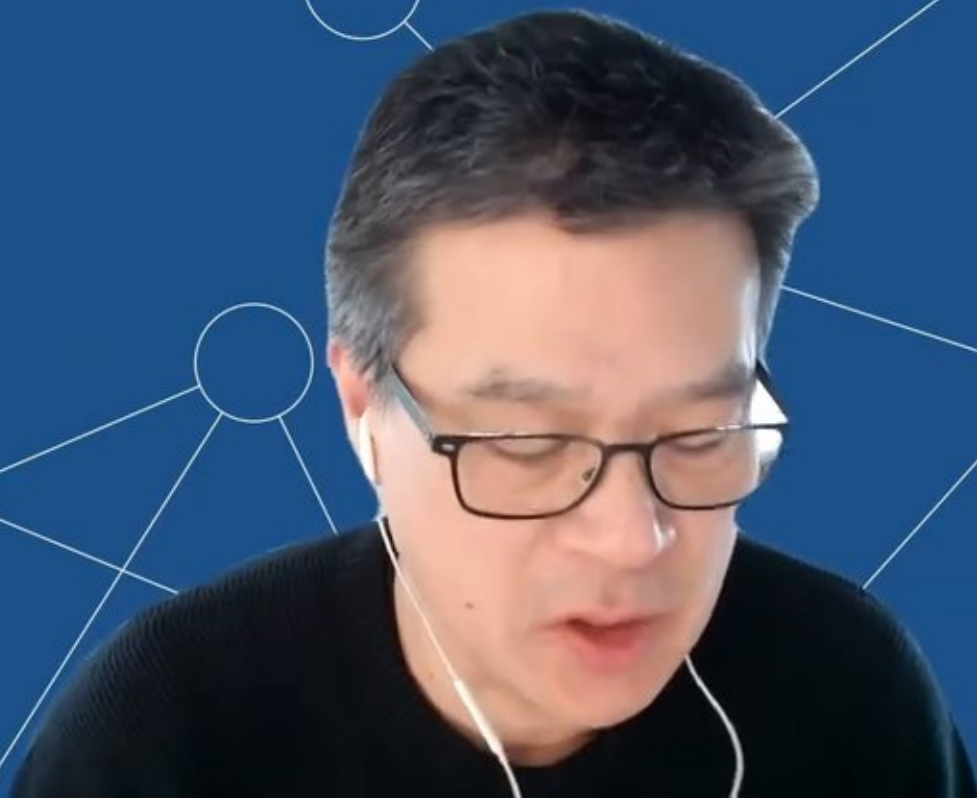












































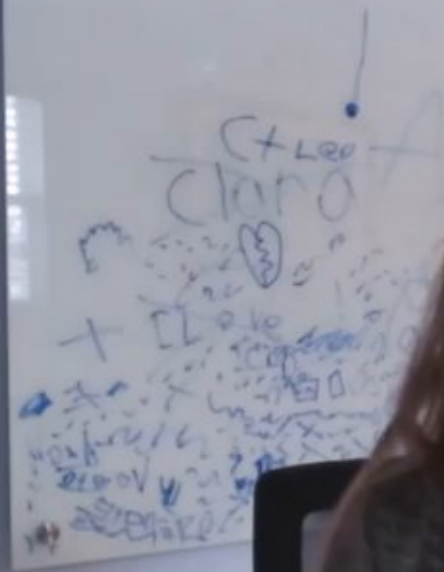
































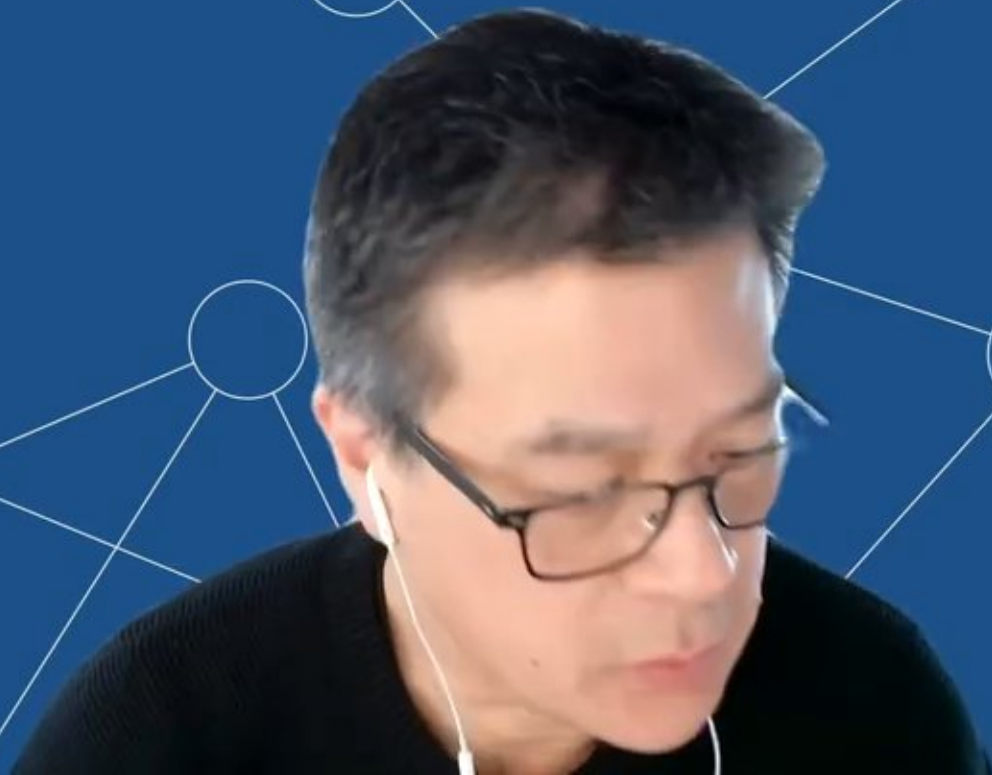






























Andrea Beckel-Mitchene...



























































