Future Clinical Uses of OCT for Neurodegenerative Diseases

Bang V Bui

The University of Melbourne, Parkville, VIC, Australia

Financial disclosure: N/A

THE UNIVERSITY OF MELBOURNE

Outline

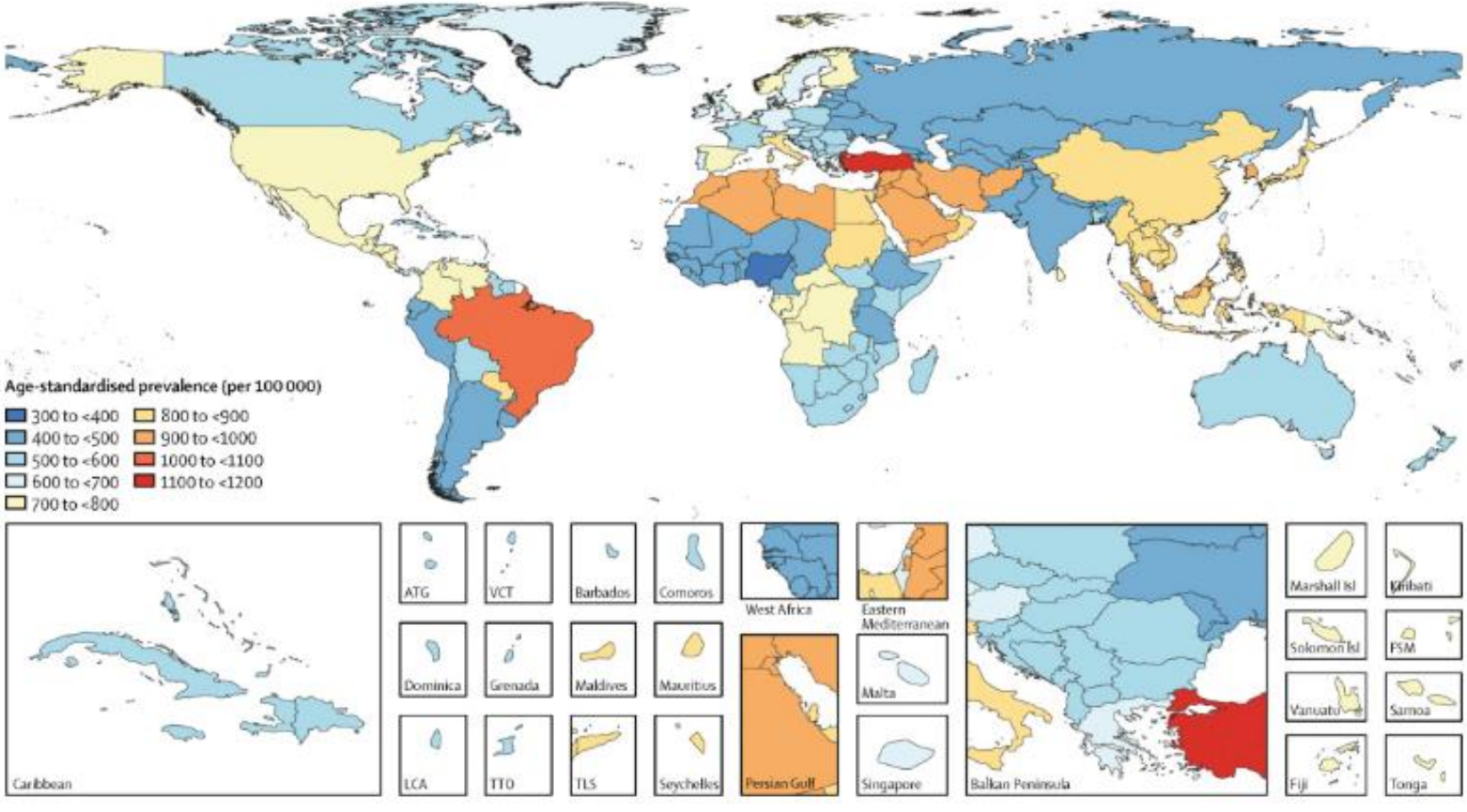
- Dementia
- How the eye might be involved?
- What OCT changes are expected?
- Where things are headed?

Dementia

- growth in life expectancy increased prevalence of chronic diseases, such as Alzheimer's disease (AD)
- 50 million people in the world living with dementia, 10 mill new each year
- major causes of disability and loss of independence
  - second largest contributor to total number of years living with disability (YLD)

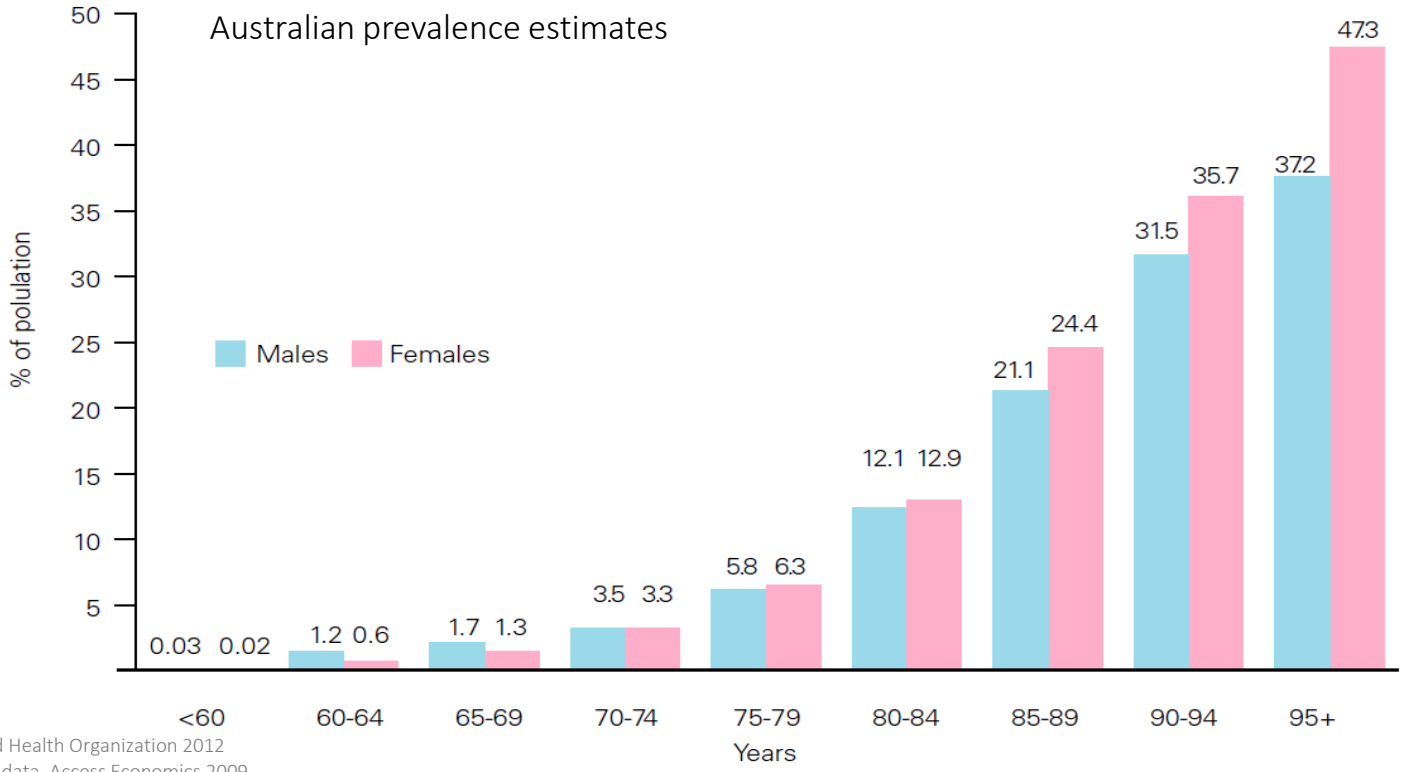
- wide physical, psychological, social, and economic impact on individual, families, carers and health care system

Alzheimer's disease is the most common form of dementia (60–70% of cases)



Alzheimer's disease

- Affects about 1 in 5 at age 85[1]

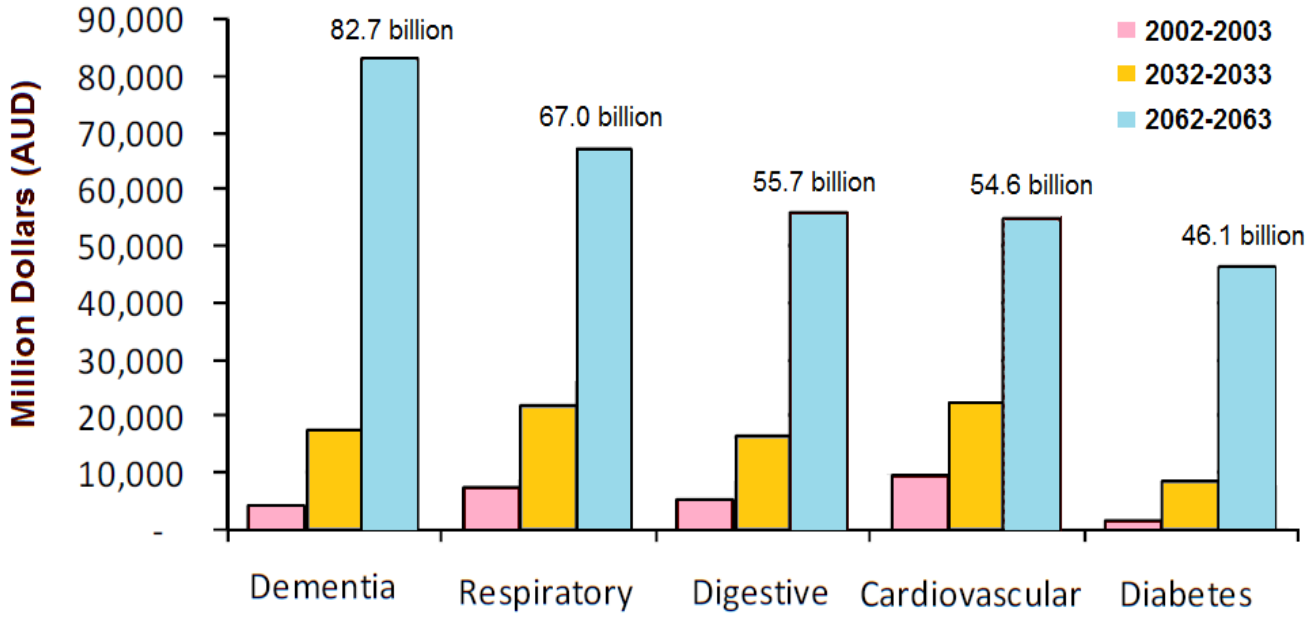


1. World Health Organization 2012
2. Table data, Access Economics 2009

Alzheimer's disease

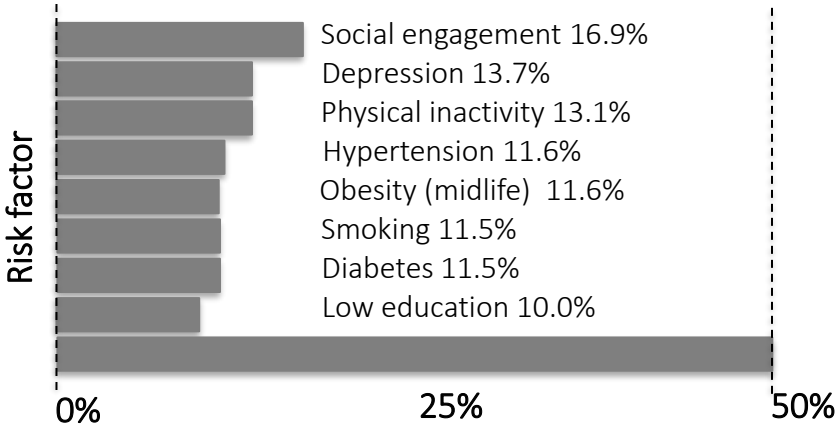
- huge economic impact

Top 5 most expensive diseases in Australia 2060



1. World Health Organization 2012
2. Table data, Access Economics 2009

Multifactorial risk factors



Metabolic factors

Diabetes
Vit D B12 deficiency
Hypertension
Folate deficiency
obesity

Lifestyle

Smoking
Low education
Depression
Sedentary lifestyle
Lack of social engagement
Psychological stress
Mental inactivity

Genetic factors

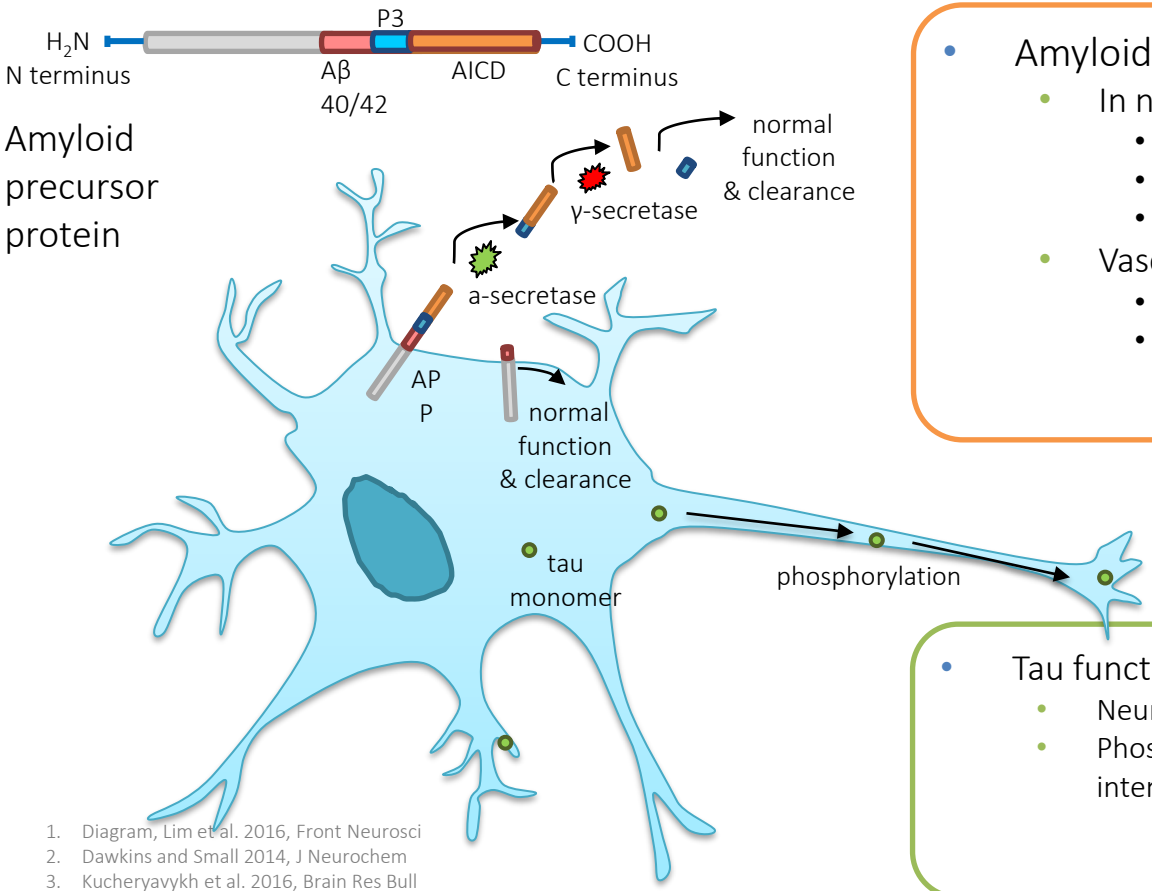
Amyloid precursor protein
Apolipoprotein E – e4
Age

Miscellaneous

Head injury
Aluminum toxicity

1. AD prevention data, Barnes and Yaffe 2011, Lancet Neurol

Amyloid Precursor Protein and Tau in health



- Amyloid in picomolar amounts
  - In neurons needed for
    - synaptic formation & repair[2]
    - Maintenance of neurons and their synapses
    - Anti-apoptosis
  - Vasculature
    - component of blood platelet
    - Important in vascular wound repair[3]

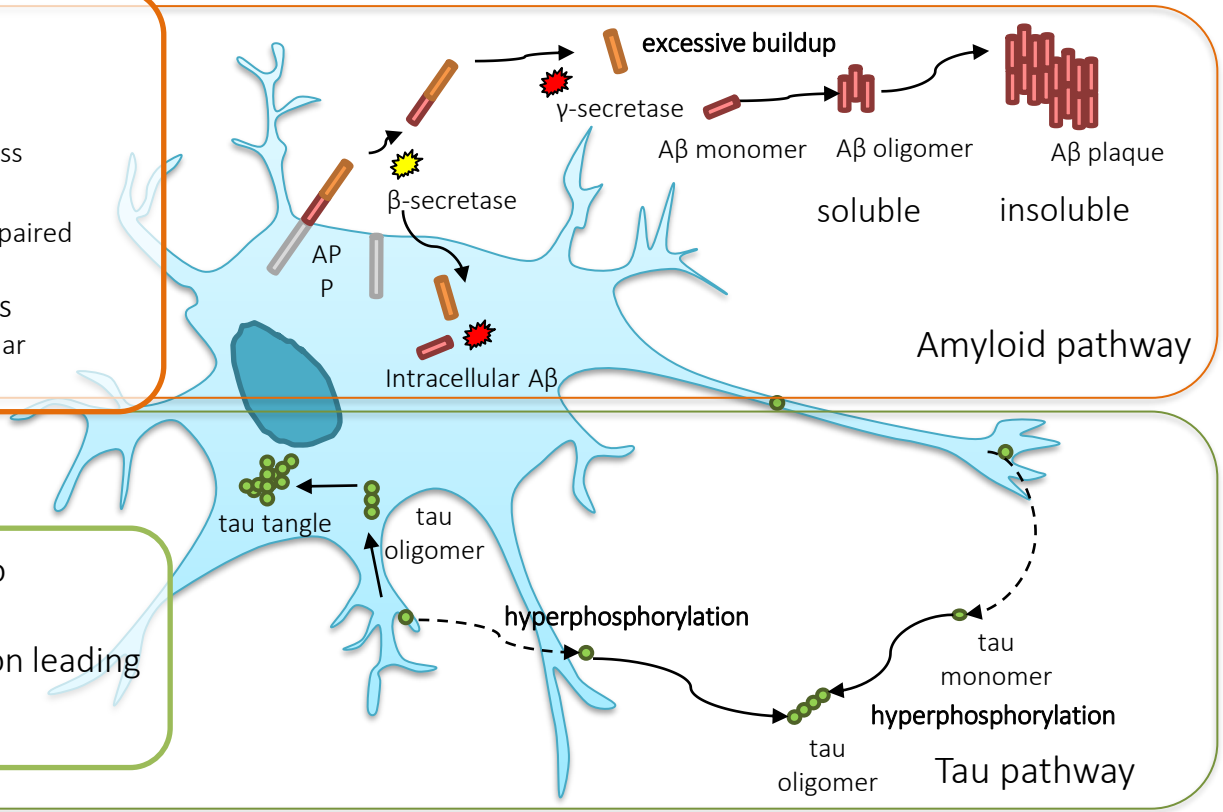
- Tau function
  - Neural microtubule stability[4]
  - Phosphorylation is normal and necessary for interaction with tubulin to form MTs

1. Diagram, Lim et al. 2016, Front Neurosci
2. Dawkins and Small 2014, J Neurochem
3. Kucheryavykh et al. 2016, Brain Res Bull
4. Johnson and Stoothoff 2004, J. Cell Sci

Amyloid Hypothesis in Alzheimer's disease

Soluble Ab is neurotoxic[1]

- Intracellular (apoptosis)
  - cytosolic: lysosome
  - mitochondria: oxidative stress
- Extracellular
  - synaptic dysfunction and impaired transmission
- Near and around blood vessels
  - Cant be cleared neurovascular dysfunction



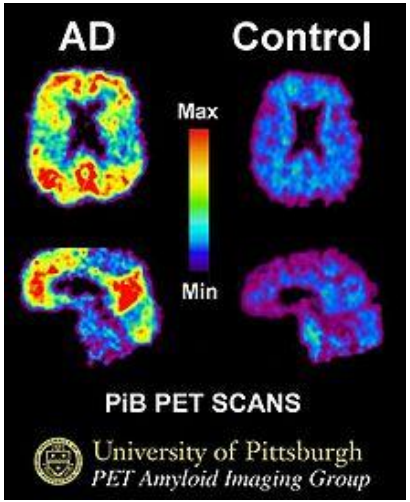
Tau hyperphosphorylation lead to filamentation and tangles

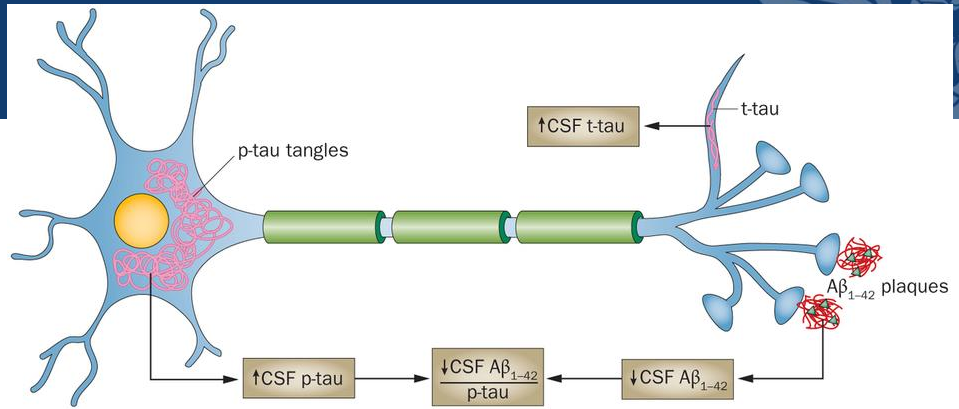
- Disrupts microtubule function leading to eventual cell apoptosis[2]

Courtesy of Jeremiah Lim

1. Mucke and Selkoe 2012, Cold Spring Harb Perspect Med
2. Wang et al. 2013, J Alz Dis

How is dementia diagnosed?





Nature Reviews | Neurology

Pathophysiological biomarkers
- "Hallmark" detection
- Cerebrospinal fluid assay
- Positron Emission Tomography

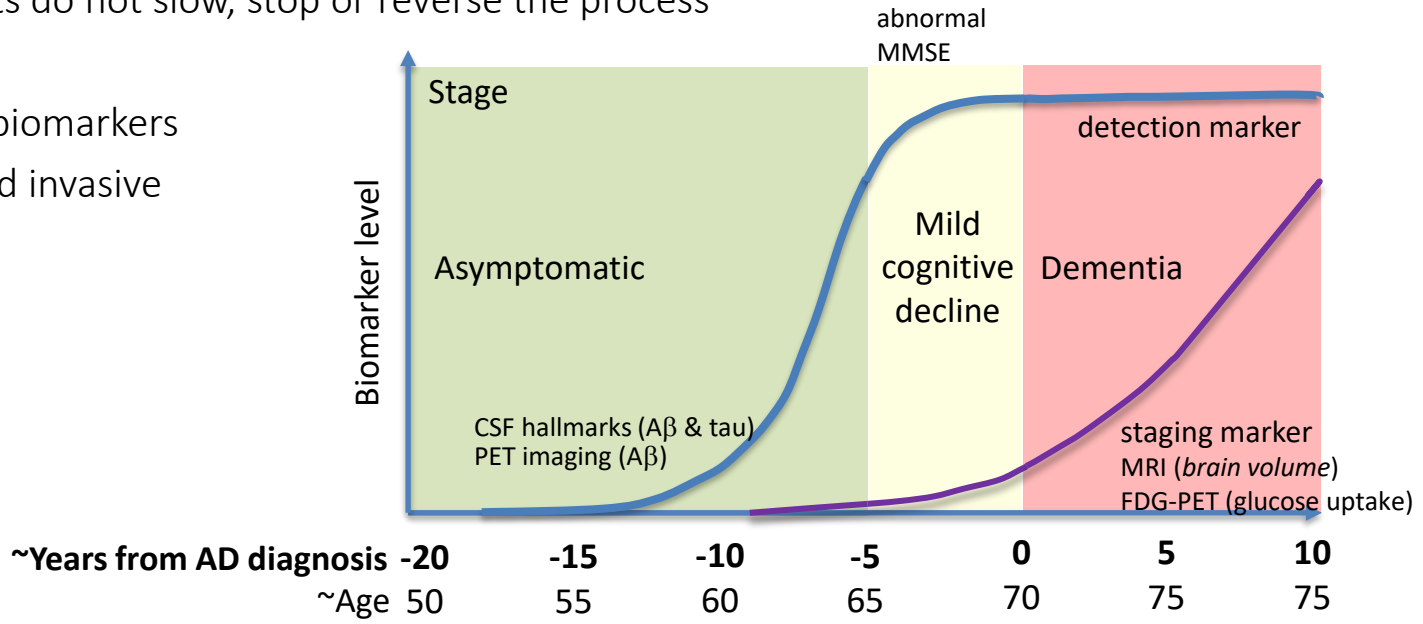
Topographical biomarkers
- Potential for staging
- Adjunct to diagnosis
- FDG-PET
- MRI

1. De Deyn 2015, Nature Reviews Neurology
2. Image, William Klunk 2008, https://commons.wikimedia.org/wiki/File:PiB_PET_Images_AD.jpg

Courtesy of Jeremiah Lim

Alzheimer's Disease stages and diagnosis

- Stages
  - Preclinical, Mild Cognitive Impairment, Clinical[1]
- Average survival of 4.6 years from clinical diagnosis[2]
- Current treatments do not slow, stop or reverse the process
- Current hallmark biomarkers
  - Expensive and invasive



1. Frisoni et al., 2012, *Nat Rev Neurol*
2. WHO 2012, Table 2.1

Amyloid accumulations are in brains and eyes of mouse AD models

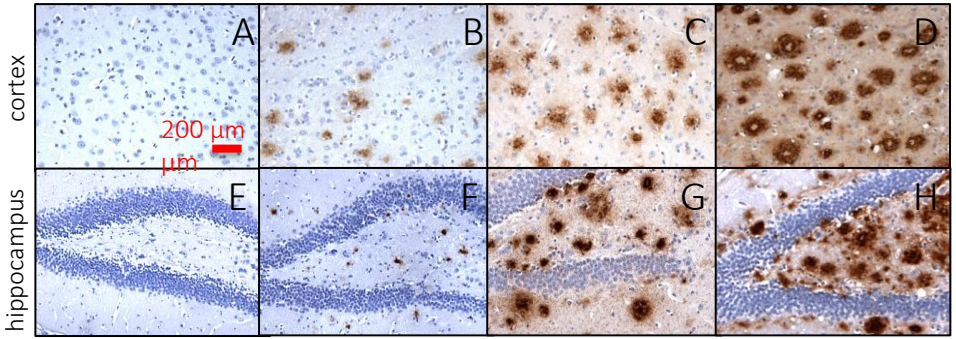
frontiers in Neuroscience

ORIGINAL RESEARCH
published: 13 August 2020
doi: 10.3389/fnins.2020.00862

Retinal Functional and Structural Changes in the 5xFAD Mouse Model of Alzheimer's Disease

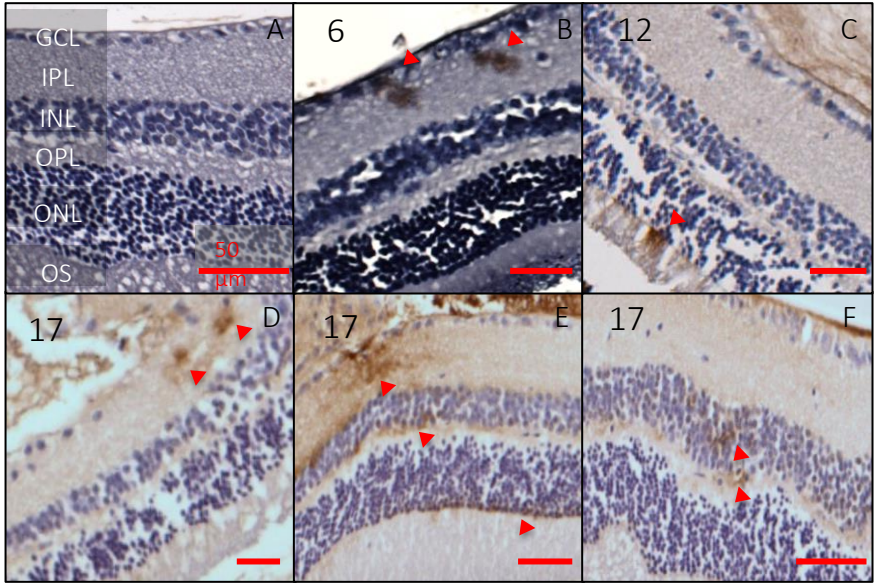
*Jeremiah K. H. Lim[1,2], Qiao-Xin Li[3], Zheng He[1], Algis J. Vingrys[1], Holly R. Chinnery[1], Jamie Mullen[4], Bang V. Bui[1] and Christine T. O. Nguyen[1]**

[1] Department of Optometry and Vision Sciences, University of Melbourne, Parkville, VIC, Australia, [2] Optometry and Vision Science, College of Nursing and Health Sciences, Flinders University, Bedford Park, SA, Australia, [3] Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia, [4] AstraZeneca Neuroscience, Cambridge, MA, United States



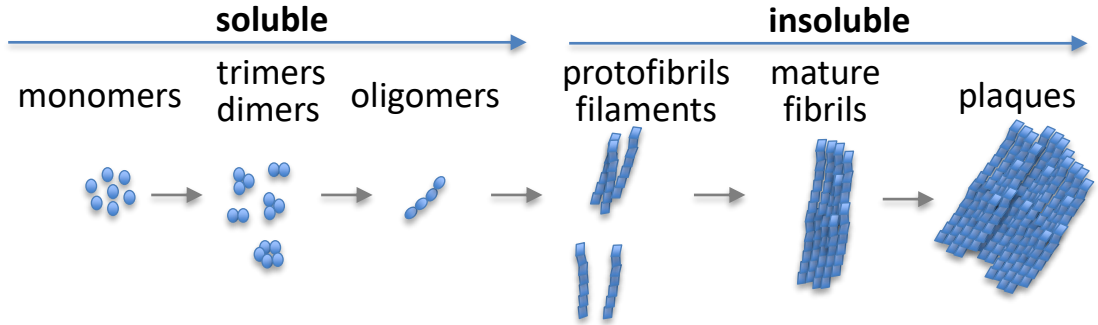
Ab deposits increase in the brain with age…

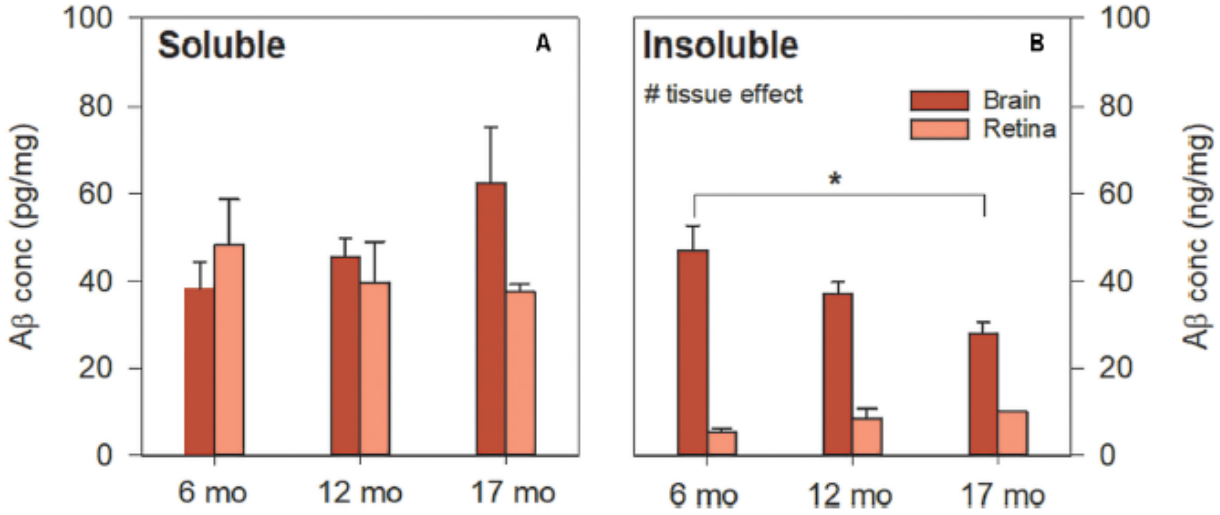
Ab deposits appear in the inner retina at all ages and in the outer retina at later stages > 12 months



Both soluble and insoluble amyloid is found in the retina

- Soluble form thought to be more toxic





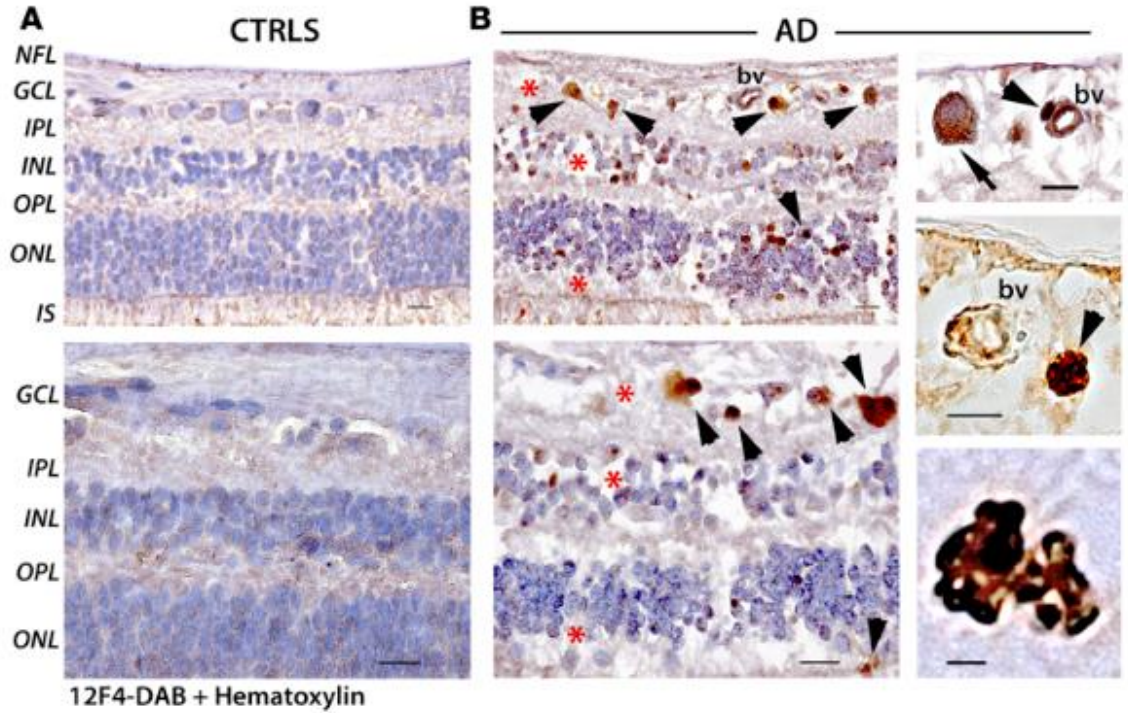
Retinal Functional and Structural Changes in the 5xFAD Mouse Model of Alzheimer's Disease

*Jeremiah K. H. Lim[1,2], Qiao-Xin Li[3], Zheng He[1], Algis J. Vingrys[1], Holly R. Chinnery[1], Jamie Mullen[4], Bang V. Bui[1] and Christine T. O. Nguyen[1]**

[1] Department of Optometry and Vision Sciences, University of Melbourne, Parkville, VIC, Australia, [2] Optometry and Vision Science, College of Nursing and Health Sciences, Flinders University, Bedford Park, SA, Australia, [3] Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia, [4] AstraZeneca Neuroscience, Cambridge, MA, United States

Amyloid accumulations are in human retinae

- In cells and blood vessels
- Particularly ganglion cells



JCI insight
CLINICAL MEDICINE

Retinal amyloid pathology and proof-of-concept imaging trial in Alzheimer's disease

Yosef Koronyo,[1] David Biggs,[2] Ernesto Barron,[3] David S. Boyer,[4] Joel A. Pearlman,[5] William J. Au,[6] Shawn J. Kile,[6] Austin Blanco,[2] Dieu-Trang Fuchs,[1] Adeel Ashfaq,[7] Sally Frautschy,[8] Gregory M. Cole,[8] Carol A. Miller,[9] David R. Hinton,[10] Steven R. Verdooner,[2] Keith L. Black,[1] and Maya Koronyo-Hamaoui[1,11]

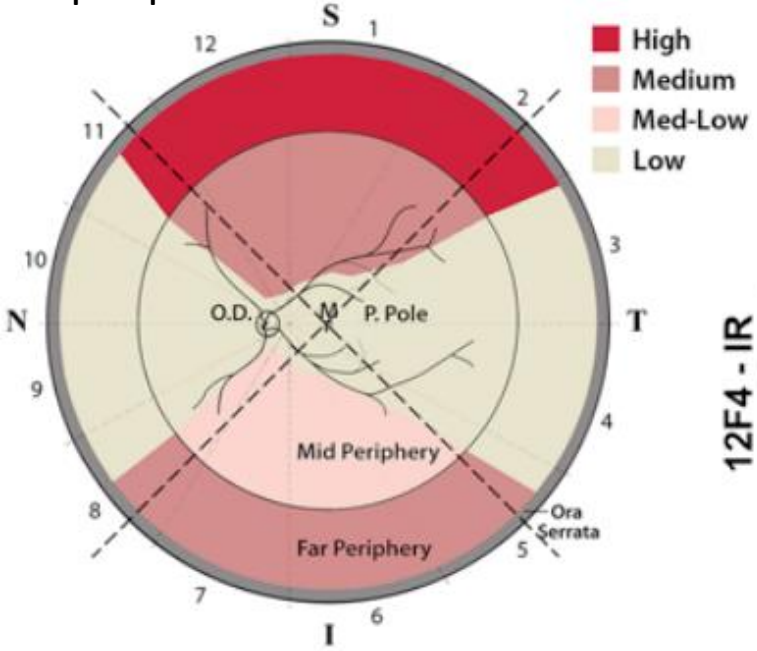
Amyloid accumulations in human retinae

JCI insight CLINICAL MEDICINE

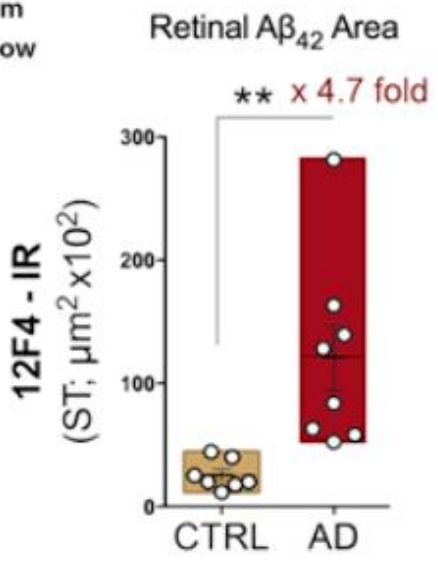
Retinal amyloid pathology and proof-of-concept imaging trial in Alzheimer's disease

Yosef Koronyo,[1] David Biggs,[2] Ernesto Barron,[3] David S. Boyer,[4] Joel A. Pearlman,[5] William J. Au,[6] Shawn J. Kile,[6] Austin Blanco,[2] Dieu-Trang Fuchs,[1] Adeel Ashfaq,[7] Sally Frautschy,[8] Gregory M. Cole,[8] Carol A. Miller,[9] David R. Hinton,[10] Steven R. Verdooner,[2] Keith L. Black,[1] and Maya Koronyo-Hamaoui[1,11]

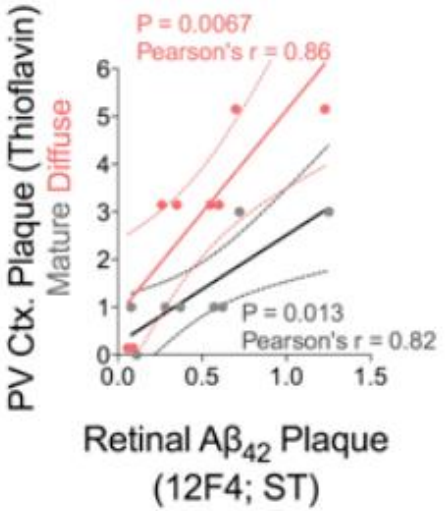
More often superior peripheral retina



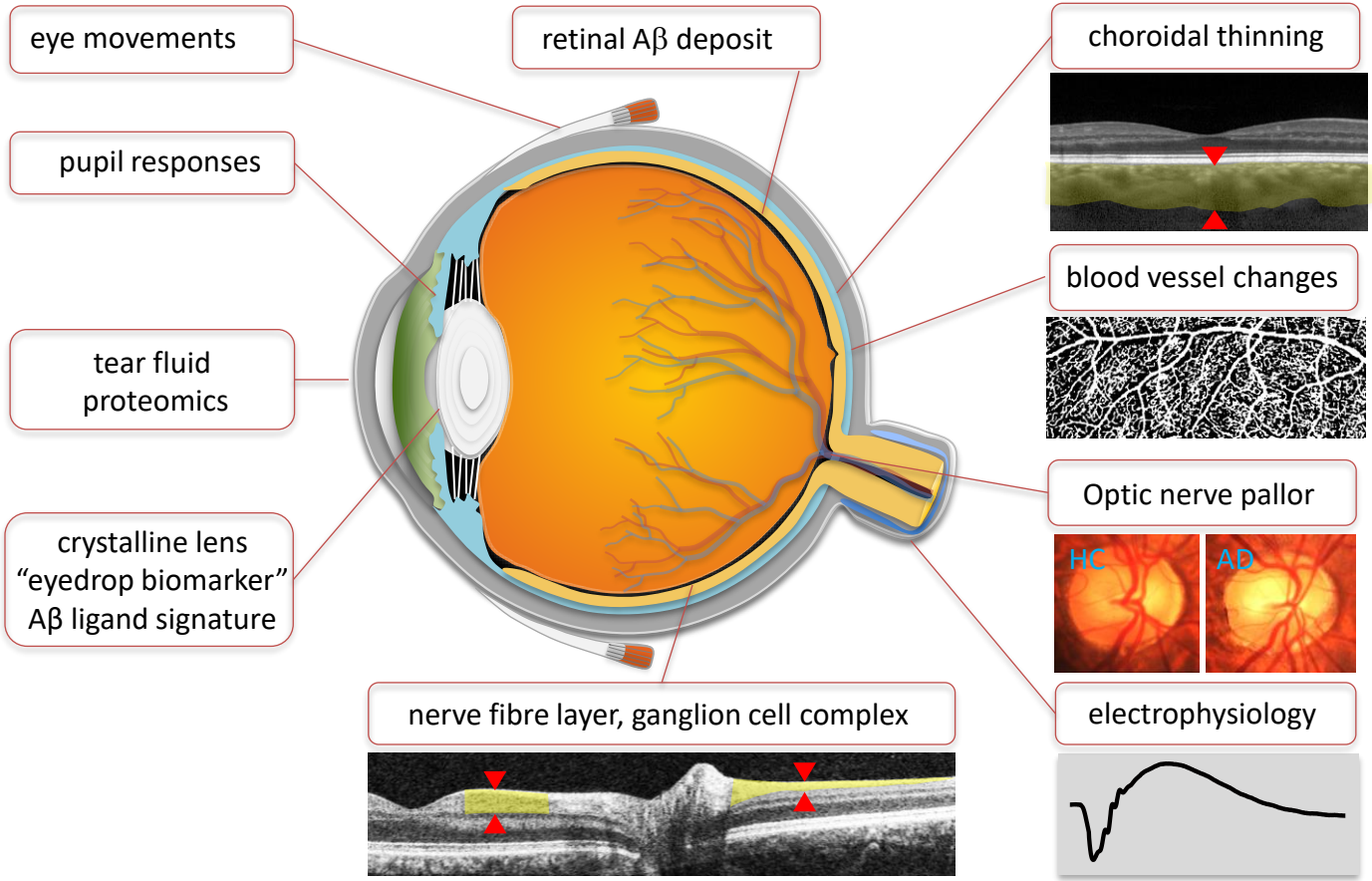
Higher amyloid in AD eyes



Retina amyloid related to brain amyloid levels



How might this manifest in the eye?



Structural and functional manifestations of AD in the visual system

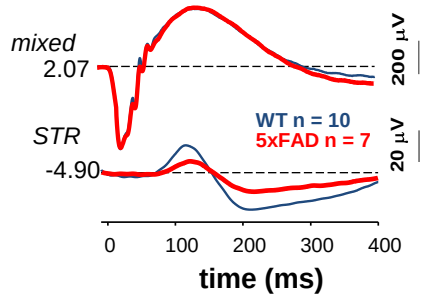
- Increasingly long list of differences: but which are specific to AD?

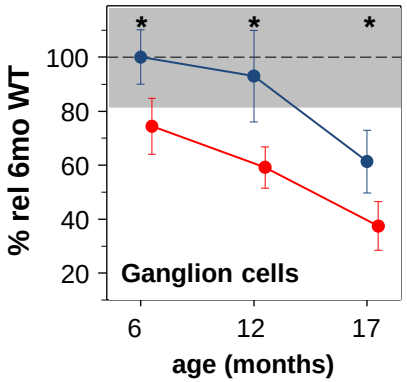
Pupil	Atypical pupil response to cholinergic antagonists
	Smaller maximum pupillary light reflex
	Increased pupillary size
Lens	Aβ in lens and aqueous humor
	Predisposition to supranuclear cataract
Retina	Decreased retinal blood flow, RNFL thinning
	RGC degeneration
	Overall reduction in RGC axon numbers
	Aβ deposition in retina
Choroid	Reduced choroidal thickness
Optic nerve	Increased cup: disk ratio and pallor

Visual acuity	Decreased visual acuity in low luminance
Contrast sensitivity	Reduced low frequencies contrast sensitivity
	Reduced reading speed at lower contrast
Color vision	Poor color discrimination
	Deficiencies most significant in tritan axis
Visual field loss	Inferior hemifield loss
Motion perception	Higher thresholds for motion detection
Depth perception and stereopsis	Reduced stereopsis, mean threshold >150 s of arc
Ocular motor function	Abnormal hypometric saccades

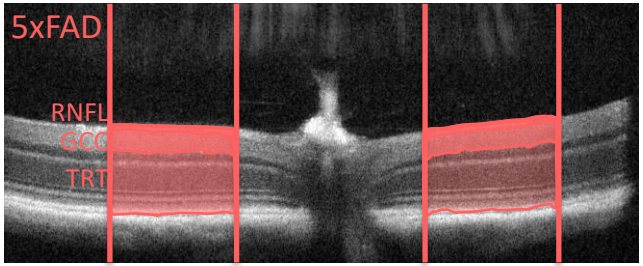
In animals with retinal amyloid deposits

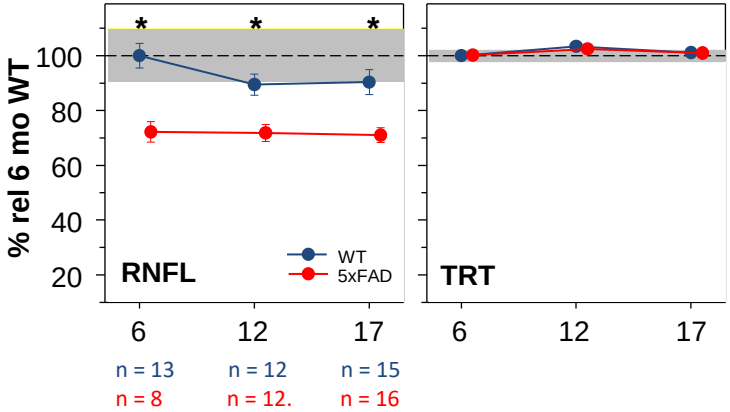
Ganglion cell responses are lost early





Retinal nerve fibre layer thins the most





Error bars: Avg ± SEM
Grey: 6mo 95% CI
* $p < 0.05$

RNFL findings in Alzheimer's disease

- More thinning in the superior
  - N=9 MMSE 24 (out of 30)
- Those with MCI also had thinning compared with controls
- Most studies consistently find RNFL thinning compared to age-matched controls
- More studies find superior and inferior thinning
  - less nasal and temporal change

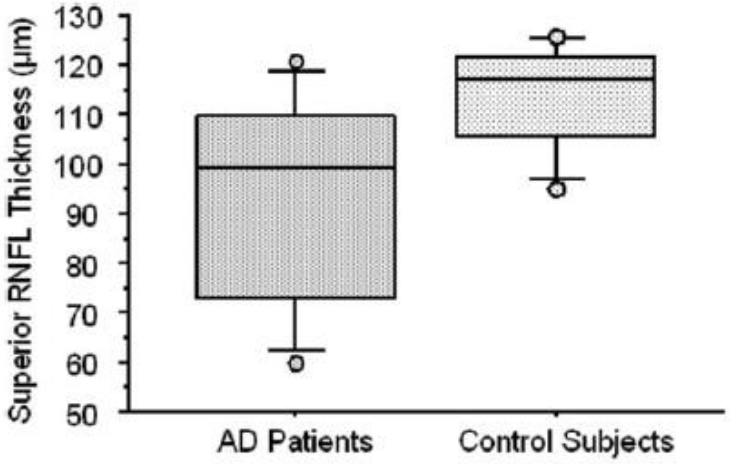


TABLE 3. Peripapillary RNFL Thickness Values in Patients with AD and Control Subjects

	AD (n = 9)	Control (n = 8)	P
Superior RNFL thickness (μm)	92.2 ± 21.6	113.6 ± 10.8	0.02*
Inferior RNFL thickness (μm)	117.0 ± 15.3	128.1 ± 11.4	0.11
Temporal RNFL thickness (μm)	67.0 ± 15.0	69.5 ± 11.1	0.70
Nasal RNFL thickness (μm)	65.7 ± 15.1	64.1 ± 7.3	0.80

Data are presented as mean ± SD.
* $P < 0.05$.

Berisha et al. Invest Ophthalmol Vis Sci. 2007;48:2285–2289) DOI:10.1167/iovs.06-1029

The biggest study to date

- Rotterdam Study, patients followed for 5 years… 2007 to 2015
  - N=3289
- Minimental state exam (MMSE)
  - score of 26 or more

- those with dementia (**prevalent**) had thinner GCL-IPL
- those with thinner RNFL higher risk of developing dementia
  - Independent of cardiovascular disease

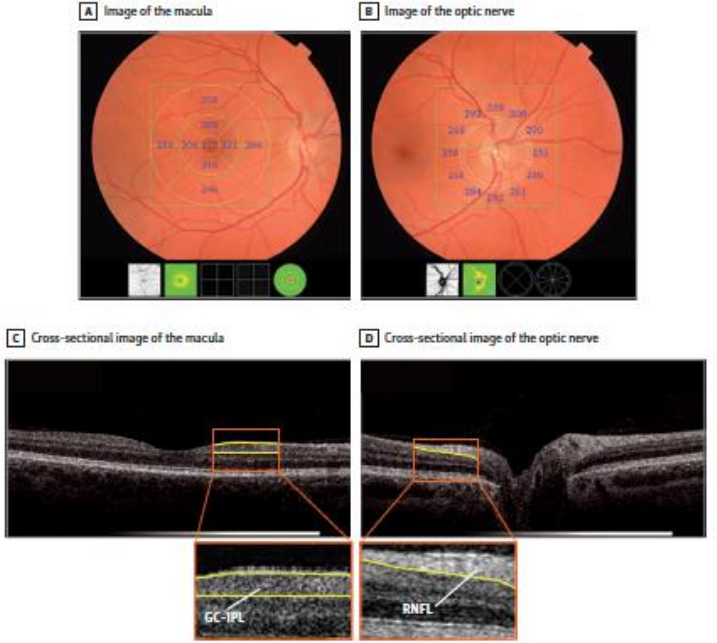
- Peripapillary RNFl thinning earlier
- Clear GCL-IPL thinning more severe disease…

JAMA Neurology | Original Investigation

Association of Retinal Neurodegeneration on Optical Coherence Tomography With Dementia
A Population-Based Study

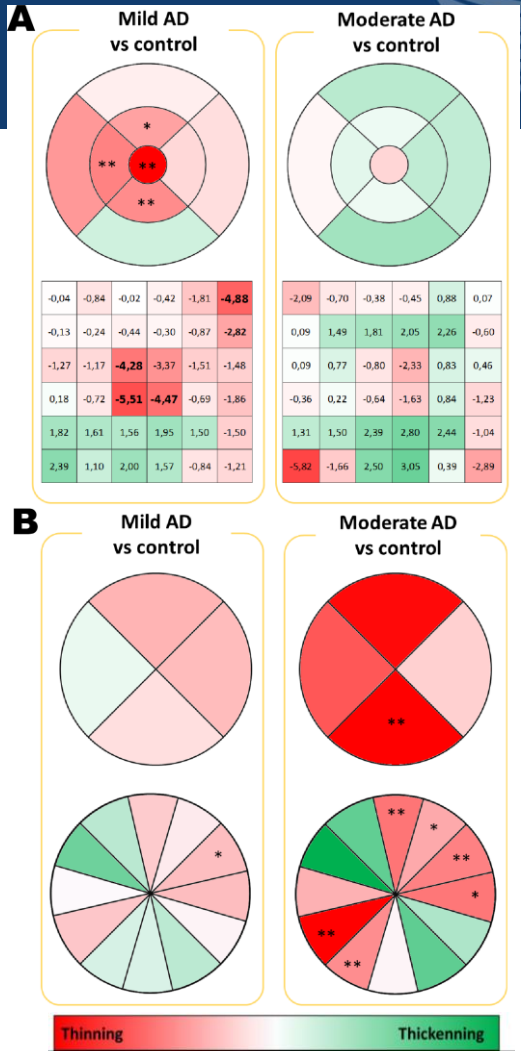
Unal Mutlu, MD, PhD; Johanna M. Colijn, MD; M. Arfan Ikram, MD, PhD; Pieter W. M. Bonnemaijer, MD; Silvan Licher, MD; Frank J. Wolters, MD; Henning Tiemeier, MD, PhD; Peter J. Koudstaal, MD, PhD; Caroline C. W. Klaver, MD, PhD; M. Kamran Ikram, MD, PhD

Figure 2. Output of the Retinal Optical Coherence Tomography



Macula thinning in Alzheimer's disease

- More variability in outcomes of studies assessing macular thinning
  - 13 out of 20 studies showed macular thinning
- Macular thinner in mild AD, but **thicker** in moderate AD
- Peripapillary RNFL show more thinning between mild and moderate AD



PLOS ONE

RESEARCH ARTICLE

Changes in visual function and retinal structure in the progression of Alzheimer's disease

Elena Salobrar-García[1,2*], Rosa de Hoz[1,3*], Ana I. Ramírez[1,3], Inés López-Cuenca[1,2], Pilar Rojas[1,4], Ravi Vazirani[1], Carla Amarante[1], Raquel Yubero[5], Pedro Gil[5], María D. Pinazo-Durán[6,7], Juan J. Salazar[1,3*], José M. Ramírez[1,2*]

OCTa difference in AD are inconsistent

- Some studies find reduced macular vessel density, larger foveal avascular zone area
  - others do not
- Peripapillary capillary density is reduced in moderate AD
  - Less nerves need fewer vessels?
- And strongly associated with the presence of Subcortical vascular cognitive impairment
  - Generalized vascular problem?

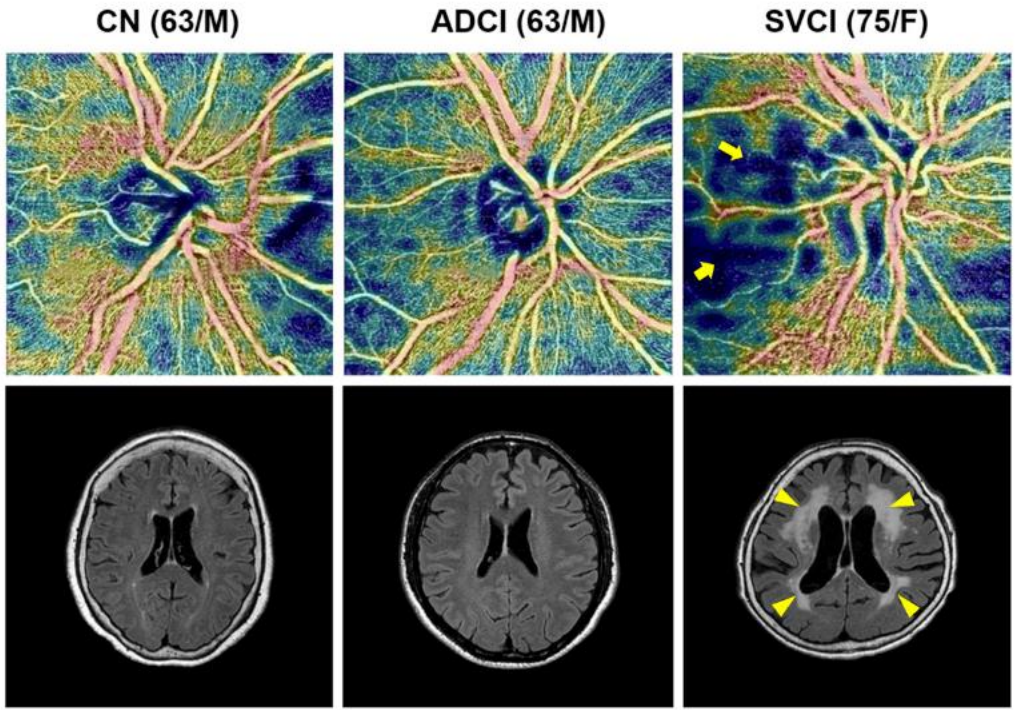
Lee et al. Alzheimer's Research & Therapy (2020) 12:73
https://doi.org/10.1186/s13195-020-00638-x

Alzheimer's Research & Therapy

RESEARCH Open Access

Optical coherence tomography angiography as a potential screening tool for cerebral small vessel diseases

Ju-Yeun Lee[1†], Jun Pyo Kim[2,3,4†], Hyemin Jang[2,3,4], Jaeho Kim[2,3,4], Sung Hoon Kang[2,3,4], Ji Sun Kim[2,3,4], Jongmin Lee[2,3,4], Young Hee Jung[2,5], Duk L. Na[2,3,4,6], Sang Won Seo[2,3,4,6,7,8], Sei Yeul Oh[9*] and Hee Jin Kim[2,3,4,6,8*]



OCTa pre-clinical AD

- Studies in Mild cognitive impairment and AD lean toward lower vessel density
- In cognitively normal subjects (MMSE 29-30)
  - those with Ab load (PET imaging) had higher vessel density, FAZ was the same
  - Is this a sign of early inflammation?
    - Soluble amyloid…

Clinical science

OPEN ACCESS

Optical coherence tomography angiography in preclinical Alzheimer's disease

Jacoba Alida van de Kreeke ,[1] Hoang-Ton Nguyen,[1] Elles Konijnenberg,[2] Jori Tomassen,[2] Anouk den Braber,[2,3] Mara ten Kate,[2] Maqsood Yaqub,[4] Bart van Berckel,[4] Adriaan A Lammertsma,[4] Dorret I Boomsma,[3] Stevie H Tan,[1] Frank Verbraak,[1] Pieter Jelle Visser[2]

Table 2 Difference in vessel densities and foveal avascular zone area between amyloid-positive and amyloid-negative participants

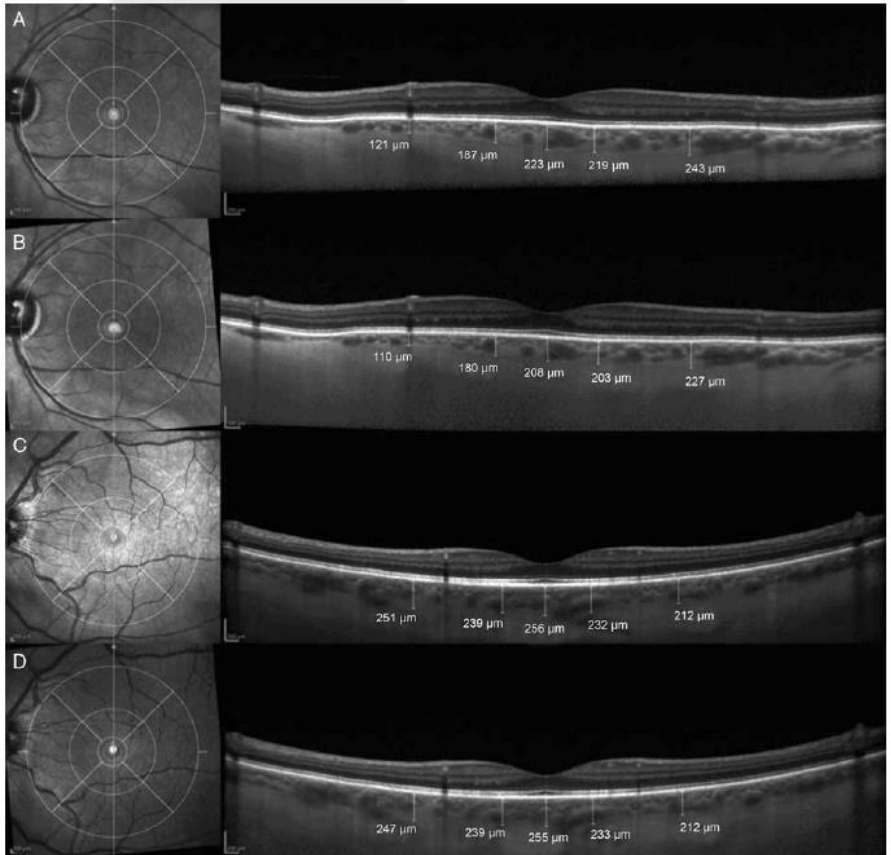
	Aβ+ versus Aβ–			
	Difference	Raw p value	95% CI	Adjusted p value
Retinal vessel density				
Inner ring macula	0.81	<0.001	0.36 to 1.26	0.002
Outer ring macula	0.50	0.012	0.11 to 0.90	0.024
Around optic nerve head	0.83	0.005	0.25 to 1.42	0.015
Foveal avascular zone (mm^2)	–0.02	0.387	–0.05 to 0.02	0.387

Choroidal thickness in AD

TABLE 3. Alzheimer Disease Patients Versus Controls: Changes in Best-corrected Visual Acuity and Psychometric Scores

	AD Patients			Controls		
	T0	T12	P	T0	T12	P
BCVA (no. ETDRS letters)	54 ± 3.8	53 ± 3.5	0.01*	57 ± 4.1	57 ± 4.2	0.7*
BCVA change	−1.3 ± 2.3			0.4 ± 2.1		
MMSE	22.5 ± 2.1	16.8 ± 2.8	< 0.0001‡	28.6 ± 1.4	28.3 ± 1.2	0.5‡

- Progression in MMSE over the course of 12 months associated with a reduction in choroidal thickness
- In mild-moderate AD
  - Why is not well understood



ORIGINAL ARTICLE

Attenuation of Choroidal Thickness in Patients With Alzheimer Disease

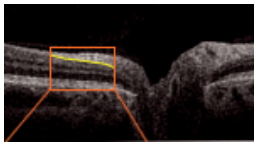
Evidence From an Italian Prospective Study

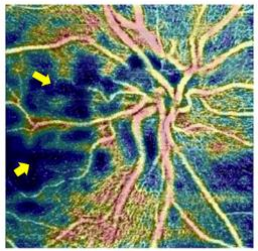
Alessandro Trebbastoni, MD, PhD, Michela Marcelli, MD,† Fabiana Mallone, MD,† Fabrizia D'Antonio, MD,* Letizia Imbriano, BSc,* Alessandra Campanelli, MD,* Carlo de Lena, MD,* and Magda Gharbiya, MD†*

Early detection of AD using OCT

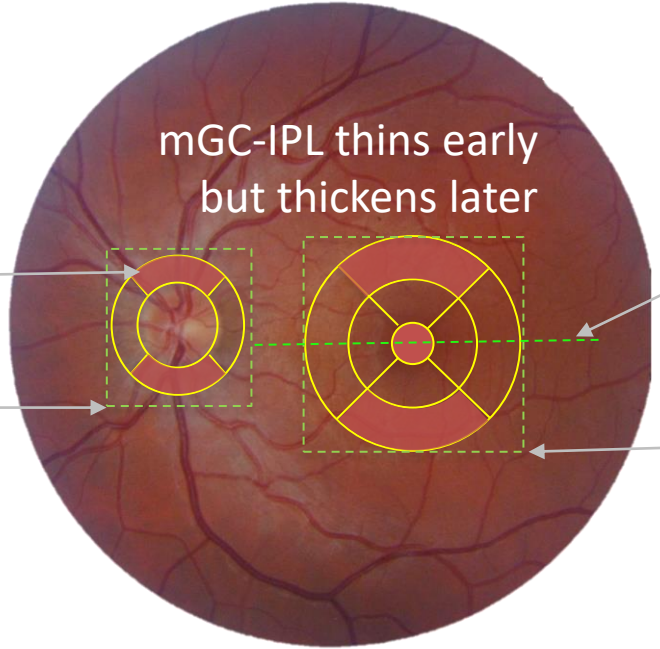
- Early detection… pRNFL thinning, mGC-IPL thickening with increase vessel density

Peripapillary RNFL thins in MCI and AD

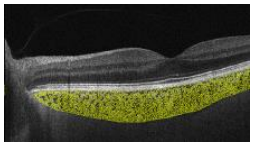


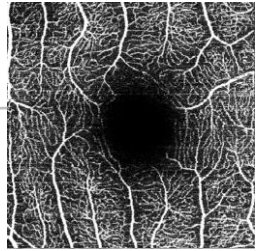


Peripapillary Vessel density more strongly associated with vascular dementia



Choroid thins with AD progression

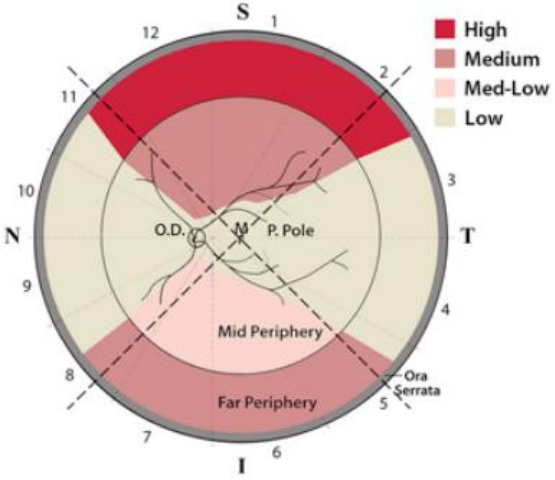


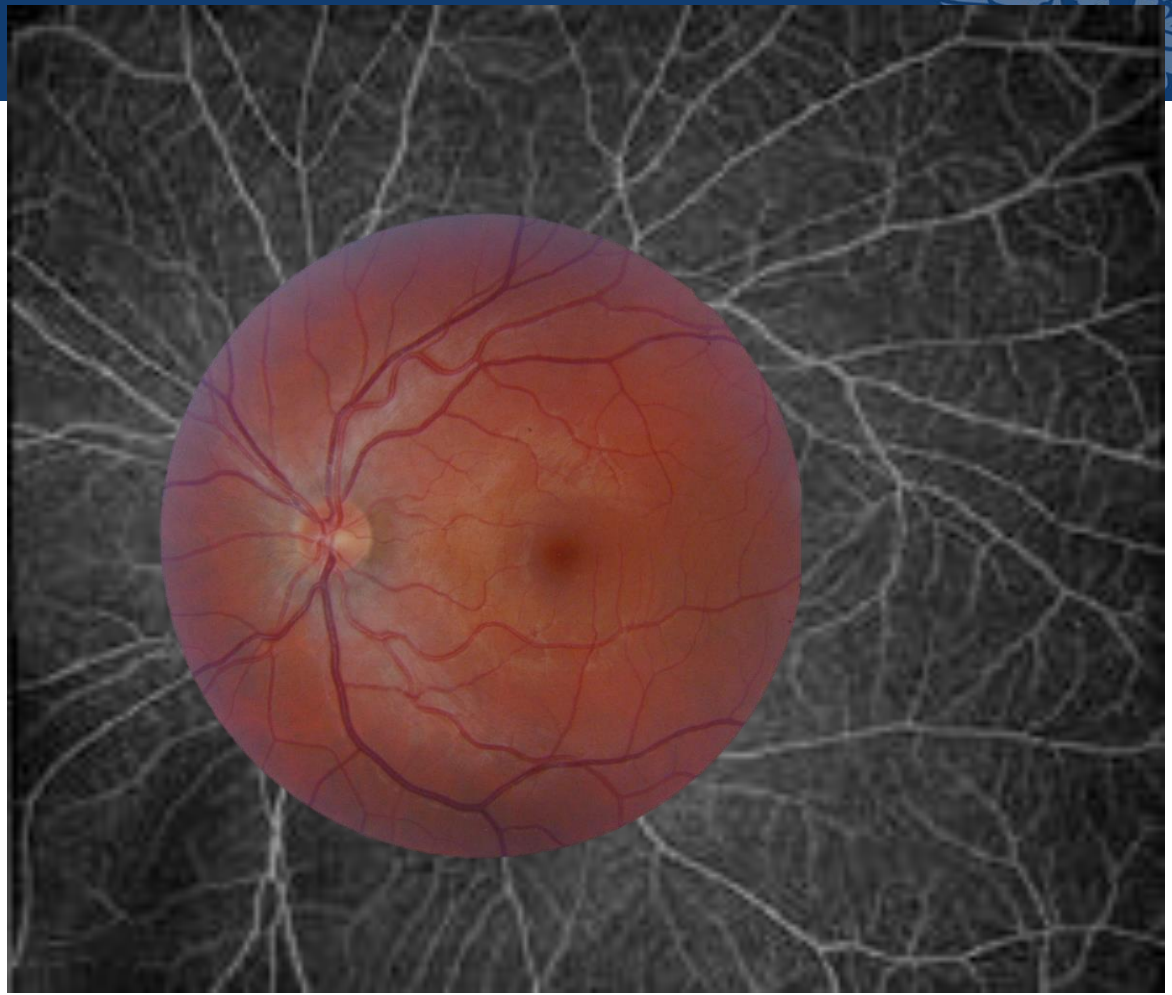


Macular Vessel density higher density in preclinical lower in MCI and AD

A more complete picture

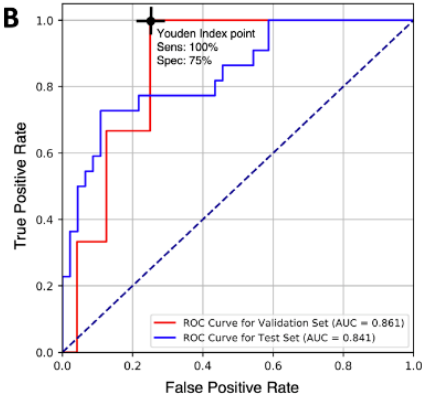
- Widefield mapping
  - OCT and OCTa montages





A more complete picture

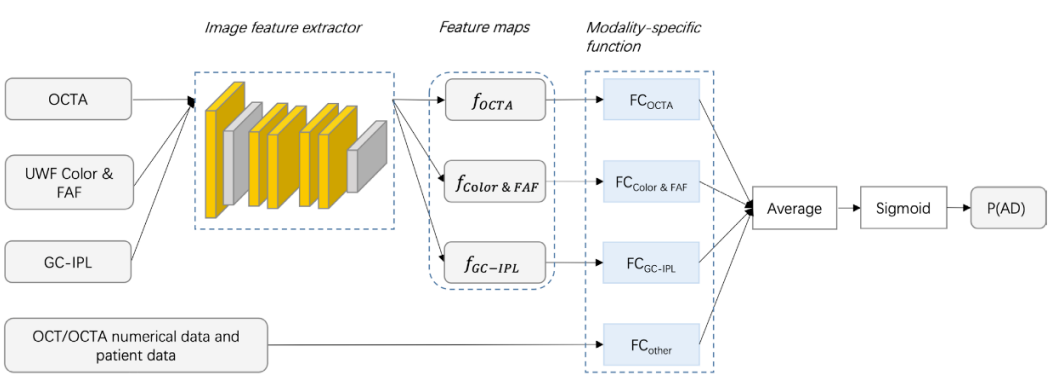
- Machine learning assisted
  - Combine OCT with other biomarkers, other imaging modalities

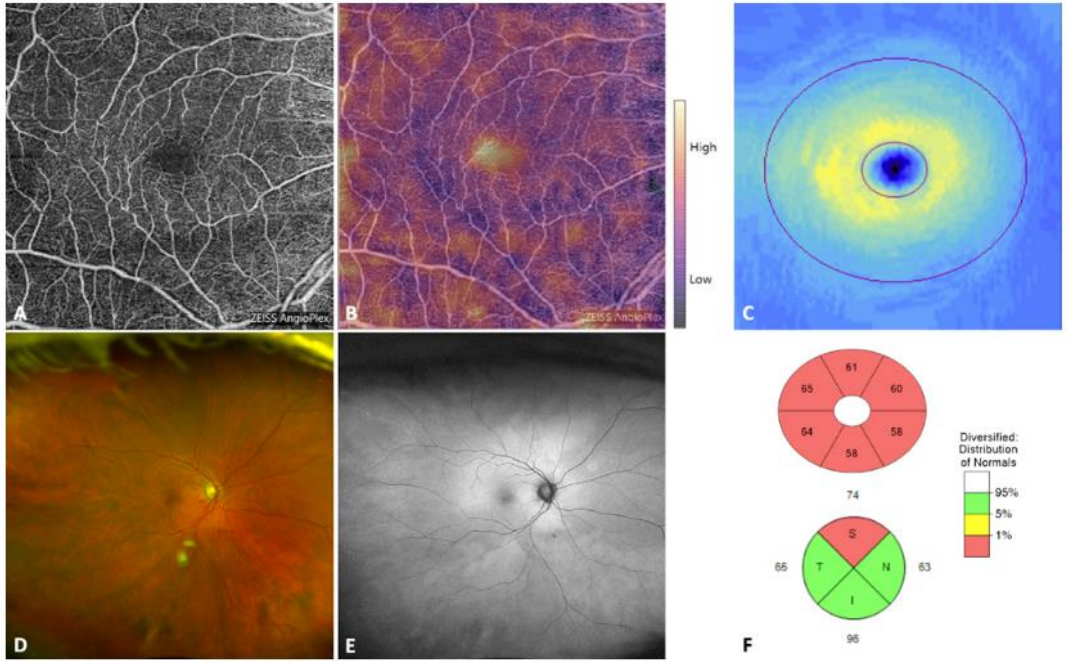


Clinical science

Convolutional neural network to identify symptomatic Alzheimer's disease using multimodal retinal imaging

C. Ellis Wisely ,[1] Dong Wang,[2] Ricardo Henao ,[3] Dilraj S. Grewal ,[1] Atalie C. Thompson,[1] Cason B. Robbins ,[1] Stephen P. Yoon,[1] Srinath Soundararajan,[1] Bryce W. Polascik,[1] James R. Burke,[4] Andy Liu,[4] Lawrence Carin,[2] Sharon Fekrat [1]





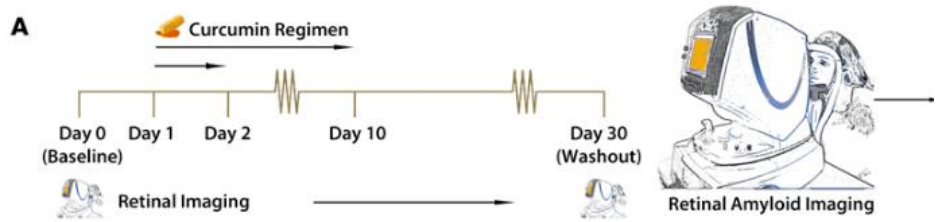
Other approaches: contrast agent

JCI insight

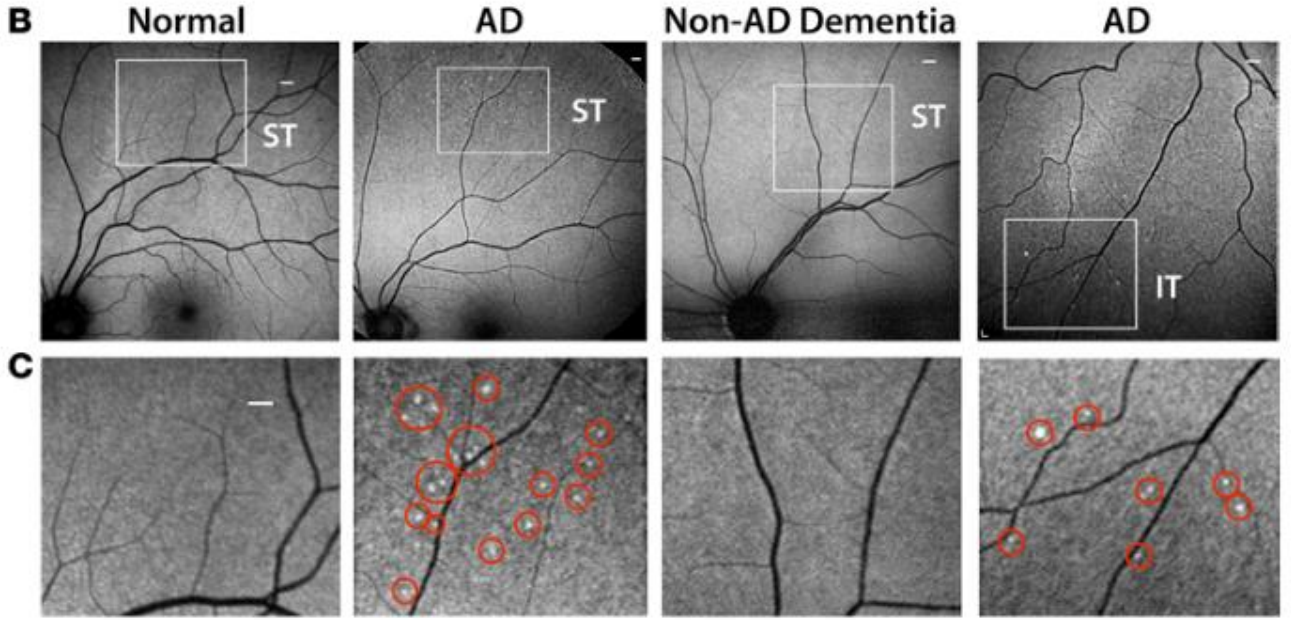
CLINICAL MEDICINE

Retinal amyloid pathology and proof-of-concept imaging trial in Alzheimer's disease

Yosef Koronyo,[1] David Biggs,[2] Ernesto Barron,[3] David S. Boyer,[4] Joel A. Pearlman,[5] William J. Au,[6] Shawn J. Kile,[6] Austin Blanco,[2] Dieu-Trang Fuchs,[1] Adeel Ashfaq,[7] Sally Frautschy,[8] Gregory M. Cole,[8] Carol A. Miller,[9] David R. Hinton,[10] Steven R. Verdooner,[2] Keith L. Black,[1] and Maya Koronyo-Hamaoui[1,11]

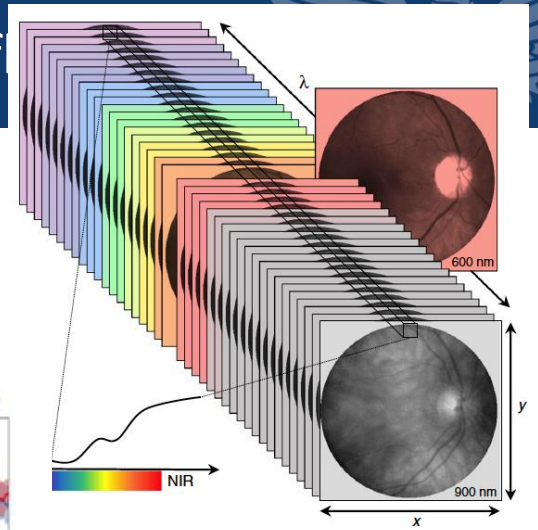


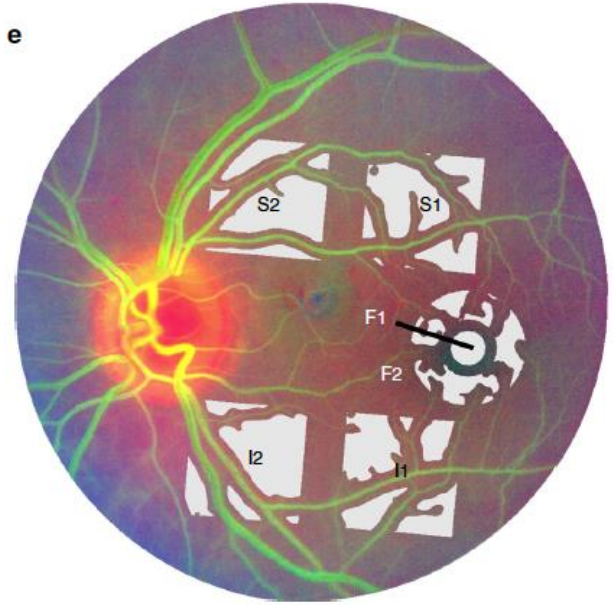
- Oral curcumin as a contrast agent

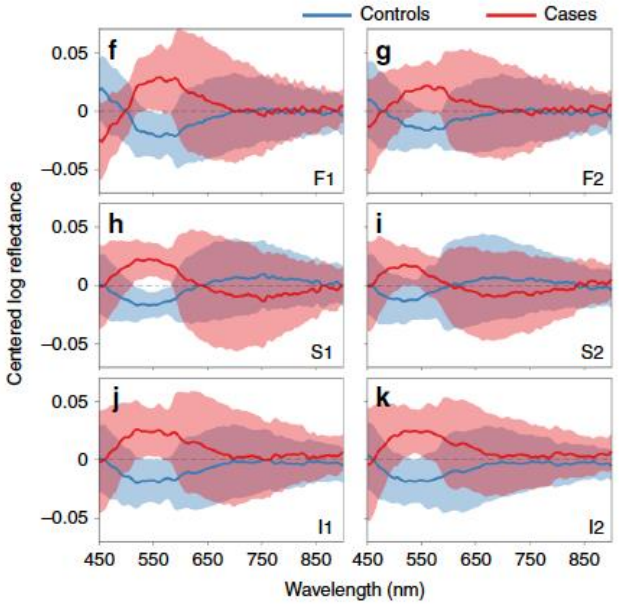


Other approaches: amyloid accumulating changes ref

- Hyperspectral imaging



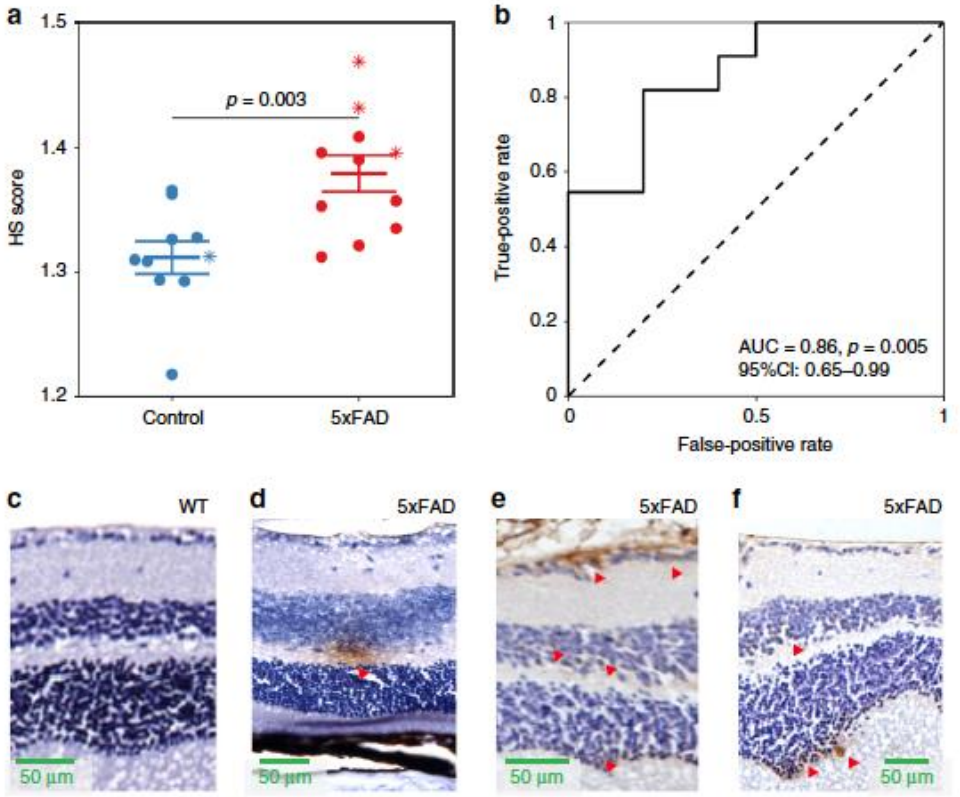




CENTRE FOR Eye Research Australia

Hyperspectral imaging in a mouse model of AD

- Identifies difference between control and mice with amyloid accumulation



nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-12242-1 OPEN

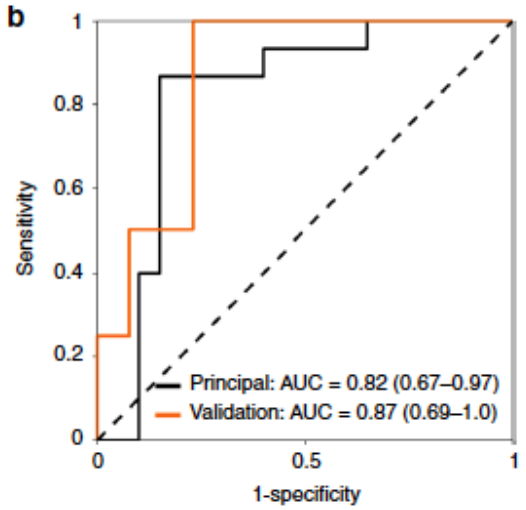
Non-invasive in vivo hyperspectral imaging of the retina for potential biomarker use in Alzheimer's disease

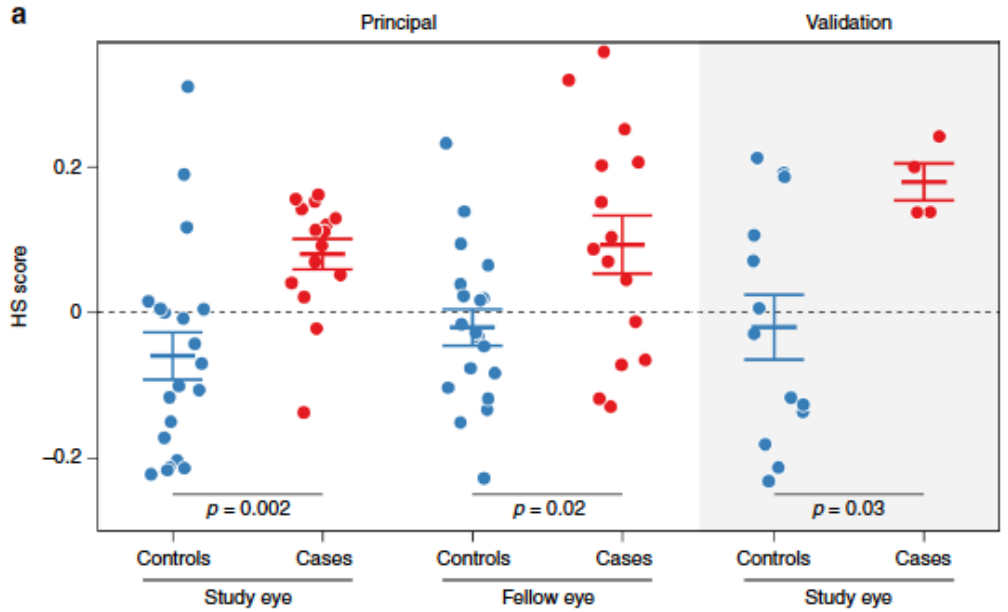
Xavier Hadoux et al.#

CENTRE FOR Eye Research Australia

Hyperspectral imaging in human AD

- PET positive
- MMSE 23





CENTRE FOR
Eye Research
Australia

Summary

- Retina manifests both soluble and insoluble amyloid beta and tau
- This produces a range of structural and functional deficit

- A growing number of studies, albeit with small sample sizes are identifying distinct retinal changes in specific locations that differentiate Alzheimer's disease risk from other conditions

- Utility of advanced OCT and OCTa imaging places eyecare and optometry in a position to help fight the growing AD epidemic

Acknowledgements

- Support
  - NHMRC 1046203, ARC Future Fellowship 130100388
  - National Institutes of Health – NEI RO1EY019939
  - Bayer GOAP, SPARK

CENTRE FOR Eye Research Australia

Australian Government Australian Research Council

Australian Government National Health and Medical Research Council NHMRC

GOAP Global Ophthalmology Awards Program from Bayer

NIH National Eye Institute Research Today...Vision Tomorrow