Whole Brain Structural Connectivity Models for Preclinical Investigation of Alzheimer Pathologies

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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:

**Molecular:** aggregation of Aβ, abnormal tau

**Cellular:** altered intracellular signaling networks, neuron loss, gliosis (astrocytes, microglia, oligodendrocytes), loss of presynaptic and postsynaptic proteins

**Circuits:** deficits in synaptic plasticity, excitation/inhibition imbalance

**Networks:** structural changes (white matter damage, atrophy), functional connectivity (default mode network)

**Clinical symptoms (dementia)**

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

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

Single cell
Resolution: submicron
Electron Microscopy
Animal Models

Human Connectome Project

Allen Mouse Connectivity Atlas

Open Connectome Project
Functional Connectivity Alterations in AD

Default Mode Network

Decreasing DMN Connectivity in Dominantly-Inherited AD

DEFAULT ACTIVITY

AMYLOID DEPOSITION

ATROPHY

METABOLISM DISRUPTION

Buckner et al J. Neurosci. 2005

Does normal connectivity predict pathology? Network degeneration hypothesis
Prion-like propagation of pathology in neurodegenerative diseases

- Amyloid-β deposits (senile plaques)
  - Image of amyloid-β deposits

- Tau inclusions (neurofibrillary tangles)
  - Image of tau inclusions

- α-Synuclein inclusions (Lewy bodies)
  - Image of α-synuclein inclusions

- TDP-43 inclusion (ALS)
  - Image of TDP-43 inclusion

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 Pipeline

Stereotaxic Injection
- Viral tracer

Image Acquisition: STP

Preprocess
- Projection Image

Data Processing
- Alignment
- Gridding
- 3-D Reference Space
- 3-D Projection Data Grid

Signal Detection
- Segmentation Mask

QC and Expert Annotation of Injections

Web Presentation: Injection Search, 2-D Images, 3-D Brain Explorer
rAAV2.1-hSyn-EGFP-WPRE into Primary Motor Cortex (MOp)
Primary injection location: Primary motor area
Primary injection location: Primary motor area
Whole Brain Coverage: 424 Injection Sites

All injections

Isocortex

Olfactory Areas, Cortical Subplate

Hippocampal Formation

Striatum, Pallidum, Hypothalamus

Thalamus, Midbrain

Cerebellum, Pons, Medulla

Number of Injections

Injection Volume (mm$^3$)

Unique Structures
Injection Experiments
Missed Structures

Injection Volume (mm$^3$)
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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- Are there (and what are the) alterations in structural network properties in AD mice? Are they related to measurable pathologies?
Rodents have a functionally defined default mode network

- Sforazzini et al., NeuroImage 2014;87:403-415
- Hanbing Lu et al. PNAS 2012;109:3979-3984
- 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?

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*

Cells with red nuclei project to CAV2-Cre injection site

Whole brain inputs and outputs

Whole brain projections (GFP)
Whole brain projection mapping from vulnerable brain regions
Mapping structural connectivity in a mouse model of AD (APP/PS1) with simultaneous measures of Aβ 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.
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