Clinicopathologic Heterogeneity of Neurofibrillary Tangle Patterns

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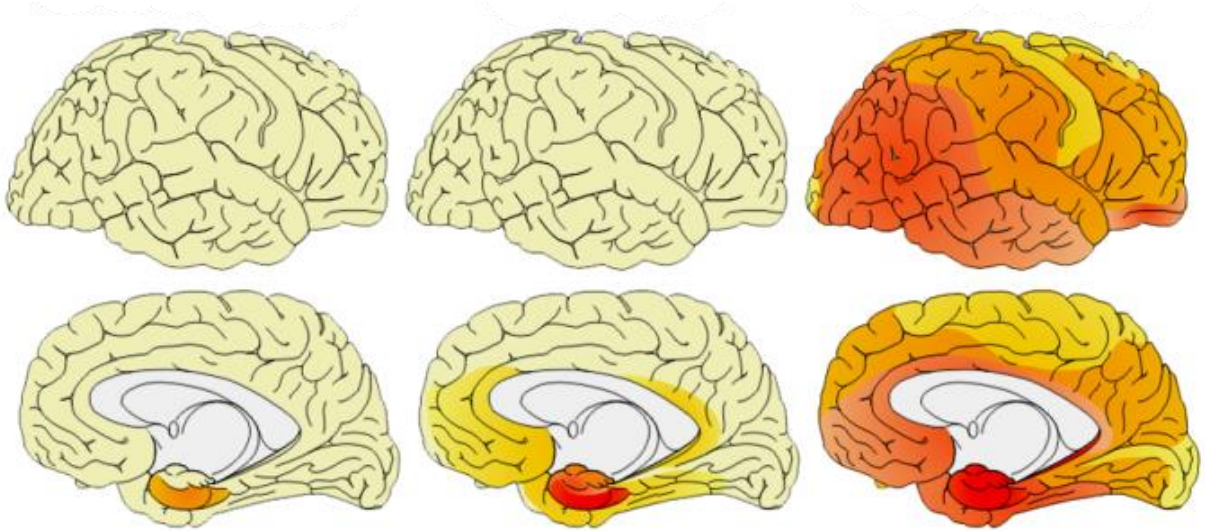
Neurofibrillary tangle (NFT) progression

Stage 1&2 **Stage 3&4** **Stage 5&6**

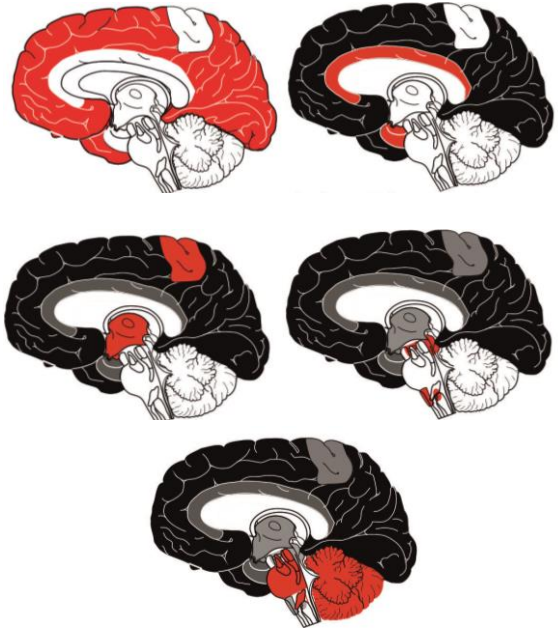


Entorhinal → **Limbic** → **Neocortex**

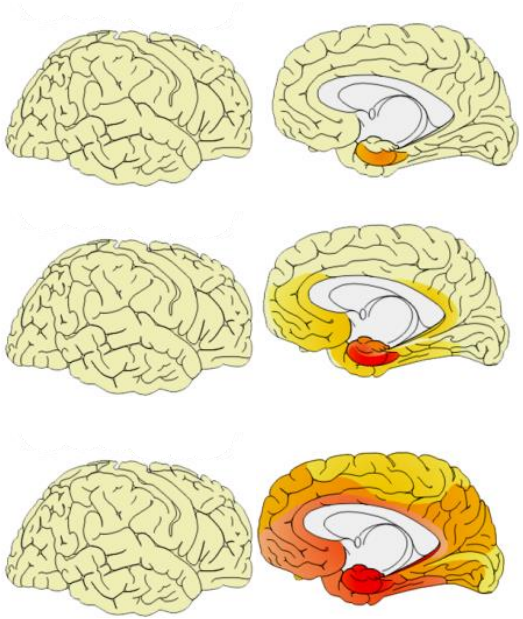
(Braak & Braak, *Acta Neuropathol 1991*)

NIA-AA neuropathologic consensus recommendations - ‘ABC’ criteria

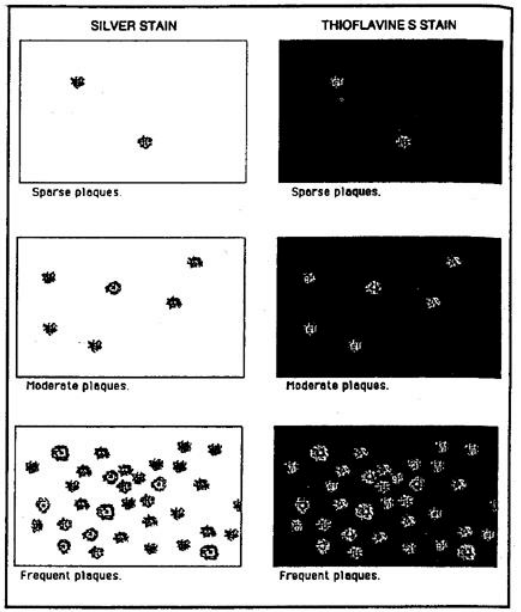
Thal amyloid phase
(A)



Braak tangle stage
(B)



CERAD neuritic plaques
(C)



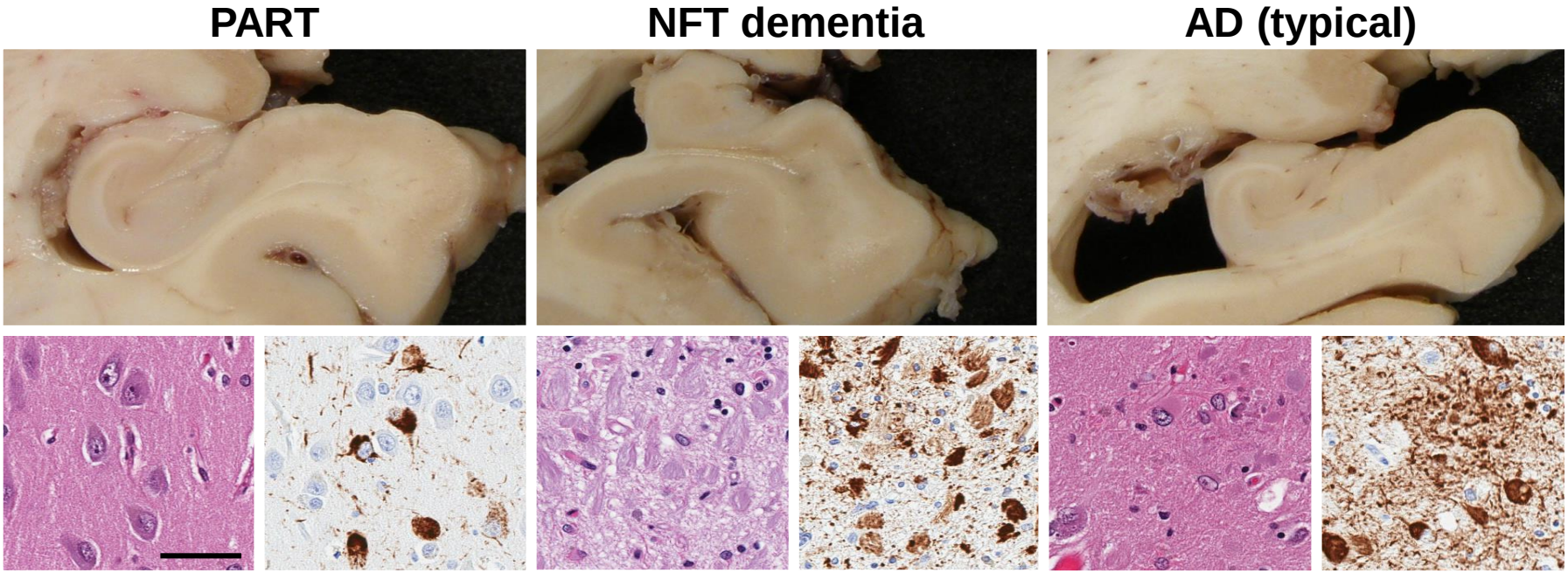
(McKhann GM *et al.*, Alz & Dem 2011; Hyman B *et al.*, Alz & Dem 2012)

“ABC” criteria and Primary Age-Related Tauopathy

AD neuropathologic change			Braak (B)	
Thal (A)	**CERAD (C)**	**0, I-II**	**III-IV**	**V-VI**
0	None	Not related	Not related	Not related
1-2	None-Sparse	Low	Low	Low
	Moderate-Frequent	Low	Intermediate	Intermediate
3	Any	Low	Intermediate	Intermediate
4-5	None-Sparse	Low	Intermediate	Intermediate
	Moderate-Frequent	Low	Intermediate	High

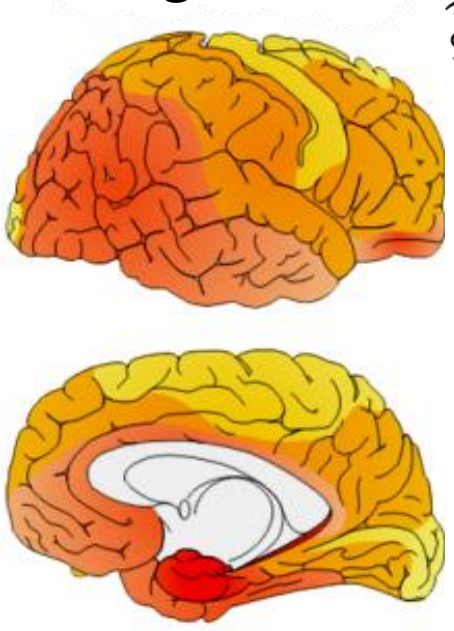
(McKhann GM *et al.*, Alz & Dem 2011; Hyman B *et al.*, Alz & Dem 2012)

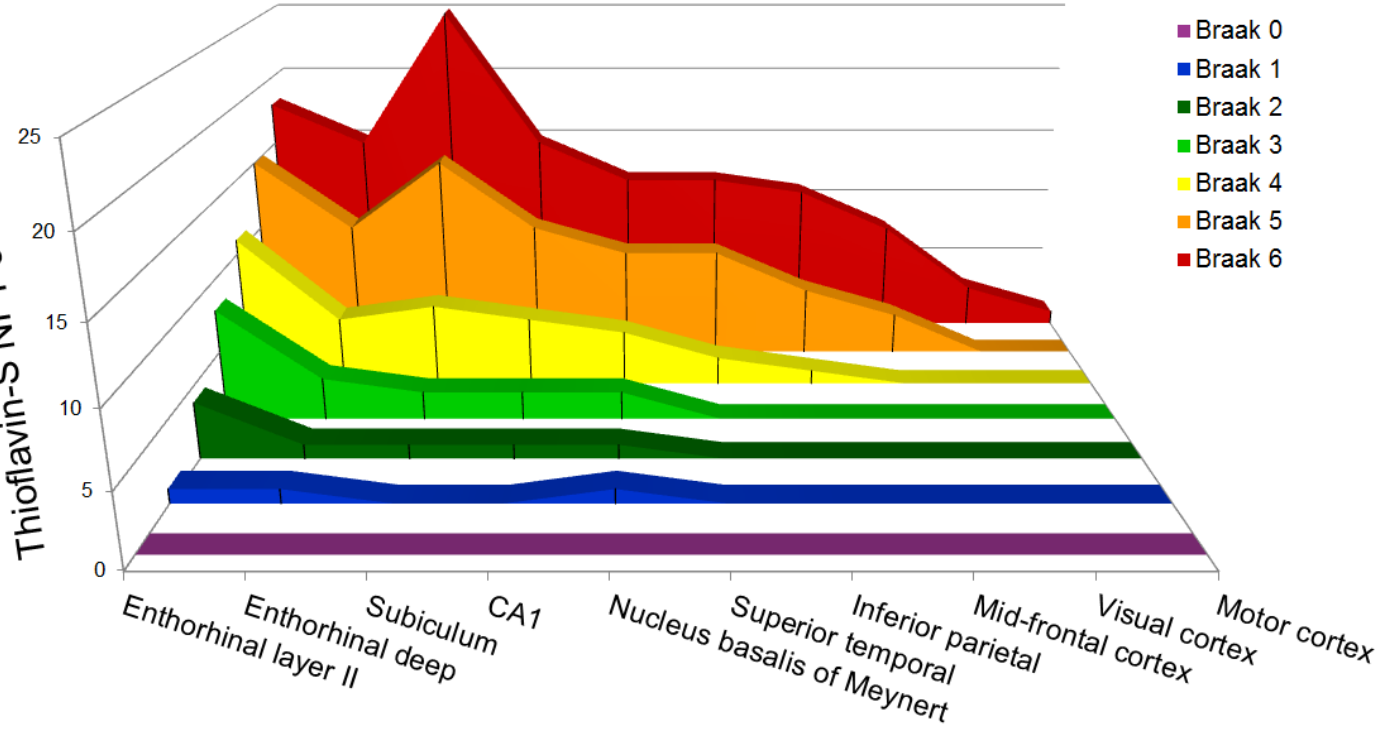
Is PART a part of Alzheimer's disease?



Advanced Braak staging

Stage V&VI





(Braak & Braak, *Acta Neuropath 199*1; Unpublished images; Unpublished data)

Atypical neuropathologic variants of AD

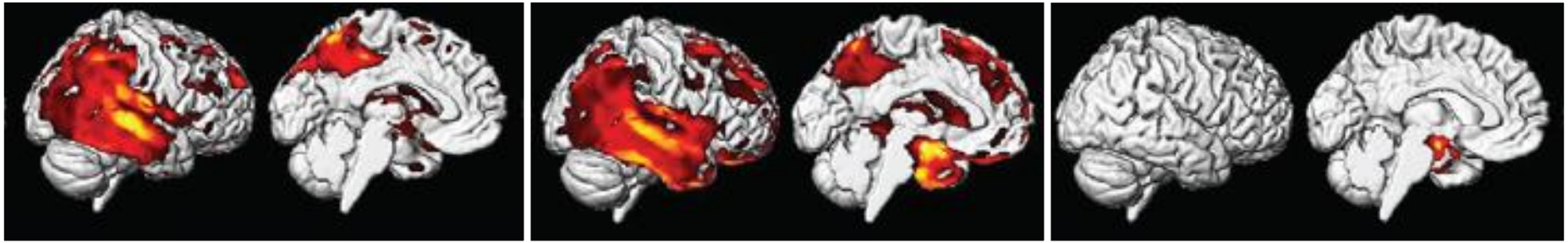
Hippocampal sparing AD

- **63% men**

Limbic predominant AD

- **69% women**

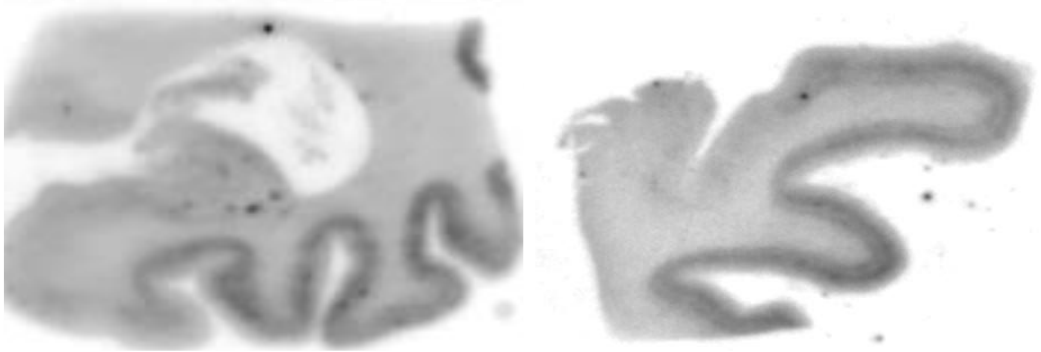
Hippocampal sparing AD | **Typical AD** | **Limbic predominant AD**



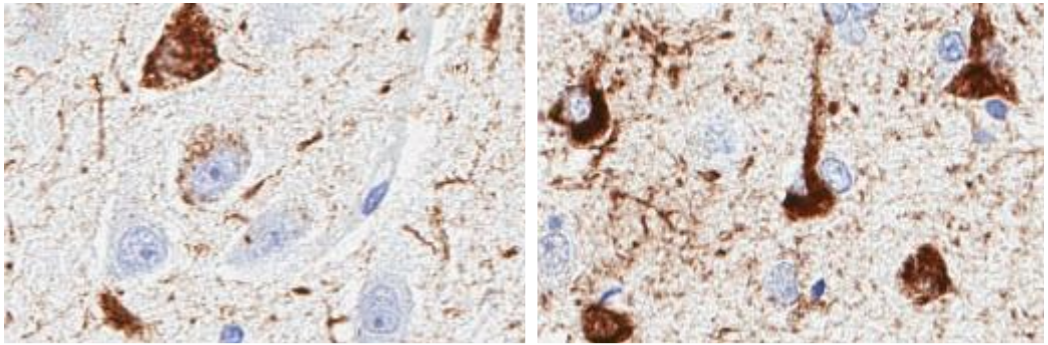
(Murray *et al*., Lancet Neurology 2011; Whitwell *et al*., Lancet Neurology 2012)

Hippocampal sparing AD presenting as semantic dementia

Autoradiography (AV1451)



Tau pathology (PHF1)



(Lowe *et al*., Acta Npath Comm 2016)

Disproportionate frequency of autopsy-confirmed AD cases across six decades

	Men	Women
Age at death		
50-59 years (%)	13/23 (57%)	10/23 (43%)
60-69 years (%)	99/154 (64%)	55/154 (36%)
70-79 years (%)	271/494 (55%)	223/494 (45%)
80-89 years (%)	312/743 (42%)	431/743 (58%)
90-99 years (%)	50/197 (25%)	147/197 (75%)
100+ years (%)	0/5 (0%)	5/5 (100%)
Significance tested using chi-square test (p<0.001)		

- Men were disproportionately affected in their 60s
- Women were disproportionately affected in their 90s, and were solely represented in the centenarians

(Murray *et al*., AAIC 2016)

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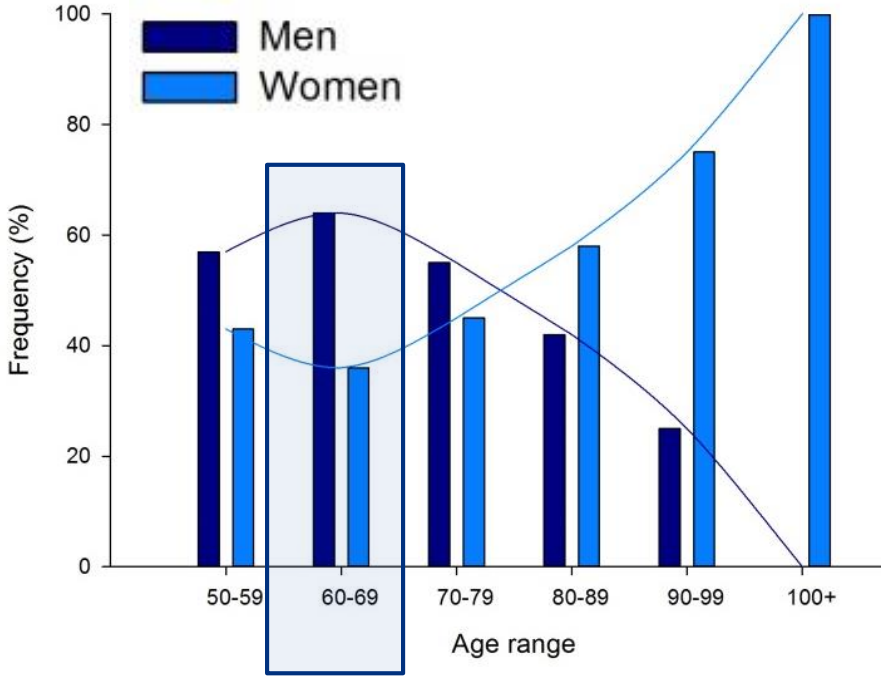

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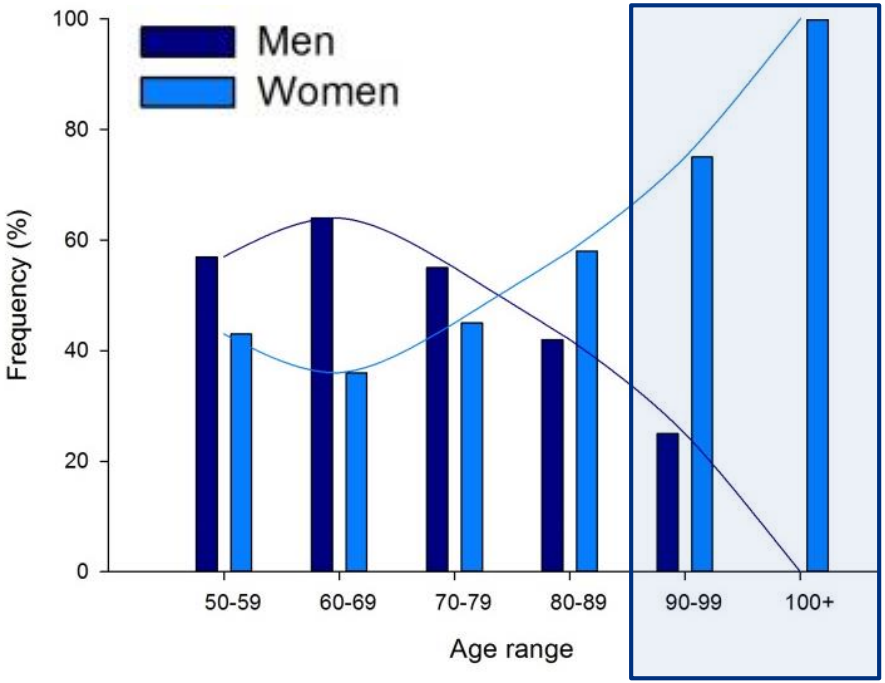

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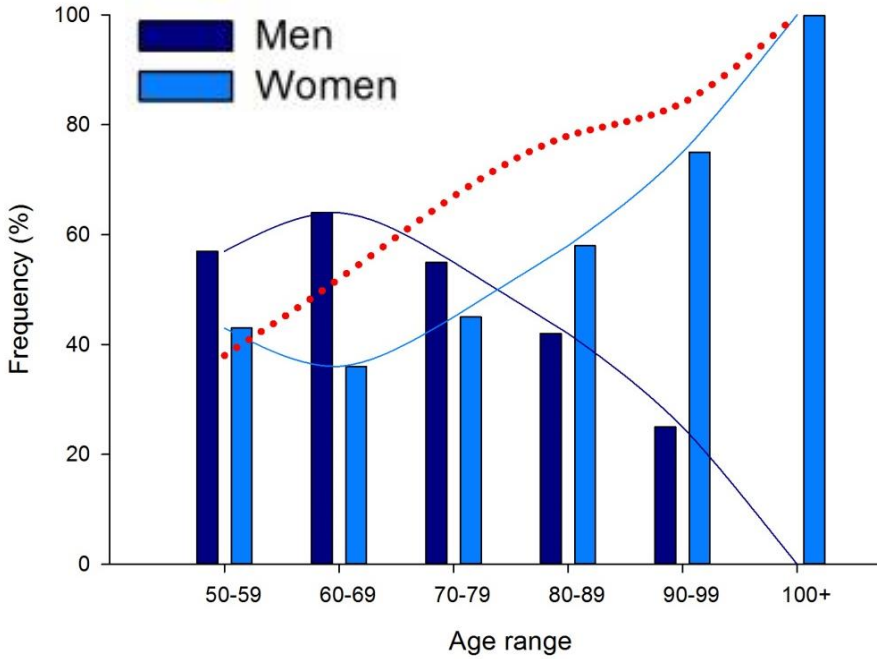
(Murray *et al*., AAIC 2016)

Disproportionate frequency of autopsy-confirmed AD cases across six decades

	AD clinically
Age at death	
50-59 years (%)	8/21 (38%)
60-69 years (%)	68/136 (52%)
70-79 years (%)	272/406 (67%)
80-89 years (%)	485/624 (78%)
90-99 years (%)	149/177 (84%)
100+ years (%)	5/5 (100%)
Significance tested using chi-square test (p<0.001)	



- In an autopsy-confirmed AD cohort, diagnostic accuracy of clinically diagnosed AD dementia increased with age

(Murray *et al*., AAIC 2016)

Summary and Conclusions

- Medial-temporal-associated, insidious tau pathology (*i.e.*, PART) may follow an aging trajectory distinct from AD
- The stereotypic progression of tau pathology does not necessarily imply a uniform severity of neuroanatomical involvement
- Atypical AD variants underscore the phenotypic heterogeneity that may impact biomarker studies
- Atypical AD variants were identified to not only differ based on neuropathologic pattern, but demonstrated demographic and clinical differences

Summary and Conclusions

- Men were disproportionately affected in their 60s, while women were overwhelmingly affected in their 90s and 100s
- Our study suggests that the rate of non-AD diagnosis in autopsy-confirmed AD cases was more common in men, especially in those who died before the age of 70s
- We investigated an autopsy-confirmed AD series regardless of clinical diagnosis, it should be noted that autopsy series can be biased by the individuals who graciously donate their tissue or that of their loved one

Acknowledgments

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