MAYO CLINIC

Paradoxical Aging in Alzheimer's disease: A Clinicopathologic Perspective

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Mayo Clinic Florida

MCI Symposium
January 19, 2020

@DrNeuroChic

Disclosure

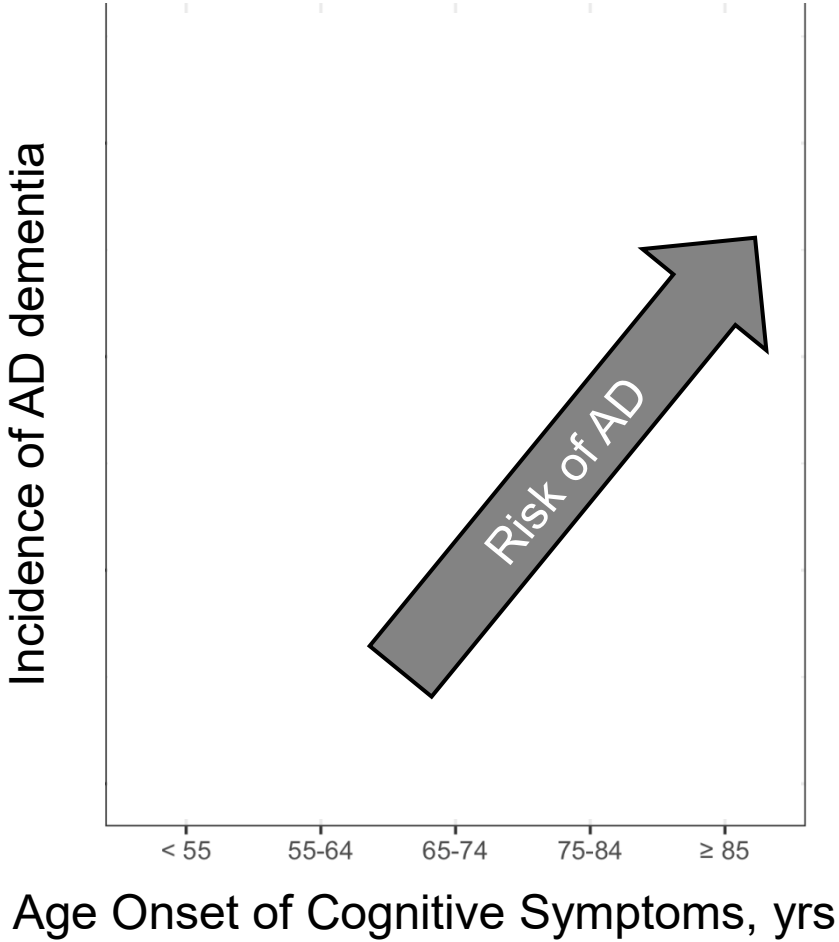
Relevant Financial Relationships

None

Off-Label/Investigational Uses

None

Punchline



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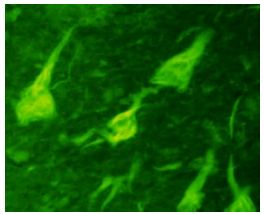
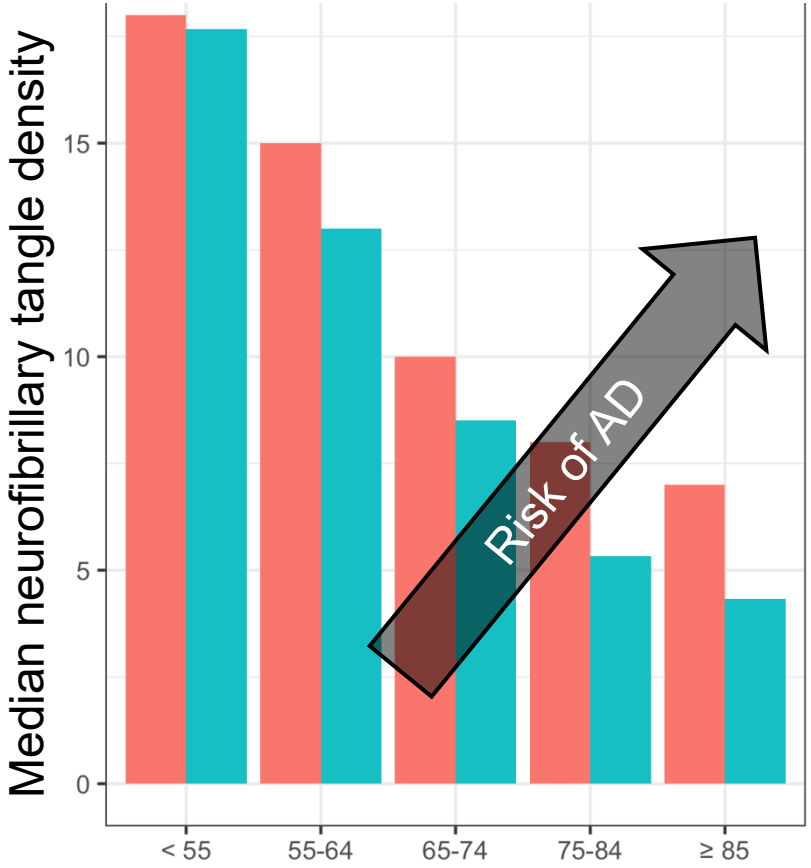
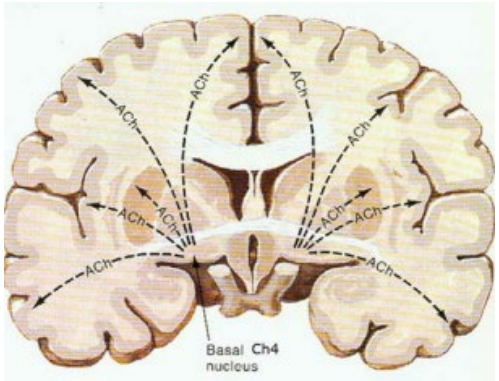




Brain region

Cortex

nbM



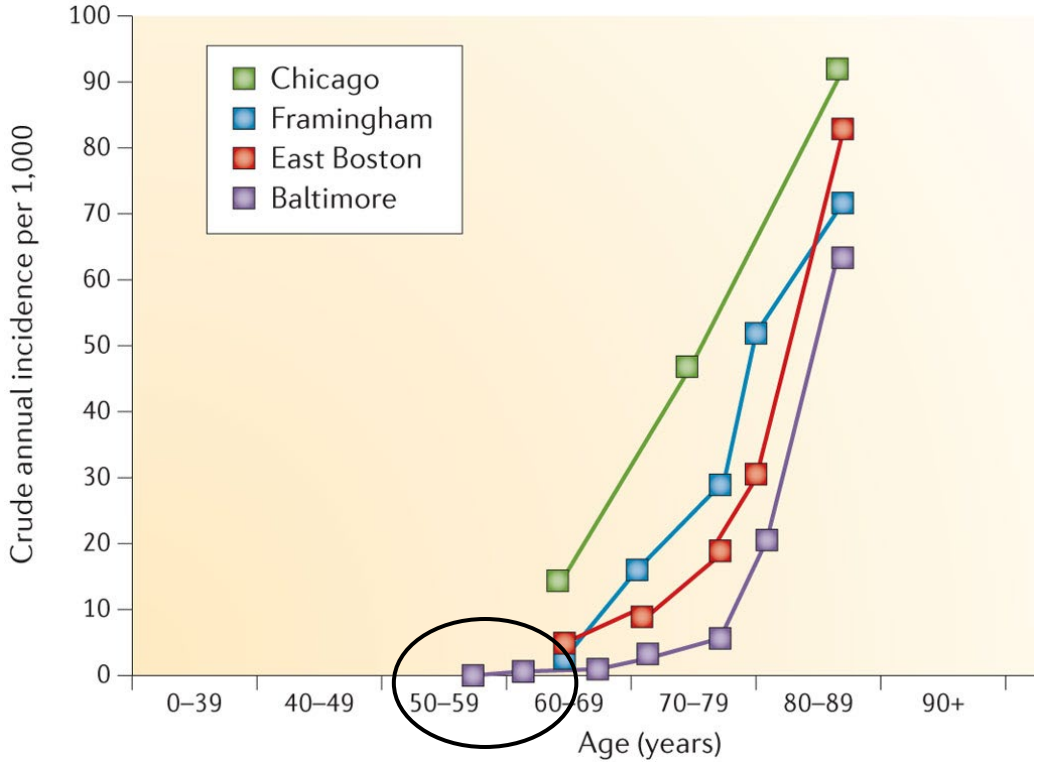
nbM – nucleus basalis of Meynert

Liesinger *et* al., Acta Neuropathologica 2018

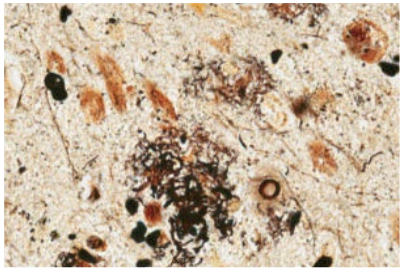
Hanna Al-Shaikh *et al*., JAMA Neurology 2019

dementia

Risk of AD exponentially increases with age



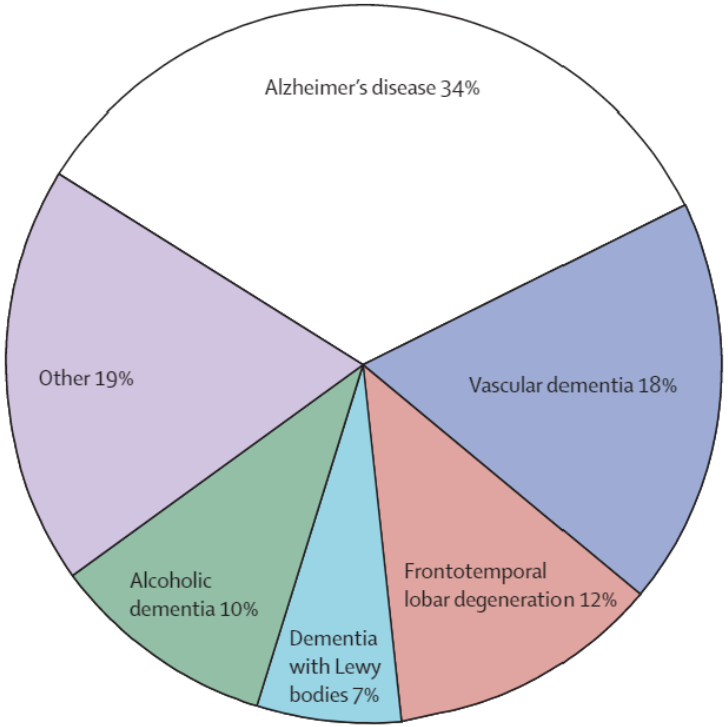
Neuropathologic AD



Masters et al. Nature Reviews Disease Primers 2015

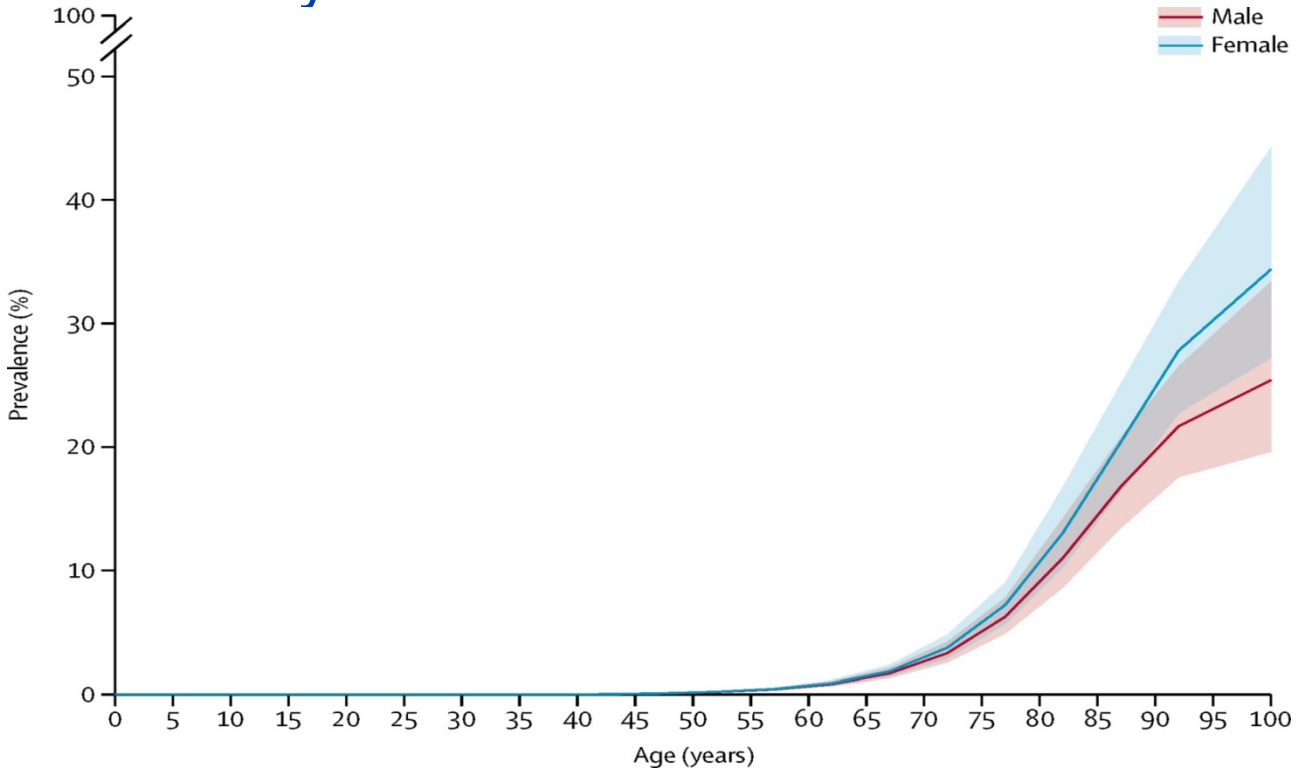
Young onset dementia

- Most common form of young onset dementia is AD
- Formerly presenile dementia
- Why 65 years of age?
  - Sociologic partition related to retirement age
  - Biological relevance?



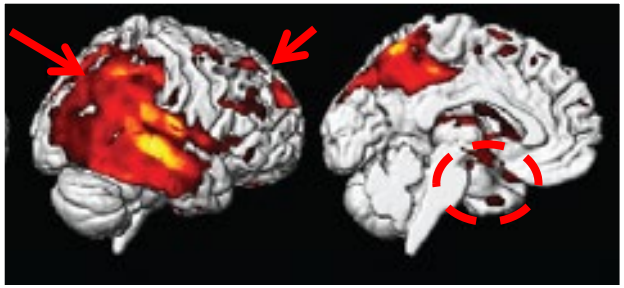
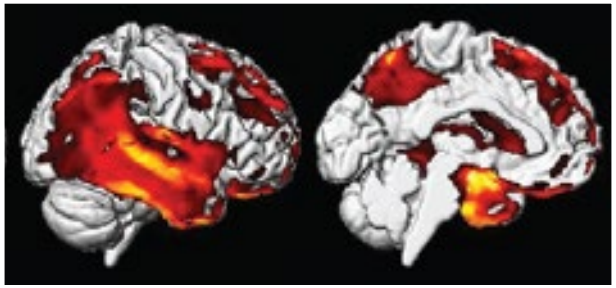
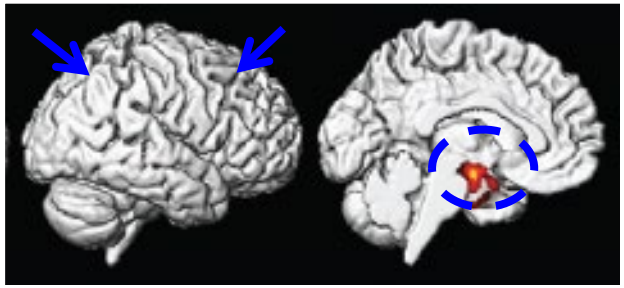
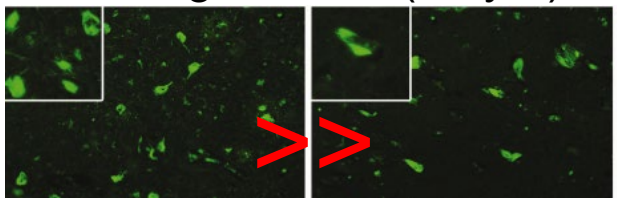
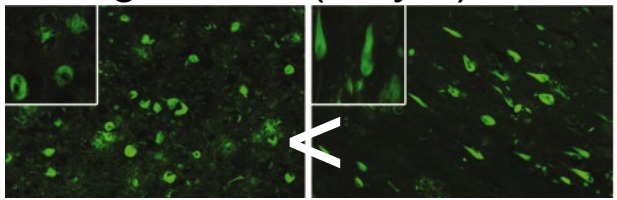
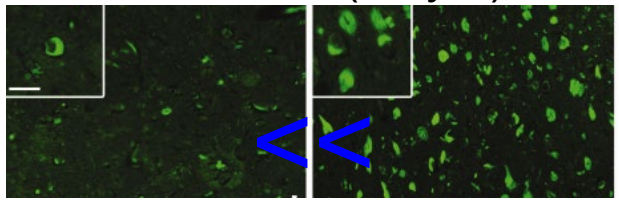
Rossor et al., Lancet Neurology 2010; Harvey et al., JNNP 2003

Global age-standardized prevalence of AD dementia and other dementias by sex



GBD 2016 Dementia Collaborators, Lancet, Neurology 2019

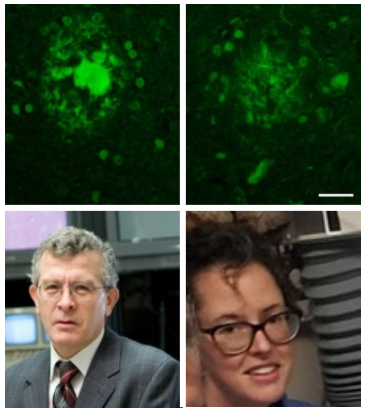
Neuropathologic subtypes of AD underlie clinical heterogeneity

Hippocampal sparing AD	Typical AD	Limbic predominant AD
		
▪ 43% women	▪ 55% women	▪ 69% women
▪ Younger onset (63 yrs)	▪ Age onset (69 yrs)	▪ Older onset (76 yrs)
		
Frontal cortex > Hippocampus	Frontal cortex < Hippocampus	Frontal cortex << Hippocampus

Murray *et al.*, Lancet Neurology 2011; Whitwell *et al.*, Lancet Neurology 2012; Josephs *et al.*, Annals Neurology 2015

Aβ plaque differences

- Ceiling effect at 50

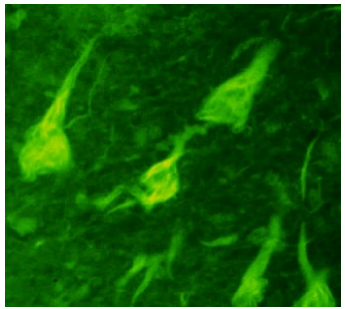


- Steadily decrease with age
  - Similar across sexes
  - Similar across regions

(Liesinger *et al.*, Acta Neuropath 2018)

Tangle observations in men

- No maximum count



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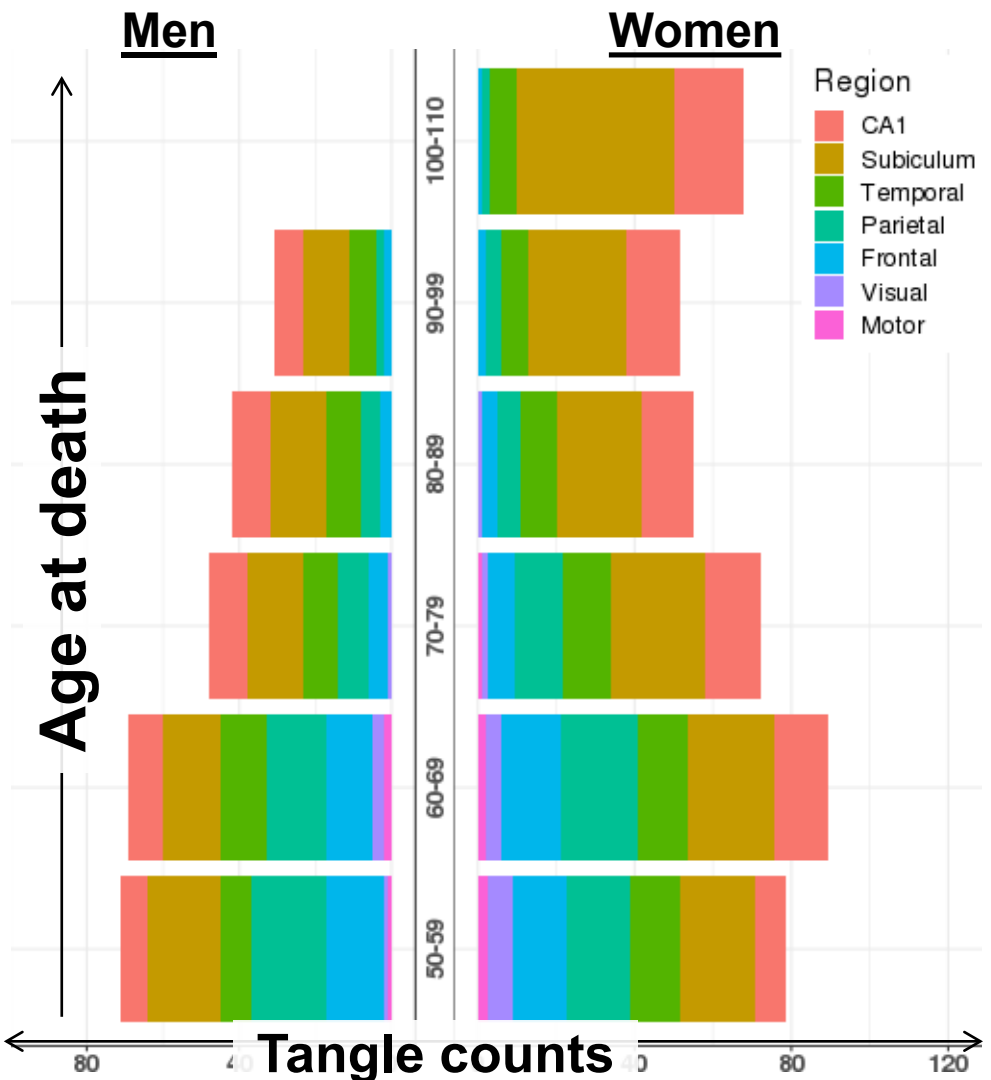

Tangle observations in men

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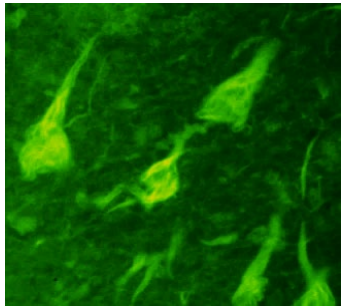
- In men, overall pattern of a steady decrease in severity with increasing age



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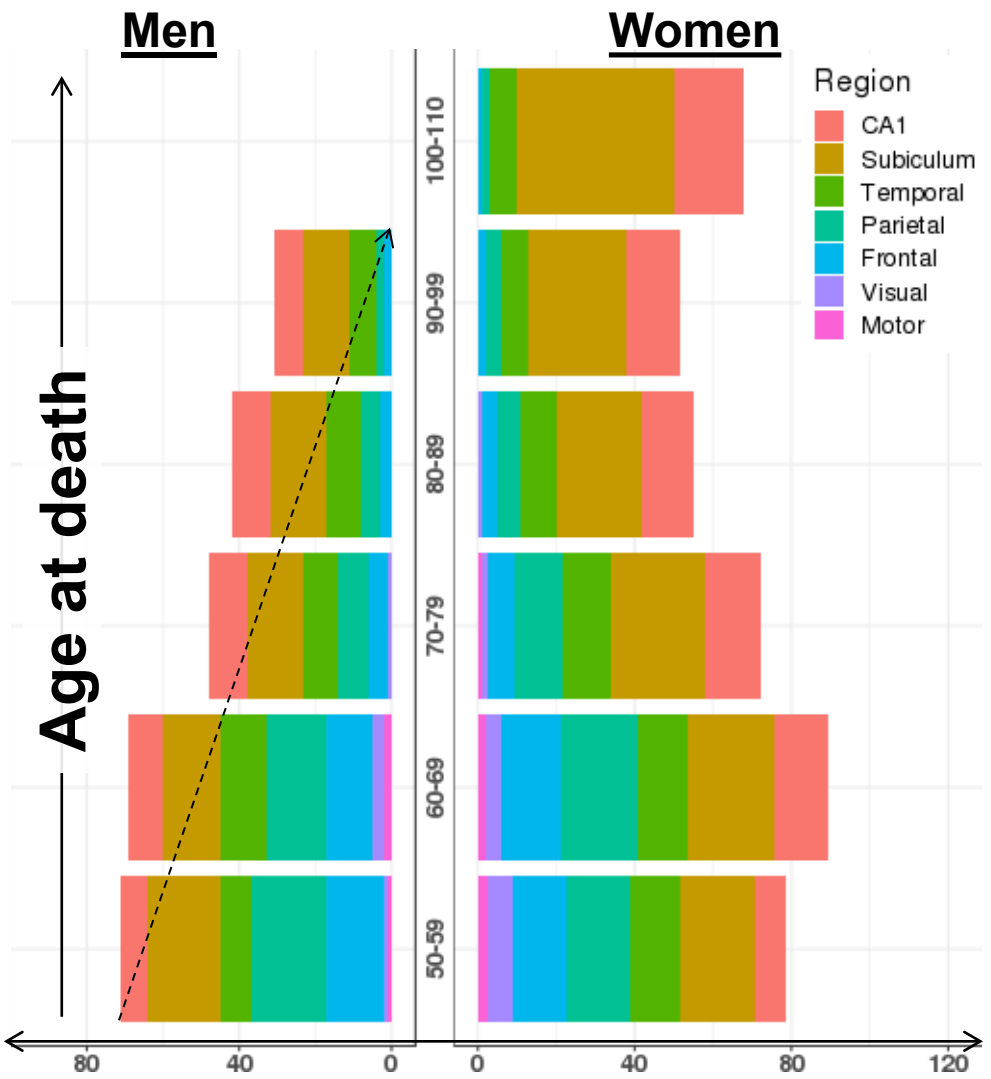

Tangle observations in men

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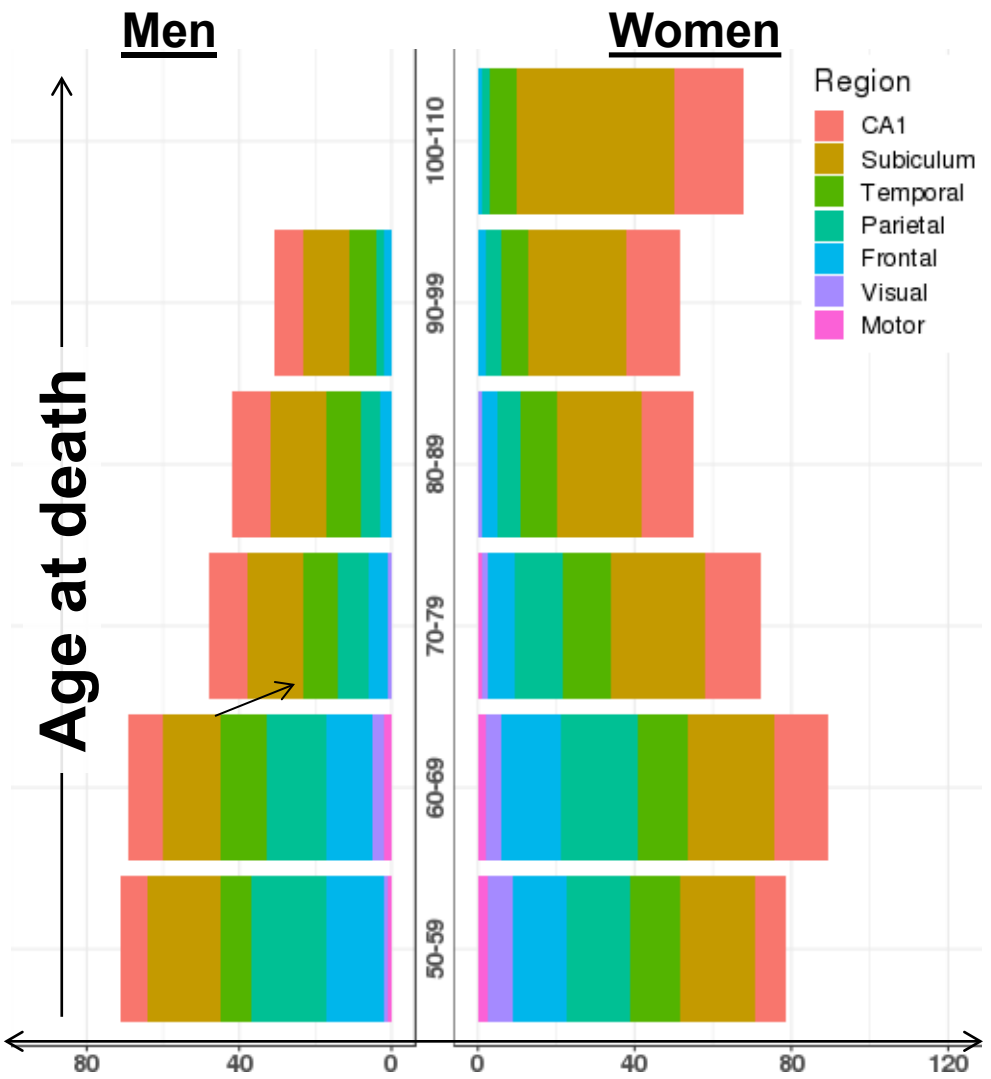
- Tangle counts remained higher in the neocortex in their 50s and 60s, with more than a two-fold decrease observed in their 70s onwards



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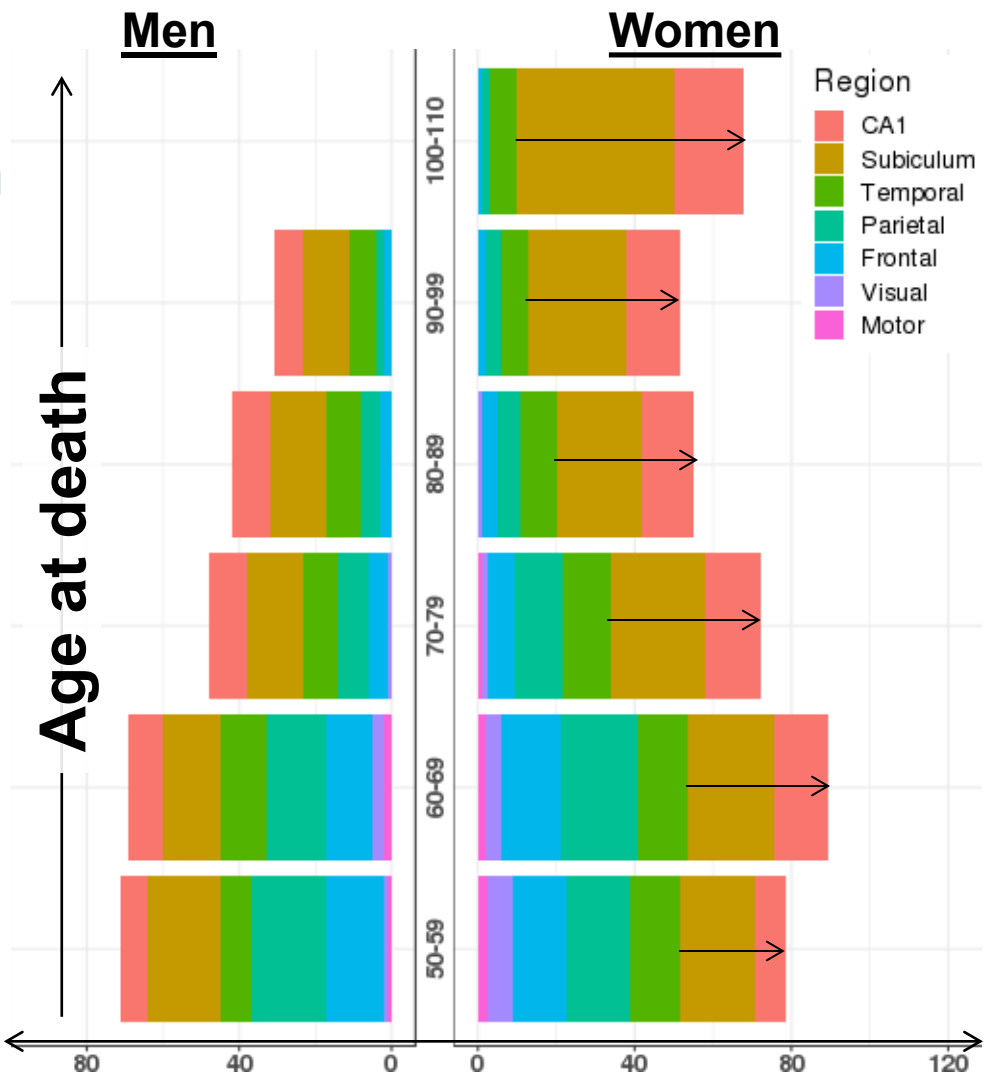
Tangle observations in women

- In women, tangles increased steadily in hippocampal subregions with increasing age



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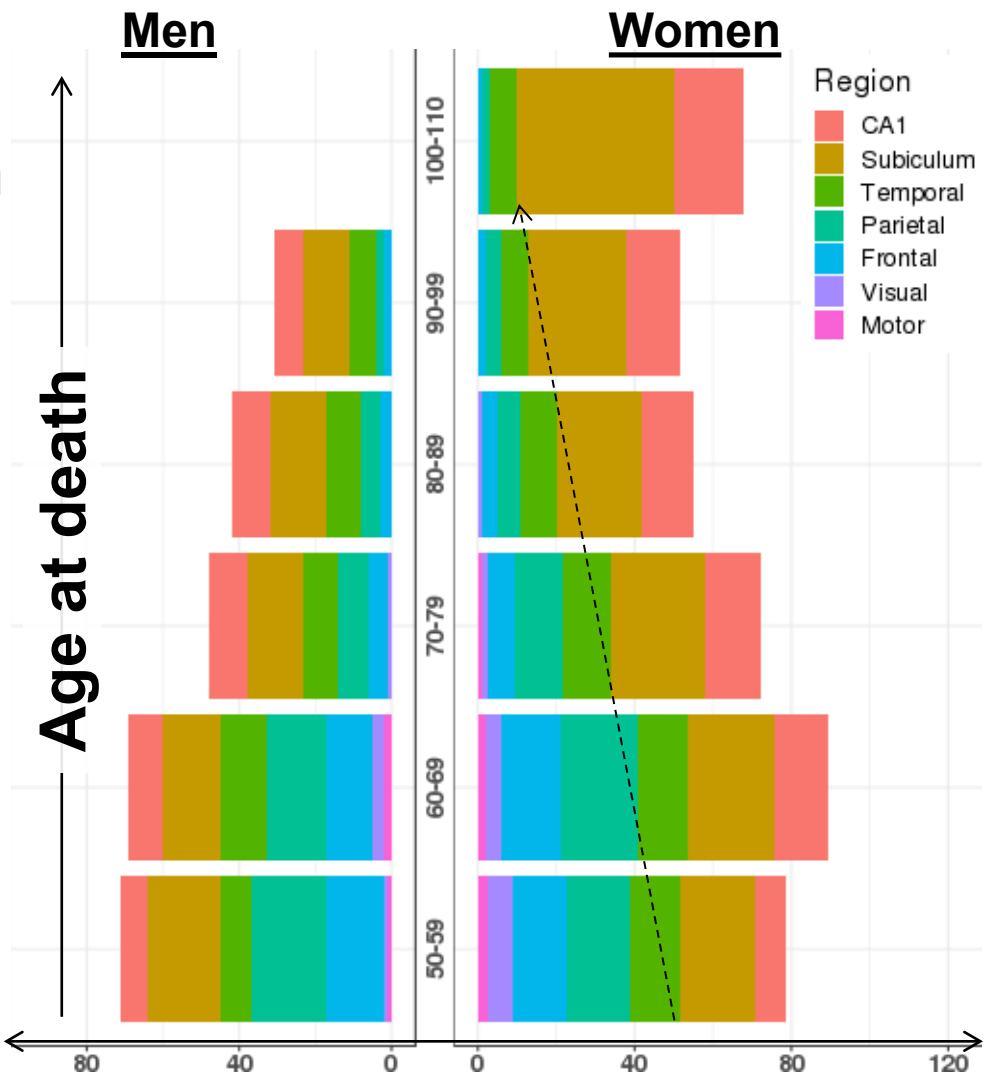
Tangle observations in women

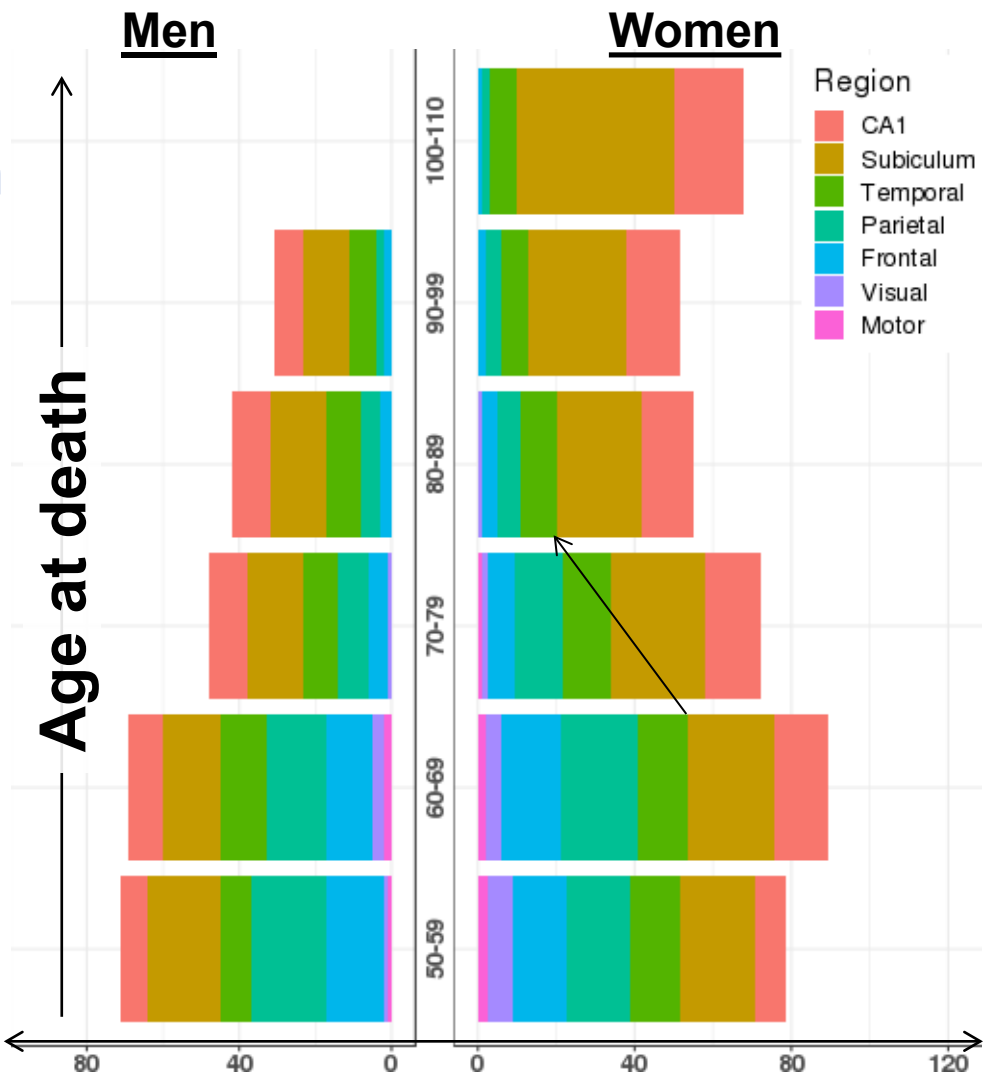
- In women, tangles increased steadily in hippocampal subregions with increasing age
- Similar to men, tangle severity decreased in the neocortex with increasing age



(Liesinger *et al.,* Acta Neuropath 2018)

Tangle observations in women

- In women, tangles increased steadily in hippocampal subregions with increasing age
- Similar to men, tangle severity decreased in the neocortex with increasing age
- A two-fold decline was observed for women in their 80s onwards



(Liesinger *et al.,* Acta Neuropath 2018)

Choose your own adventure...

Aerial perspective

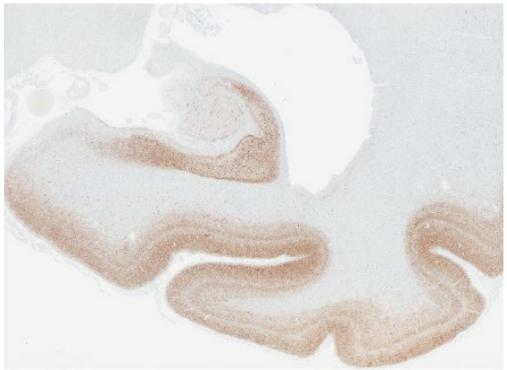
Subway level

Photo credit: Manuel Gutjahr

Cortical tau uptake inversely associates with age onset

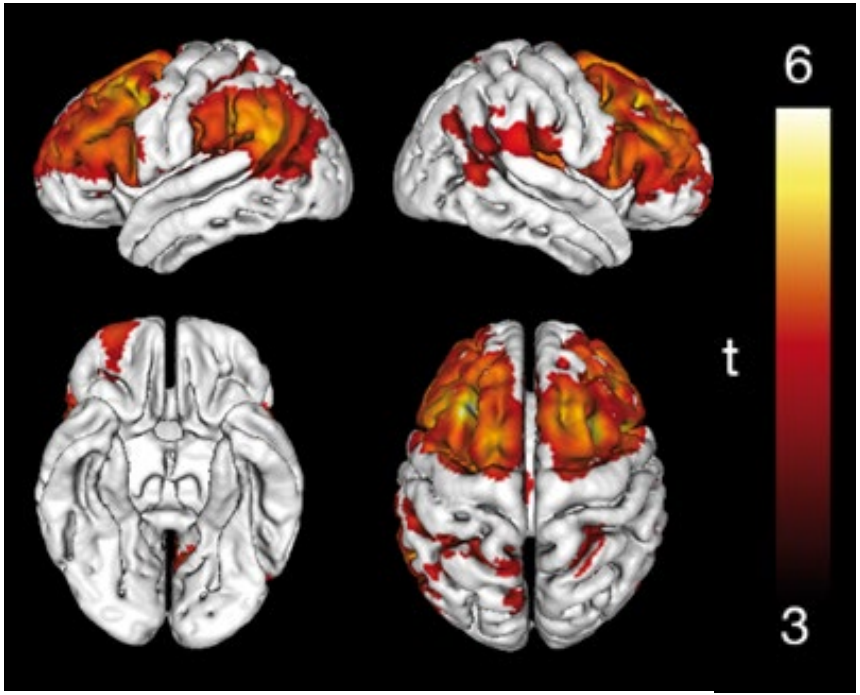
- Young onset AD (<65) compared to late onset AD (≥65) yielded a distinct pattern of higher tau PET (flortaucipir) retention

Autoradiography



Tau immunostain

Voxelwise comparison: <65 vs. ≥65

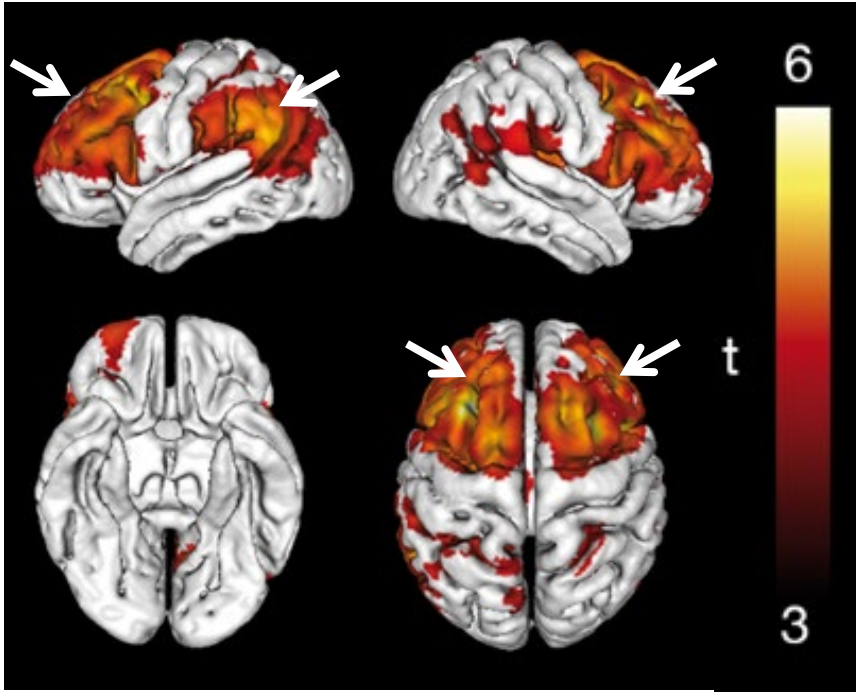


Lowe et al., Acta Npath Comm 2016; Schöll et al., Brain 2017

Cortical tau uptake inversely associates with age onset

- Young onset AD (<65) compared to late onset AD (≥65) yielded a distinct pattern of higher tau PET (flortaucipir) retention
- When compared against each other, the young onset AD group exhibited greater uptake than the late-onset group in prefrontal and premotor, as well as in inferior parietal cortex

Voxelwise comparison: <65 vs. ≥65



Schöll et al., Brain 2017

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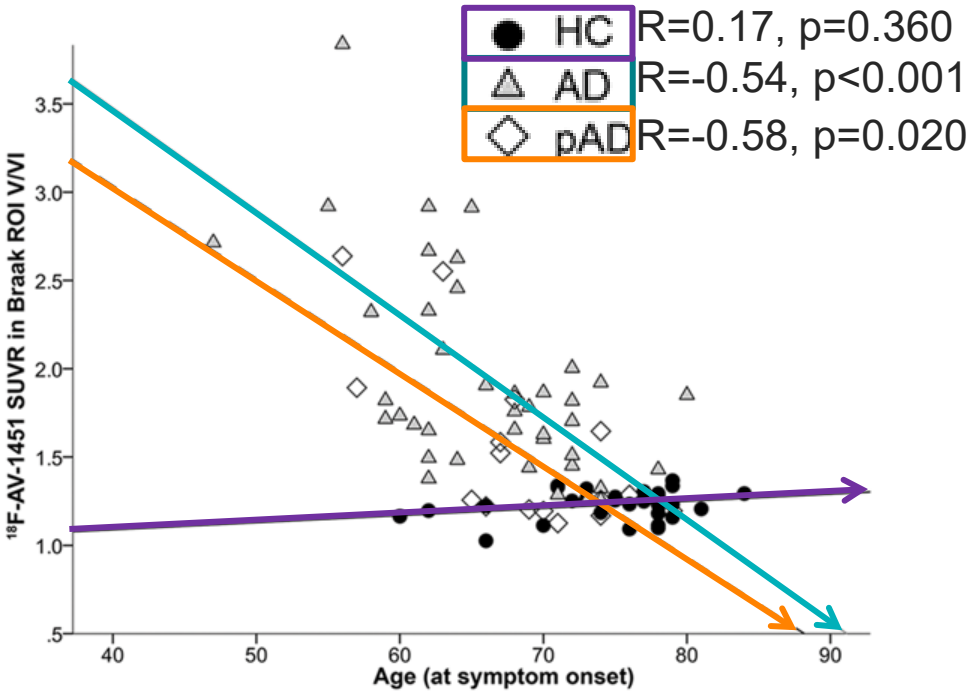

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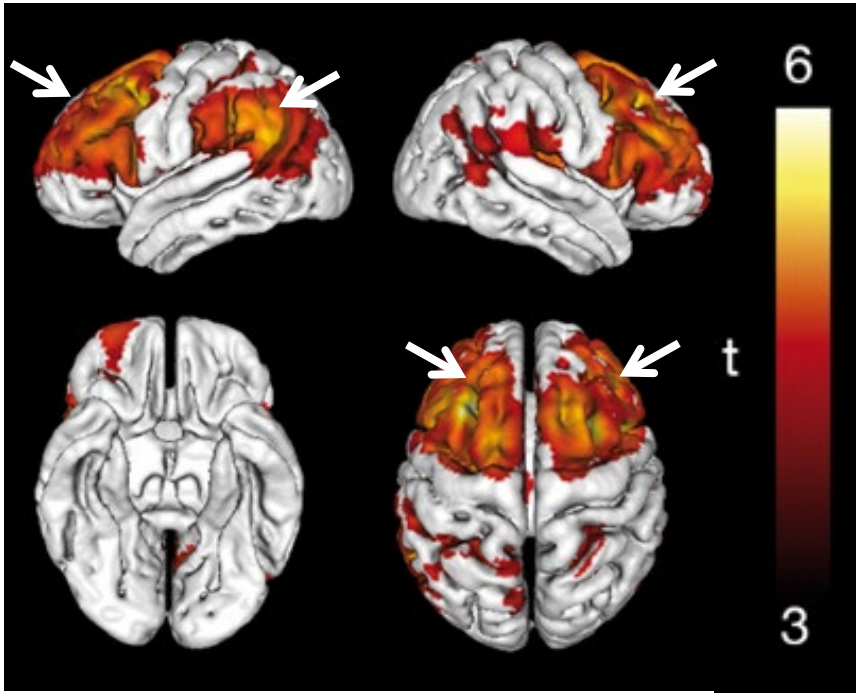
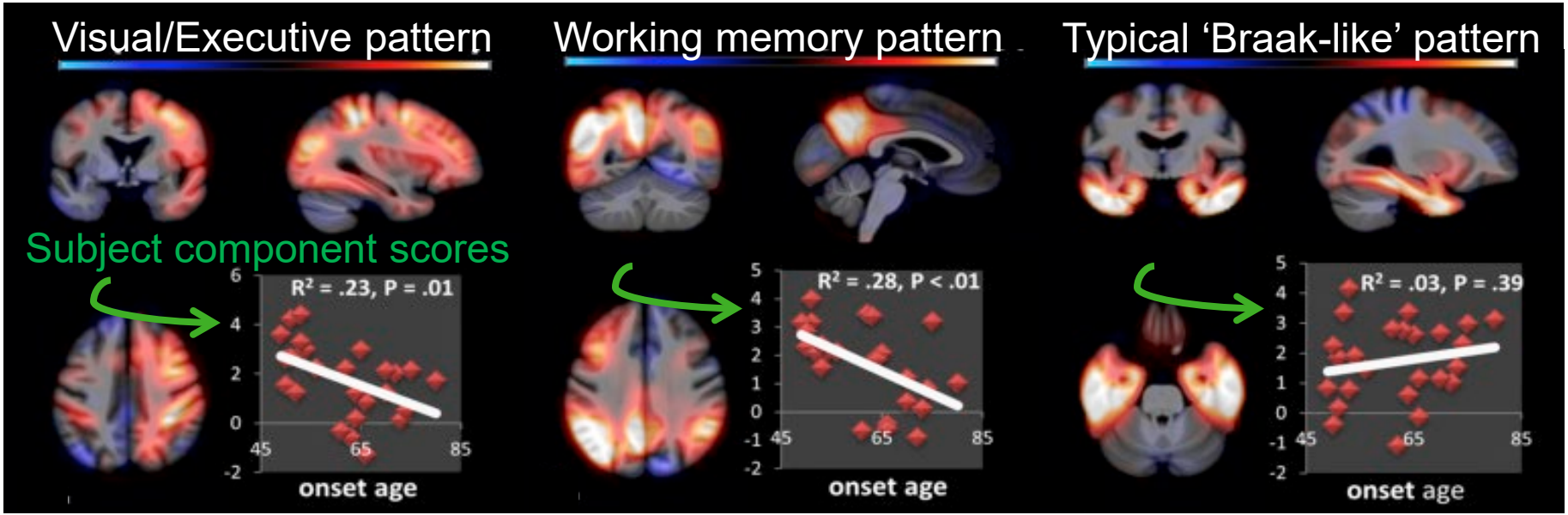


HC-Healthy control, pAD-prodromal AD

Schöll et al., Brain 2017

Spatial patterns of Tau PET



- Using a data-driven approach, spatial patterns of tau PET uptake were identified
- Atypical, non-Braak-like patterns associated with younger age onset

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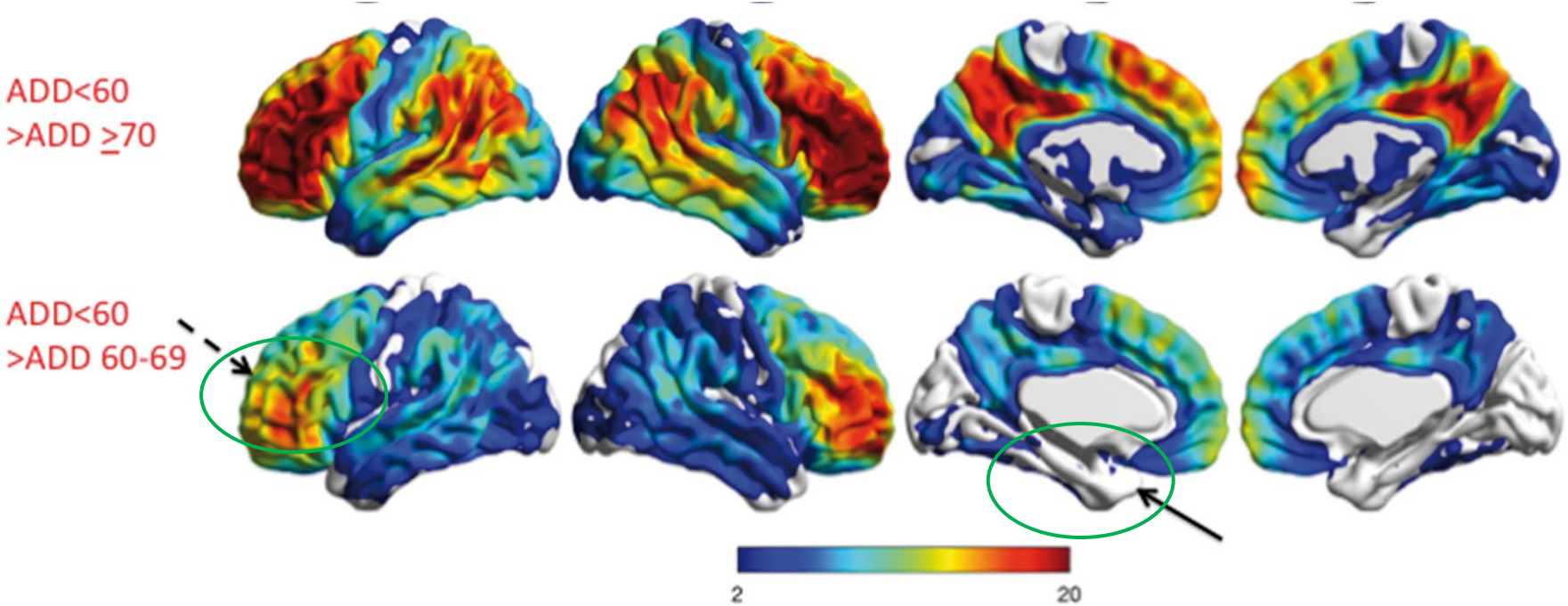
Jones et al., Cortex 2017

Does an age cutoff of 65 matter?



Lowe et al., Brain 2018

Does an age cutoff of 65 matter?

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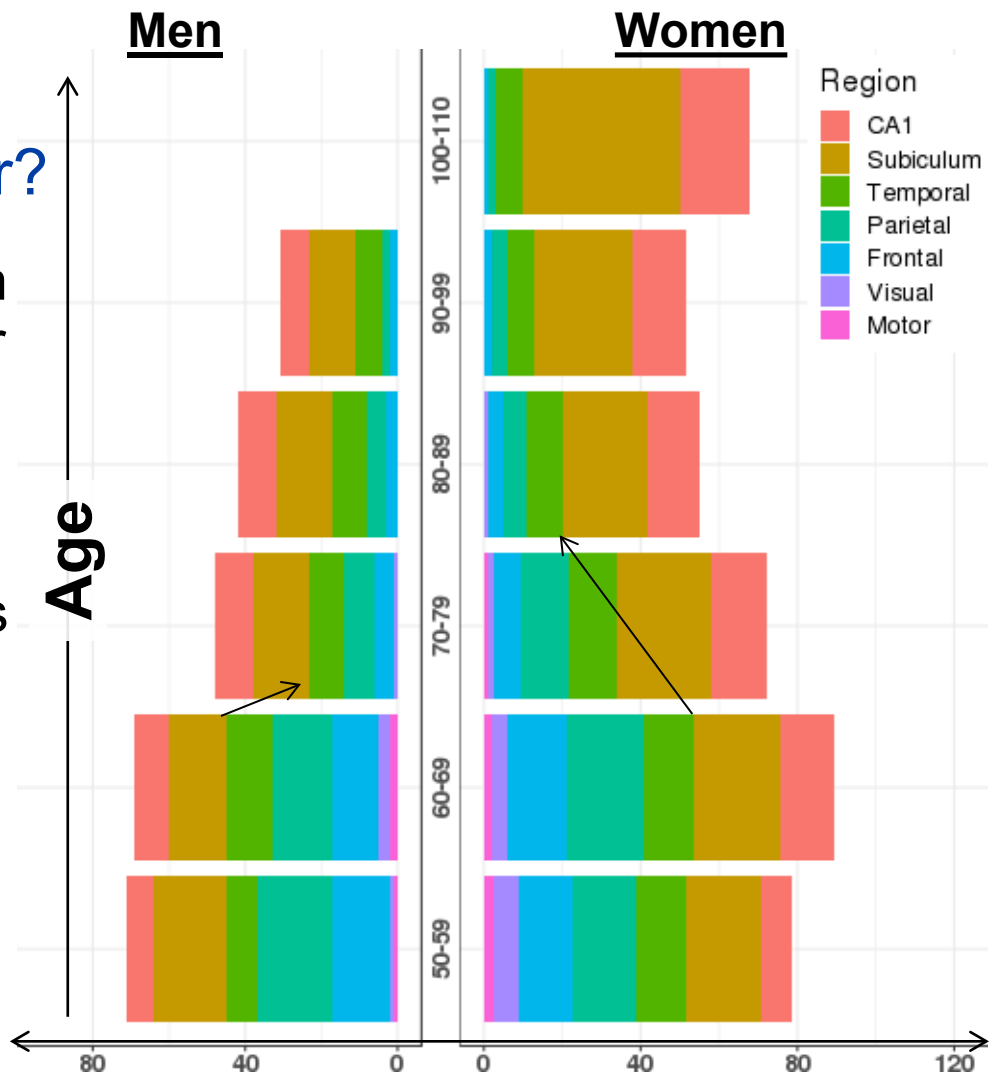
- In women, a two-fold decline was observed in their 80s onwards



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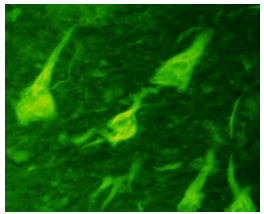
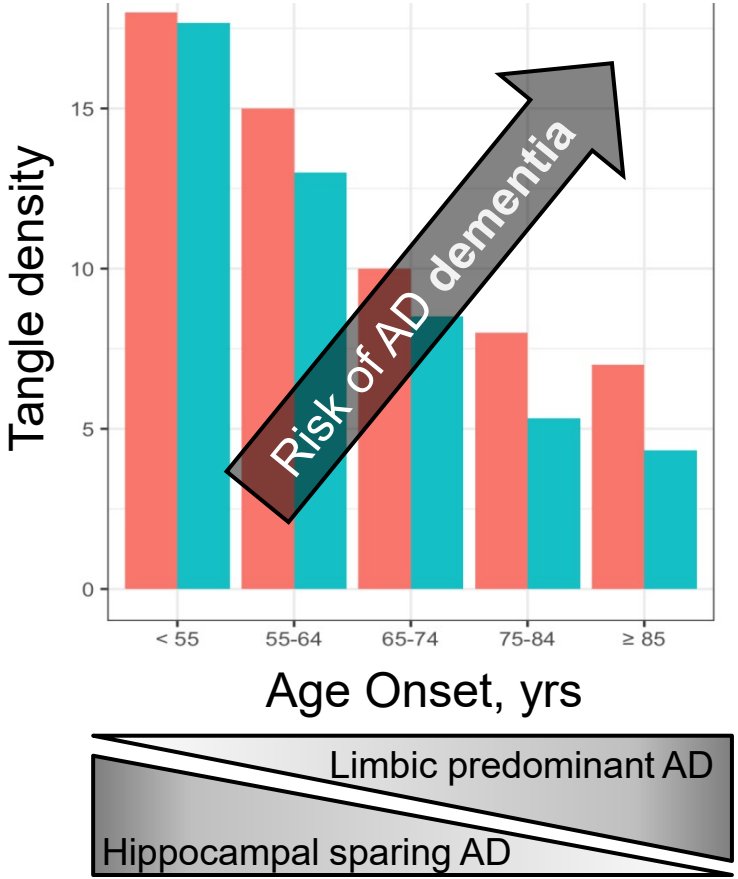
Summary





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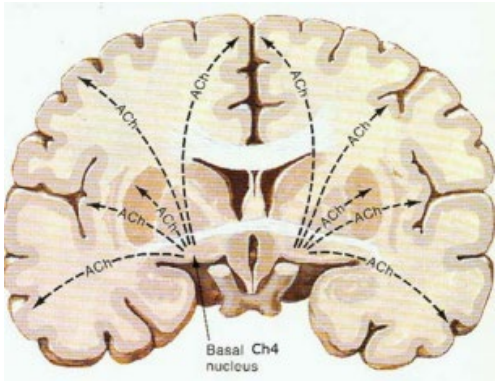

Liesinger *et* al., Acta Neuropathologica 2018

Hanna Al-Shaikh *et al*., JAMA Neurology 2019

Points of consideration

- Nomenclature: Young onset AD vs. Early onset AD
- Stratification vs. Adjustment
- Clinical trial inclusion/exclusion and interpretation of results
- Severity differences in neurofibrillary tangle accumulation
  - Late onset AD patients may die from other age-related conditions
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Grant support:

- Florida Department of Health, Ed and Ethel Moore on Alzheimer's disease (6AZ01,8AZ06)
- Clinicopathologic and Neuroimaging Differences in AD subtypes (R01-AG054449)
- Alzheimer's Association (AARG-17-533458)
- Mayo ADRC grant (P30-AG062677)

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- Sydney Labuzan
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- Kelly M. Ross
- Jessica Tranovich

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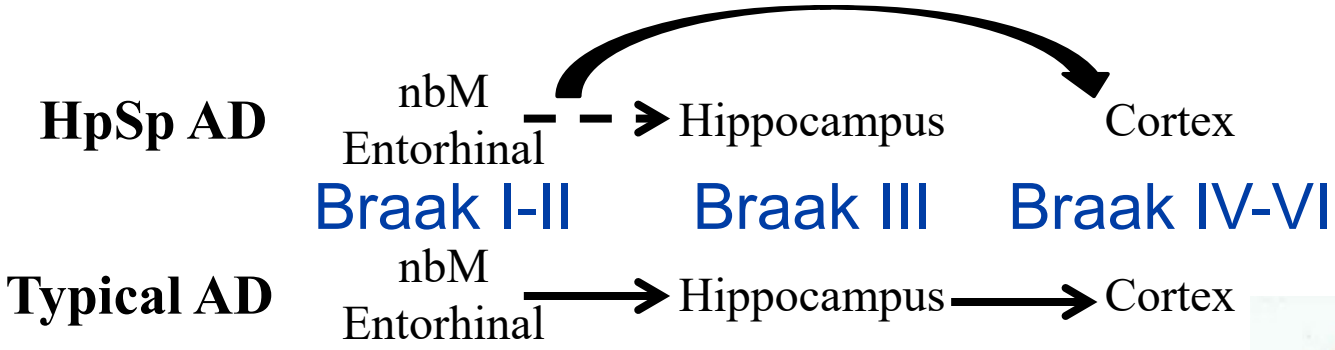
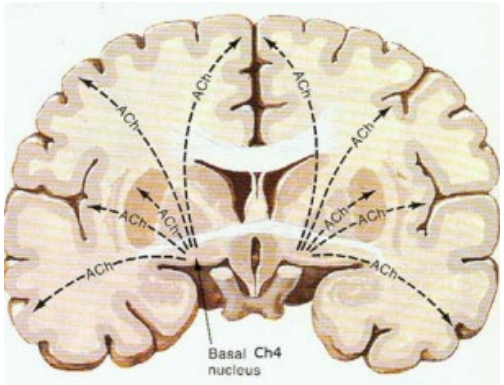
- Dennis W. Dickson
- Shunsuke Koga
- Michael DeTure
- Monica Castanedes-Casey
- Virginia R. Phillips
- Ariston Librero
- Rachel Harwood

Collaborators:

- Neill R. Graff-Radford
- Ranjan Duara
- Nilufer Ertekin-Taner
- Rickey E. Carter
- Owen A. Ross
- Val J. Lowe

Why is the cortex more vulnerable in young onset AD?
Theoretical wave of neurofibrillary tangle vulnerability





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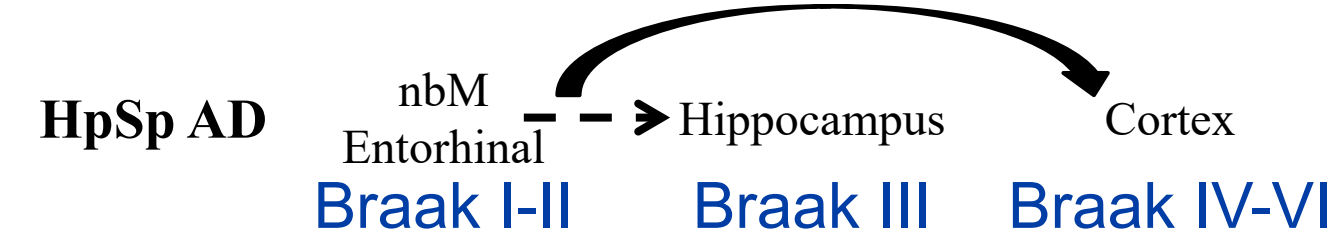
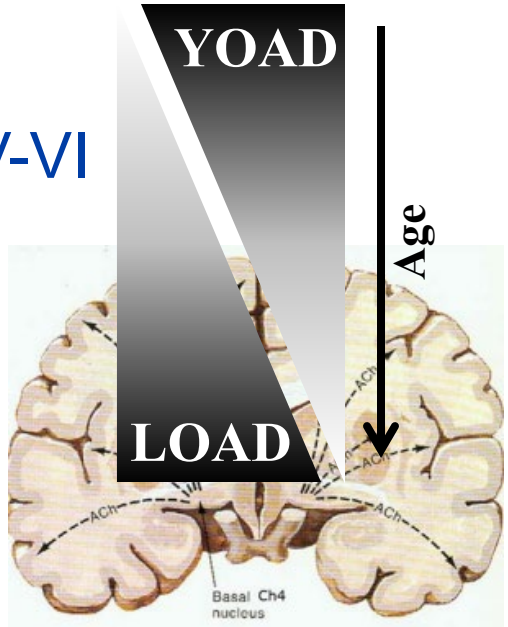
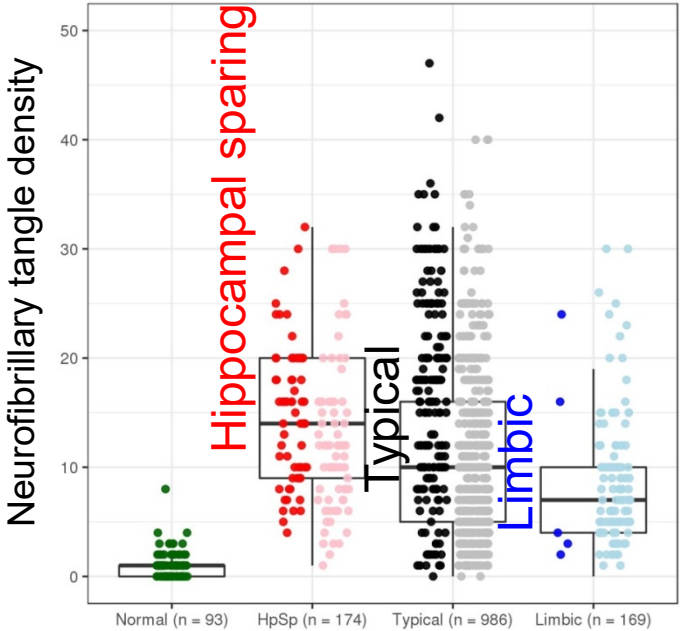




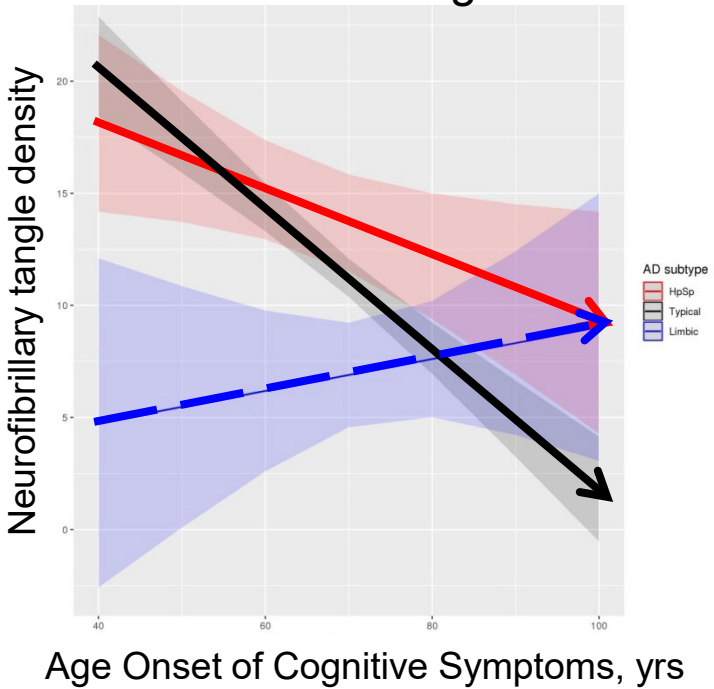
Hanna Al-Shaikh *et al*., JAMA Neurology 2019

Impact of age on neurofibrillary tangle accumulation in nbM

Lesion differences among subtypes

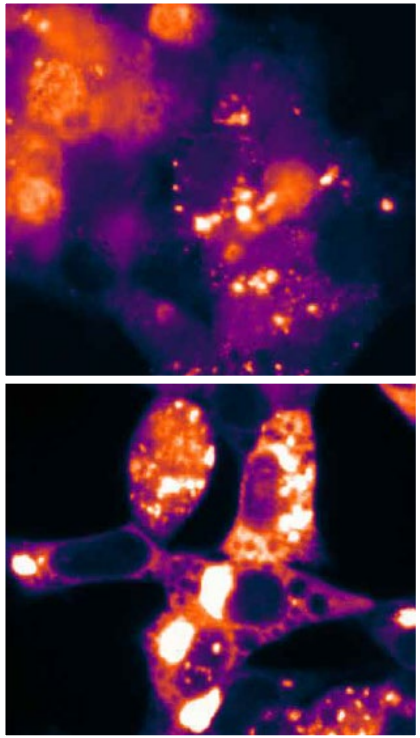


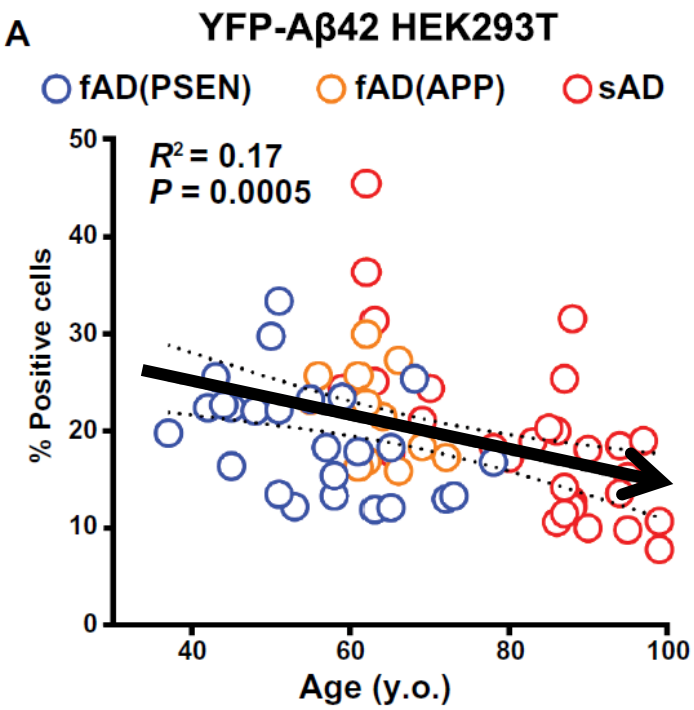
Interaction with Age Onset

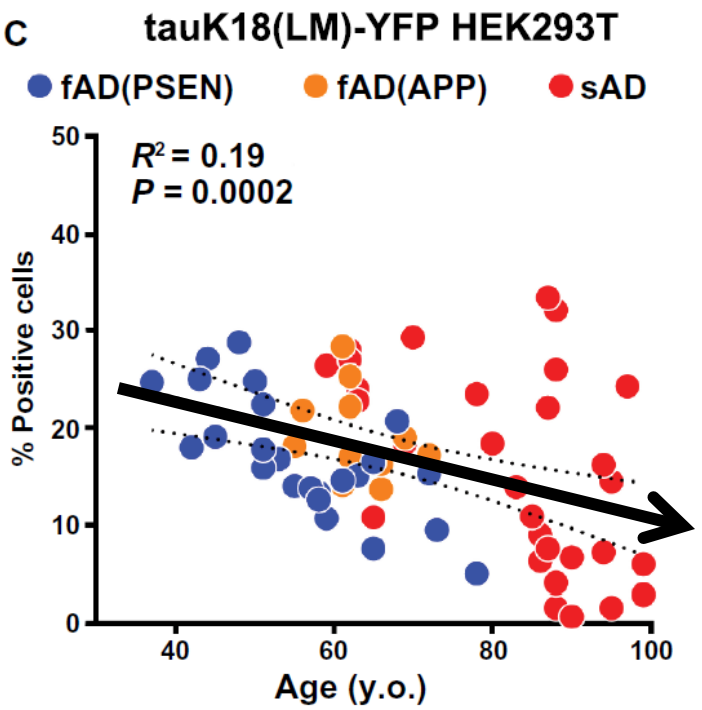


Hanna Al-Shaikh *et al.*, JAMA Neurology 2019

Self-propagating conformers of tau and Aβ decline with age

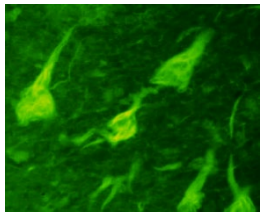


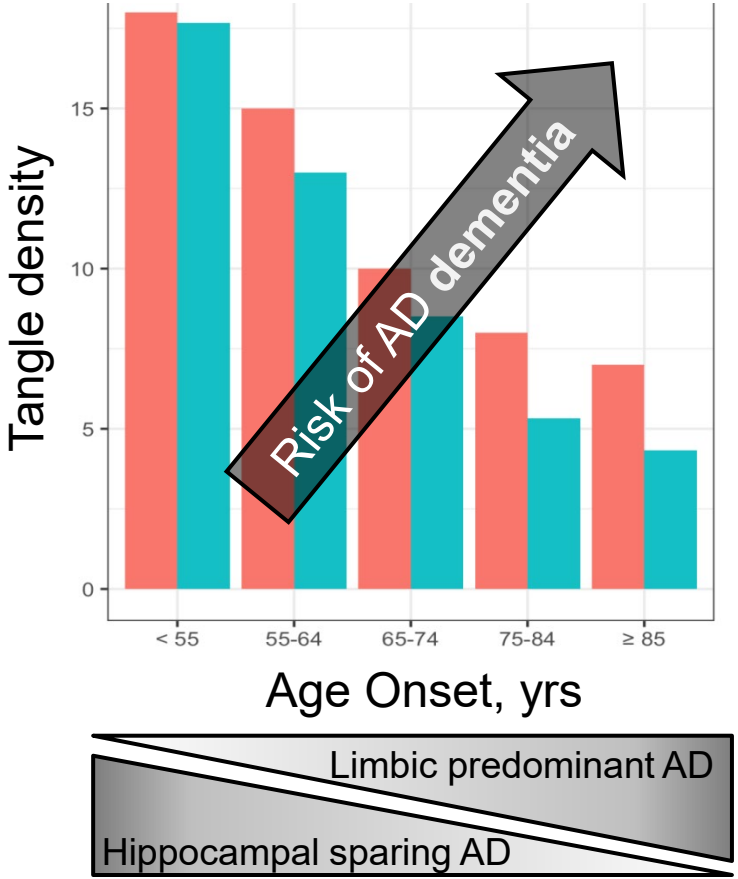




Aoyagi & Condello et al., Sci Transl Med 2019

Summary





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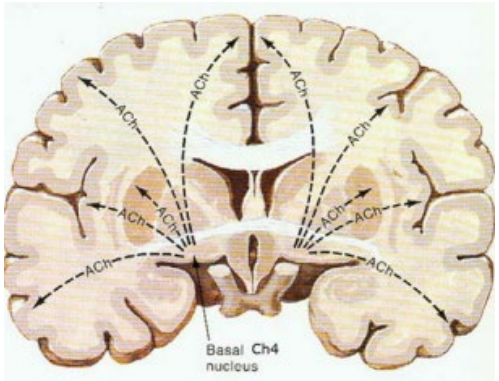

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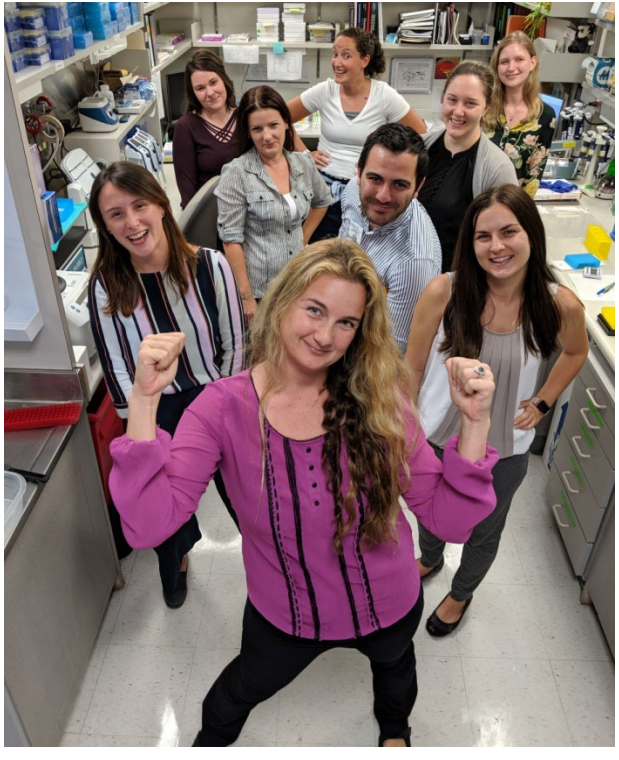
- Nilufer Ertekin-Taner
- Rickey E. Carter
- Owen A. Ross
- Val J. Lowe



MAYO CLINIC

Thank you for your time and attention!