

Whole Brain Structural Connectivity Models for Preclinical Investigation of Alzheimer Pathologies

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Assistant Investigator



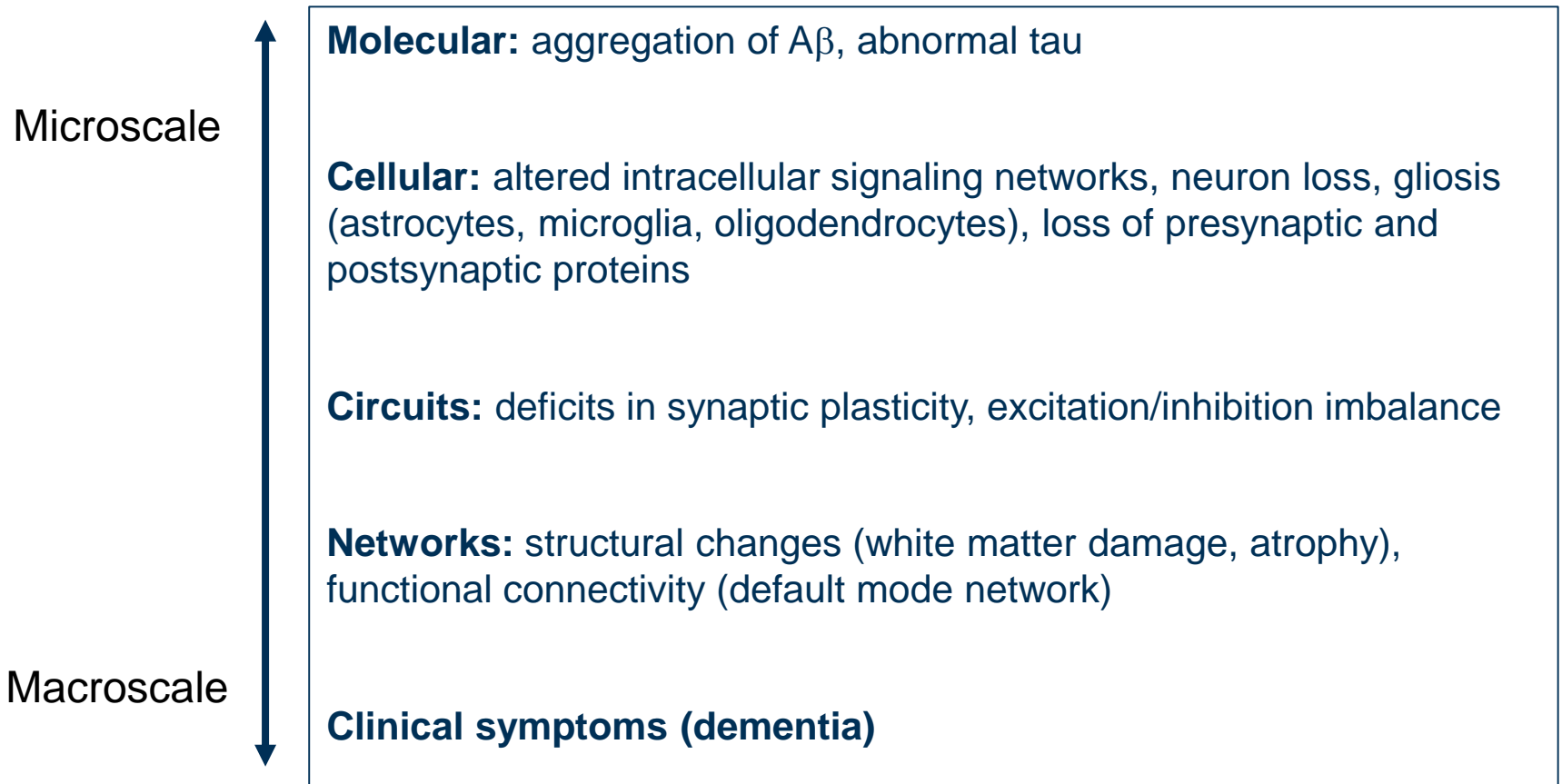
ALLEN INSTITUTE *for*
BRAIN SCIENCE

Overview

- **Multi-scale Alzheimer disease pathologies**
- **Anatomical connectome mapping projects**
- **The Allen Mouse Connectivity Atlas**
- **Connectivity maps in mouse models of disease**



Alzheimer's Disease Pathologies – Types and Scales:

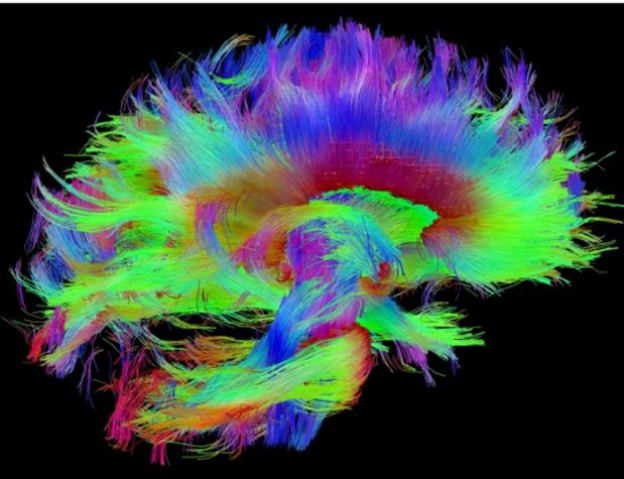


Causal relationships between amyloid- β (or other pathologies) and large-scale network failure are not known.



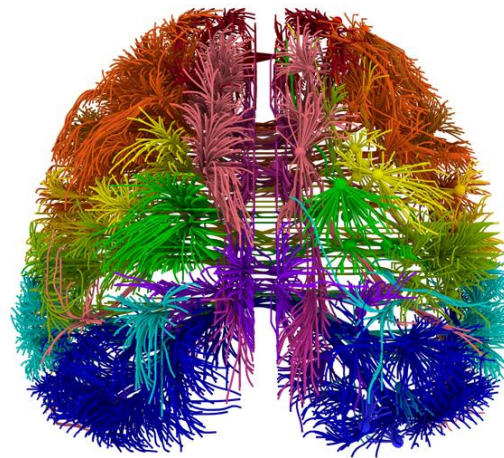
Anatomical Connectomes: Types and Scales

Macroscale ← → Mesoscale ← → Microscale



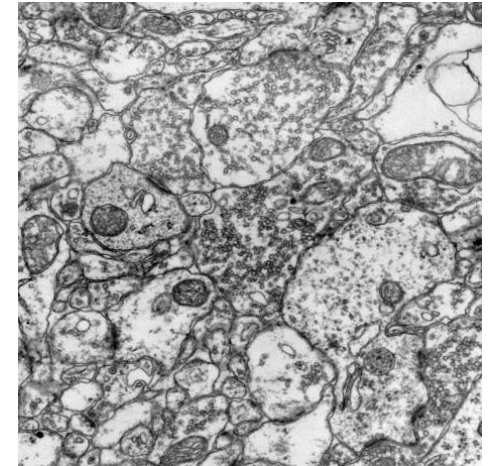
Inter-areal
Resolution: mm
MRI, DTI
Humans

Human Connectome Project



Cell populations, inter-and intra-areal
Resolution: μms (100s cells)
Tracers; Light Microscopy
Animal Models

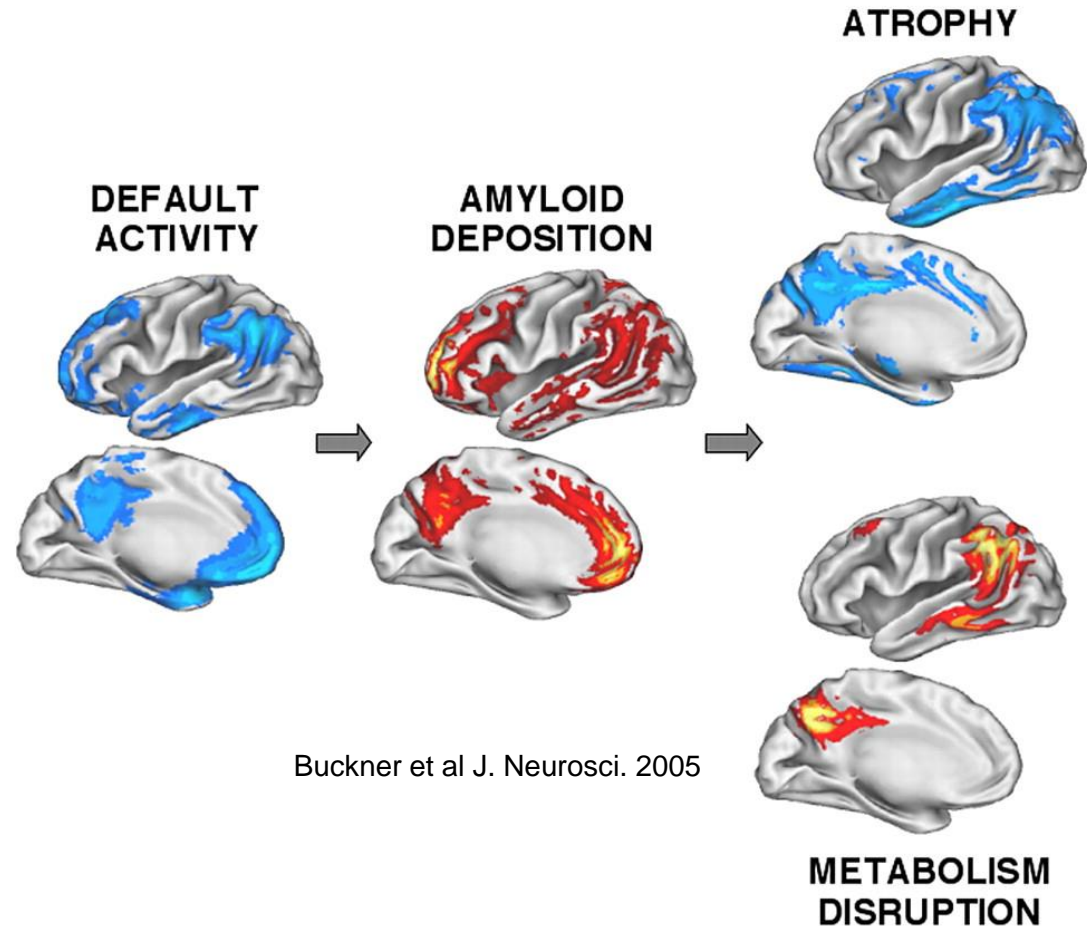
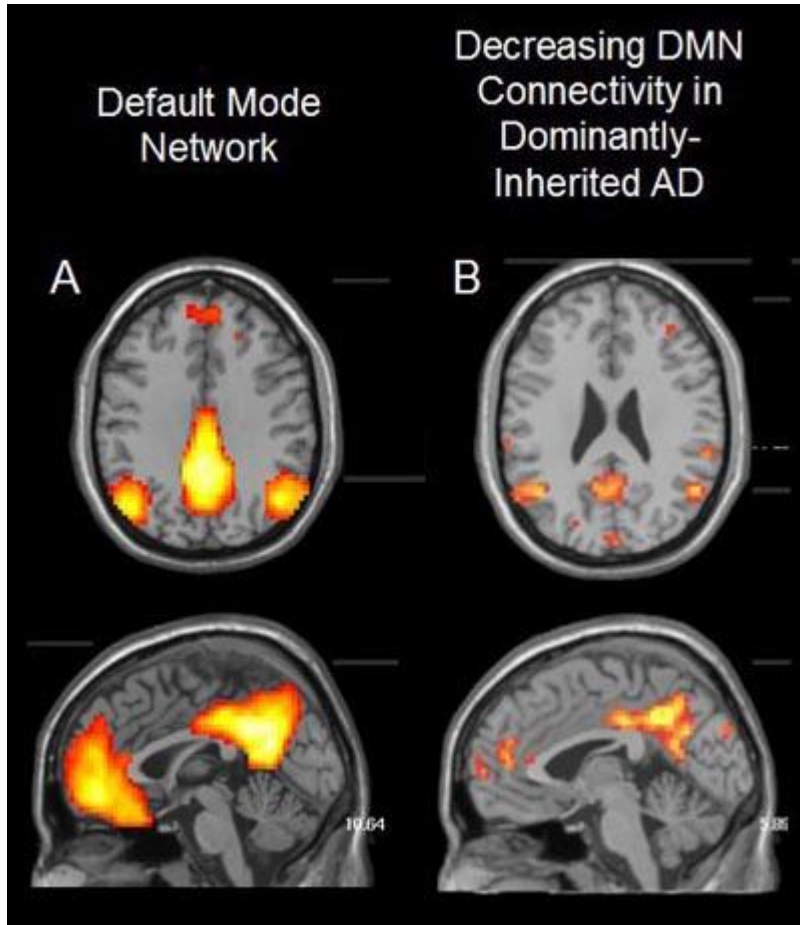
Allen Mouse Connectivity Atlas



Single cell
Resolution: submicron
Electron Microscopy
Animal Models

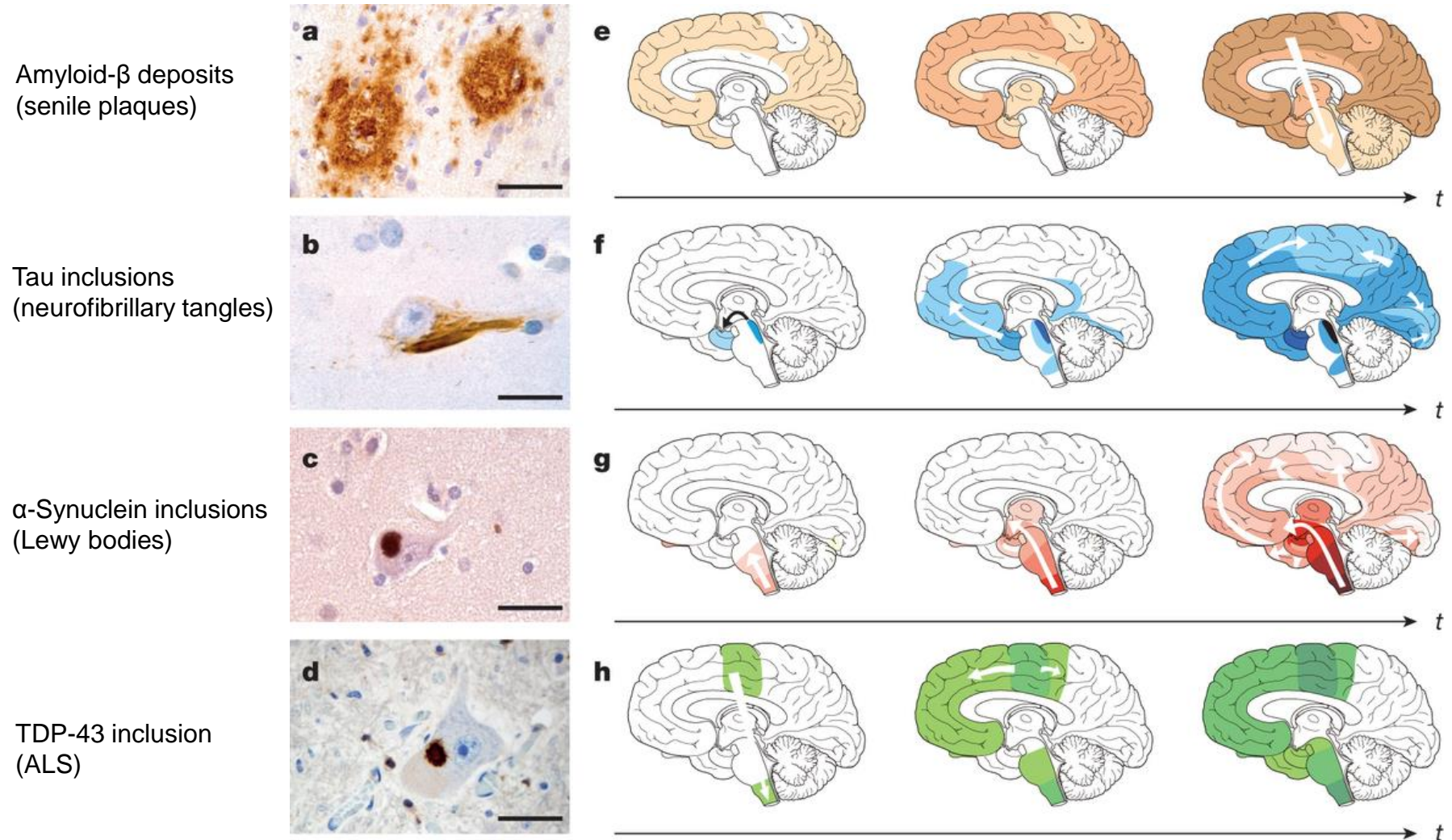
Open Connectome Project

Functional Connectivity Alterations in AD



Does normal connectivity predict pathology? Network degeneration hypothesis

Prion-like propagation of pathology in neurodegenerative diseases



Mouse Alzheimer Project Questions

- Can we understand large scale network alterations and selective vulnerability observed in human patients by using mouse models of Alzheimer's disease?
- Can we predict (model) the progression of pathology using “normal” connectivity in mice?
- Can we identify specific types of projection neurons most vulnerable to pathology and instrumental to disease progression?
- Are there (and what are the) alterations in structural network properties in AD mice? Are they related to measurable pathologies?



Allen Mouse Connectivity Atlas

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BRAIN ATLAS

ALLEN BRAIN ATLAS

DATA PORTAL

HOME

GET STARTED

HELP

MOUSE CONNECTIVITY ▾

Search...



PROJECTION

BDA/AAV COMPARISON

TRANSGENIC CHARACTERIZATION

REFERENCE DATA

BRAIN EXPLORER

DOCUMENTATION

HELP

- Source Search
- Target Search
- Spatial Search

Filter Source Structure(s) ?

Filter Mouse Line

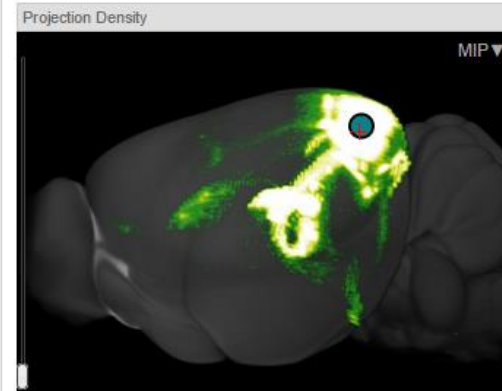
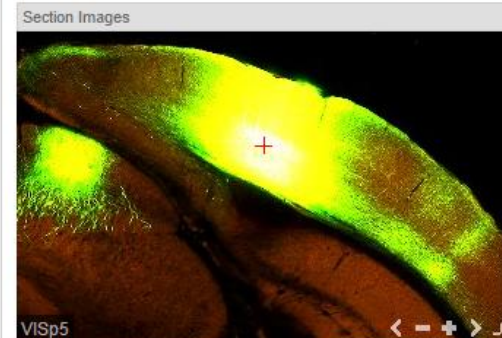
Primary Structure Only

Search Results [Permalink](#)

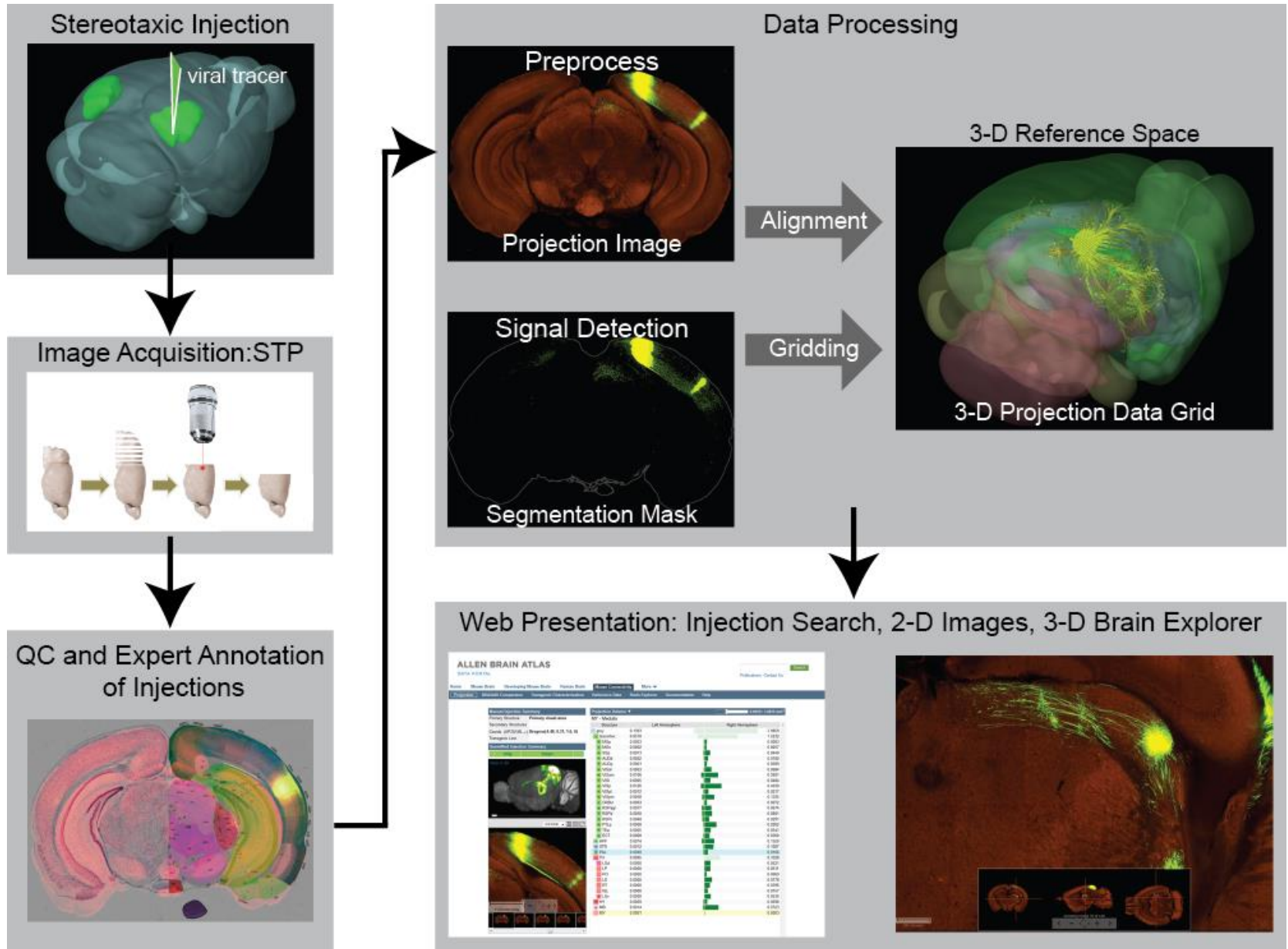


<i>Injection Structure(s)</i> ▾	Mouse Line	Inj Site Vol
<input checked="" type="checkbox"/> VISp	C57BL/6J	0.518
<input type="checkbox"/> VISp - VISam	Efr3a-Cre_NO1...	0.014
<input type="checkbox"/> VISp - VISal	Nr5a1-Cre	0.027
<input type="checkbox"/> VISp - VISam	C57BL/6J	0.784
<input type="checkbox"/> VISp	Nr5a1-Cre	0.015
<input type="checkbox"/> VISp	C57BL/6J	0.528

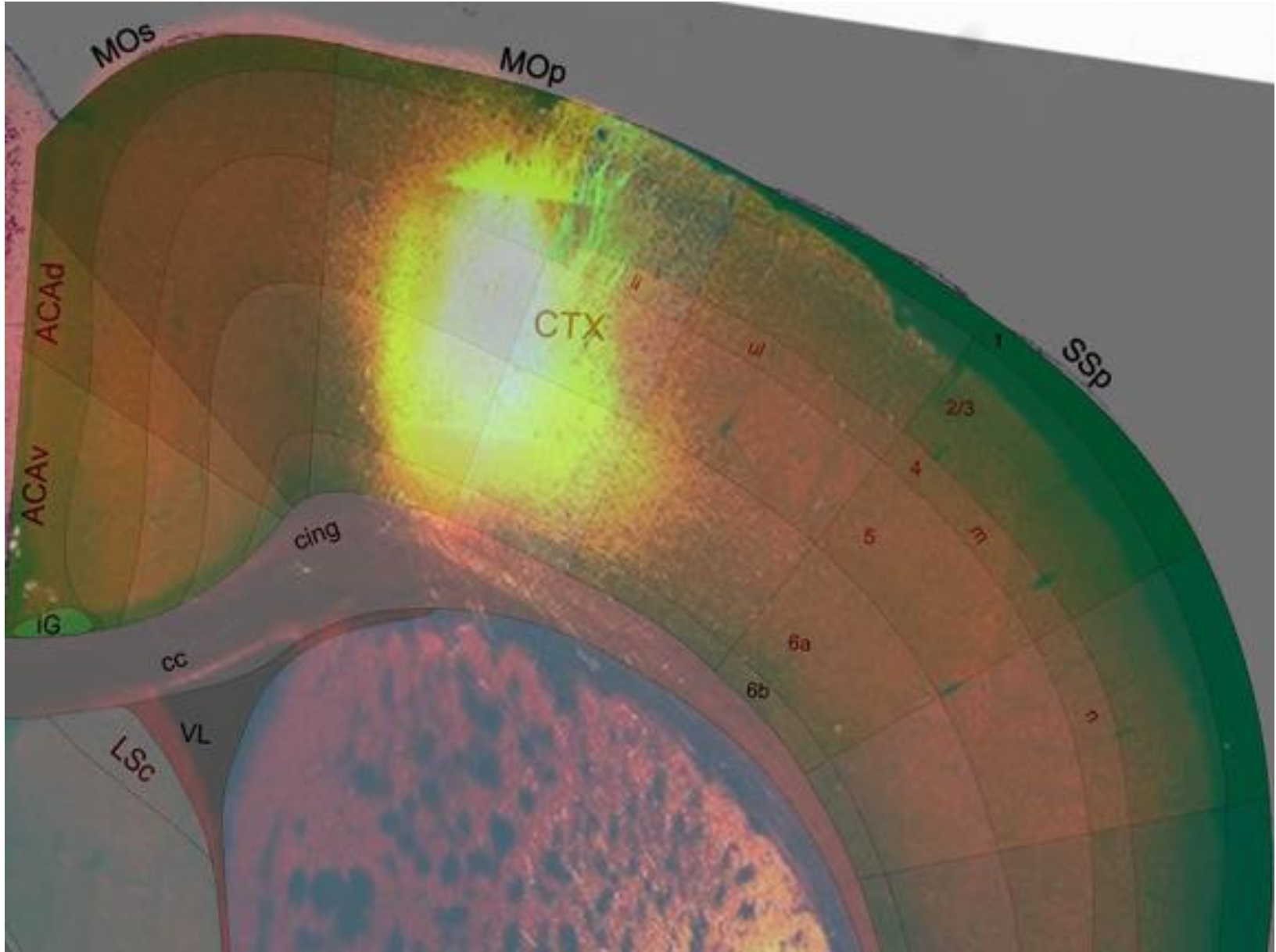
Experiment 307593747 - VISp

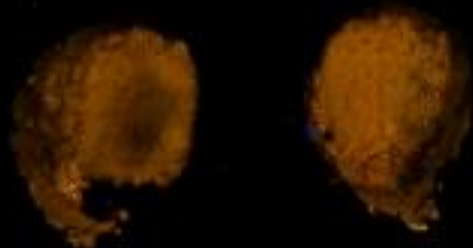


Allen Mouse Connectivity Atlas Pipeline






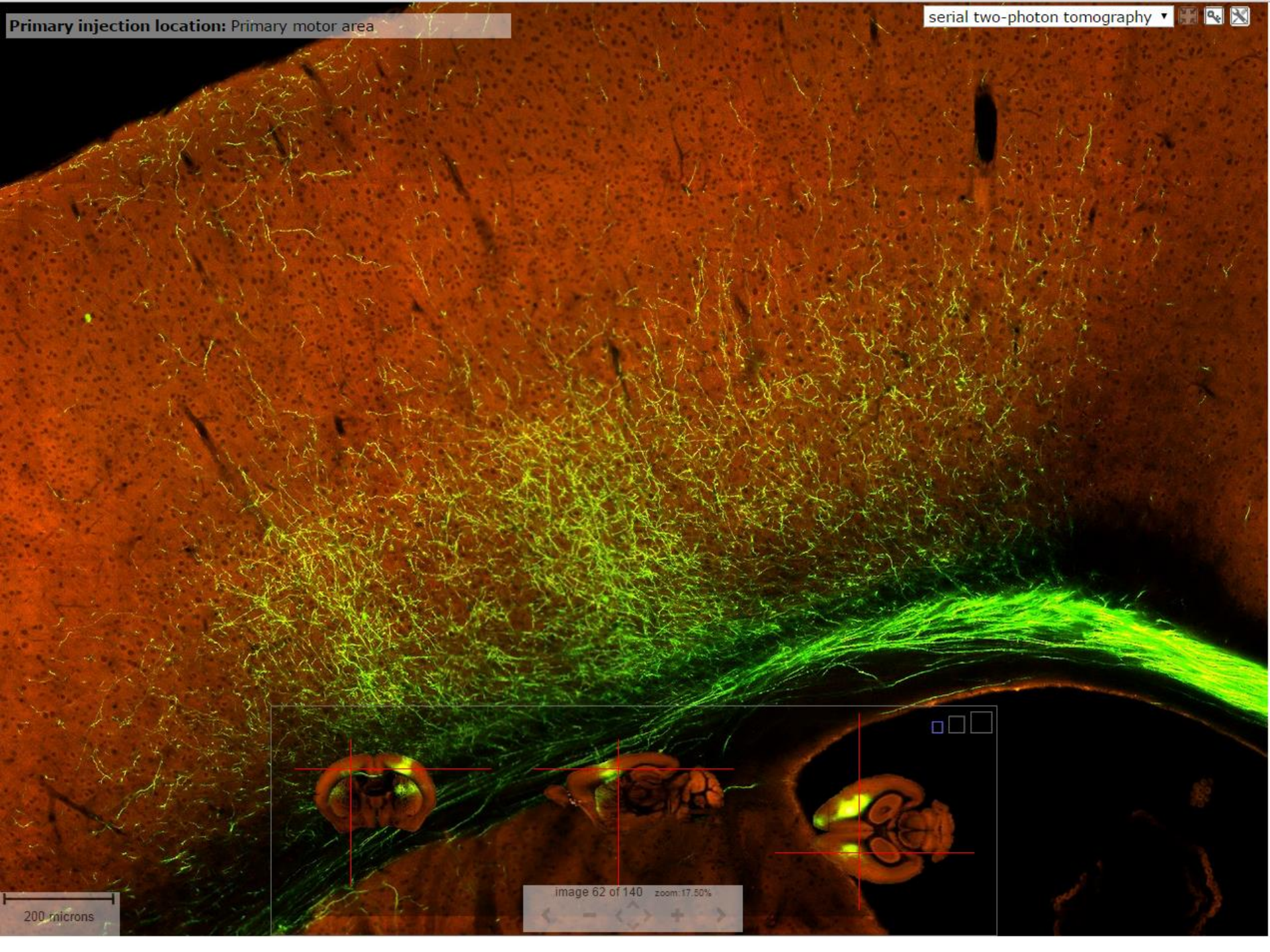
rAAV2.1-hSyn-EGFP-WPRE into Primary Motor Cortex (MOp)







Primary injection location: Primary motor area

serial two-photon tomography   



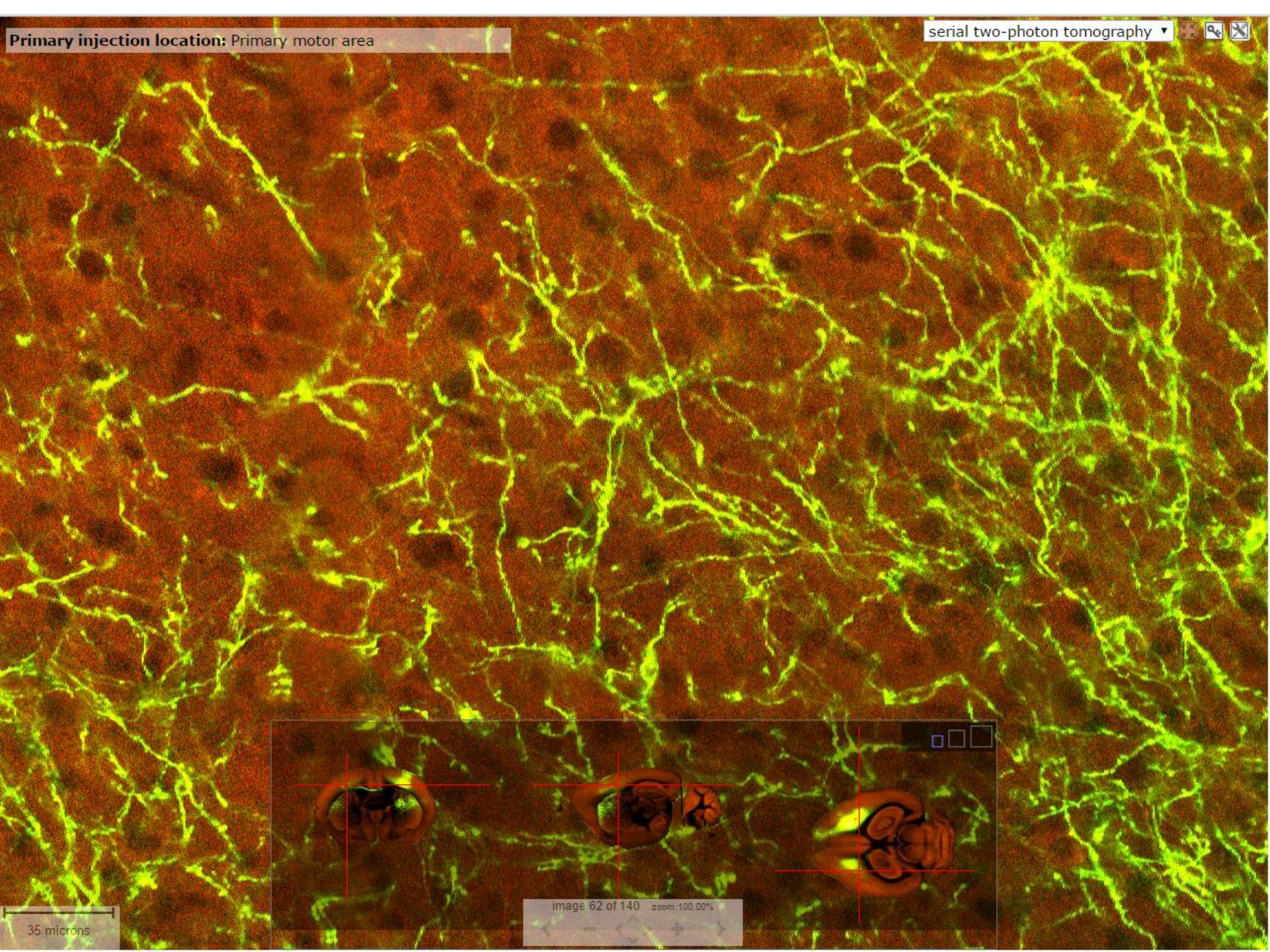
200 microns

image 62 of 140 zoom: 17.50%




Primary injection location: Primary motor area

serial two-photon tomography



35 microns

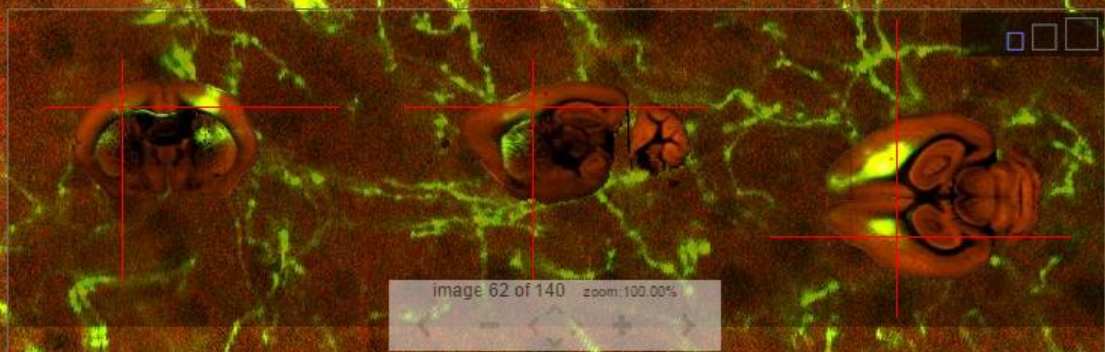
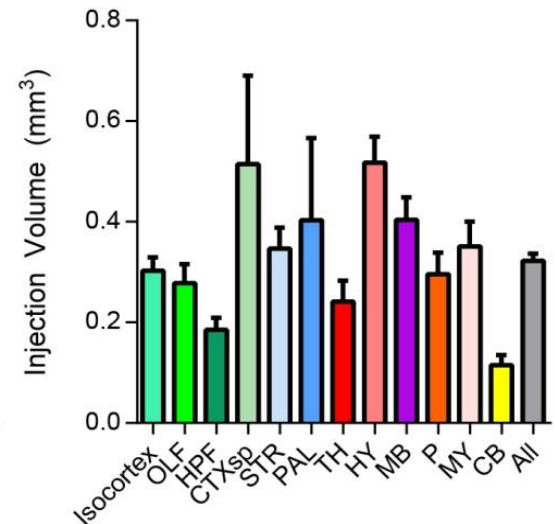
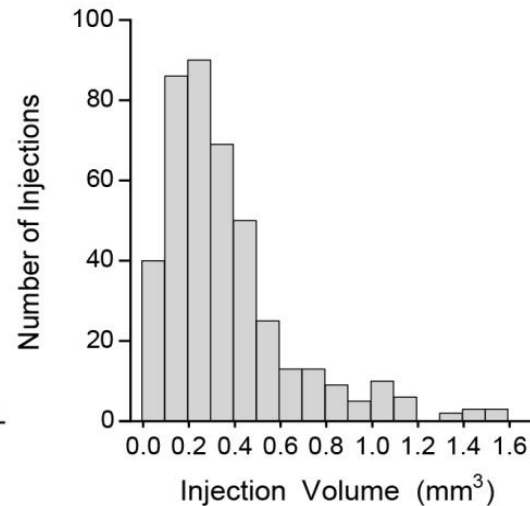
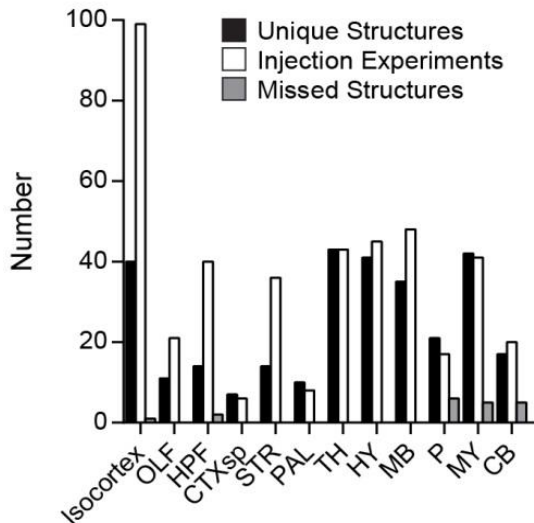
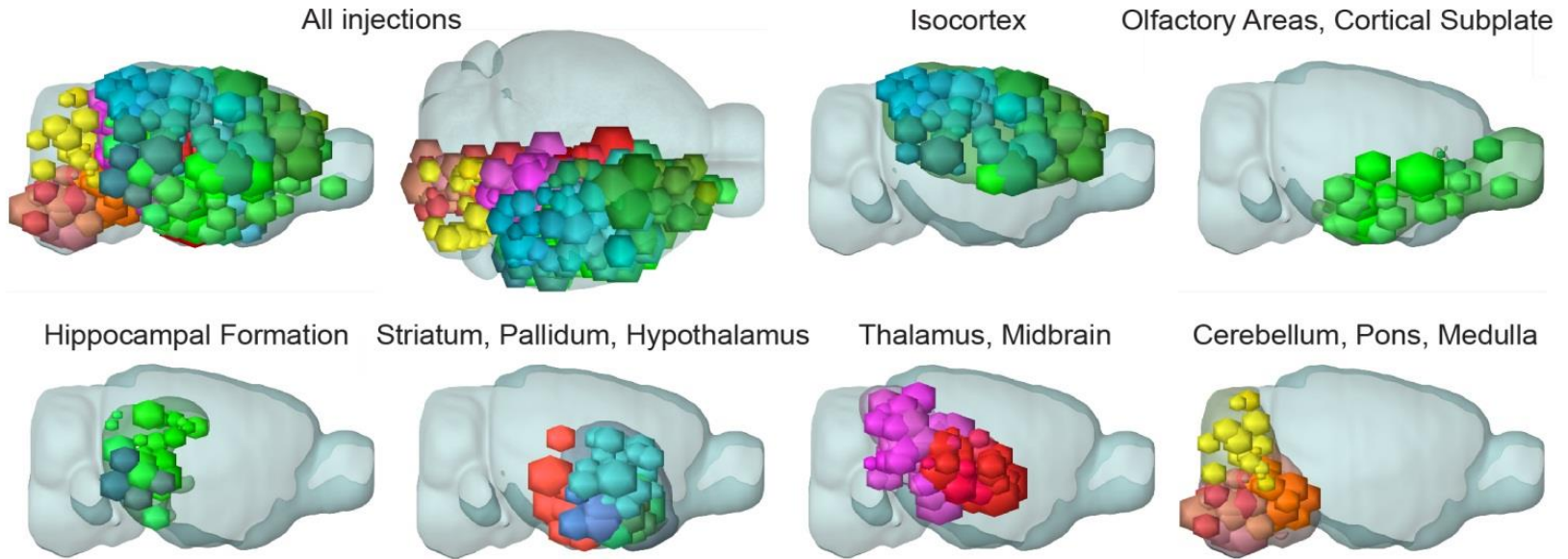


image 62 of 140 zoom:100.00%

Whole Brain Coverage: 424 Injection Sites



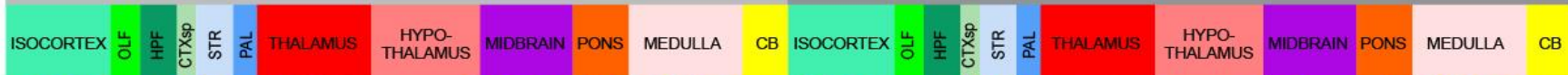
3.5 -2.0 -0.5



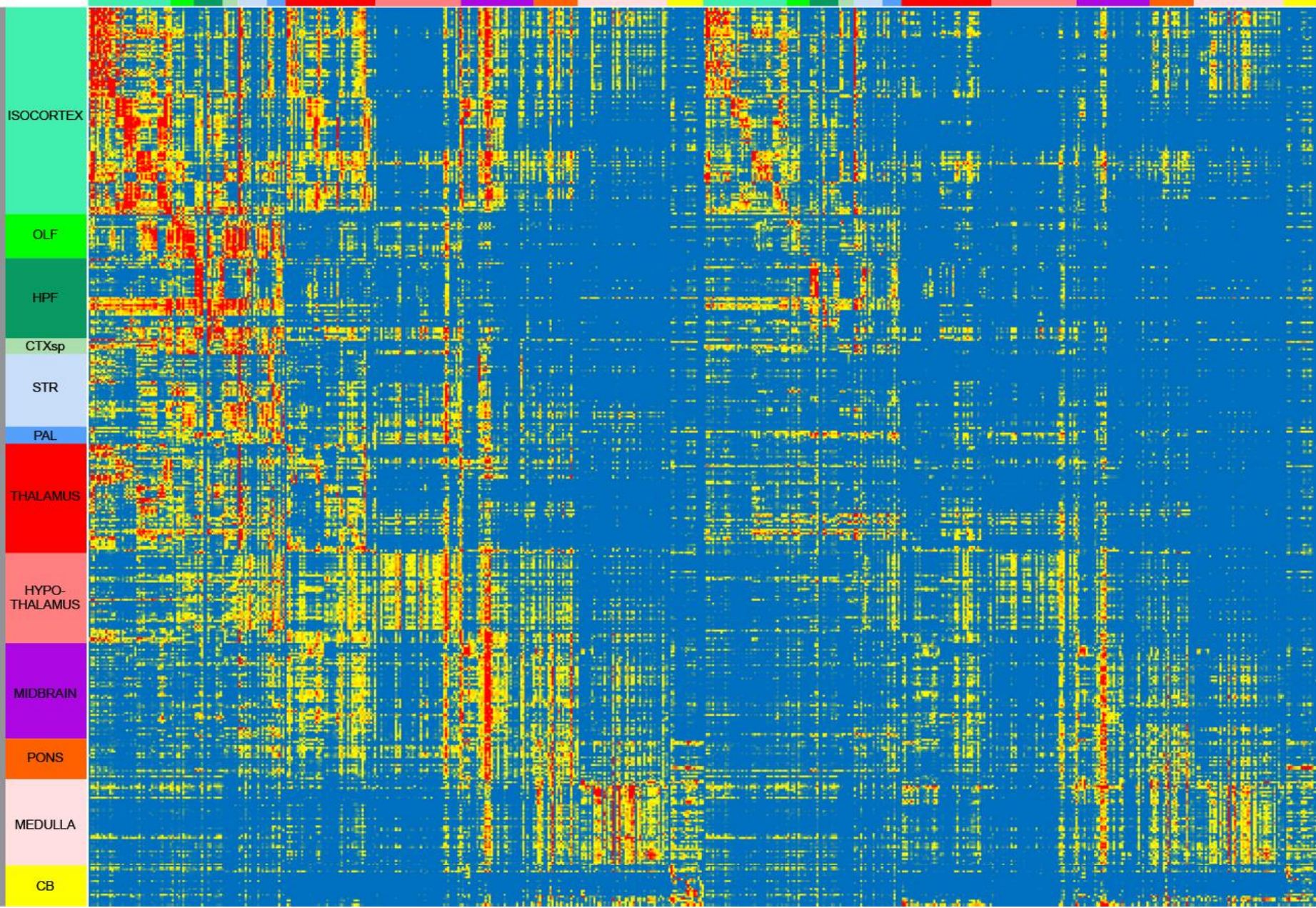
LOG10

TARGET: RIGHT HEMISPHERE (IPSI LATERAL)

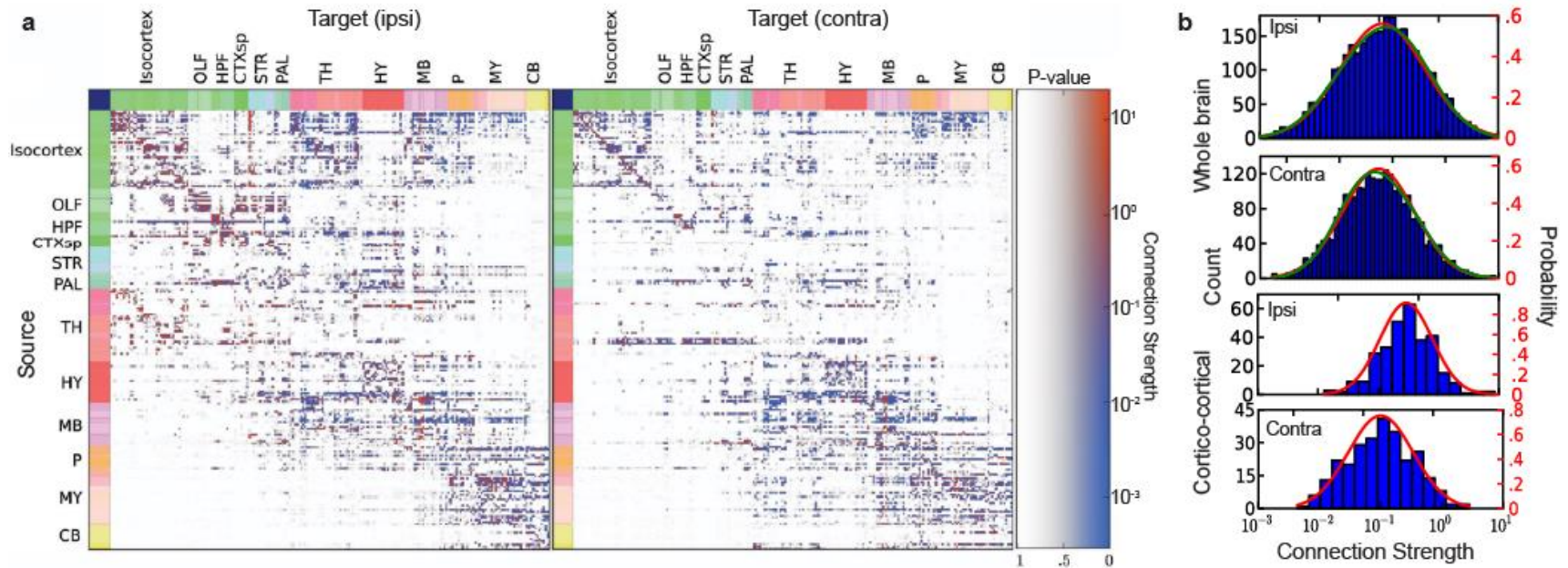
TARGET: LEFT HEMISPHERE (CONTRALATERAL)



SOURCE (INJECTIONS)



Interareal Connectivity Model and Analyses



Allen Mouse Connectivity Atlas – A Mesoscale Projectome

Features:

- Whole-brain coverage
- Single axon resolution
- High-precision co-registration of all datasets into a common 3D space
- Quantifiable
- Retaining realistic 3D spatial location and topography of projection targets as well as fiber tracts
- Cre-line based cell type specific projections

Enables:

- Computational network analysis: sub-networks, motifs, hubs, etc.
- More refined delineation of anatomical boundaries in 3D: improving traditional chemo- and cytoarchitecture based brain atlases
- Anterograde (from sources) and virtual retrograde (from targets) searches and comparisons

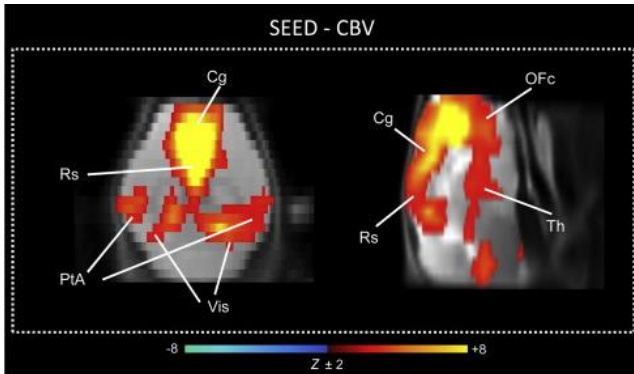
Alzheimer Project Questions

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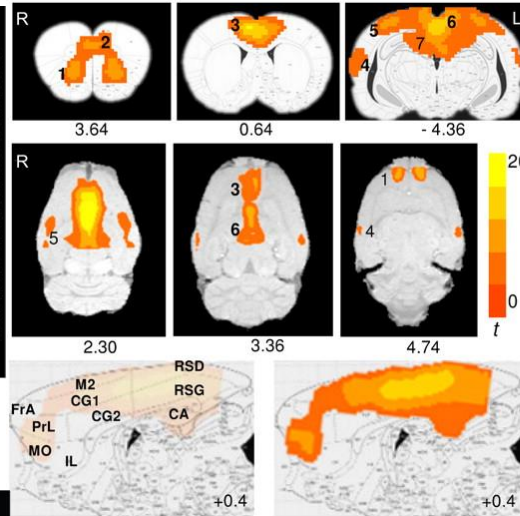


Rodents have a functionally defined default mode network

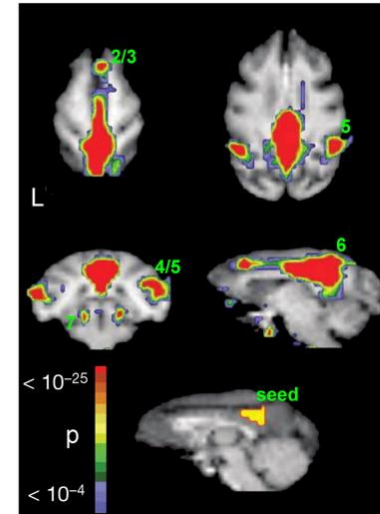
Mouse DMN



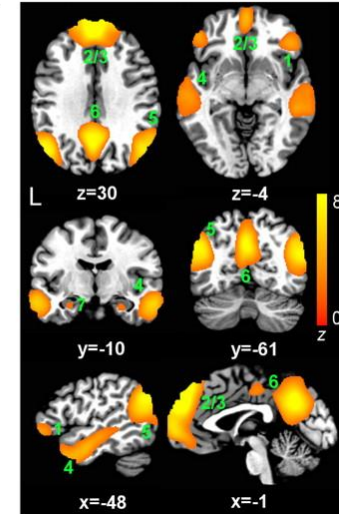
Rat DMN



Monkey DMN

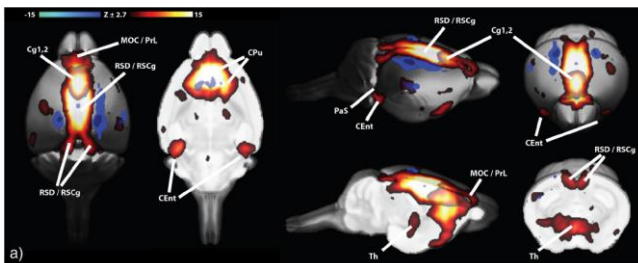


Human DMN



Hanbing Lu et al. PNAS 2012;109:3979-3984

- Sforazzini et al., NeuroImage 2014;87:403-415



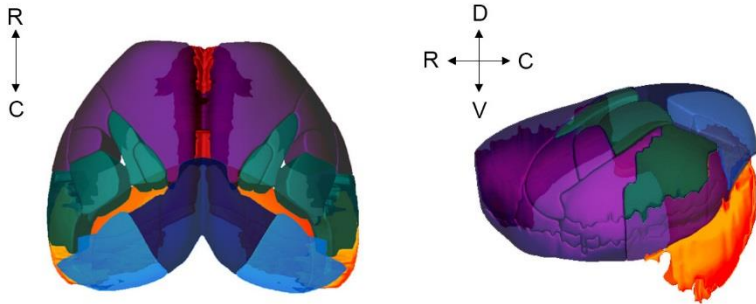
Zerbi et al., NeuroImage 2015;123:11-21

Do Alzheimer's disease mouse models have altered DMN connectivity?
Does the spread of amyloid pathology follow anatomical connections in the DMN?

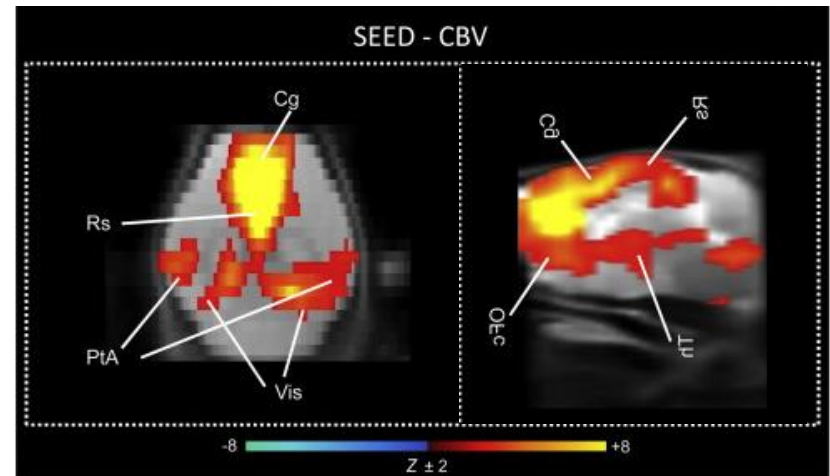
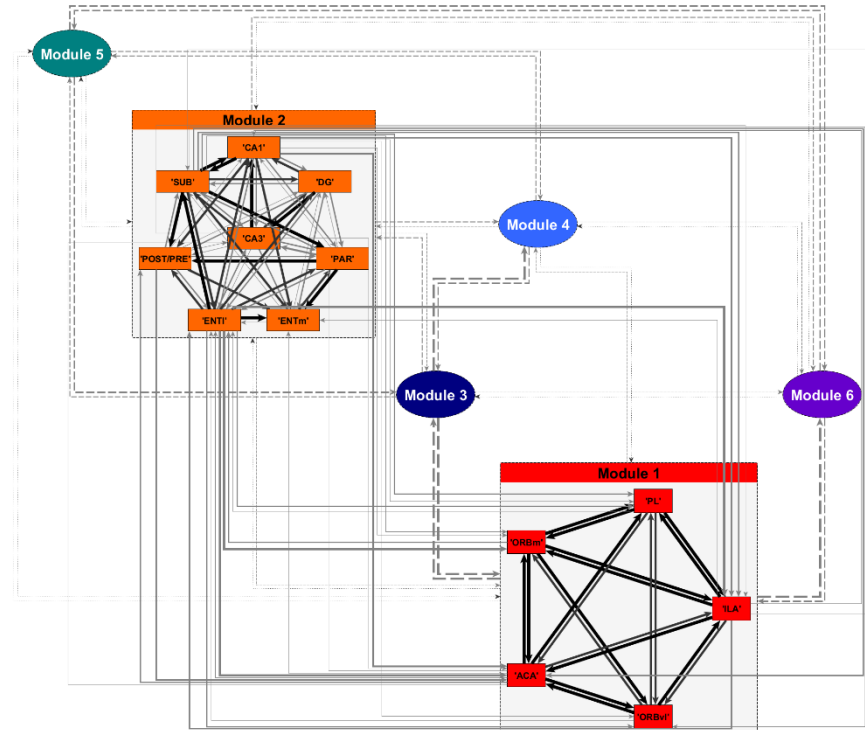
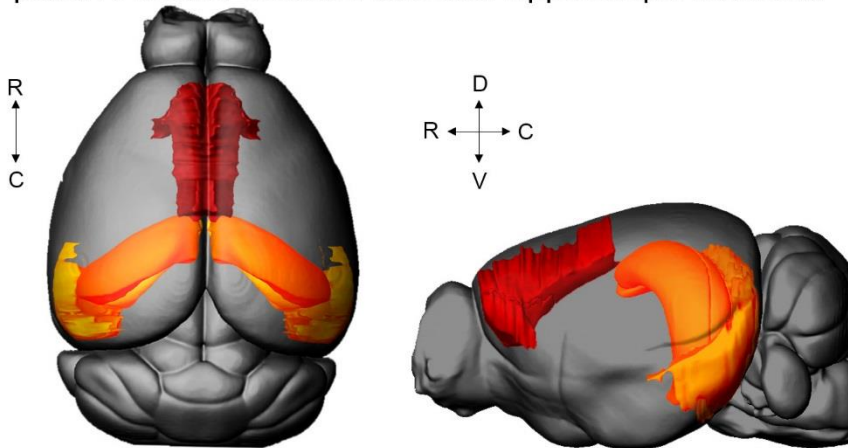
Anatomical Correlate of Mouse DMN?

Module 1	Module 2	Module 3	Module 4	Module 5	Module 6
ACA	CA3	VISpm	VISpl	SSp-ul	ORBI
ORBvl	PAR	VISam	VISpor	SSp-ll	AI
ILA	DG	RSPd	VISp	SSp-bfd	MOs
ORBm	CA1	RSPagl	VISl	AUDd	GU/VISC
PL	POST/PRE	RSPv		AUDp,v	MOp
	ENTm				SSs
	ENTl				SSp-n
	SUB				SSp-m
					TEa/PER/ECT

cortical and hippocampal structural modules



putative mouse default mode and hippocampal networks

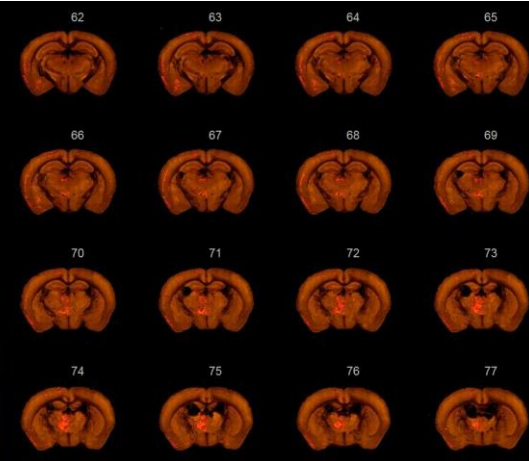
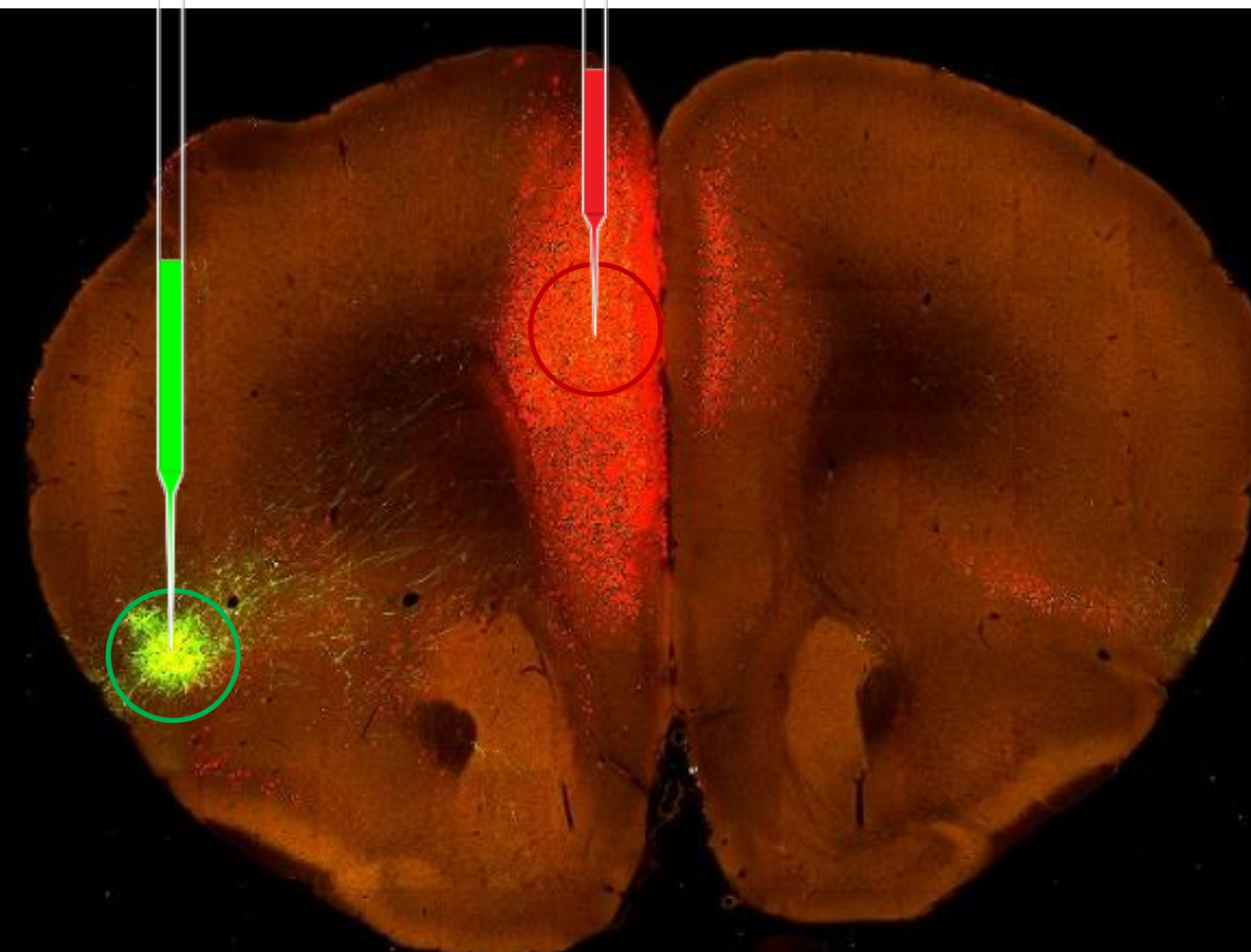


Genetic tools to label specific classes of neurons

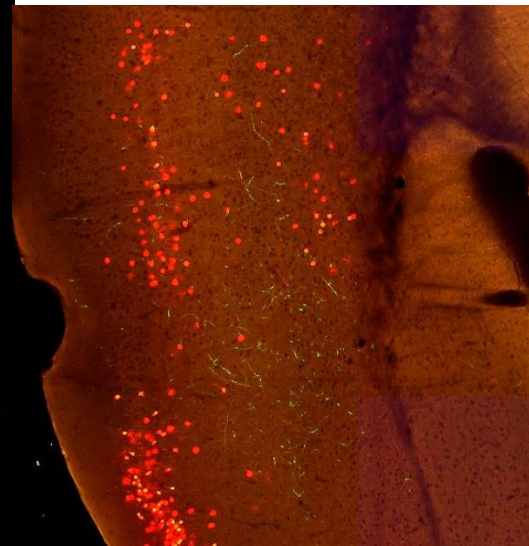
AAV1-FLEX-EGFP
Only expressed in Cre+ cells

CAV2-Cre: *Retrograde virus*

Whole brain inputs and outputs



Whole brain projections (GFP)

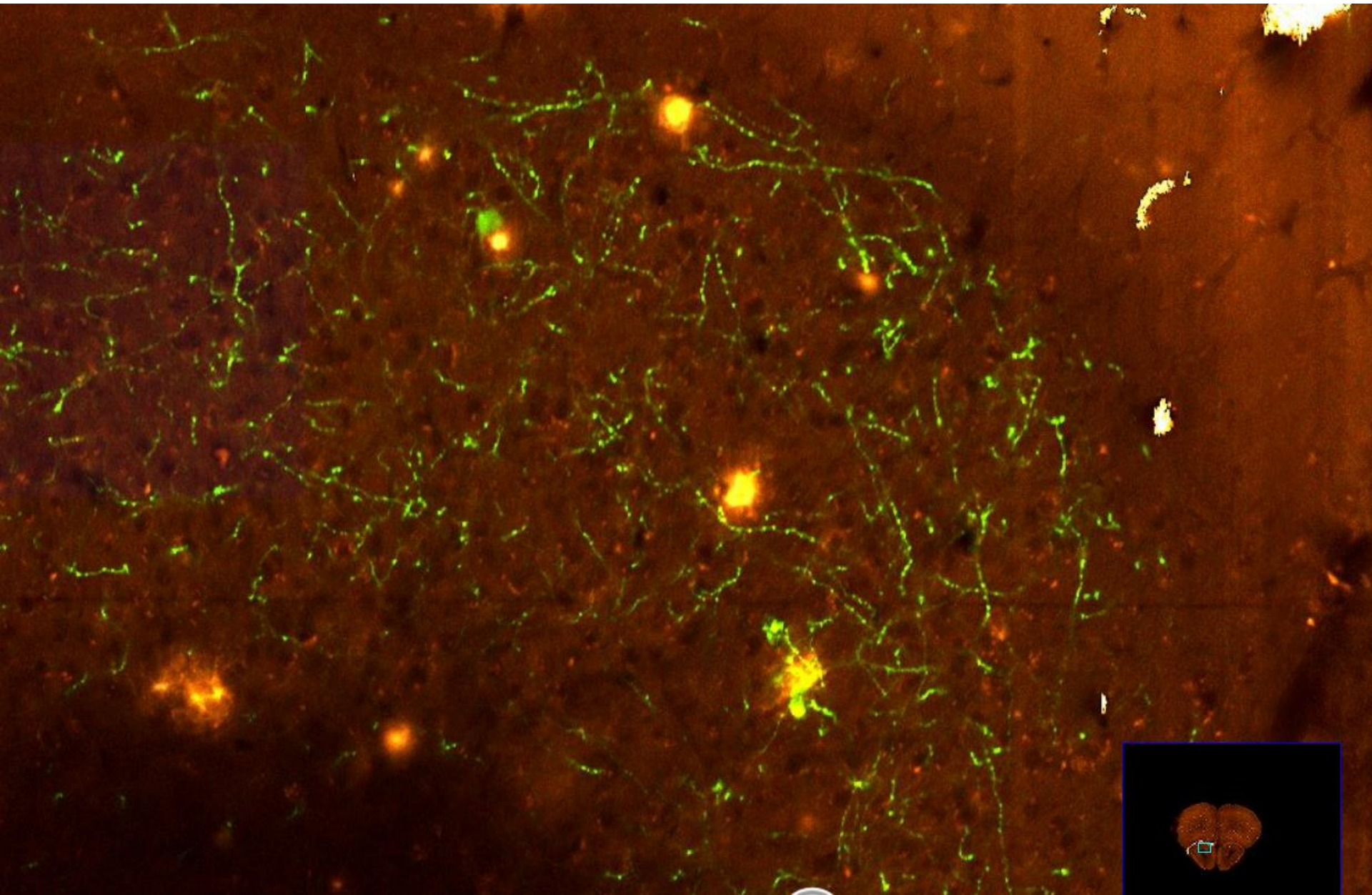


Cells with red nuclei project to CAV2-Cre injection site

Whole brain projection mapping from vulnerable brain regions



Mapping structural connectivity in a mouse model of AD (APP/PS1) with simultaneous measures of A β pathology



Mesoscale Connectivity in Alzheimer's Disease: Future Product Summary

- Mapping whole brain projections in large-scale disease relevant networks in a mouse model of AD
- Mouse model enables multi-scale analyses of long distance structural connectivity changes with other microscale pathologies
- Build a computational model to predict disease progression and test further hypotheses.
- Platform is robust and flexible enough for additional mouse models.





THANK YOU

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Hongkui Zeng
NIA R01AG047589

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