Neurodegenerative lesions in young and very old people

Juan C. Troncoso, M.D
Johns Hopkins University School of Medicine
Department of Pathology
troncoso@jhmi.edu

World Congress of Neurology
Santiago , Chile
1 November 2015

Juan C. Troncoso, M.D
Johns Hopkins University School of Medicine

Support:

- Johns Hopkins University Alzheimer's Disease research Center (NIH AG
- BrightFocus Foundation

Other Disclosures: None

LEARNING OBJECTIVES

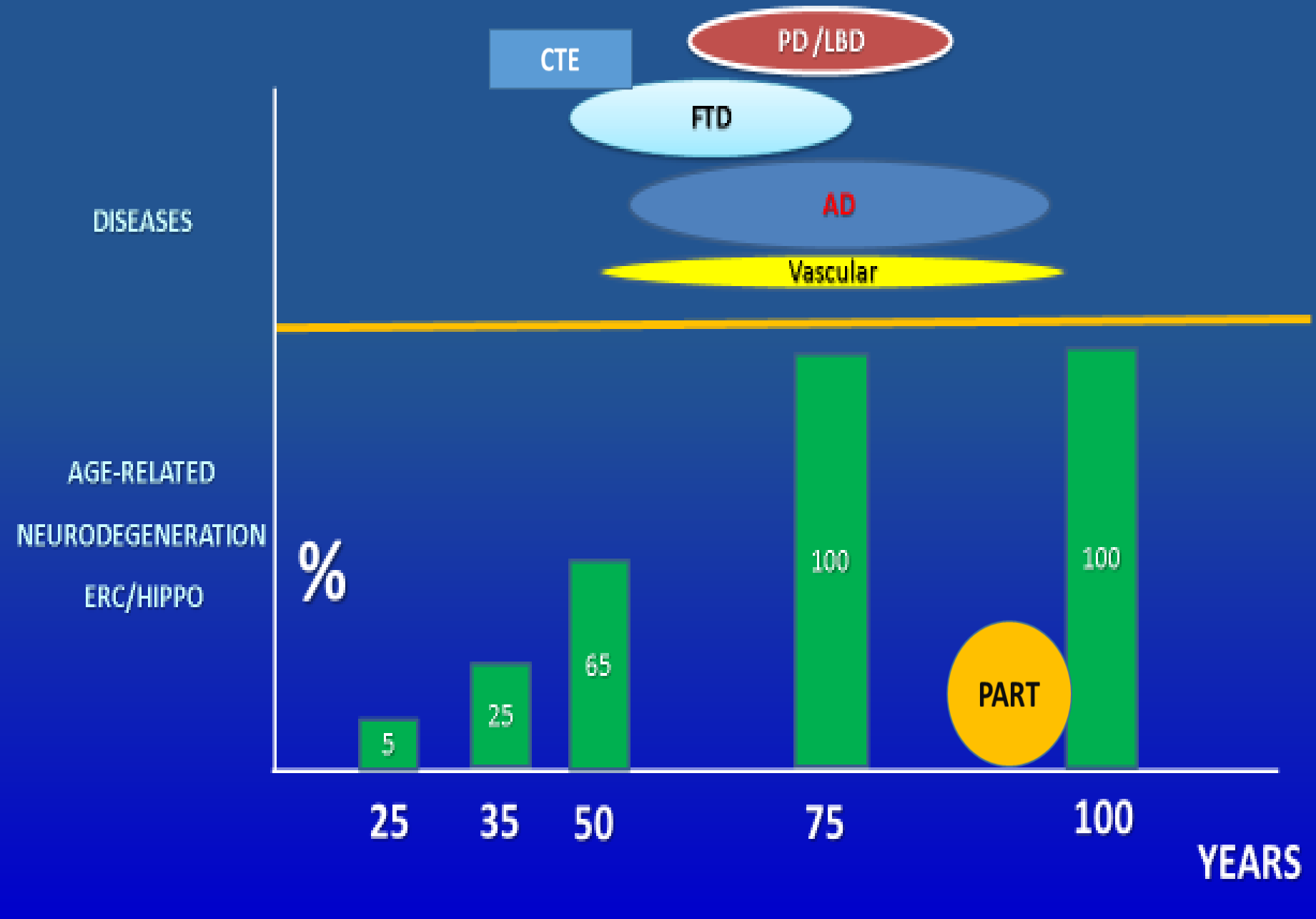
- Degenerative lesions of the brain start early in life (>30 years)
- Tau lesions are frequent in the locus coeruleus, entorhinal cortex, and hippocampus in young subjects
- Aβ amyloid lesions appear as early as 40 years of age
- Onset of Aβ lesions is related to ApoE genotype
- Tau lesions are independent of ApoE genotype
- Primary age-related tauopathy (PART) is common in older subjects (>85 years) who do not have Alzheimer's disease

KEY MESSAGE

- FUNCTIONAL DECLINE AND NEURODEGENERATION OF THE BRAIN STARTS EARLY IN LIFE

- EVEN IF YOU ESCAPE:
  ALZHEIMER'S, PARKINSON'S, LEWY BODY DISEASE,
  AND FRONTO-TEMPORAL DEMENTIA,
  THE BRAIN WILL STILL BE ABNORMAL IN OLD AGE.

AGING AND AGE-RELATED DISEASES



Source of Autopsy Brains

ADRC
n = 349

BLSA
(> 85 years)
n= 182

PDRC
n = 274

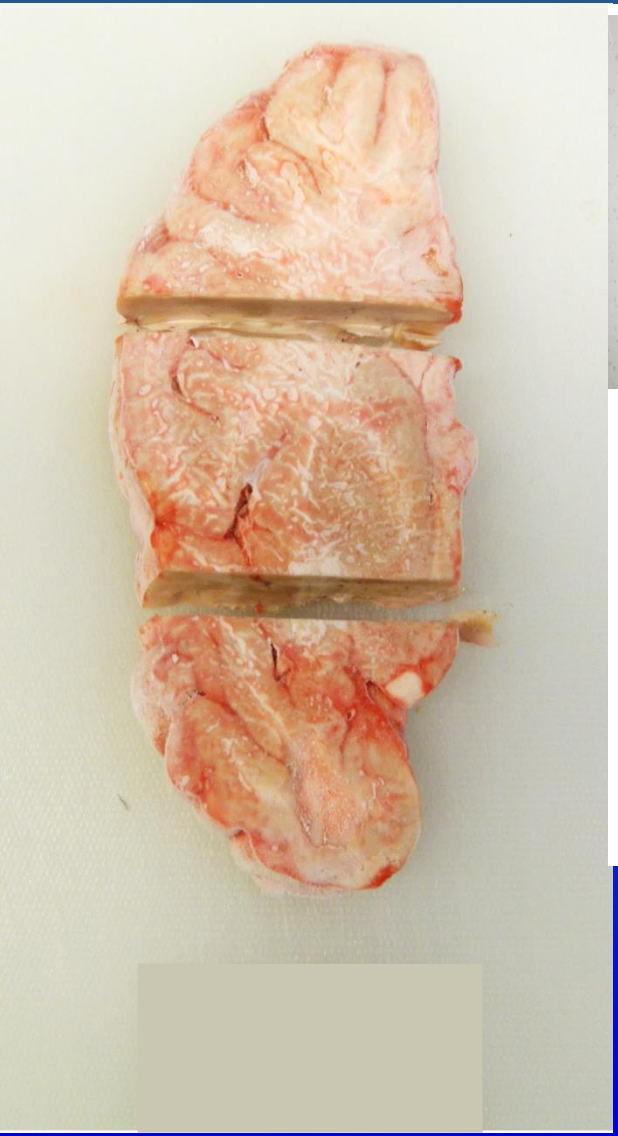
OCME & LIEBER
INSTITUTE
(20-50 YEARS)
n = 295

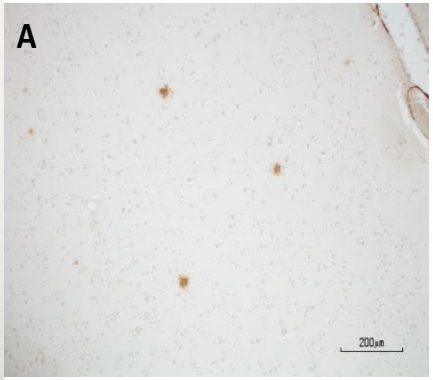
Methods:
Tau & Abeta
immunostains

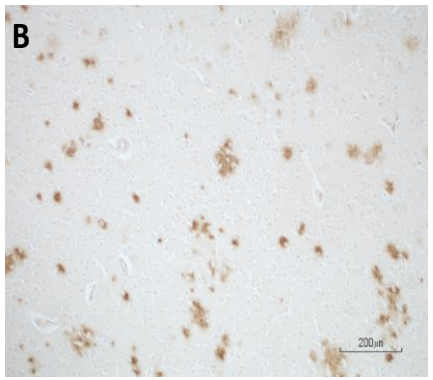
Subjects 20 to 50 years of age

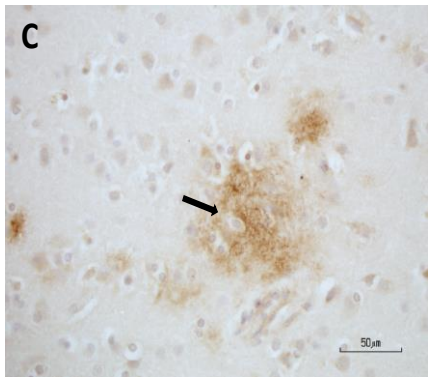
Ages (years)	Total	Males	Females	White	AA	Other
20-29	33	25	8	22	8	3
30-39	59	36	23	41	14	3
40-50	96	61	35	67	28	1
	188	122	66	130	50	7

Aβ Study (large tissue blocks)

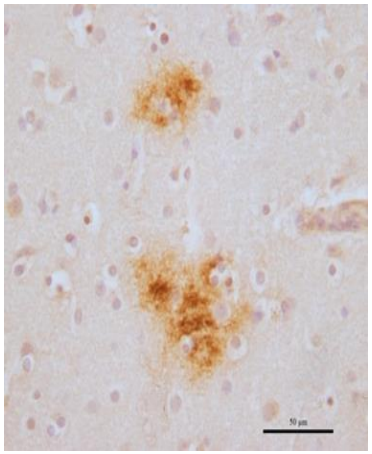








- Diffuse Aβ deposits in cerebral cortex
- Scant vascular Aβ
- No neuritic plaques
- No astrocytic proliferation
- No microglial reaction



Aβ deposits (6E10 ICC)

Study #	Age & Sex	Race	Aβ								
			Hippo	Trans-ERC	ERC	ITG	Fr	SMTG	IP	OCC	Vas
65	49 M	W	+	+	+	+++	+++	+++	+++	+++	+
7	46 F	W	+	+	+	++	+++	+++	+++	+++	--
2	47 F	AA	--	+	+	+	+	+	+	+	++
78	47 M	W	--	--	--	+	+	+	+	+	--
165	40 M	W	--	--	--	++	+	+	+	+	--
217	48 F	W	--	+	+	+++	++	++	++	+/-	+
252	44 M	AA	+	+	+	+++	++	+++	+++	+	--
136	44 M	AA	--	+++	++	+++	++	+++	++	++	--
280	43 M	W	+	n/a	++	n/a	++	+++	+++	+	+
206	45 F	W	--	+++	+++	n/a	++	+	+	+	+
215	45 F	W	--	++	--	++	+	+++	+	++	--
272	47 M	W	--	--	--	+	+	--	+	+	--
73	43 M	W	n/a	n/a	n/a	n/a	++	+++	++	--	--

ApoE Alleles (40-50 year old)

Race / ApoE Allele	E2	E3	E4
White n = 67	13 (6.8%)	93 (48.4%)	28 (14.6%)
AA n = 28	7 (3.6%)	38 (19.8%)	11 (5.7%)
Other n = 1	0	2 (1%)	0
All n = 96	20 (10.4%)	133 (69.3%)	39 (20.3%)

Aβ deposition and ApoE genotypes

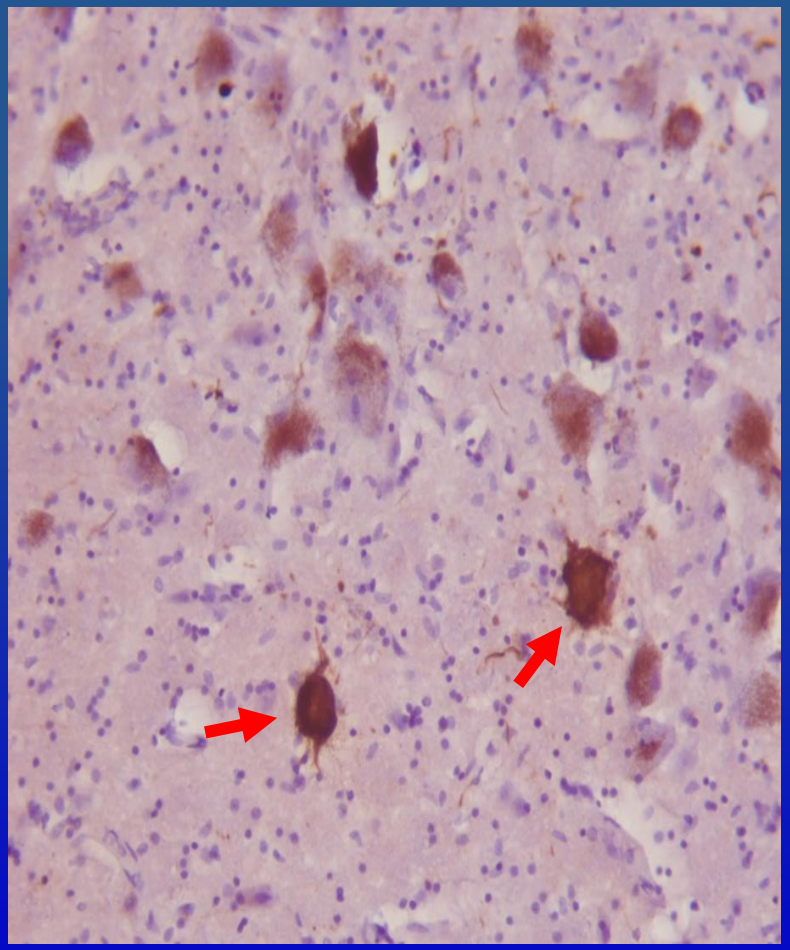
Study #	Age & Sex	Race	Aβ									ApoE
			Hippo	Trans-ERC	ERC	ITG	Fr	SMTG	IP	OCC	Vas	
65	49 M	W	+	+	+	+++	+++	+++	+++	+++	+	E4/E4
7	46 F	W	+	+	+	++	+++	+++	+++	+++	--	**E4/E3**
2	47 F	AA	--	+	+	+	+	+	+	+	++	**E4/E4**
78	47 M	W	--	--	--	+	+	+	+	+	--	**E4/E3**
165	40 M	W	--	--	--	++	+	+	+	+	--	**E4/E3**
217	48 F	W	--	+	+	+++	++	++	++	+/-	+	**E4/E3**
252	44 M	AA	+	+	+	+++	++	+++	+++	+	--	**E4/E3**
136	44 M	AA	--	+++	++	+++	++	+++	++	++	--	**E3/E4**
280	43 M	W	+	n/a	++	n/a	++	+++	+++	+	+	**E4/E4**
206	45 F	W	--	+++	+++	n/a	++	+	+	+	+	**E3/E4**
215	45 F	W	--	++	--	++	+	+++	+	++	--	**E3/E4**
272	47 M	W	--	--	--	+	+	--	+	+	--	**E3/E4**
73	43 M	W	n/a	n/a	n/a	n/a	++	+++	++	--	--	**E3/E4**

ApoE Genotypes (40-50 year old)

ApoE Genotype	n	Aβ (+) n, %		Aβ (-) n, %	
2/2	2	0		2	
2/3	13	0		13	
2/4	3	0		3	
3/3	46	0		46	
3/4	28	10	36%	18	64%
4/4	4	4	100%	0	0 %
Total	96	13	13.5%	83	86.4%

Tau Lesions in Locus Coeruleus n = 55

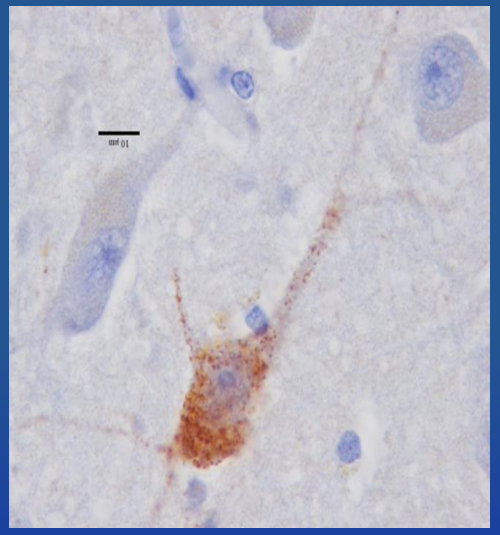
Age	#	Tau (+)
20-29	9	55.5 %
30-39	17	58.8 %
40-50	29	100 %

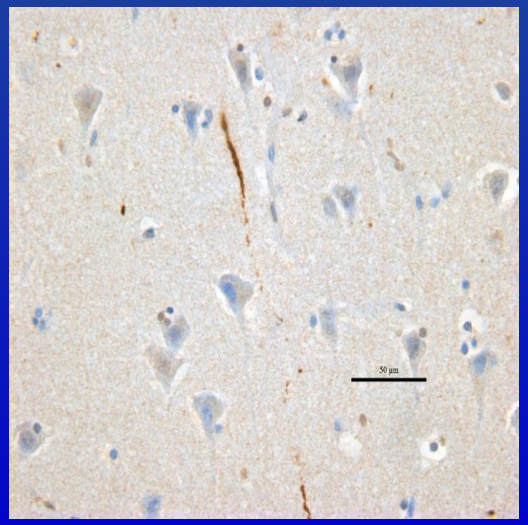


Tau Lesions in Hippocampus & ERC

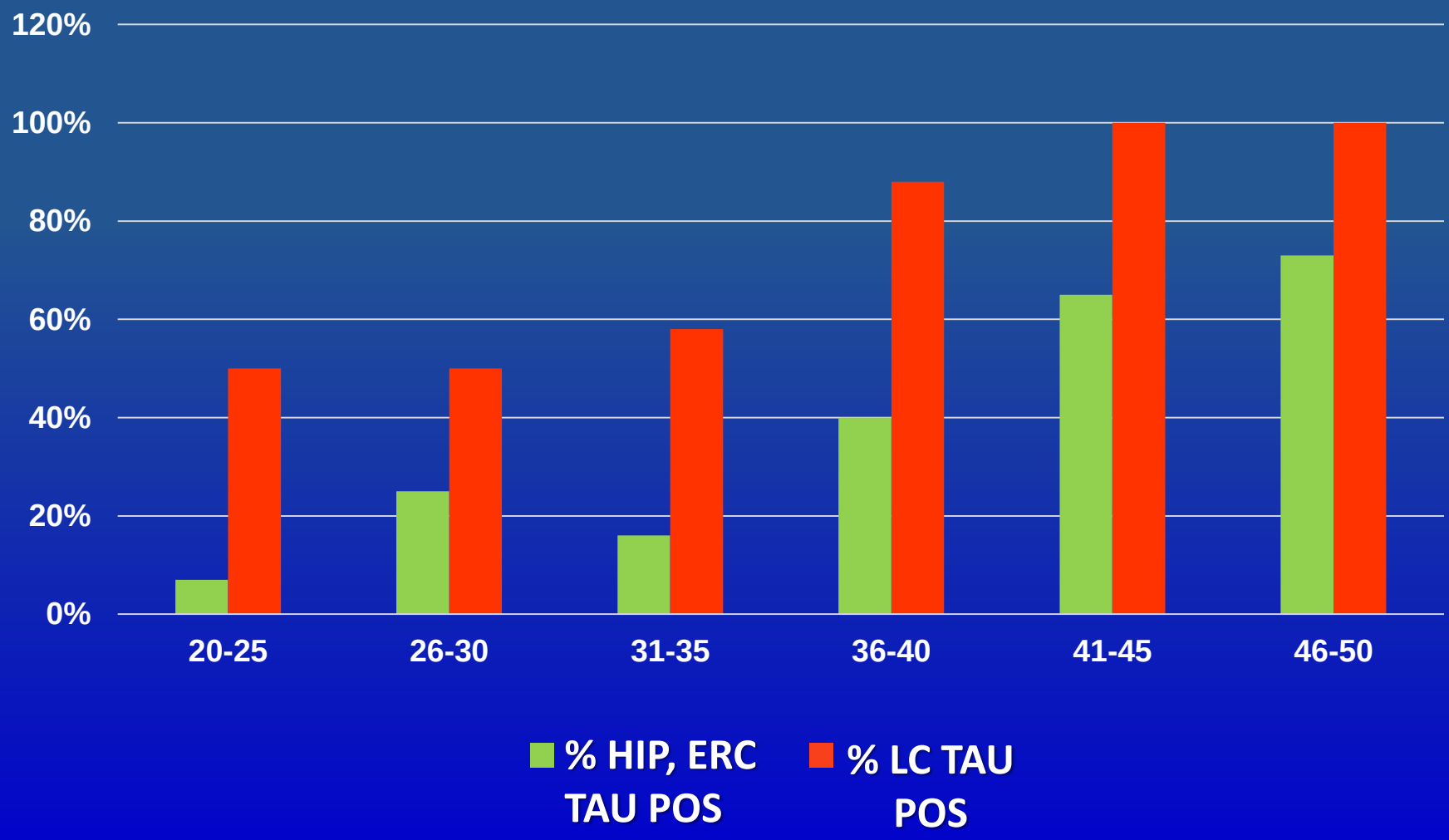
n = 135

Age	n	Tau (+)	%
20 - 29	23	2	8.7 %
30 - 39	41	10	24.3 %
40 - 50	71	40	56.3 %





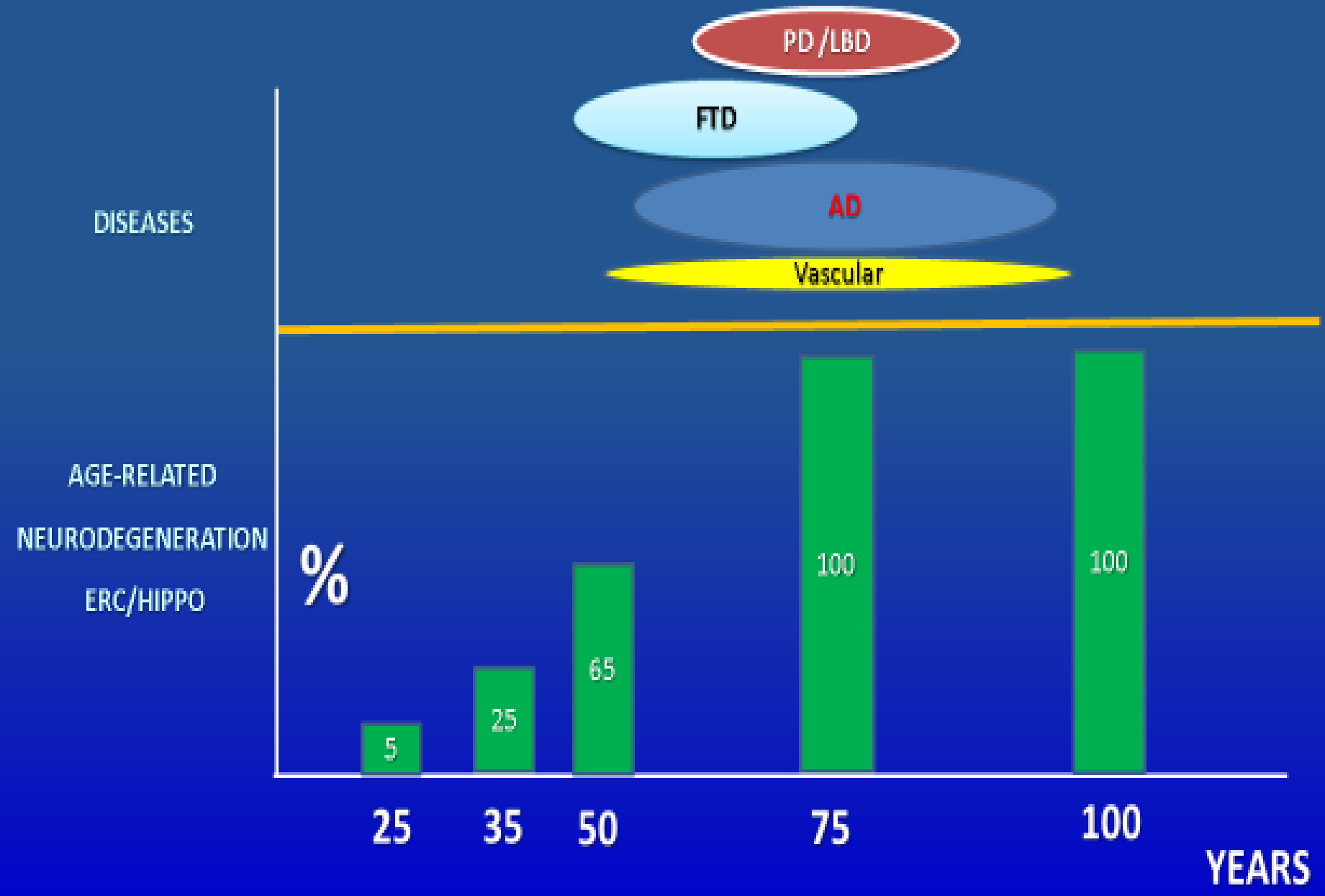
TAU LESIONS IN HIPPO/ERC & LC



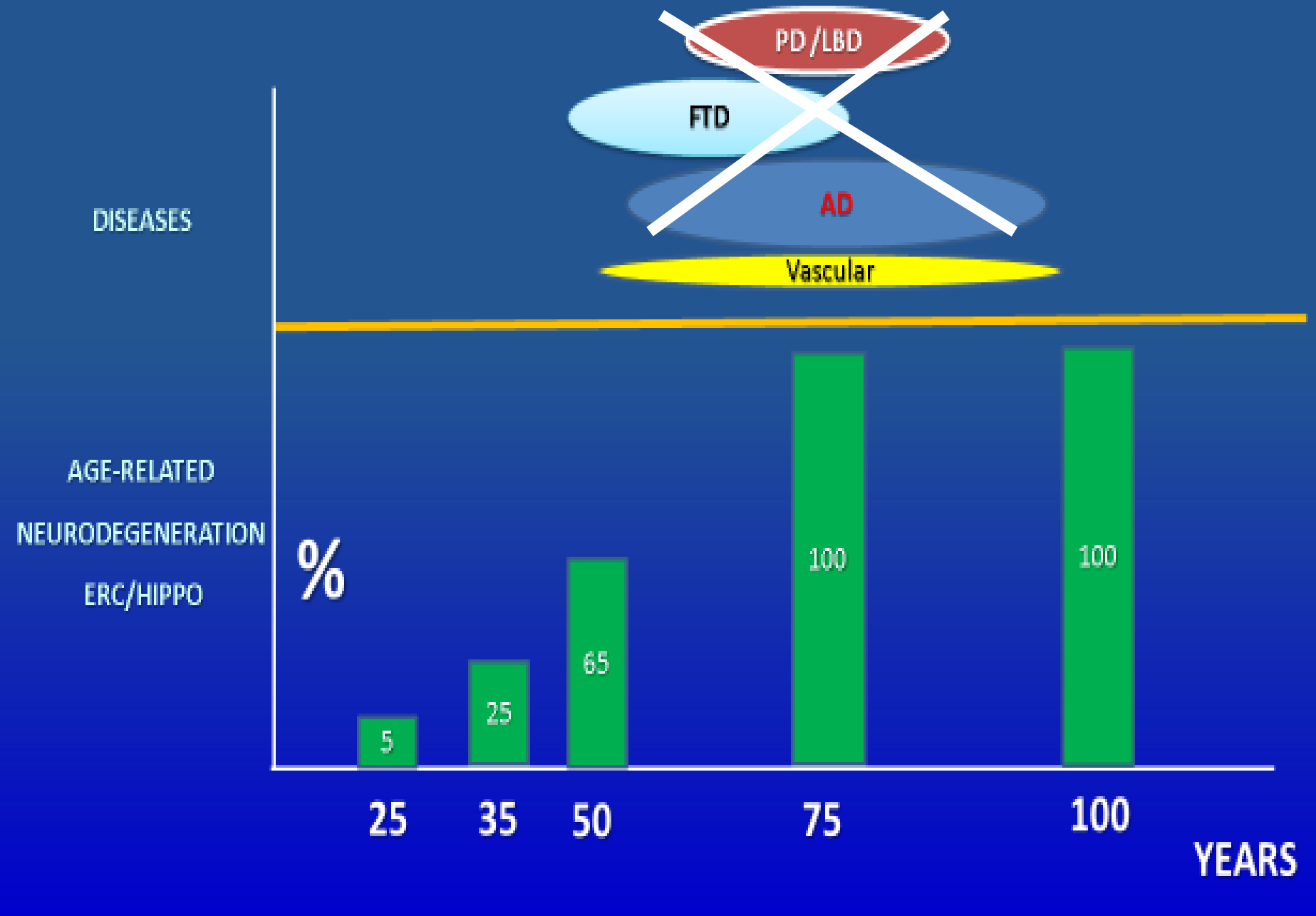
Conclusions I

- Aβ lesions, a hallmark of Alzheimer's, begin in the 5th decade of life, many years before onset of cognitive decline
- Aβ deposition in neocortex precedes Tau lesions
- Tau lesions of brain stem and ERC/hippocampus begin very early in life and appear independent of disease
- Tau lesions appear independent of ApoE genotype
- Tau lesions do not necessarily overlap with Aβ lesions
- Disease-independent tau lesions may be proxies for neuronal changes underlying age-associated cognitive decline

AGING AND AGE-RELATED DISEASES

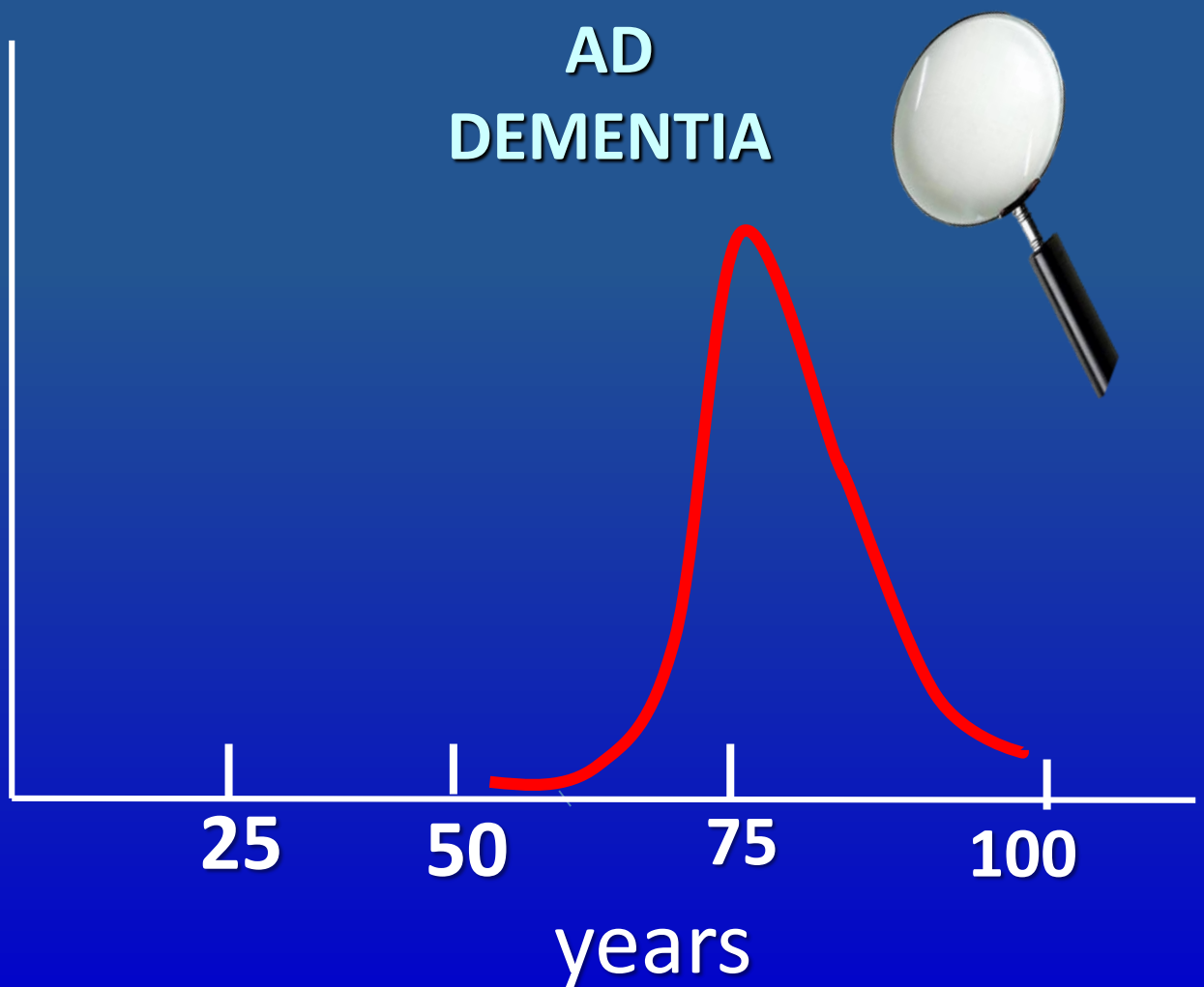


AGING AND AGE-RELATED DISEASES

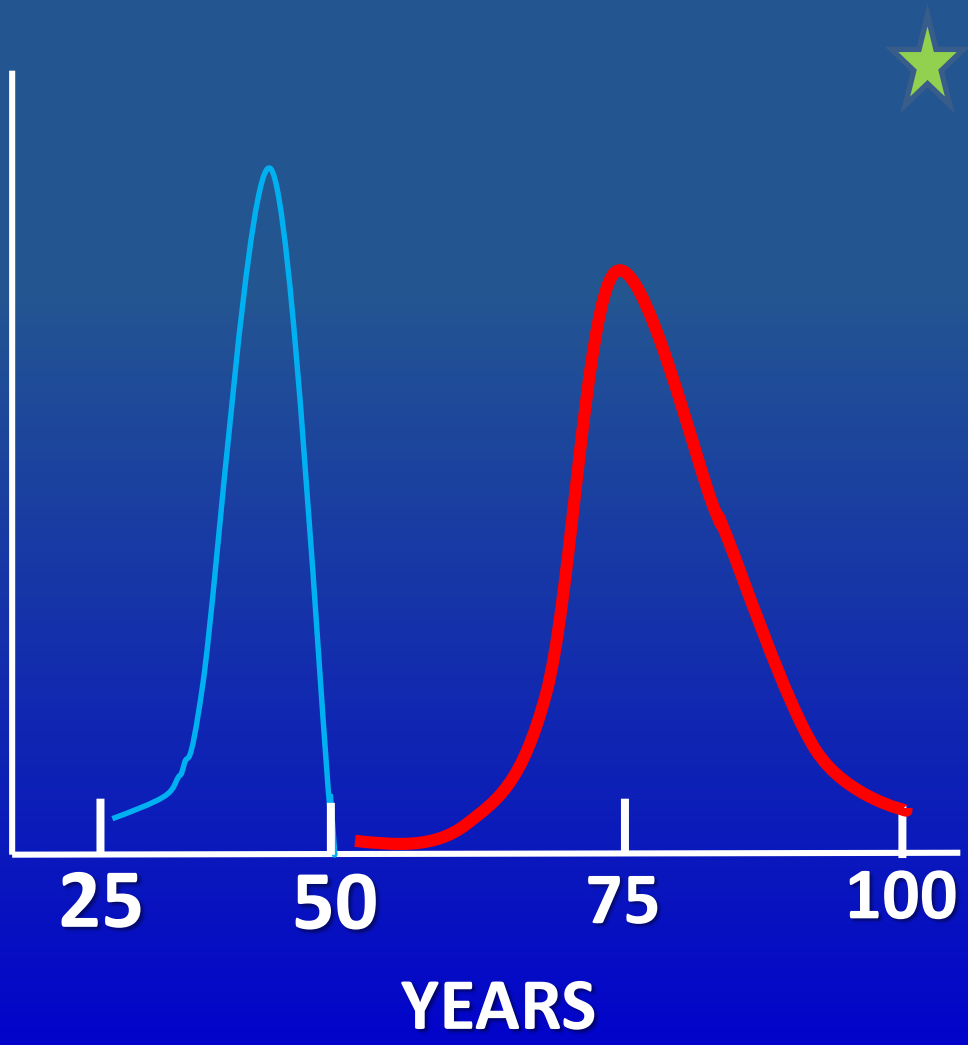


PART

Primary age-related tauopathy

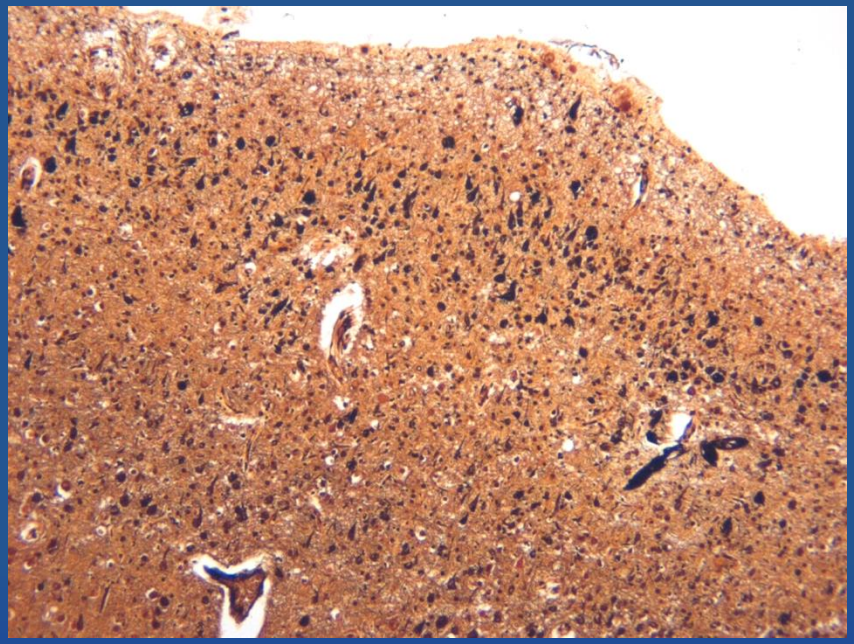


A 101 year-old with Dementia

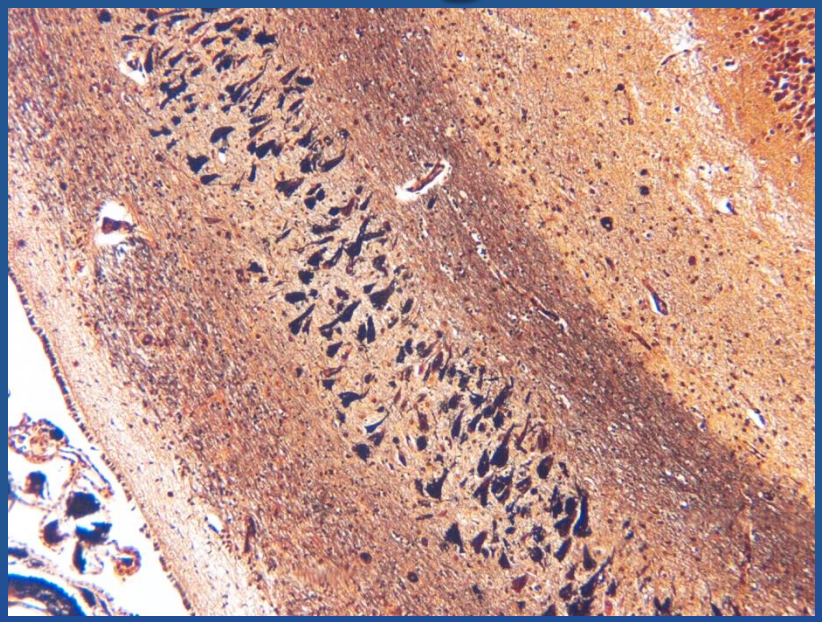


- 101 y/o woman
- 10 year of dementia
- Clinical Dx. AD
- Old occipital infarcts
- Tau / NFT Braak III
- No Neuritic plaques or Aβ deposits
- No Lewy bodies

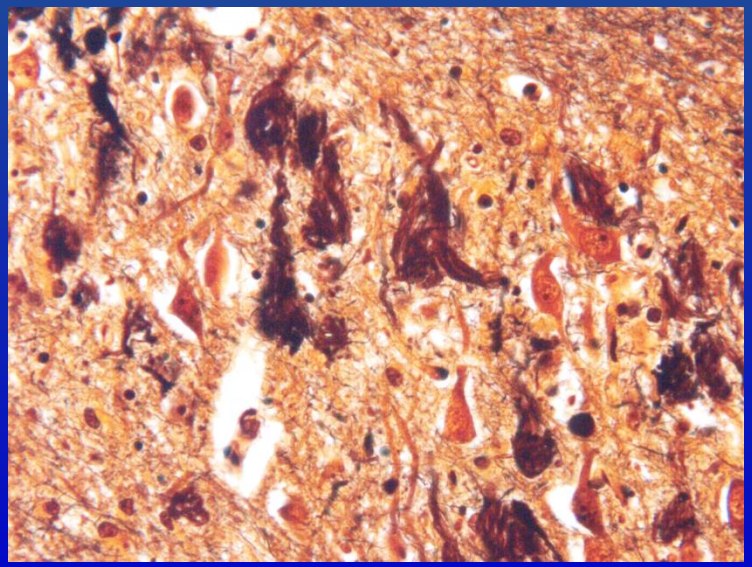
Microscopic findings



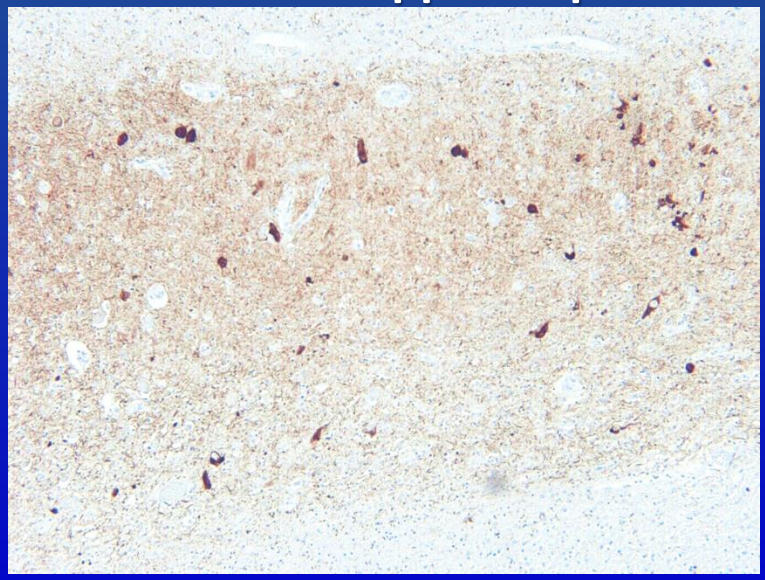
Hirano – Entorhinal



Hirano – Hippocampus



Tangles and Ghost Tangles Hippocampus

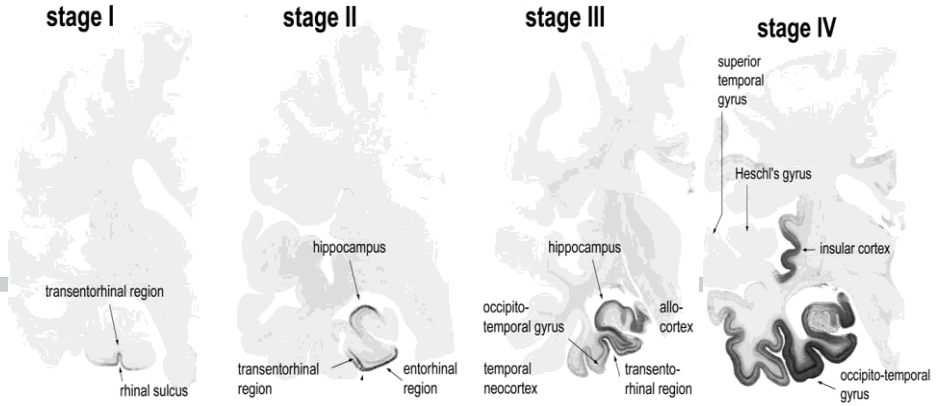


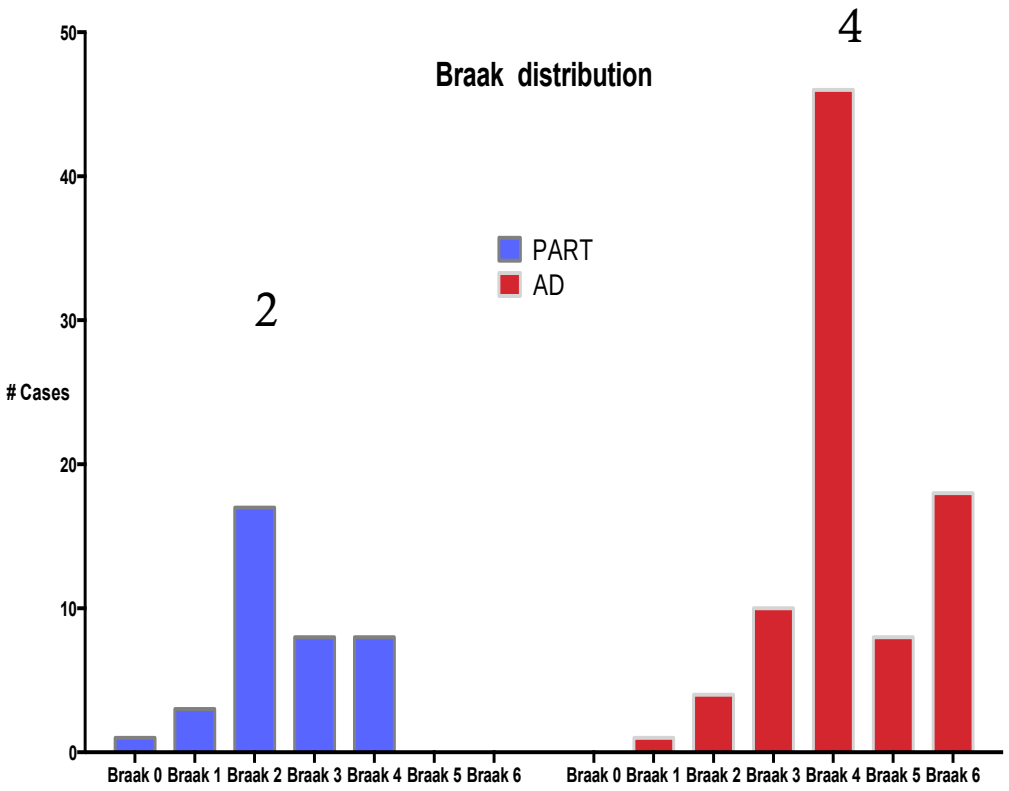
Tau – Hippocampus

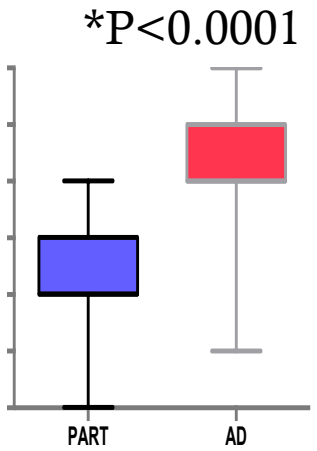
BLSA autopsies of subjects ≥ 85 years of age (n = 182)

	PART No Alzheimer's or degenerative pathology c/s vascular	Alzheimer's pathology c/s vascular	Other pathologies
Number of subjects	37 (20%)	87 (48%)	58 (32%)
Age (SD) years	92 (4.4)	93 (4.6)	
CDR (0-3) mean	0.77	1.29	
MMSE (30-0) mean	23.7	21.19	

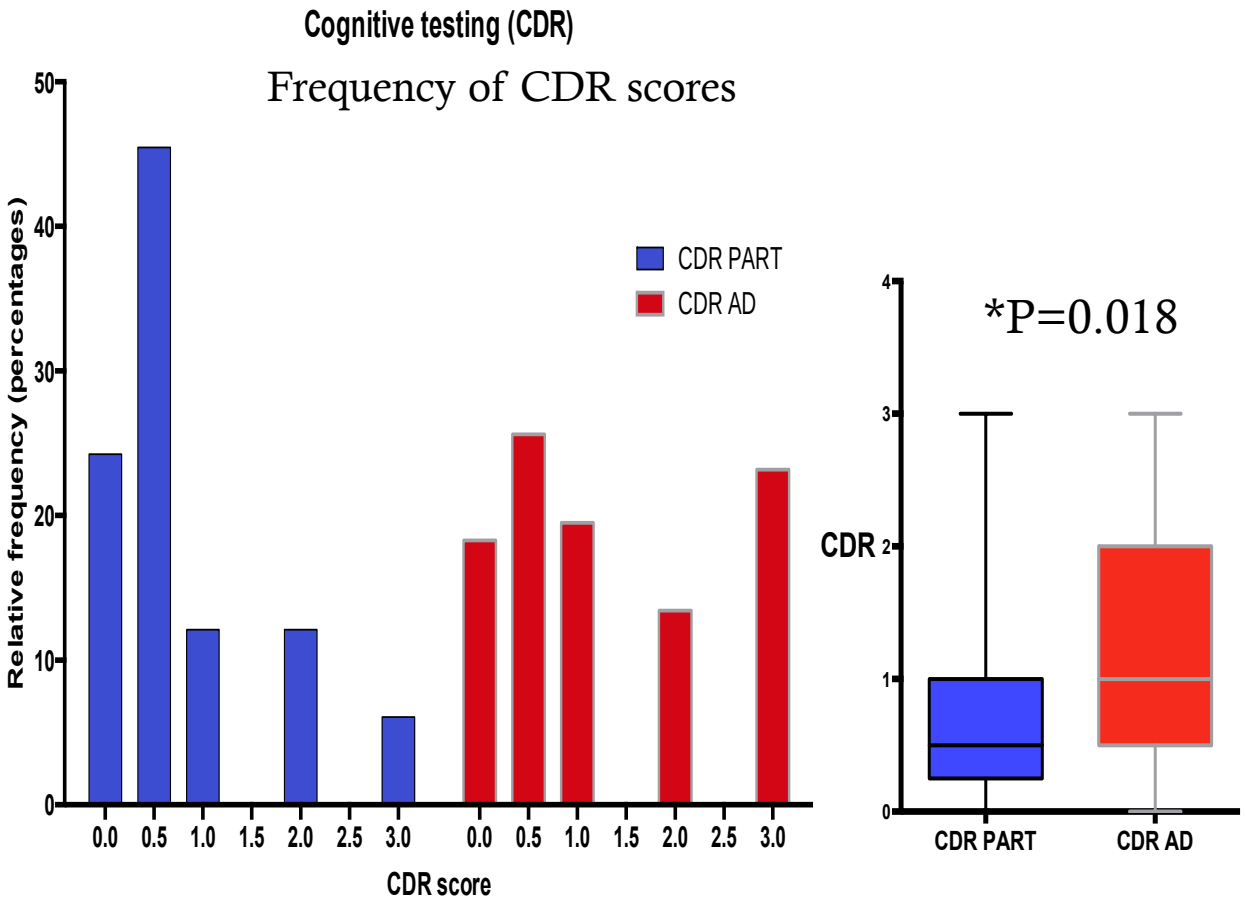
Braak stage distribution



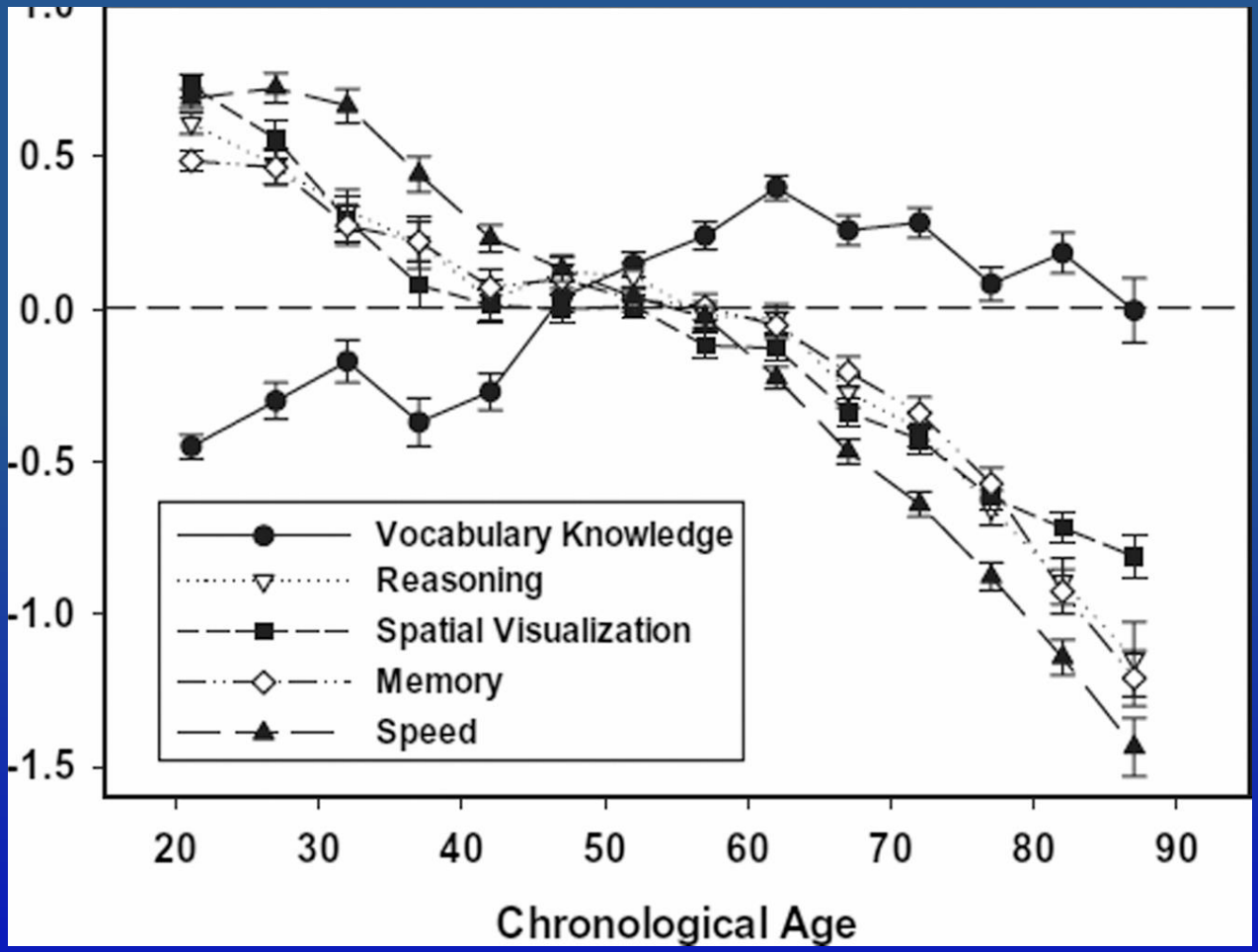




Cognitive testing (CDR) Distribution in BLSA



Cognition , Memory & Age



Salthouse et al 2010

Conclusions II

FUNCTIONAL DECLINE AND NEURODEGENERATION OF THE BRAIN STARTS EARLY IN LIFE

EVEN IF YOU ESCAPE:
ALZHEIMER'S, PARKINSON'S, LEWY BODY DISEASE, FRONTO-TEMPORAL DEMENTIA, THE BRAIN WILL STILL BE ABNORMAL IN OLD AGE

Primary age-related tauopathy (PART) is common in older subjects (>85 years) who do not have Alzheimer's disease

REFERENCES

- Braak, H. et al. 2011. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. J Neuropathol Exp Neurol. 70:960-969.
- Corder, E. H., et al. 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 261:921-923.
- Driscoll, I., & Troncoso, J. 2011. Asymptomatic Alzheimer's disease: a prodrome or a state of resilience? Curr Alzheimer Res. 8:330-335.
- J F. Crary et al 2014. Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathologica. 128:755-766.
- Jellinger et al 2015. PART, a distinct tauopathy, different from classical sporadic Alzheimer disease. Acta Neuropathologica. 129(5):757-62.
- C. Duyckaerts et al 2015. PART is part of Alzheimer disease. Acta Neuropathologica. 129(5):749-56.
- Pletnikova et al 2015. Alzheimer Lesions in the Autopsied Brains of People 30 to 50 Years of Age. Cognitive and Behavioral Neurology. (3):144-152.