In search of eye imaging biomarker in dementia moue models:

Understanding the role of tau/Aβ protein in the retina

Alzheimer Society Research Program Exchange

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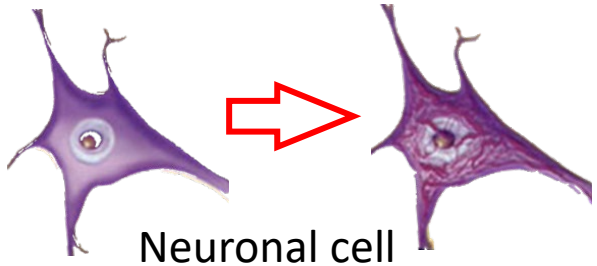
Alzheimer Society CANADA

SFU SIMON FRASER UNIVERSITY

Research themes

Hyperphosphorylation

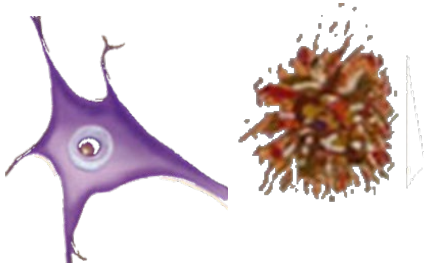


Neuronal cell

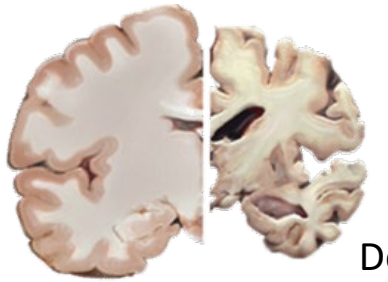
Retinal Tau pathology

Retina **Amyloid** pathology

Amyloid deposition



Imaging the Alzheimer's-related eye pathologies using mouse model



Healthy brain

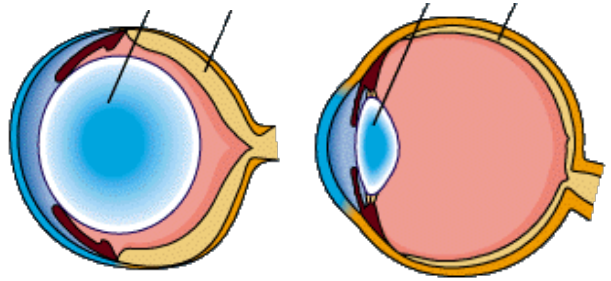
Demented brain

Connection to the brain pathology

Live imaging for clinical translation

Mouse eye

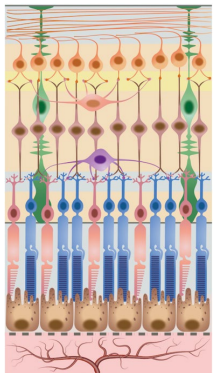
Human eye



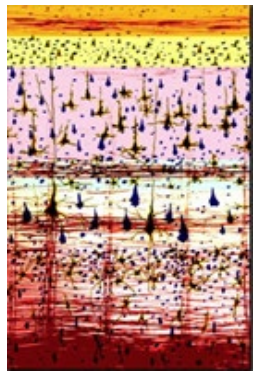
Motivation – Why use retinal imaging for AD

- The retina is an extension of the central nervous system (CNS)

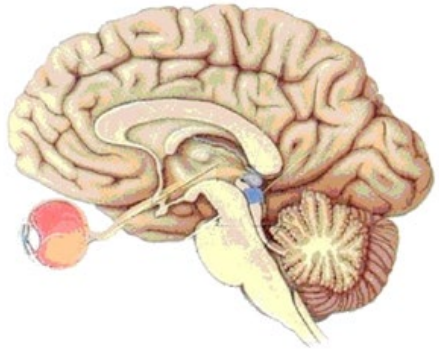
  - Sharing embryonic origin with the brain
  - Anatomically similar
  - Functionally connected
  - Easier to access and image

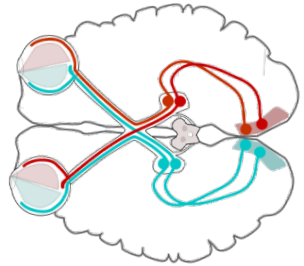


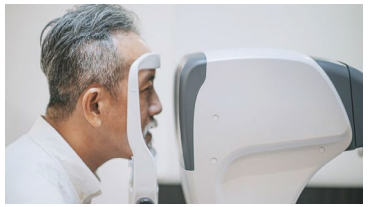
retina



cortex

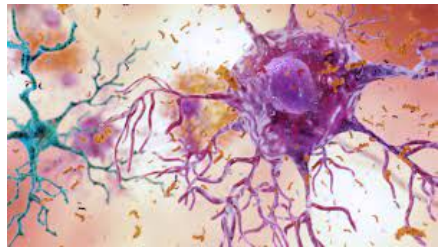


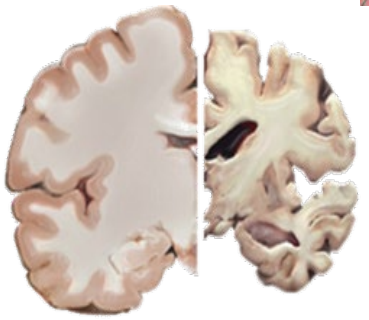




Does Alzheimer's pathology also manifest in the eye?

- Alzheimer's Disease
  - Complex multi-factorial disease, manifest multiple pathologies
  - vascular disruption,
  - Abnormal protein expression and aggregation
  - inflammation-related immune response
  - neural degeneration



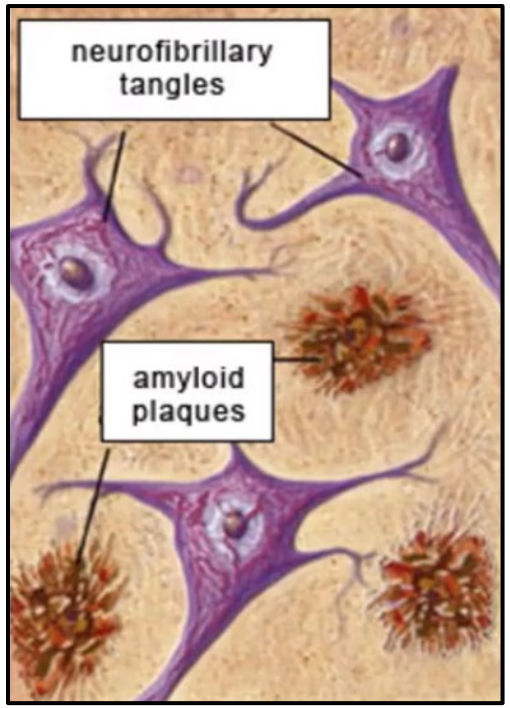


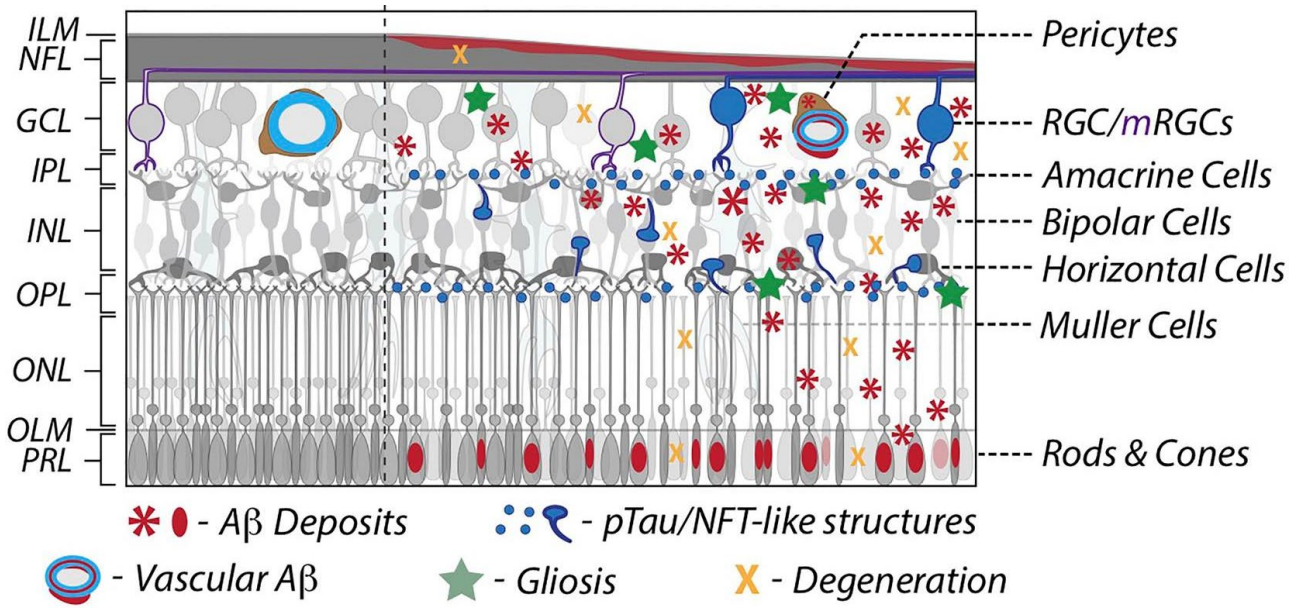
Healthy brain

demented brain

Does Alzheimer's pathology also manifest in the eye?

- Hallmarks of AD - two types of toxic proteins:
  - Amyloid precursor protein (APP) => **β-Amyloid (Aβ)** => plaques
  - Tau: microtubular associated protein (MAP) => **hyperphosphorylated (pTau)** => neurofibrillary tangles





Mirzaei, N. *et al.* (2020) '**Alzheimer's Retinopathy: Seeing Disease in the Eyes**', *Frontiers in Neuroscience*, 2020

Part 1:
Imaging Tau pathology in the retina and optical nerve

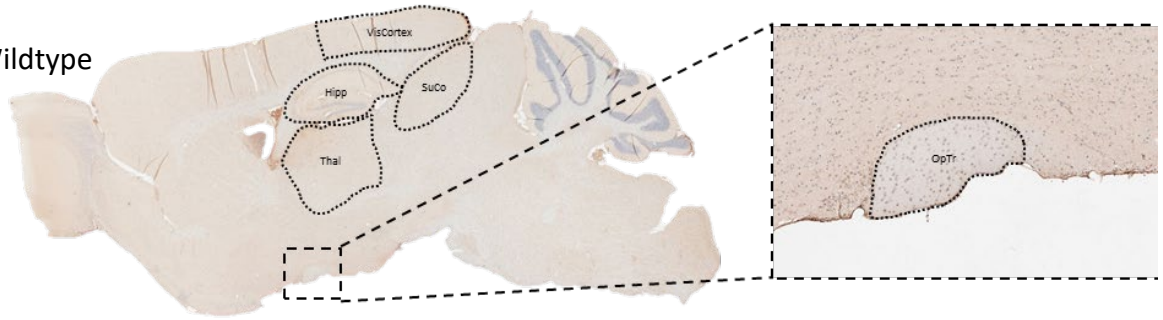
- Transgenic mouse model with Tau pathology (rTg4510)

Tauopathy in mouse brain

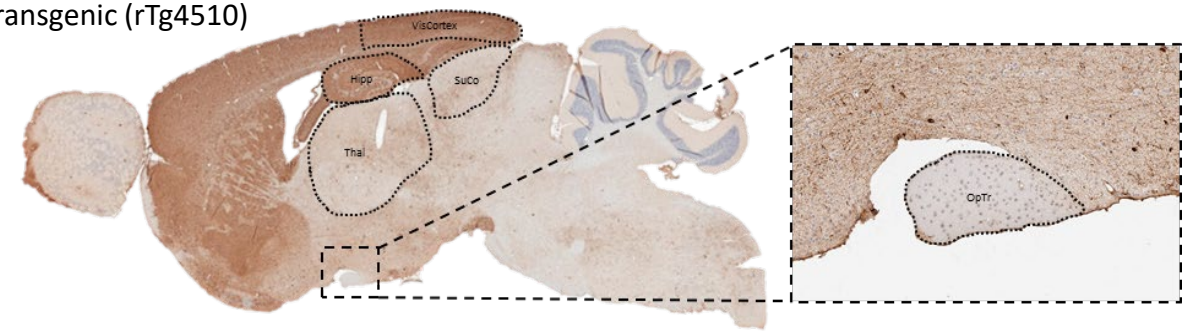
- Hyperphosphorylated (pTau) brain staining

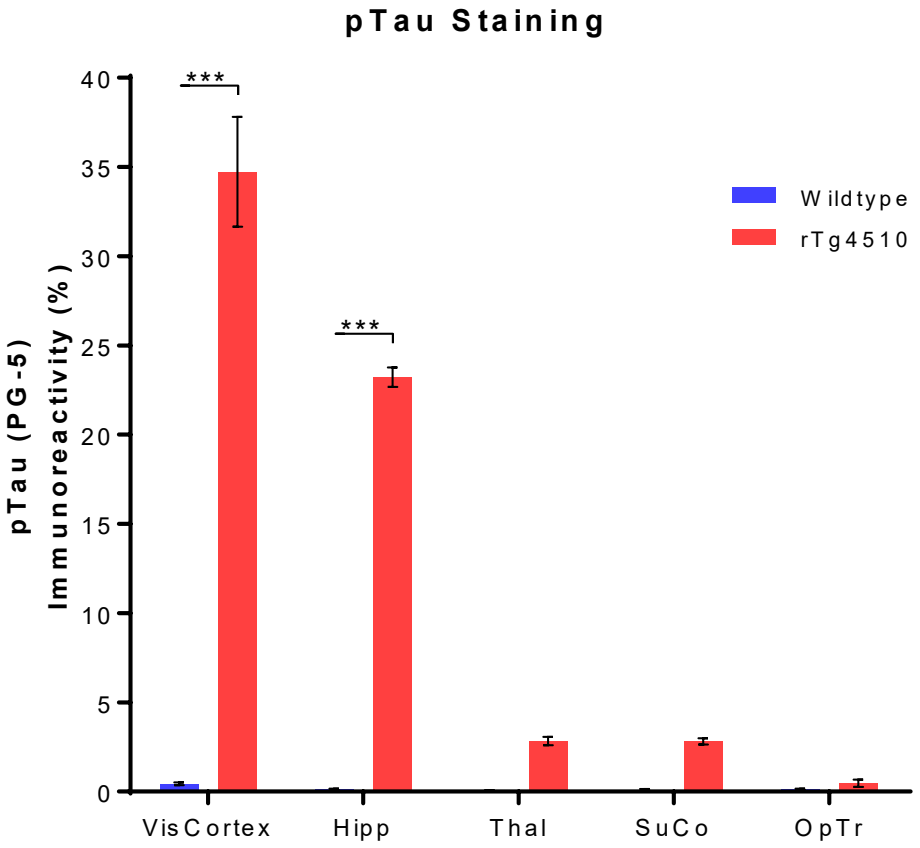
- **Cortex**
- **Hippocampus**
- **Thalamus**
- **Superior Colliculus**
- **Optical Track**

Wildtype

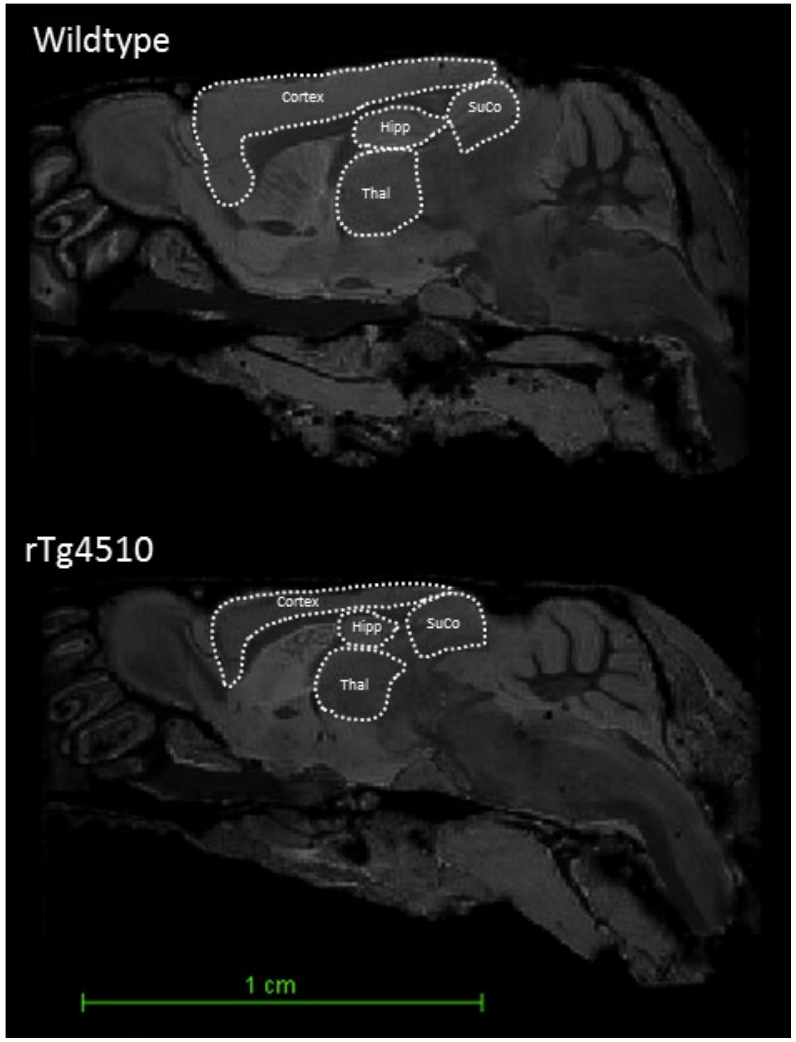


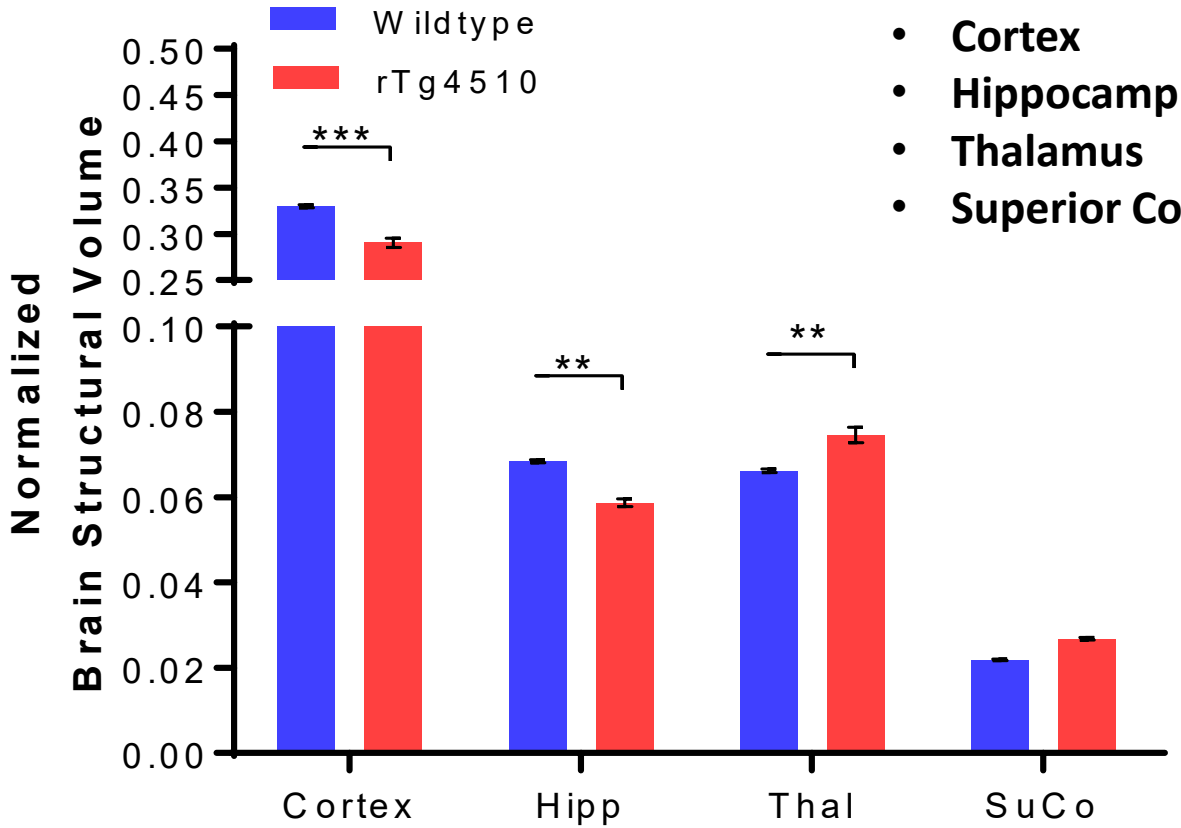
Transgenic (rTg4510)





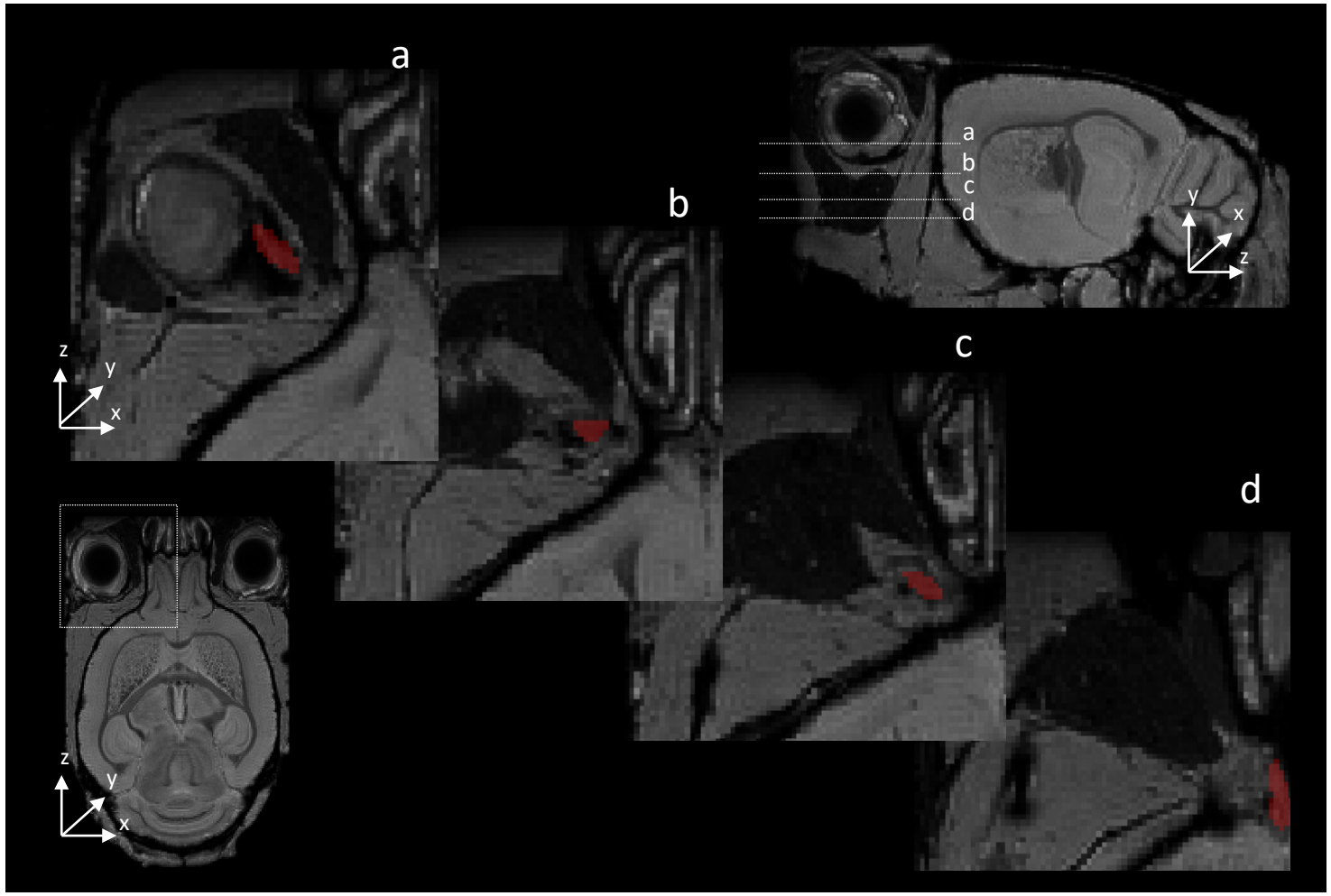
Neurodegeneration in the mouse brain

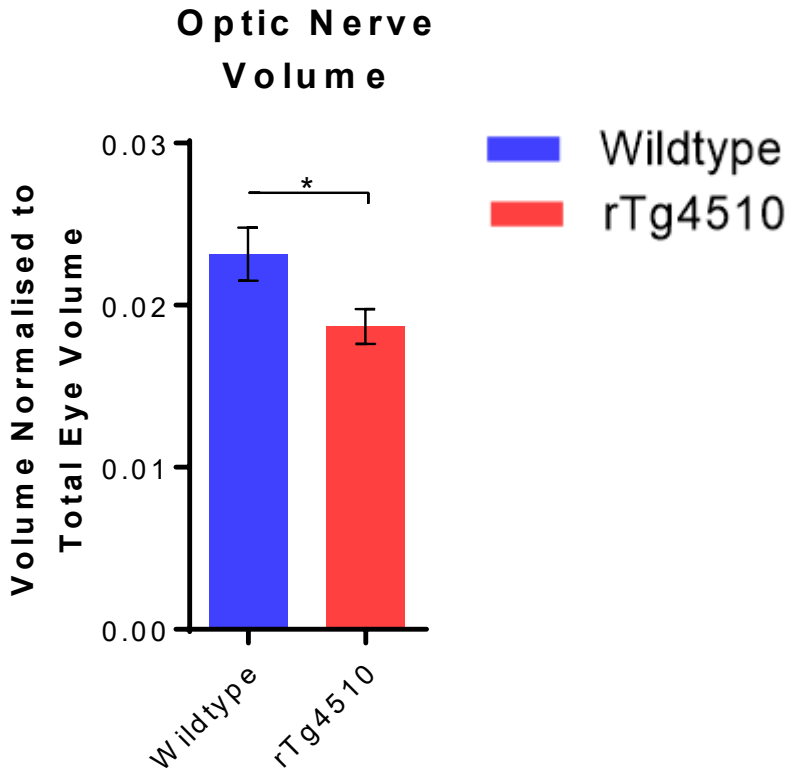




- **Cortex**
- **Hippocampus**
- **Thalamus**
- **Superior Colliculus**

Optical Nerve Volume reduction

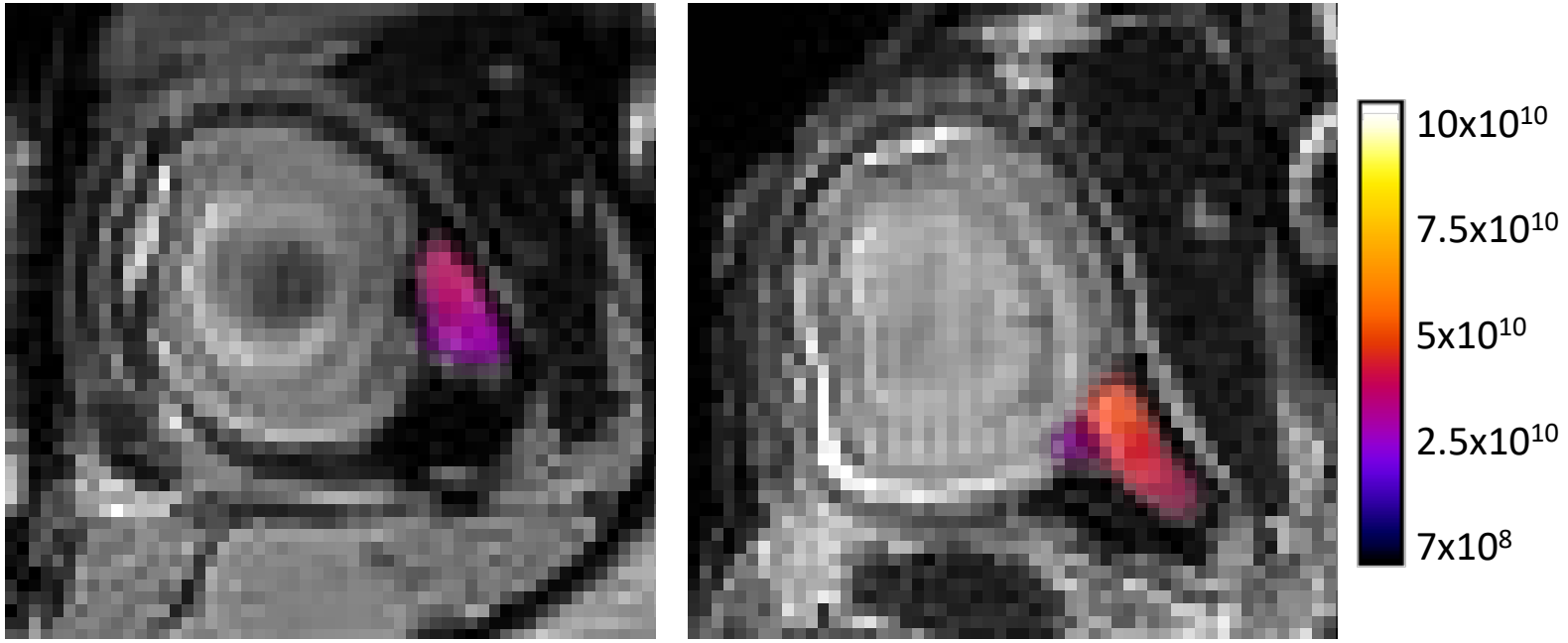


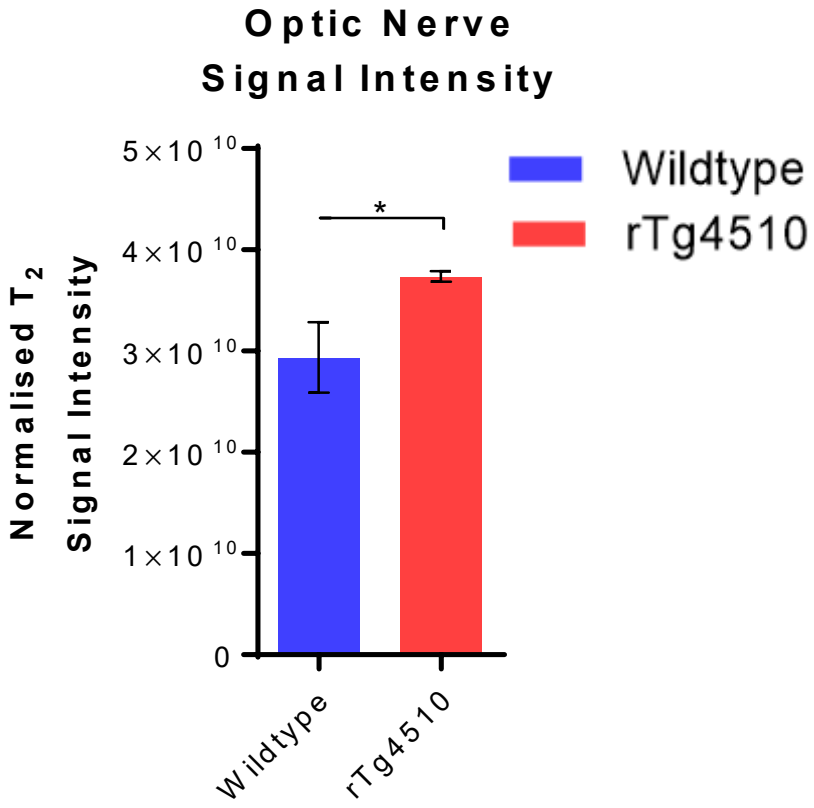


Optical Nerve Signal Intensity increase

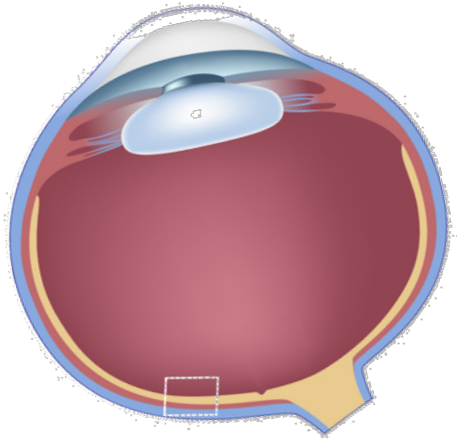
Wildtype

rTg4510

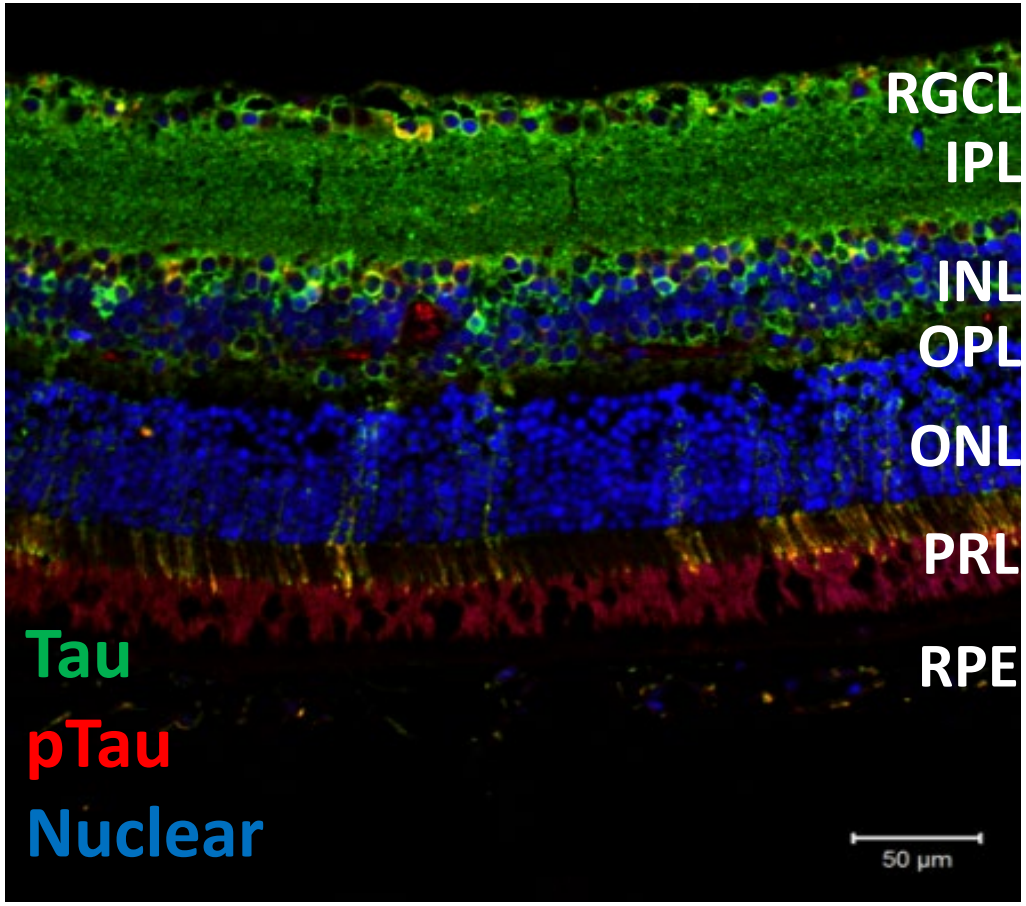




pTau deposition in the retina



- Immunohistochemically-stained retina sample



RGCL Retinal Ganglion Cell Layer
IPL Inner Plexiform Layer

INL Inner Nuclear Layer
OPL Outer Plexiform Layer

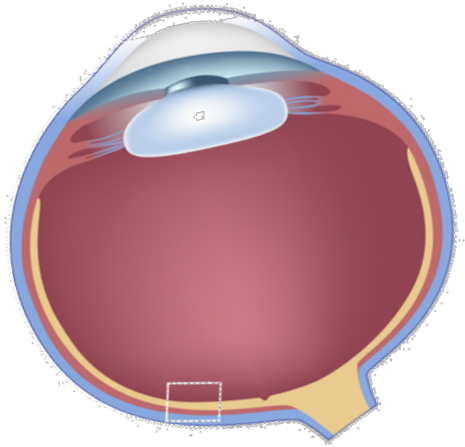
ONL Outer Nuclear Layer

PRL Photoreceptor Layer

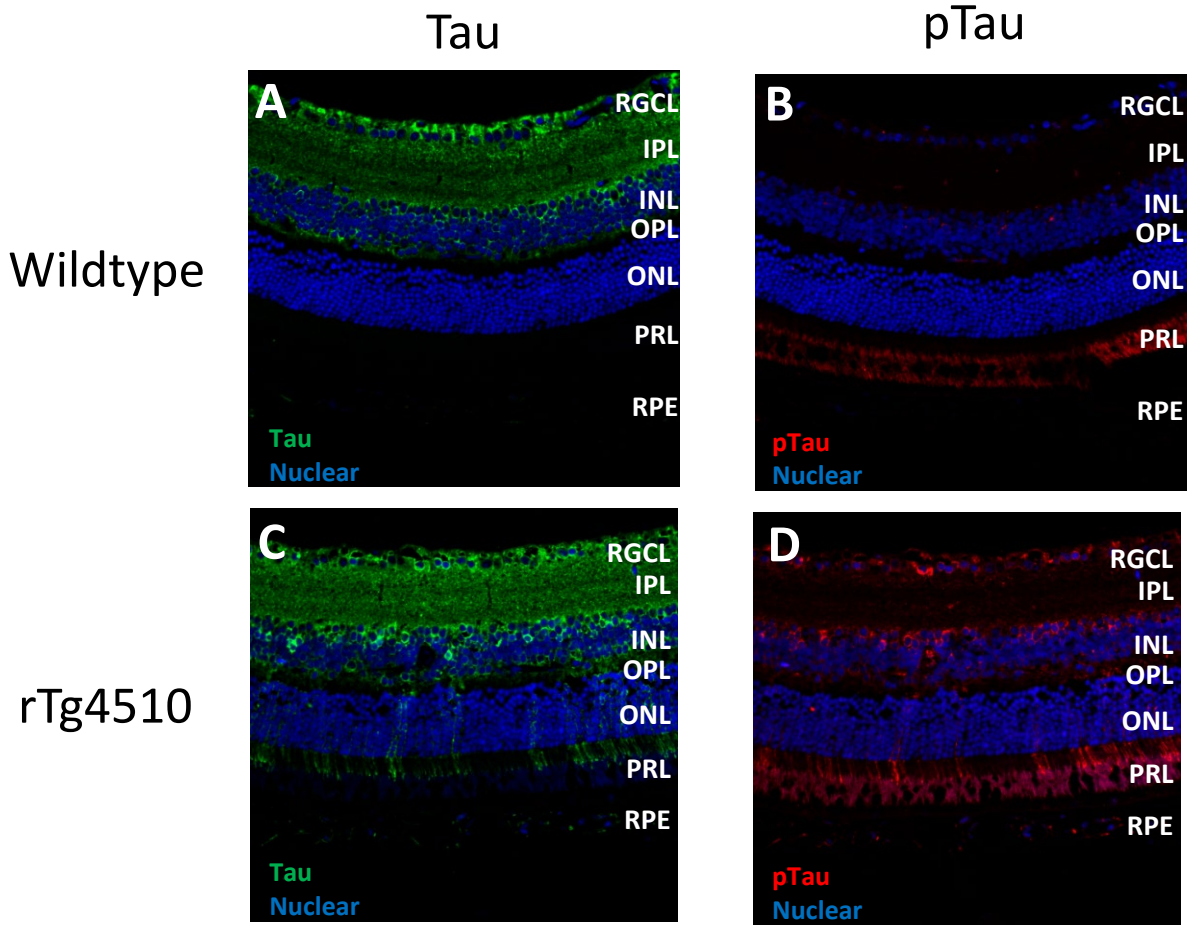
RPE Retinal pigment epithelium

Results – pTau in retina

- **pTau** in the inner retinal layer of the retina

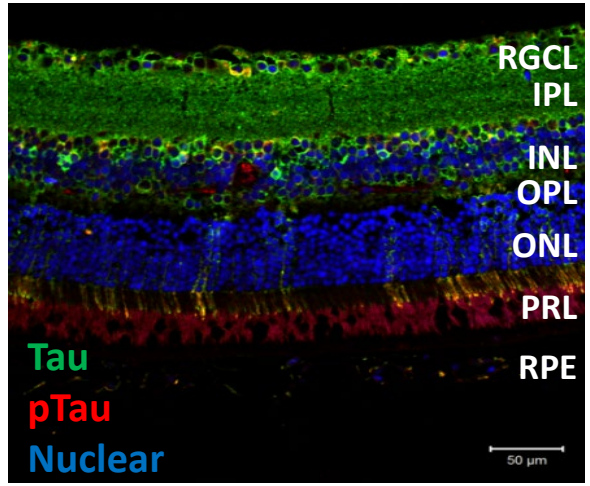


Tau
pTau
Nuclear

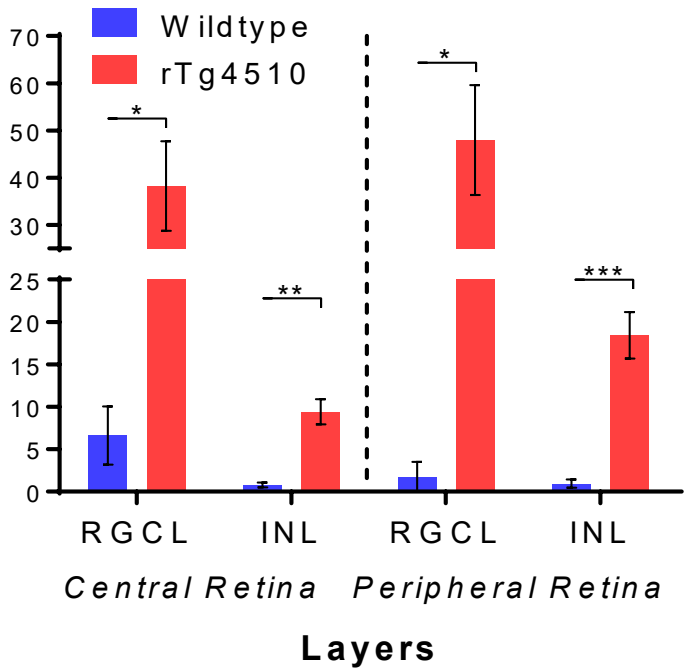


Results – pTau in retina

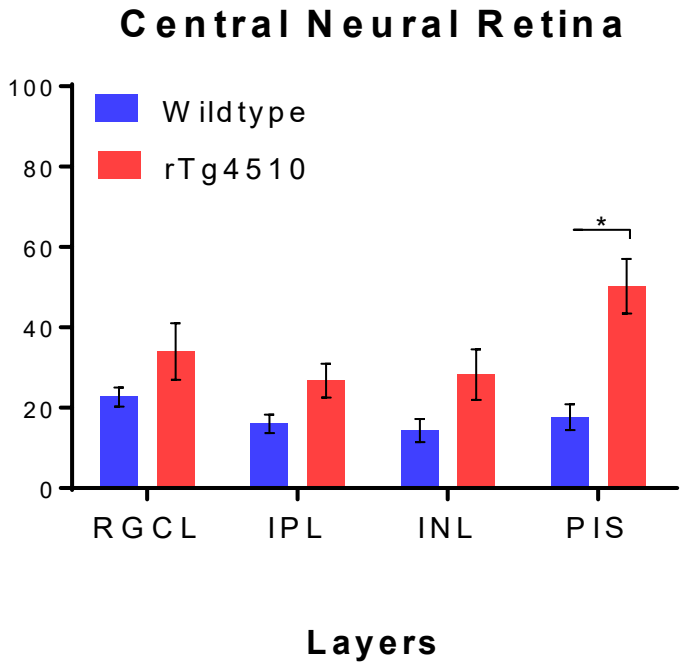
- pTau positive cell number and intensity

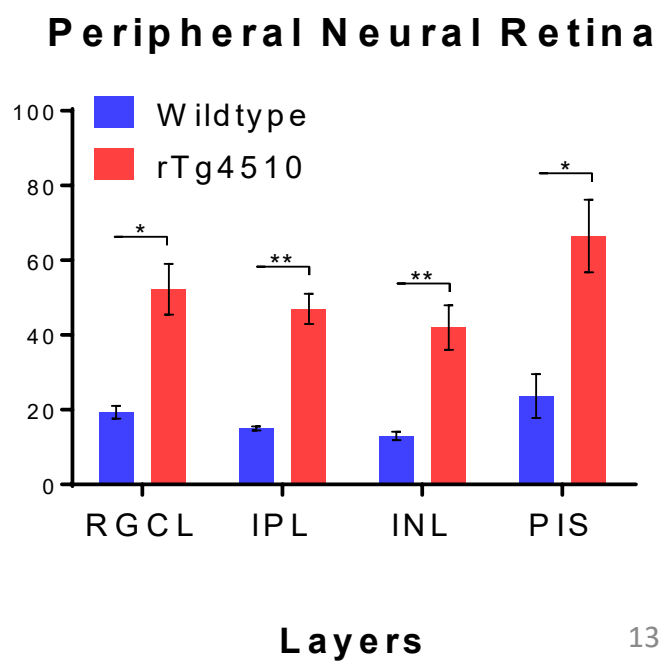


pTau immunopositive cytosolic staining cell (%)



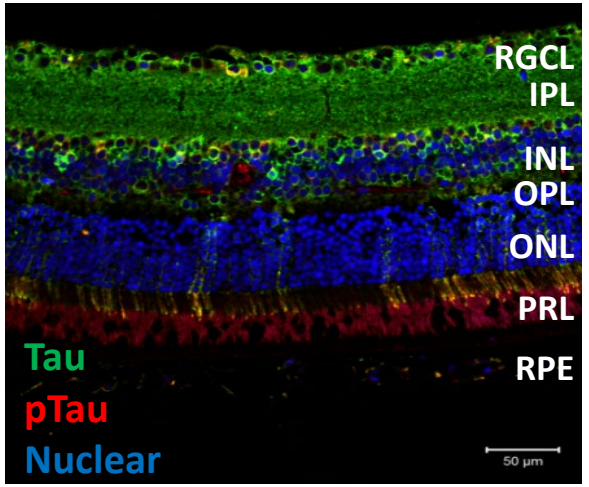
Intensity of pTau staining (Mean Intensity/Pixel)

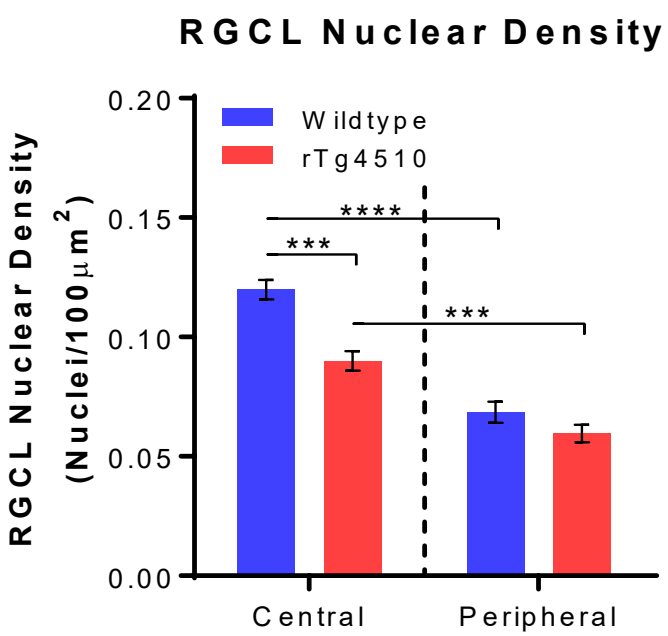


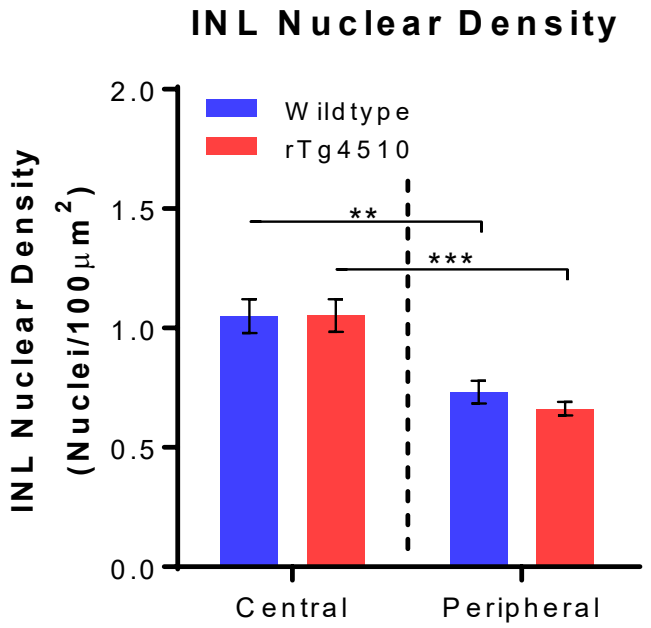


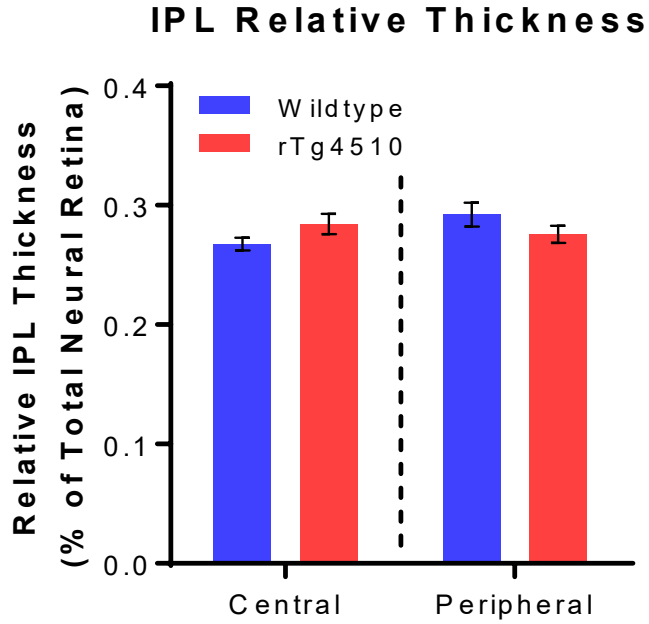
Results – neurodegeneration in retina

- Neuronal cell nuclear density
- Retina layer thickness

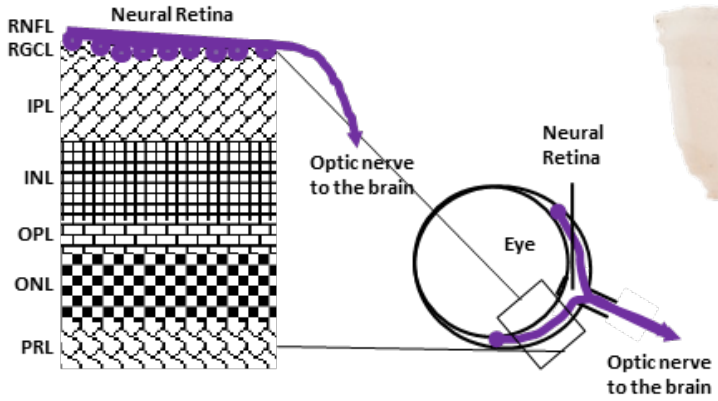


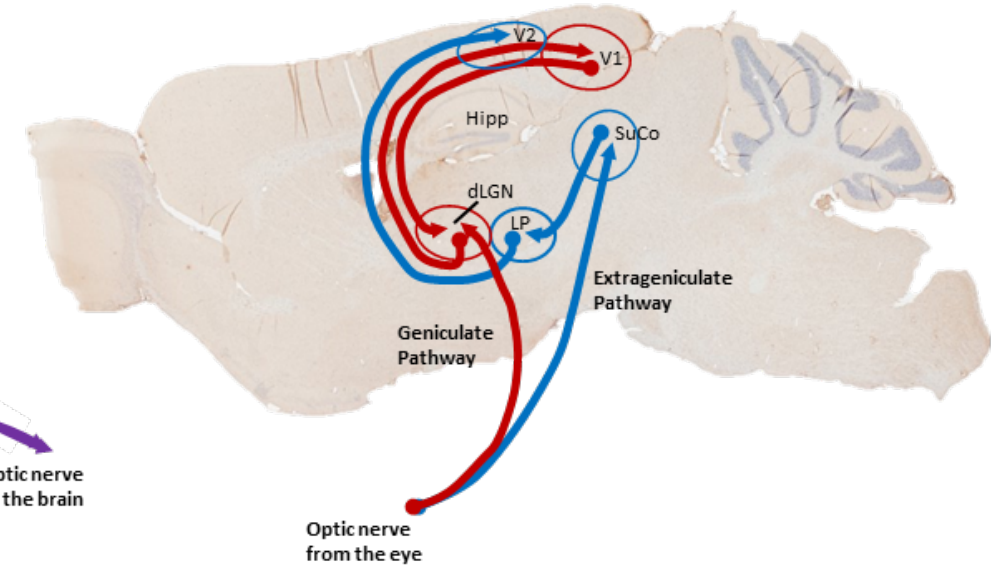


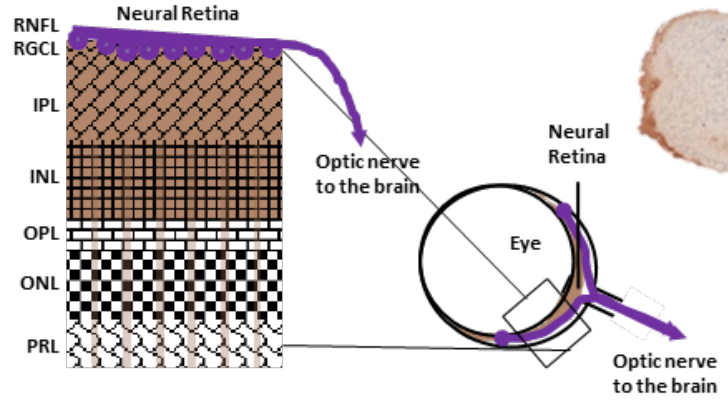


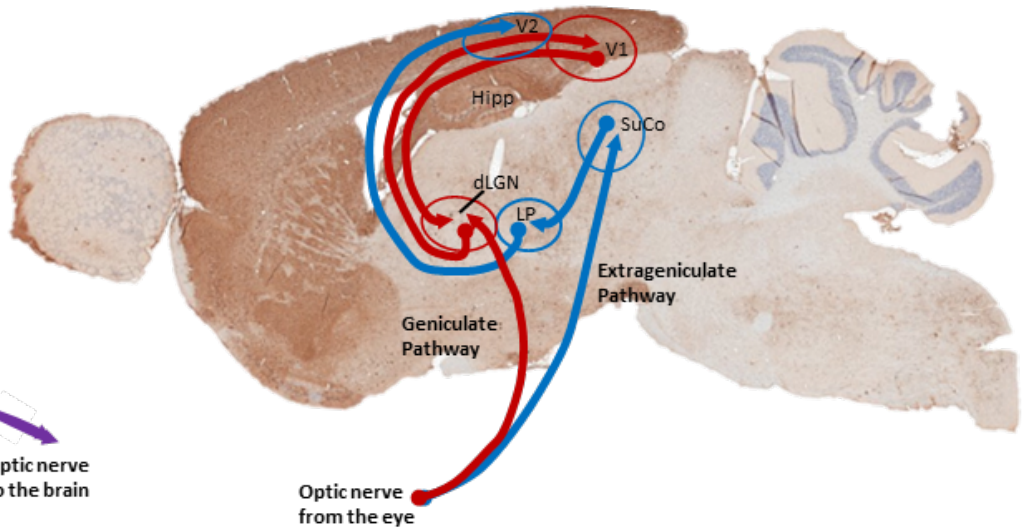


Summary of findings



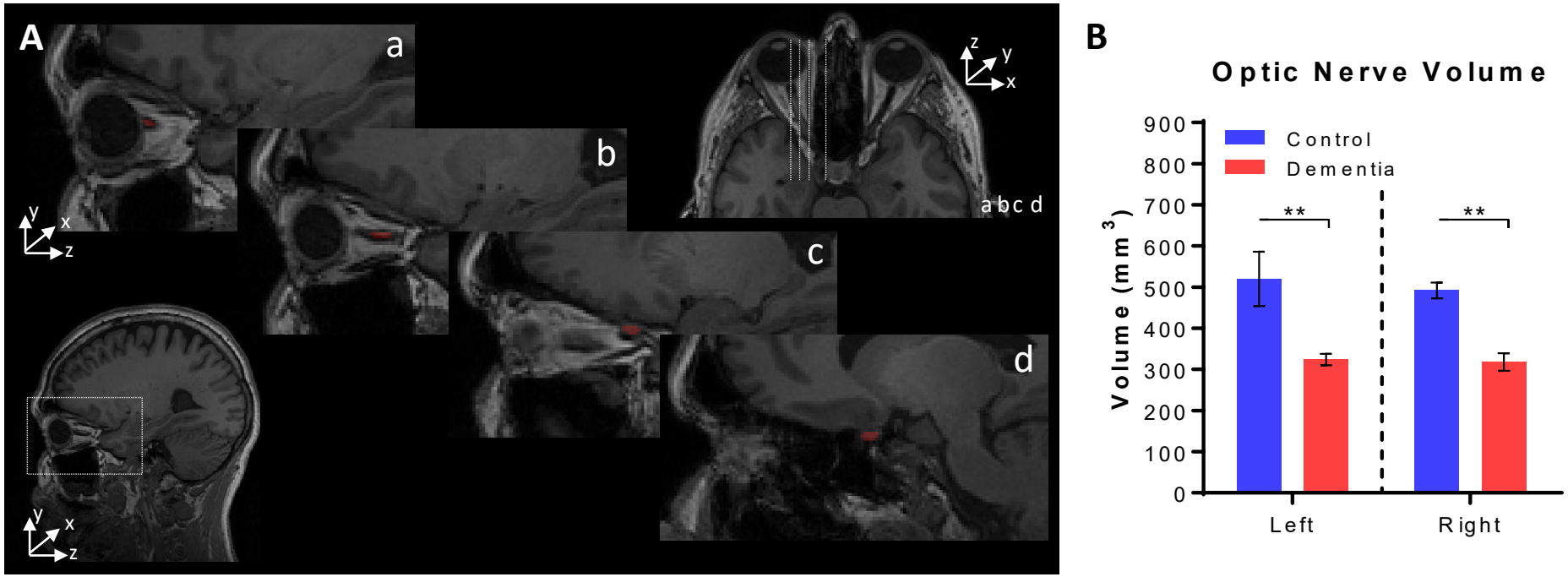






Patient data of optical nerve volume

- Atrophic changes in optic nerve volume were similarly observed in Dementia patient with Tau pathology (− 36.6 ± 2.6%).

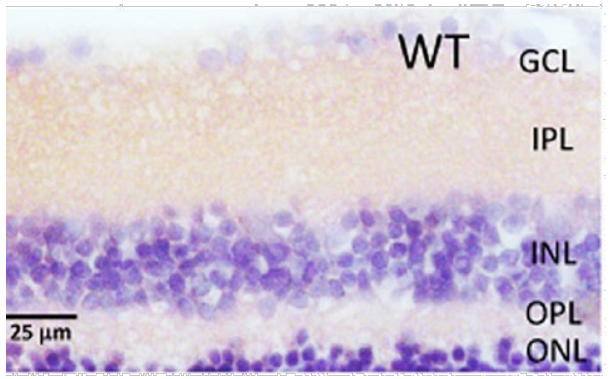


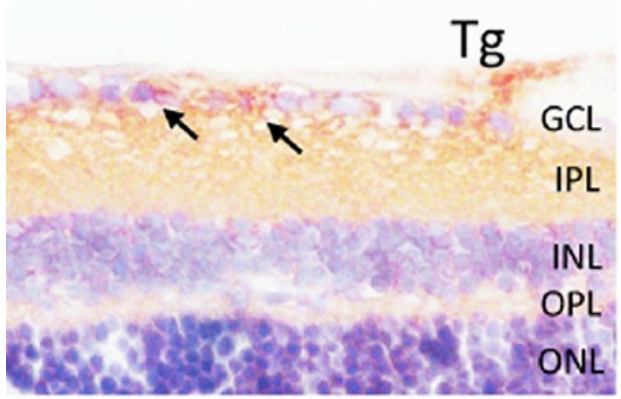
Project 2:
In vivo imaging of Aβ pathology in the retina

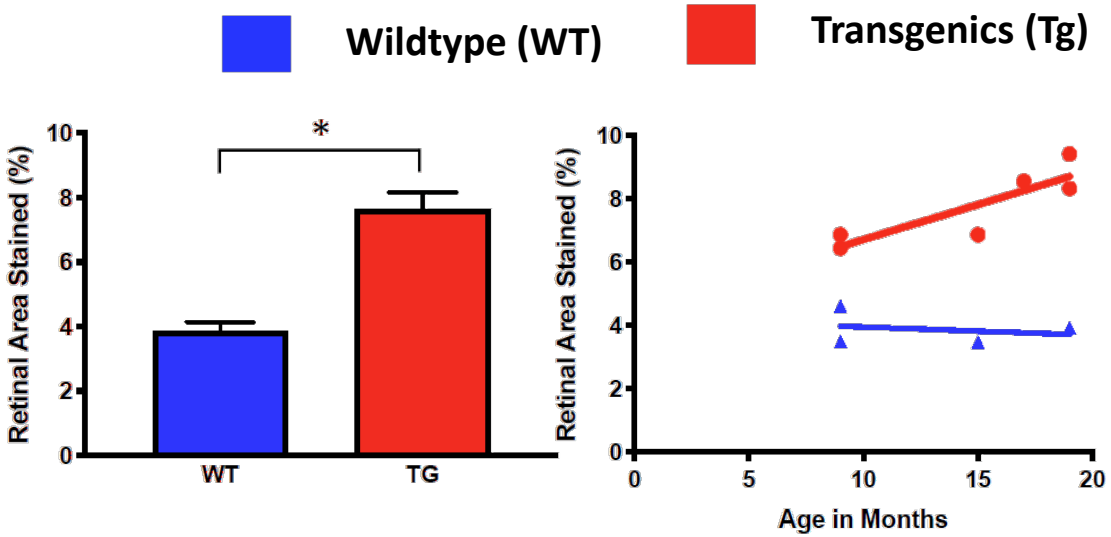
- Transgenic mouse model with Amyloid pathology (APP/PS1)

Ex vivo Aβ immunostaining in the retina

- Significantly higher *ex vivo* retinal Ab immunoreactivity in transgenic mic
- Retinal Aβ increased with age in the transgenic mice, but not in wildtype.

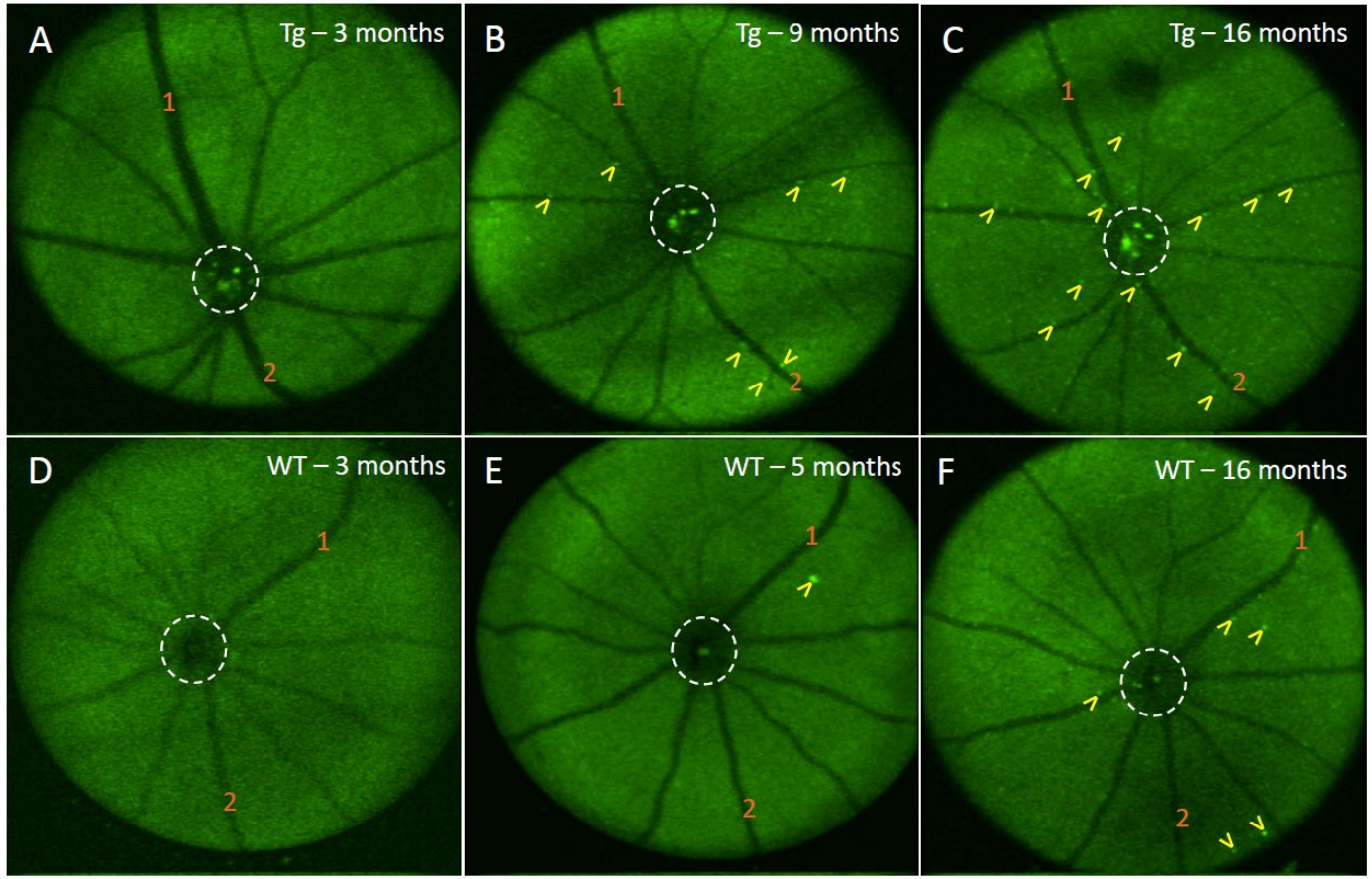


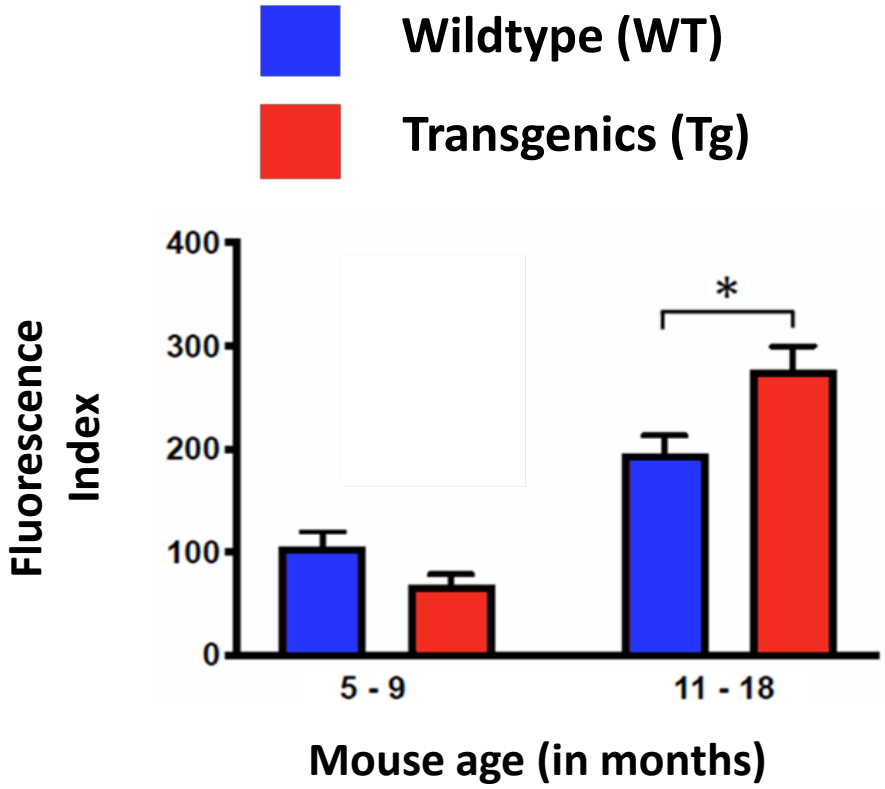




In vivo retinal fluorescence imaging

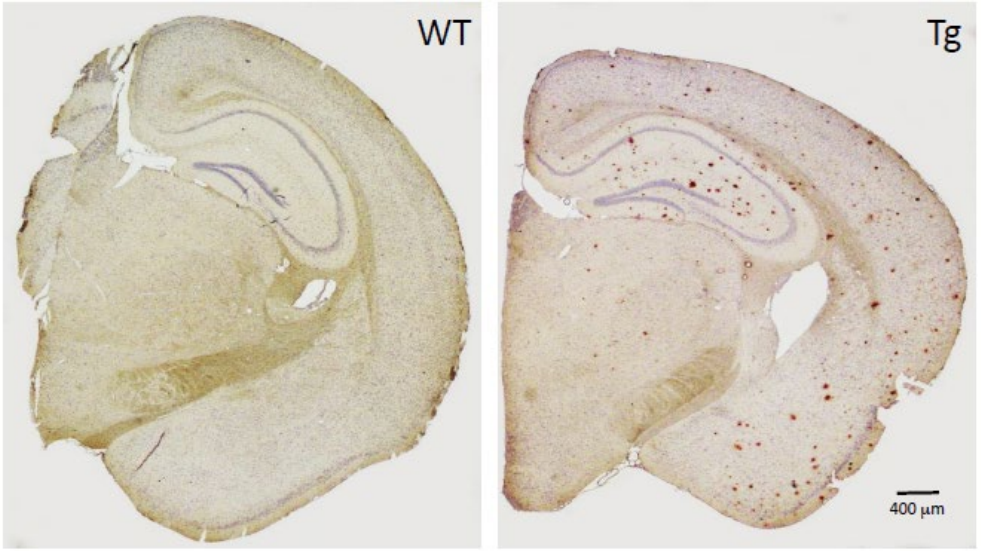
- Retinal in vivo Fluorescence After Curcumin Injection Is Higher in transgenic mouse than Wildtype Mice, and increases with age

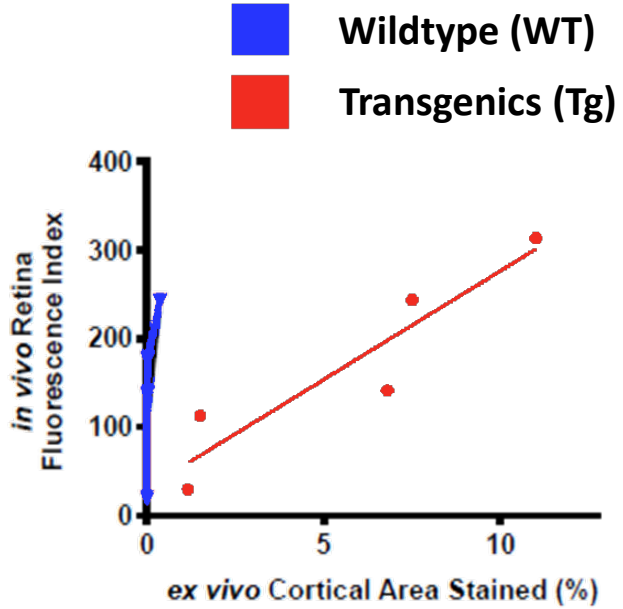




Ex vivo Aβ immunostaining in the mouse brain

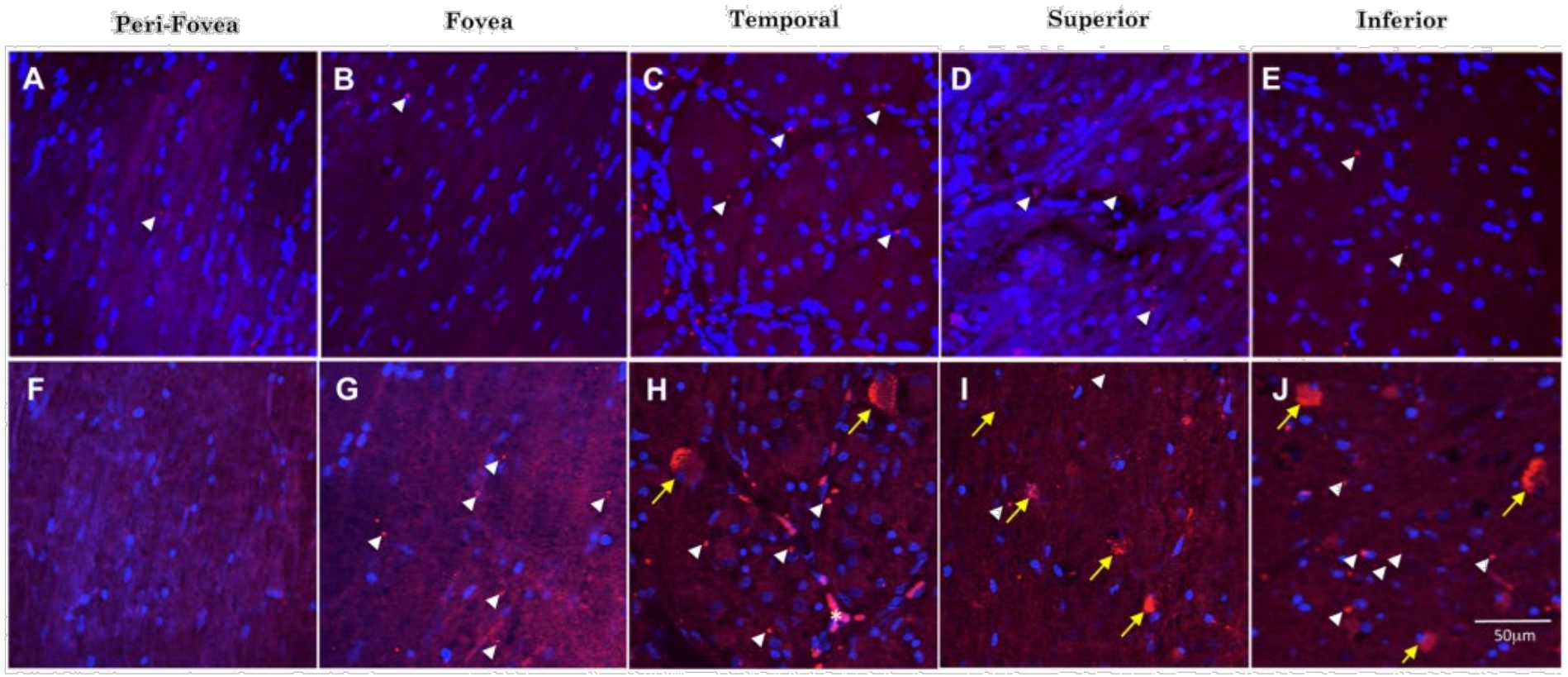
- Retinal in vivo fluorescence correlates with ex vivo cortical Aβ Loads





Connection to retinal Aβ pathology in human eye

- Levels of intracellular and extracellular Aβ retinal deposits were significantly higher in AD than controls.

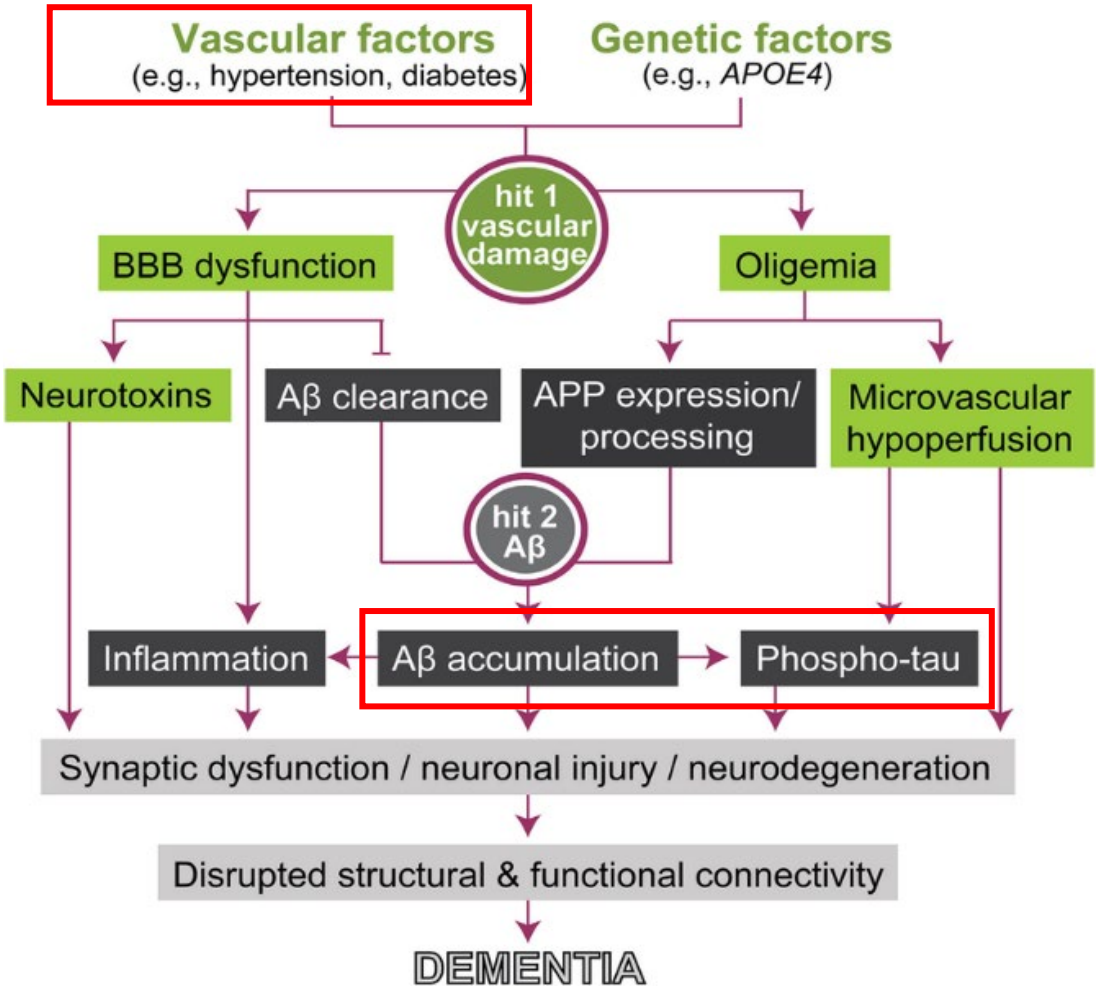


Moving forward

- Integrated non-invasive multi-modal retinal imaging
  - Retinal structural change
    - Optical coherence tomography (OCT)
  - Retinal vascular change
    - Optical coherence tomography angiography (OCTA)

AD Pathogenesis model revisited

- Two-hit hypothesis
  - First hit: **vascular pathology** is an important factor in AD pathogenesis
  - Second hit: **Aβ accumulation** and **hyperphosphorylation of Tau protein**
  - Neuronal injury and **neurodegeneration**



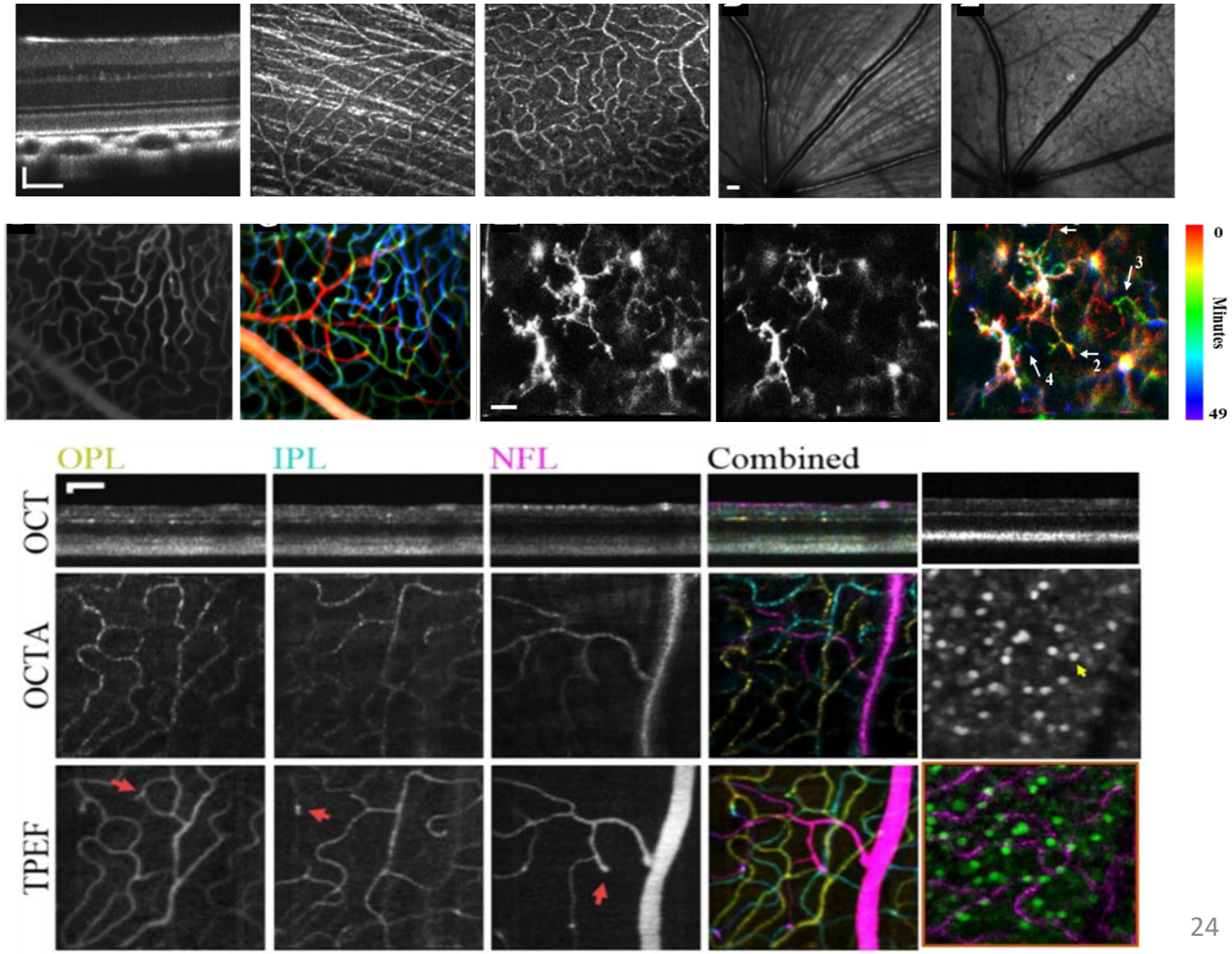
Nelson, A. R. *et al.* Neurovascular dysfunction and neurodegeneration in dementia and Alzheimer's disease. Biochim. Biophys. Acta - Mol. Basis Dis. 2016

Multi-model non-invasive retinal imaging

- Optical Coherence Tomography (OCT)
  - Structural OCT
  - OCT Angiography

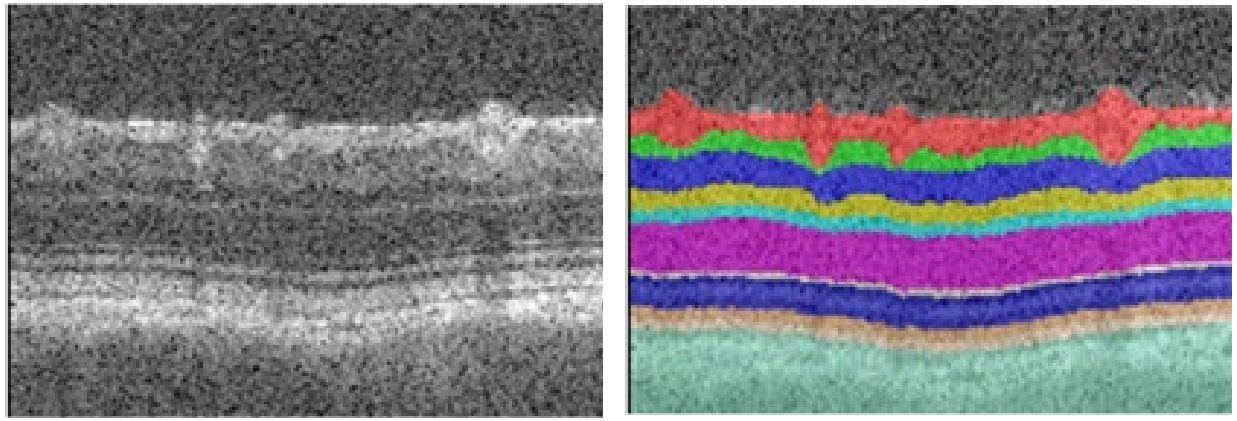
- Two-photo excited fluorescence imaging

  - Retinal angiography
  - fluorescently-labelled cells

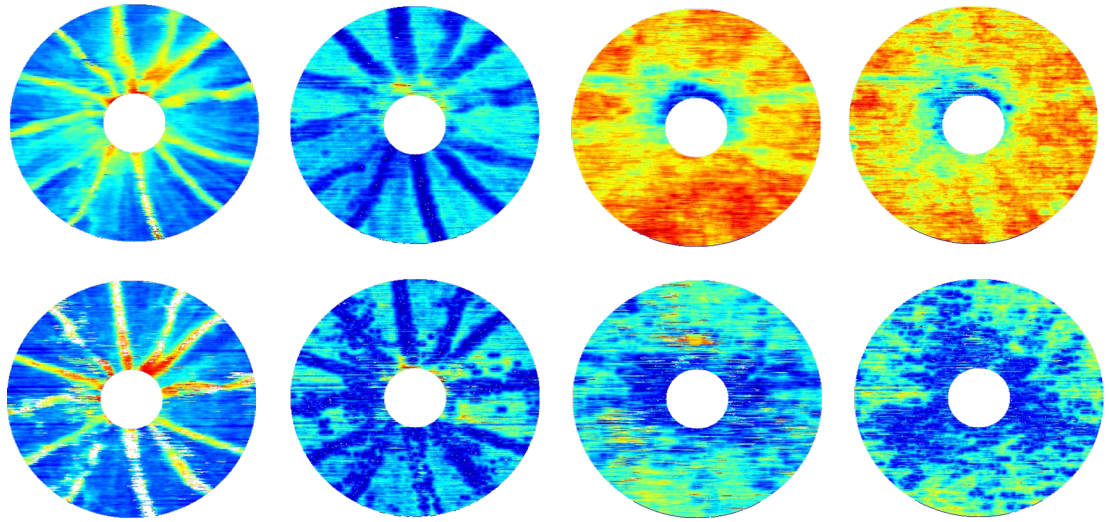


Quantitative retina morphology analysis for optical coherence tomography (OCT)

Deep-learning-based automatic retinal layer segmentation



Layer-wise retinal thickness map



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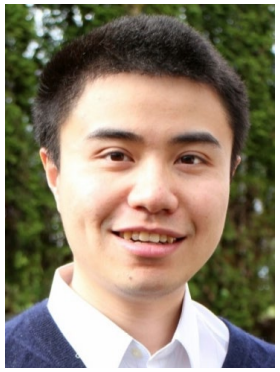
Mark Lythgoe

Imre Lengyel



Da Ma

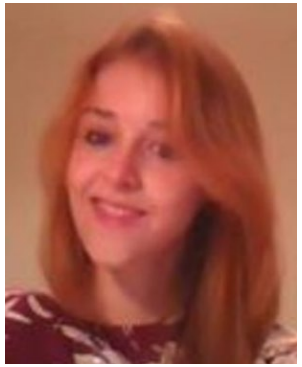
Daniel J. Wahl

Sieun Lee

Ahmad Sidiqi

Jing Cui

Ian F. Harrison



Roz Whitaker

Thank you

Q & A