In Vivo Characterization of Retinal Microvascular Impairment in Age Related Memory Loss

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UHealth
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Thomas Sydenham

Father of English Medicine

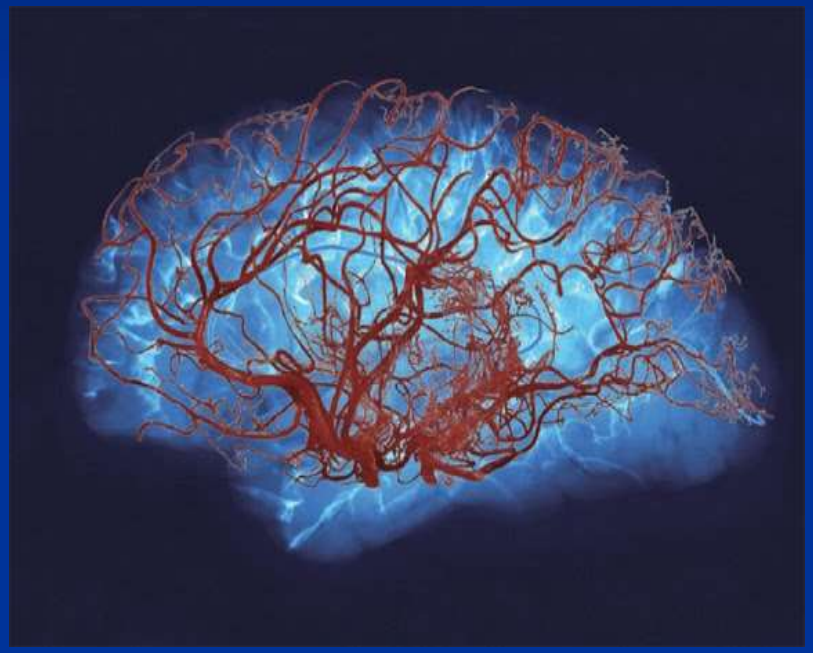
(1624-1689)

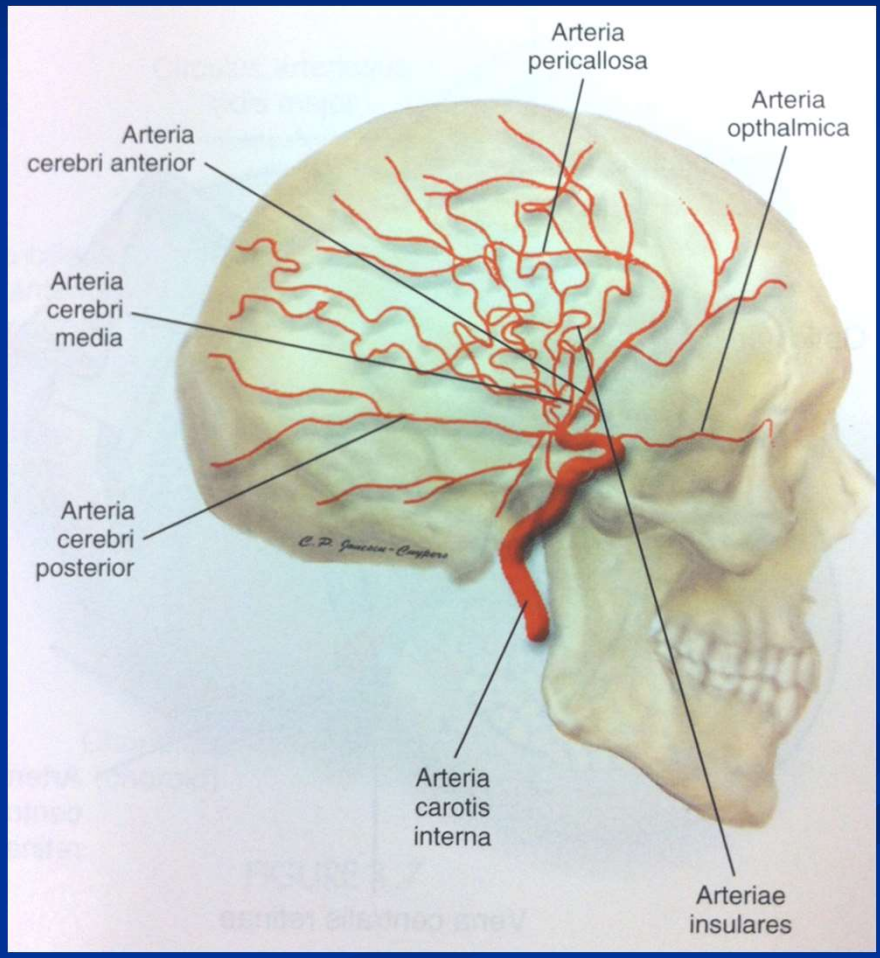
A man is as old as his arteries.

Vascular Aging

Leonard A). J R Coll Physicians Lond 1990; 24:141–143.
De Meyer T et al., Ageing Res Rev 2011; 10:297–303.
Franklin SS. J Hypertens 2002; 20:1693–1696

The vasculatures in the eye and cerebral cortex have the same main blood supply, which is the internal carotid artery (ICA)

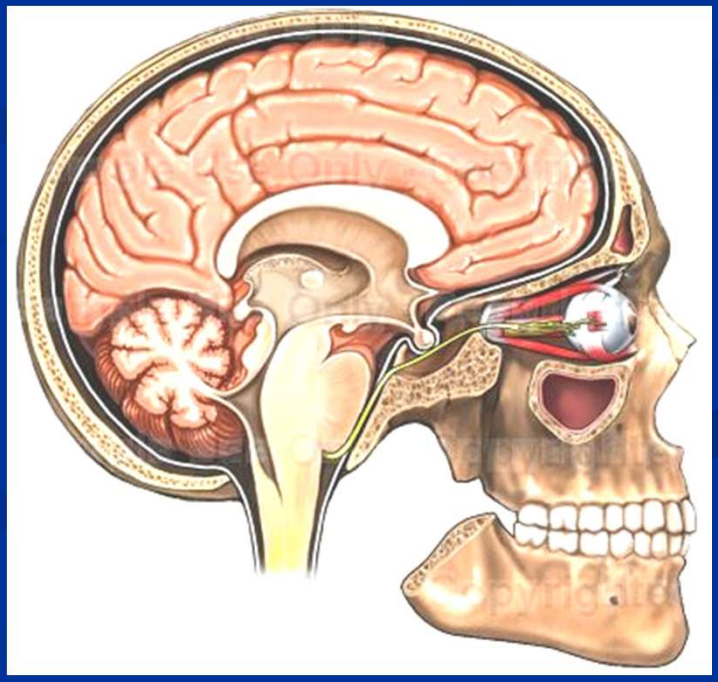


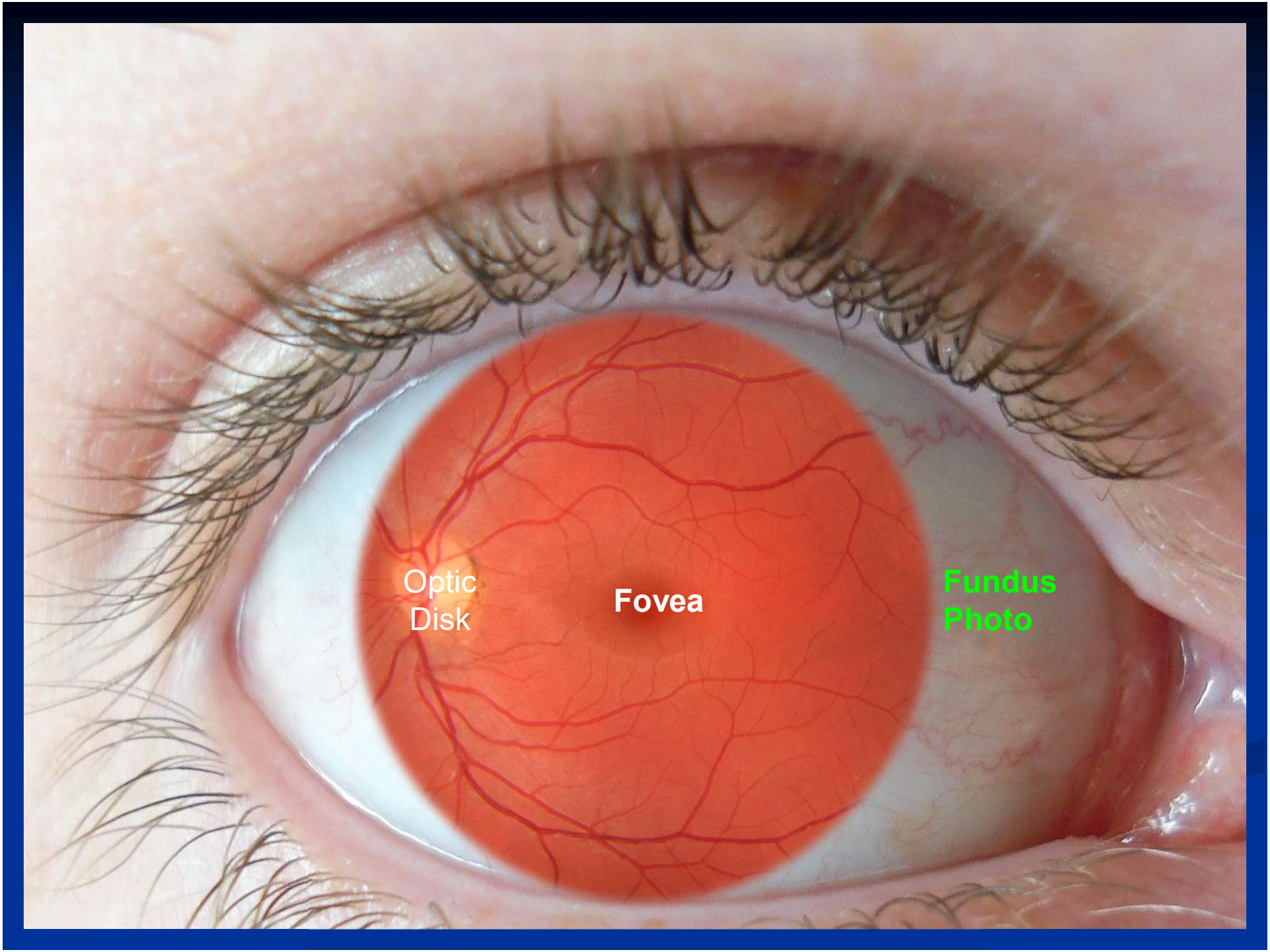


Cited from Atlas of Ocular Blood Flow

Eye is the Window of the Brain

- Retina is the extension of brain.
- Eye and brain are in similar constricted environment.
- Retinal and cerebral small vessels share similar:
  - embryological origin
  - Anatomical features
  - Blood-retinal barrier
- The transparent ocular media enables noninvasive visualization and analysis in vivo:
  - Neurodegeneration
  - Microvascular dysfunction

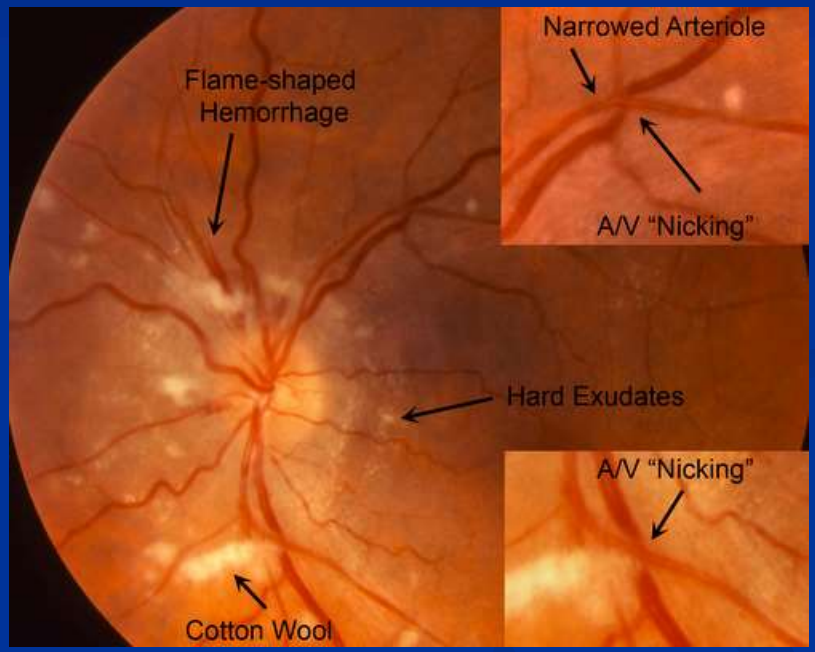



Optic
Disk
Fovea
Fundus
Photo

Retinal Microvascular Abnormalities

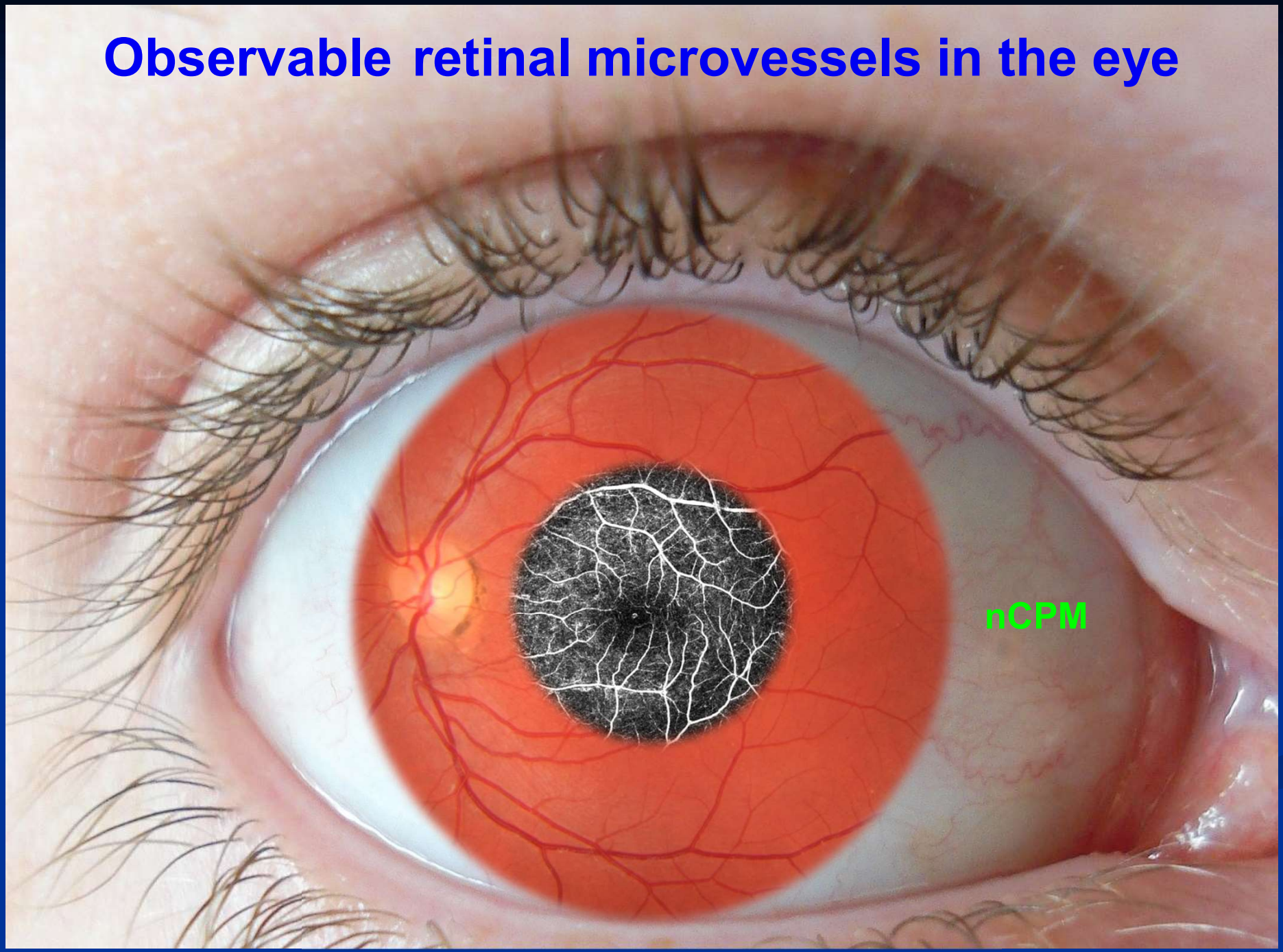
large scale epidemiologic study

- Atherosclerosis Risk in Communities Study (ARIC)
  - Strong link between the presence of retinal vascular abnormalites and both clinical (stroke) and subclinical (white matter lesions) detected on MRI
  - With and without diabetes and hypertension
- The Rotterdam Study
  - Larger venular calibers associated with an increased risk of vascular dementia
  - After adjustment of stroke and cardiovascular risk factors
- Cardiovascular Health Study
  - Total number of retinal signs reversely correlated with the executive function and gait speed
  - After adjustment of vascular risk factors



Yatsuya H. et al., .Stroke 2010; 41: 1349–1355
Wong TY et al., Lancet 2001; 358: 1134–1140
Cheung N. et al., Brain. 2010; 133: 1987–1993.
Kawasaki R. et al., Stroke. 2010; 41: 1826–1828
De Jong FJ et al., Neurology, 2011. 76 . 816–821
Dae Hyun Kim et al. Stroke. 2011;42:1589-1595

Observable retinal microvessels in the eye

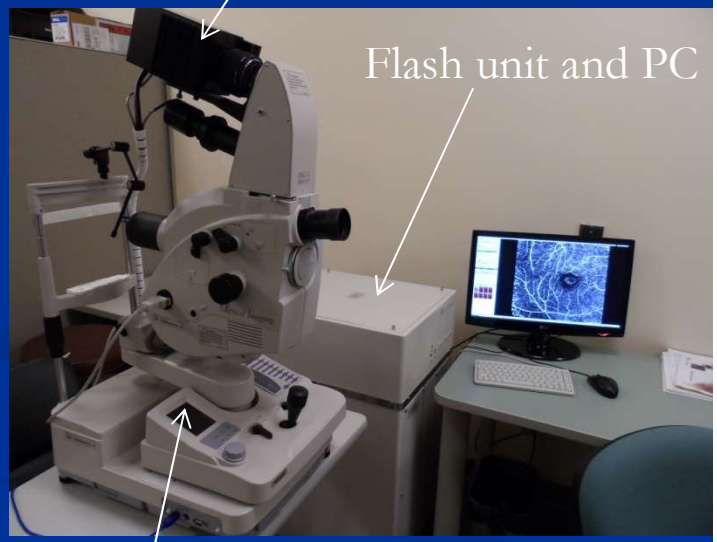


Advanced Ophthalmic Imaging Lab

- Extended infrastructure of McKnight Brain Institute
- Novel non-invasive imaging modalities
  - Retinal Function Imager (RFI)
    - quantitative analysis of microcirculation (pre-capillary arteriole, post-capillary venule)
  - Optic coherence tomography angiography (OCTA)
    - depth resolved microvascular network
  - Ultrahigh resolution optic coherence tomography (UHR-OCT)
    - tomographic intraretinal thickness analysis
  - Polarization sensitive optic coherence tomography (PS-OCT)
    - Micro-structural integrity of retinal nerve fiber layer

Retinal Function Imager (RFI)

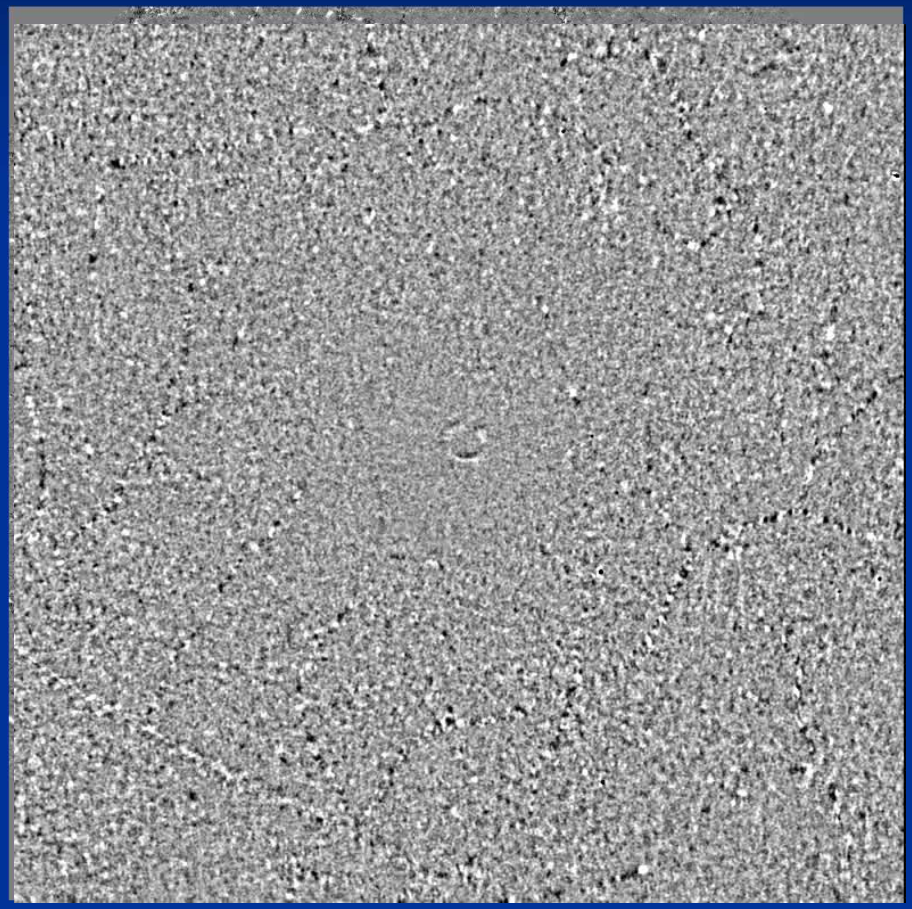
- A retinal function imager (**RFI**, Optical Imaging Ltd, Rehovot, Israel) was used to capture reflectance changes as a function of time under stroboscopic illumination.
- Hemoglobin in red blood cells was used as an intrinsic motion-contrast agent in the generation of:
  - Blood flow velocity maps
  - Microvascular network



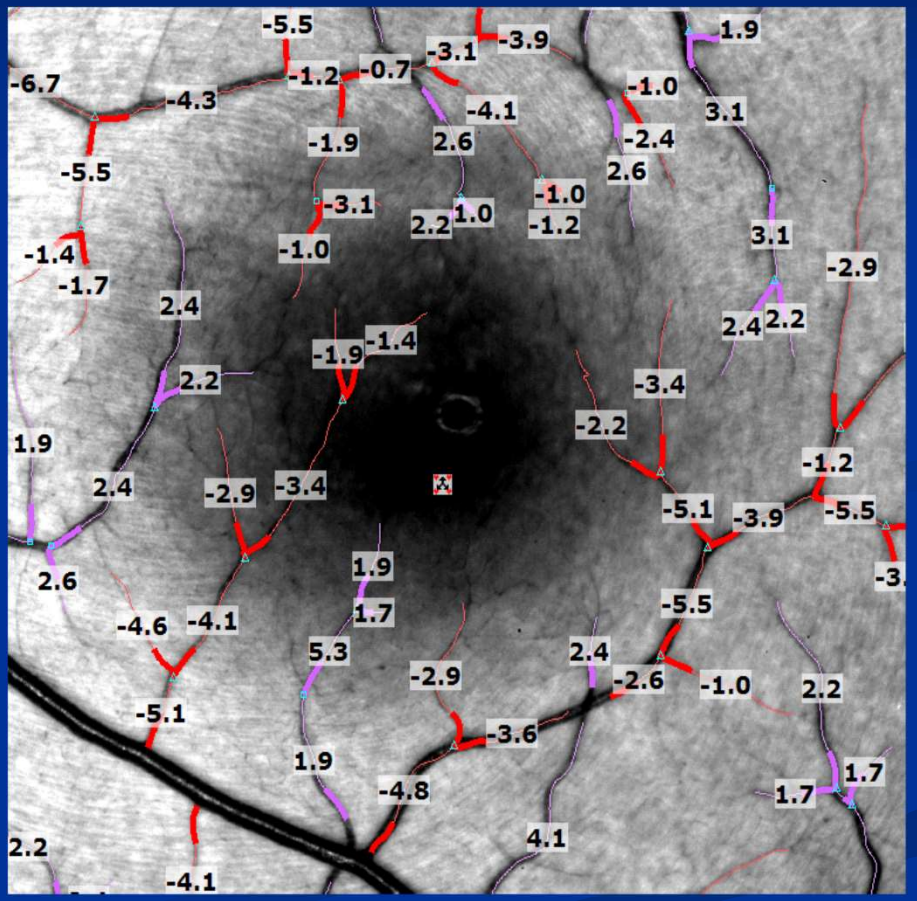
Jiang et al. Microvasc. Res. 2013;85:134-137.
Jiang et al. Microvasc Res. 2013 Epub ahead of print
Izhaky et al. Jpn. J. Ophthalmol. 2009;53:345-351.
Landa et al. Int. Ophthalmol. 2010;32:211-215

RFI blood flow measurement

Blood flow-velocity visualization



Automatic Quantification (mm/sec)



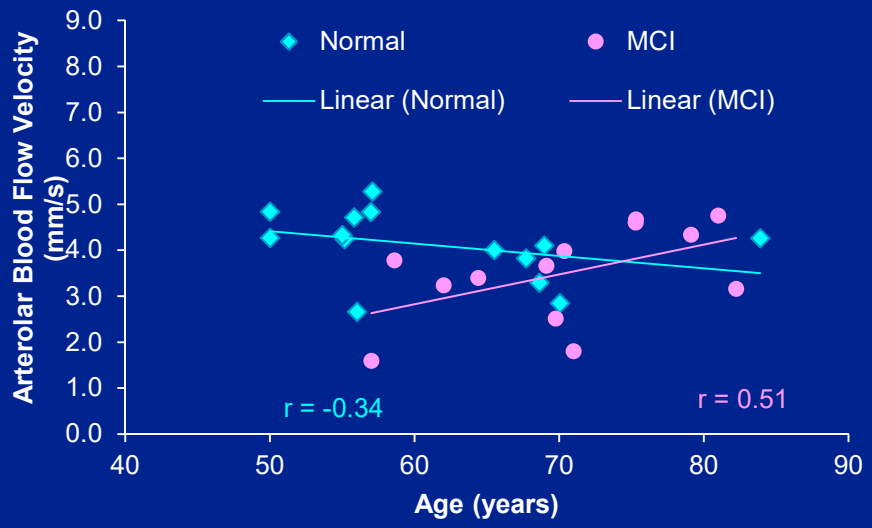
(mm/sec)

Movie from a series of 8 mages

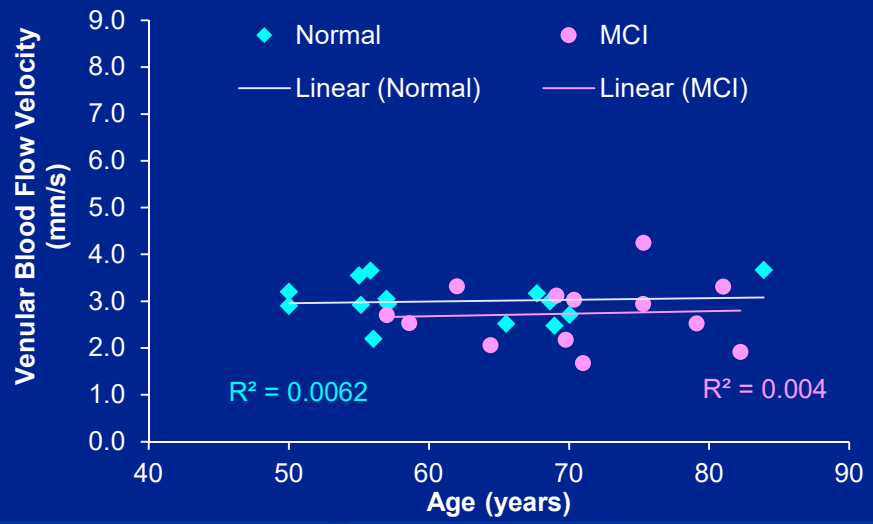
Field of view : 20 degree Image size 4.6 x 4.6 mm^2 1024 x 1024 pixels

Aging of Retinal Microcirculation

Retinal Blood Flow Velocity in Arterioles



Retinal Blood Flow Velocity in Venules

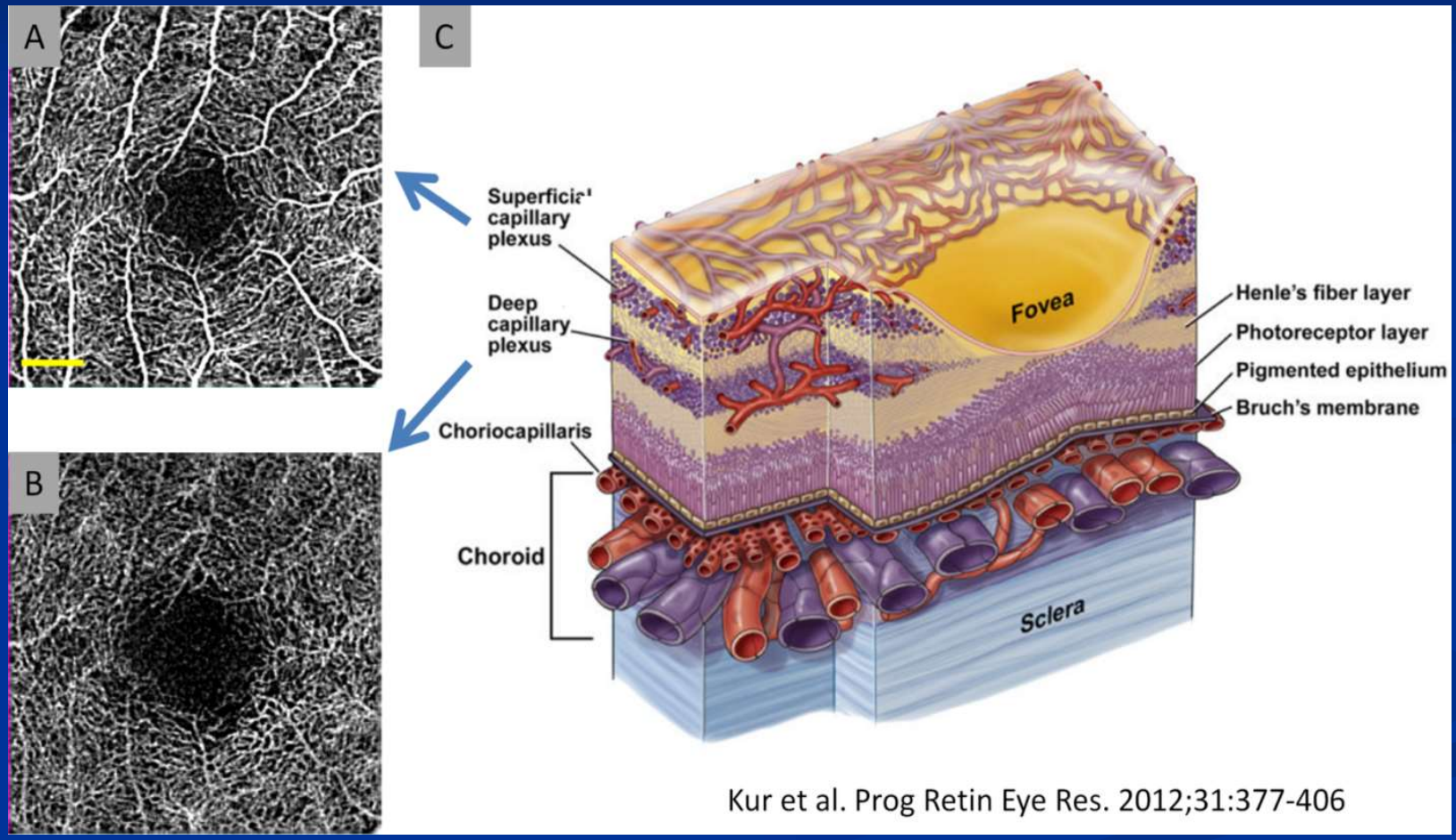


N = 28 (Normal = 14, MCI= 13)

Optic Coherence Tomography Angiography (OCTA)

http://www.zeiss.com/meditec/en_de/c/oct angiography.html

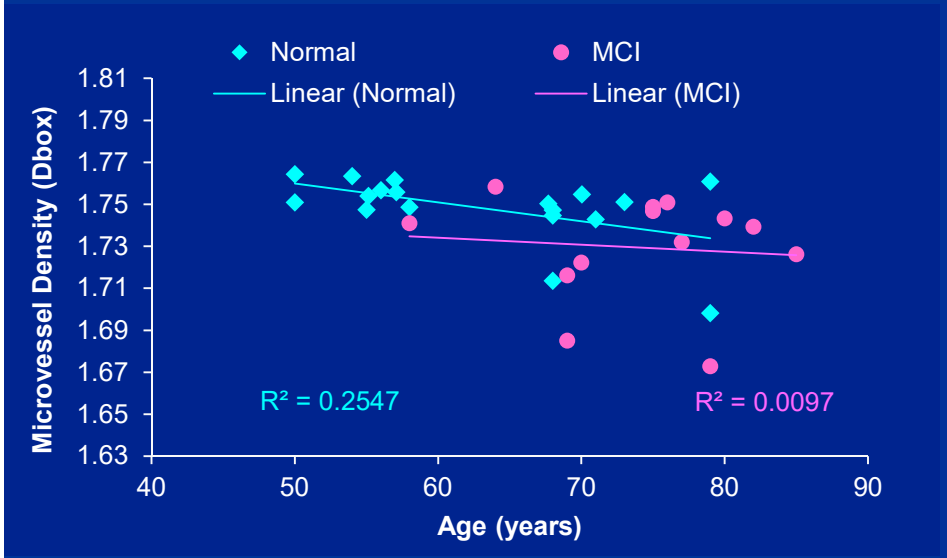
OCTA for Quantitative Analysis of Microvascular Network in Intra-retinal Layers



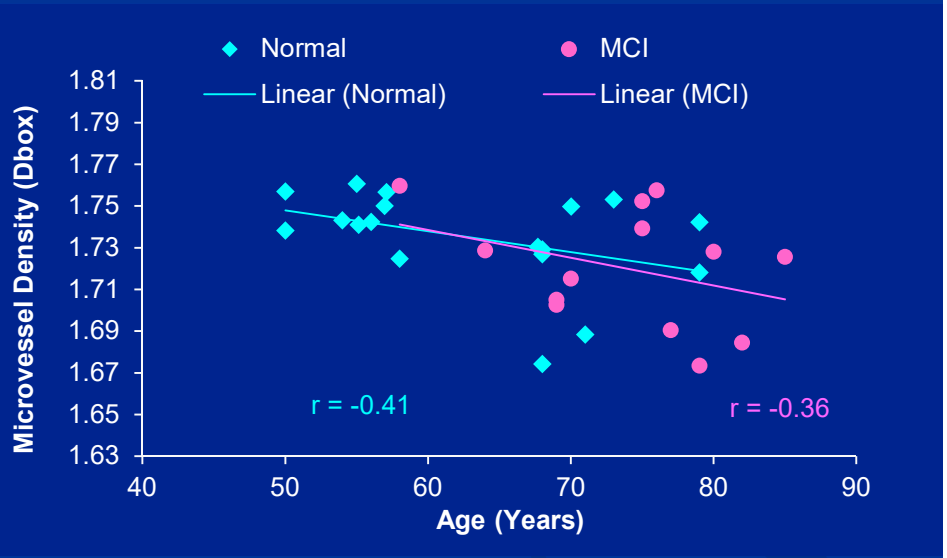
Kur et al. Prog Retin Eye Res. 2012;31:377-406

Aging of Retinal Microvessels

Retinal Superficial Capillary Plexus

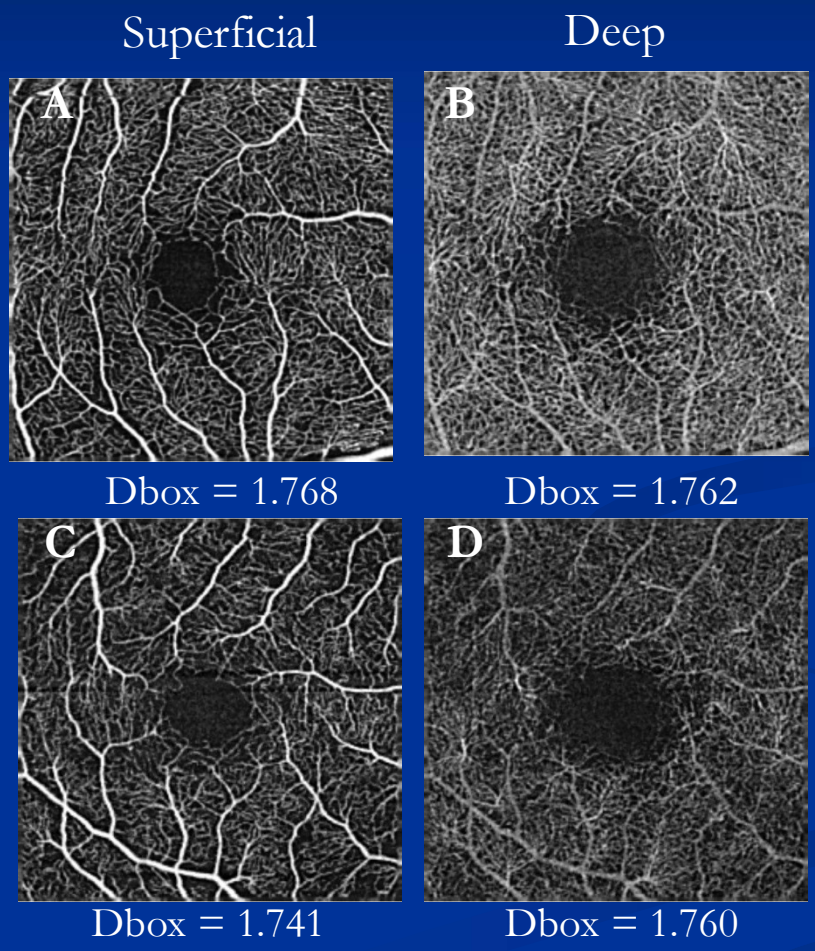


Retinal Deep Capillary Plexus

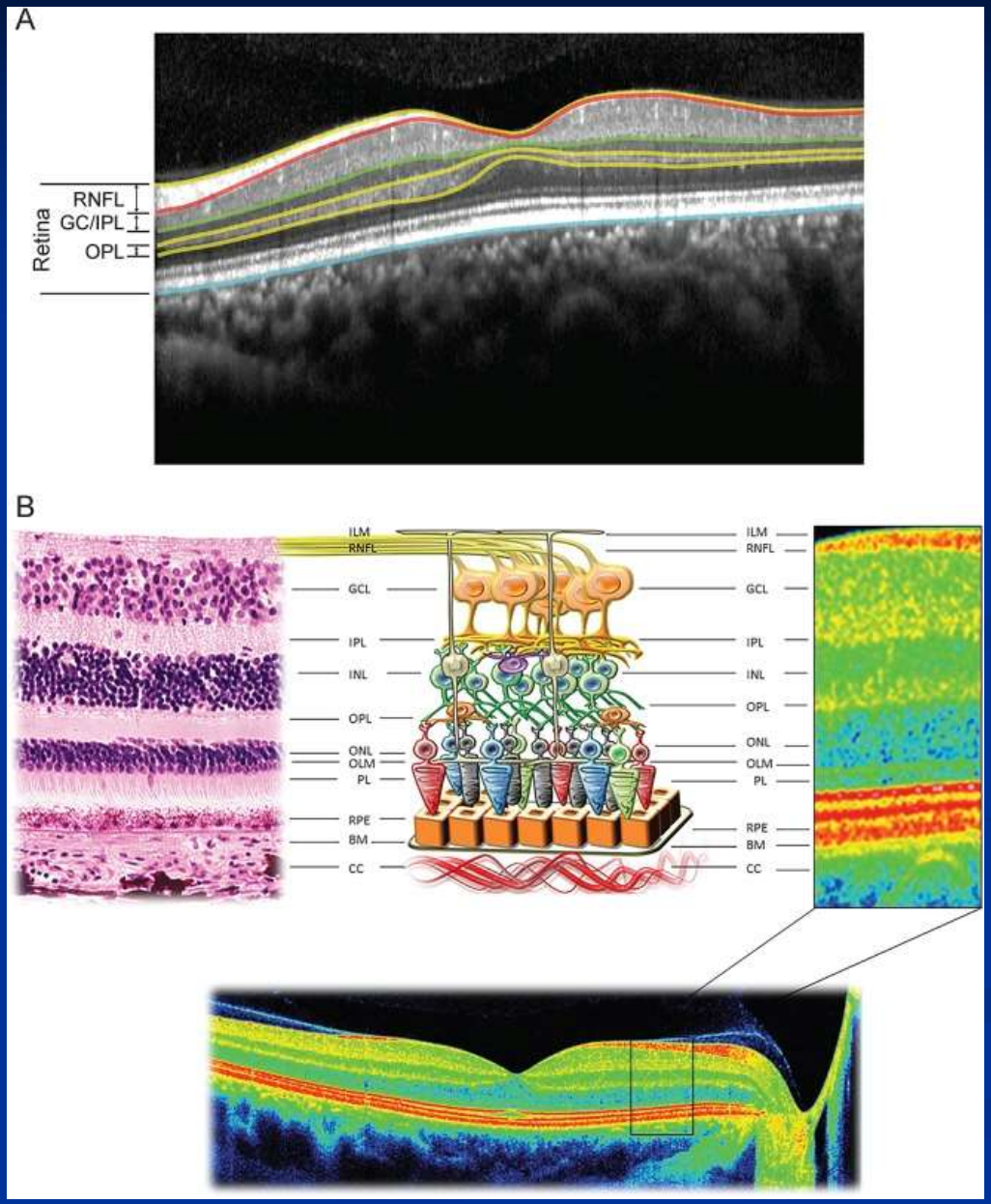


N = 31 (Normal = 18, MCI = 13)

Aging of Retinal Microvessels



Optic Coherence Tomography (OCT) of the Human Retina

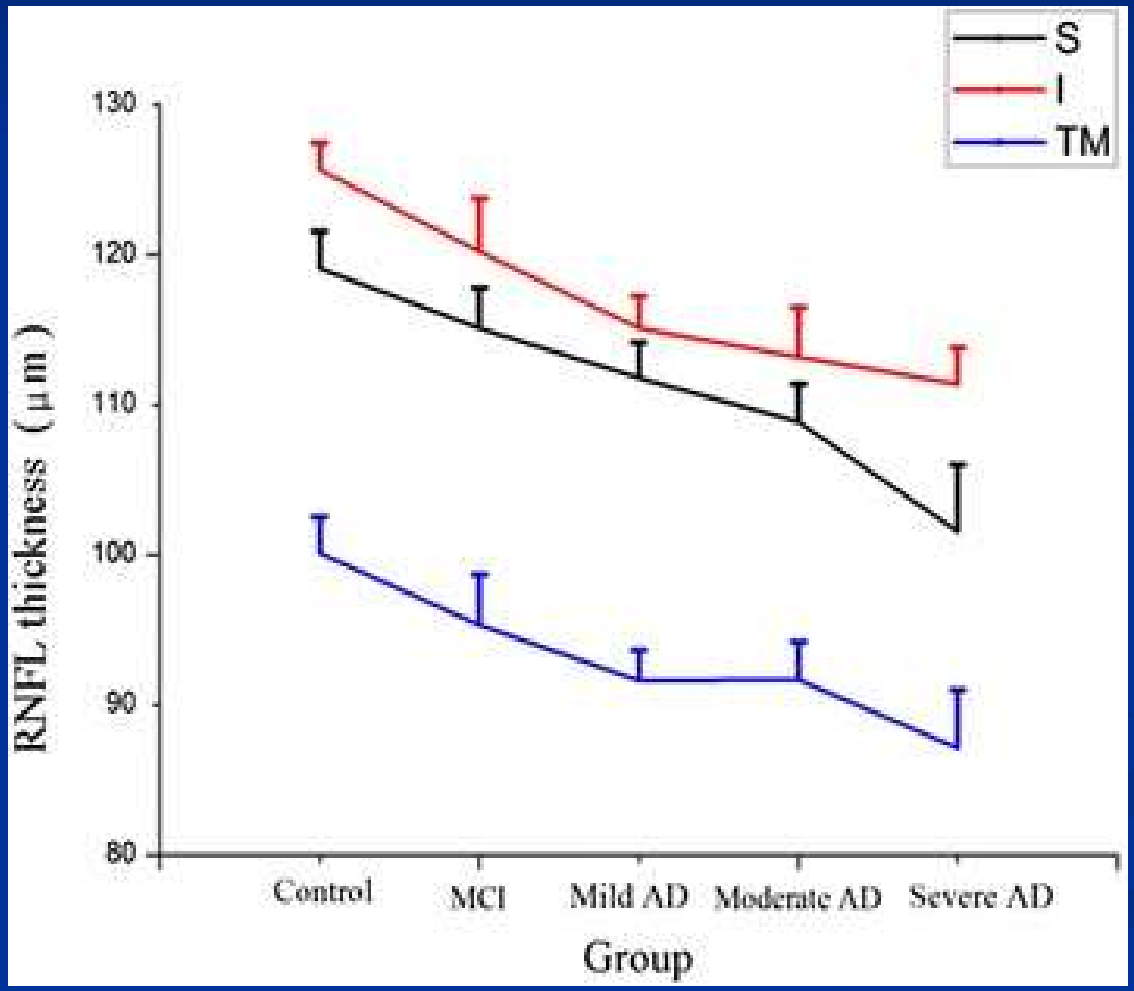


Retinal segmentation on SD-OCT

Correlation of anatomy with OCT for the human retina

Galetta SL et al., Neurol Neuroimmunol Neuroinflamm 2015 23;2(4):e13

RNFL thickness in patients with MCI, mild, moderate, severe AD and control subjects

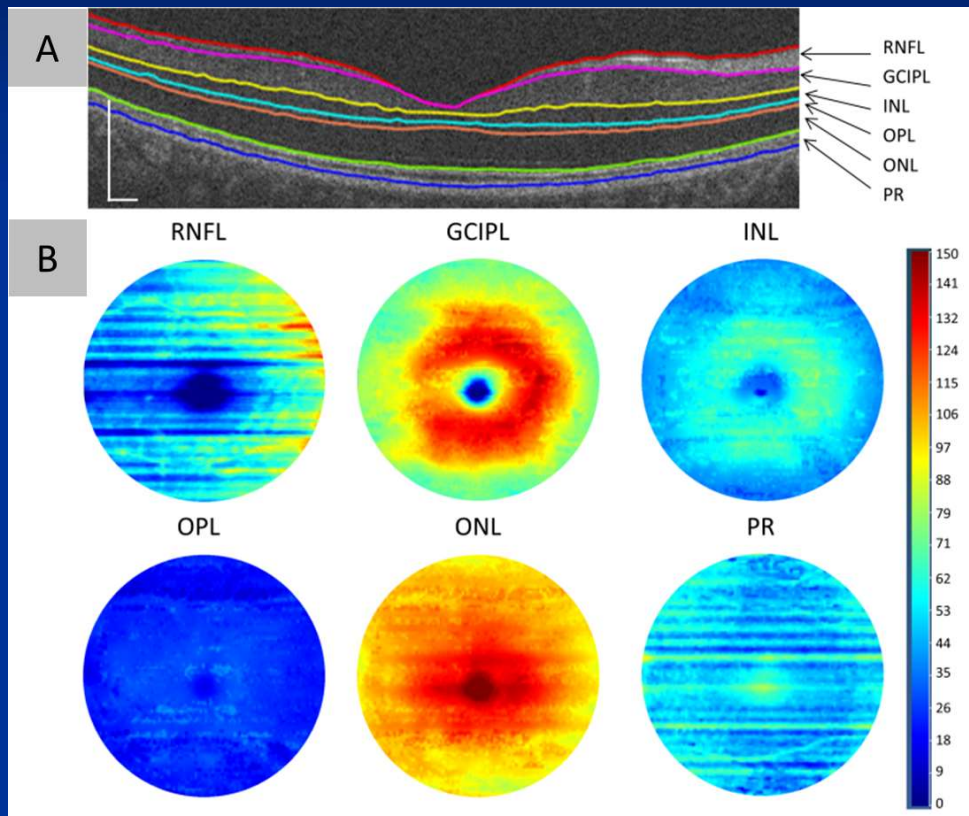


Liu D et al. BMC Neurol 2015;15:14

Ultrahigh Resolution OCT (UHR-OCT)

Axial resolution = ~ 3 μm, automated segmentation of 6 intraretinal layers

Cross-Sectional Retinal Segmented Tomographic Thickness Maps of Intraretinal Layers



RNFL: retinal nerve fiber layer;

GCIPL: ganglion cell layer + inner plexiform layer;

INL: inner nuclear layer;

OPL: outer plexiform layer;

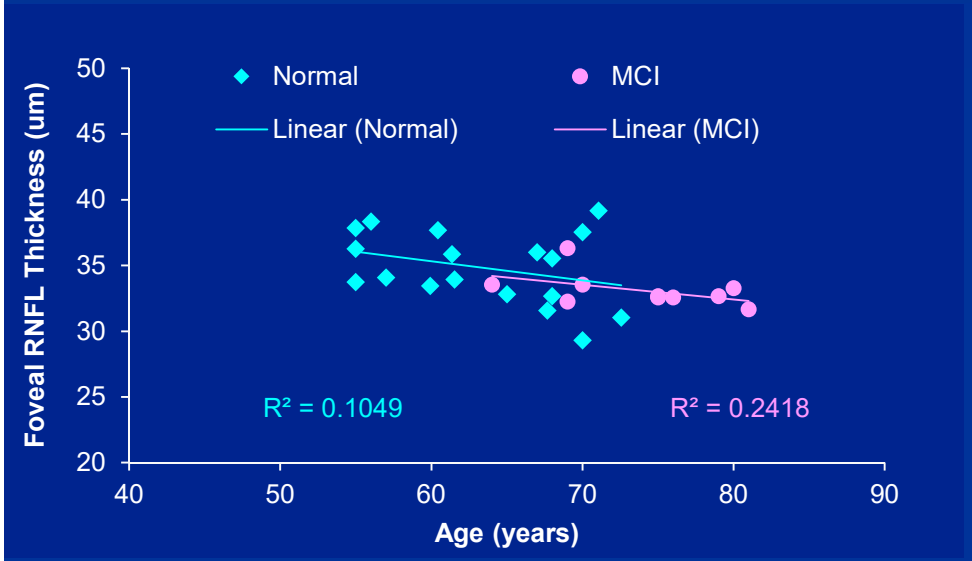
ONL: outer nuclear layer;

PR: retinal photoreceptor layer

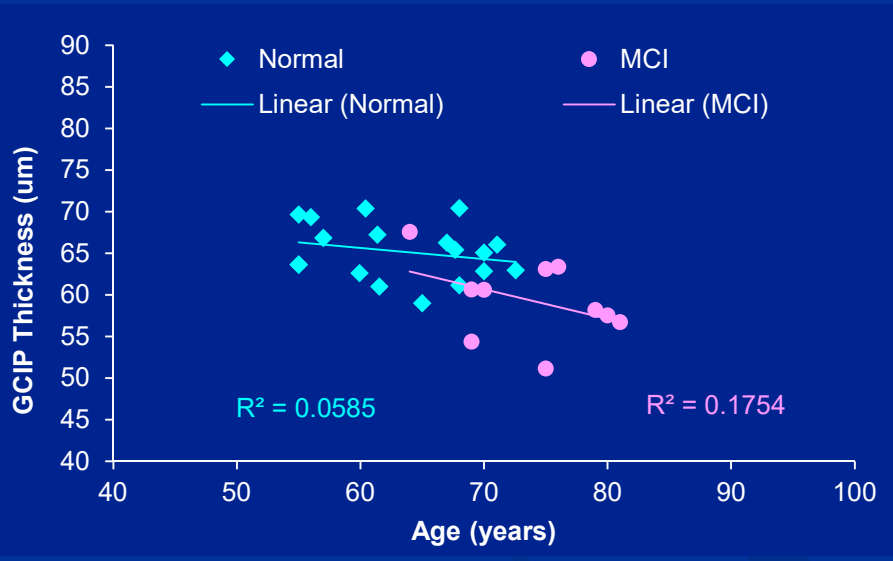
Ultrahigh resolution OCT (UHR-OCT, axial resolution = ~3 μm)
Fully-automated 3D segmentation software

Aging of Retinal Neurons

Retinal Nerve Fiber Layer (RNFL)



Retinal Ganglion Cells (GCL)

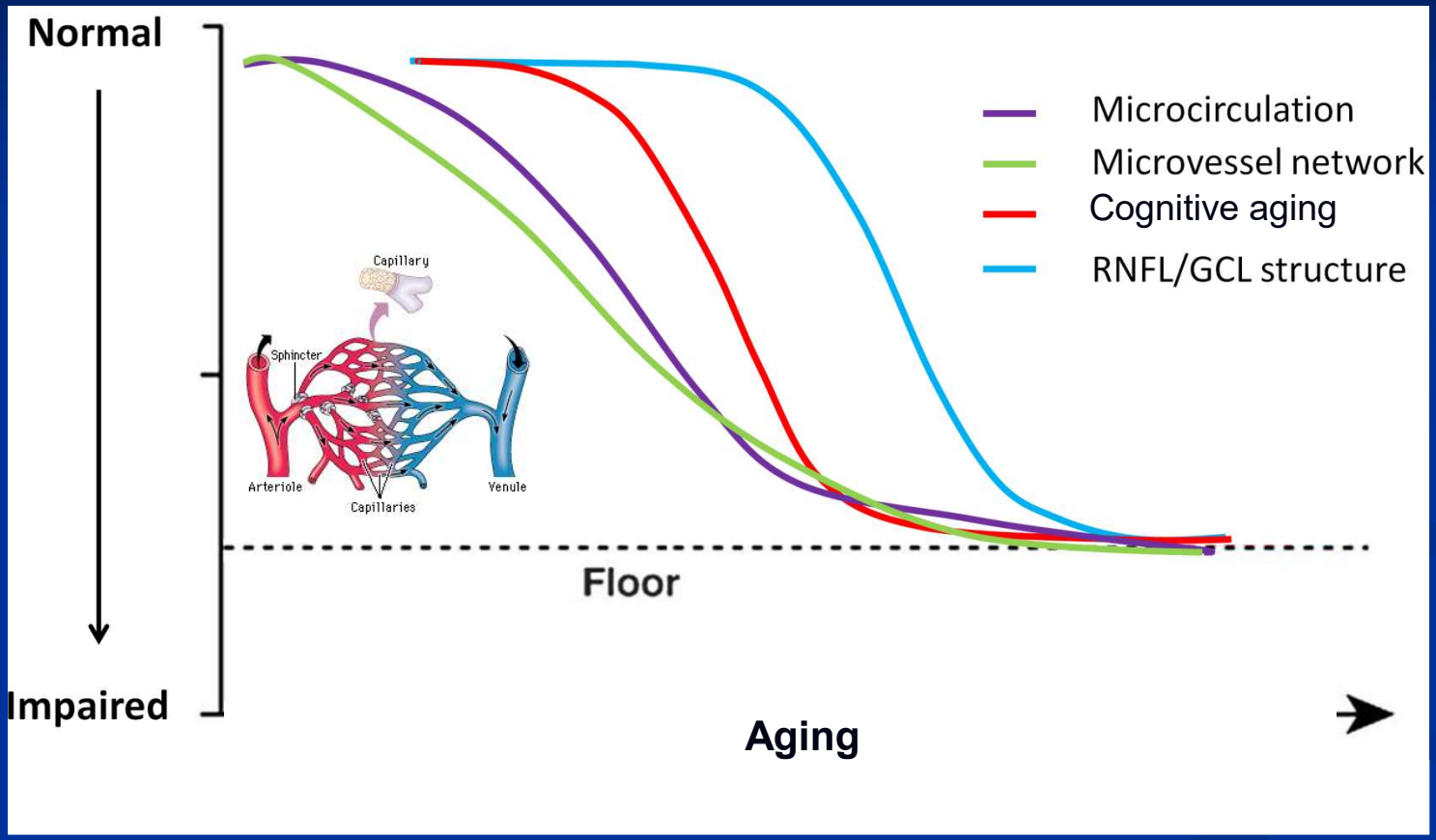


N = 28 (Normal = 18, MCI = 10)

Summary

- Vascular aging is evident in retinal microcirculation and capillary network.
- More profound vascular aging in MCI patients is apparent.
- Non-invasive novel ophthalmic imaging is promising in studying the role of vascular aging in cognitive decline.
- Future longitudinal studies with large sample size are needed.

Critical question: which happens first?



Our main hypothesis predicts that impairment initially occurs with the microvessel network and microcirculation, followed by cognitive aging and the loss of RNFL/GCL structure.

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THANK YOU

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UM RSA 2015-41

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Research to Prevent Blindness

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