# PART

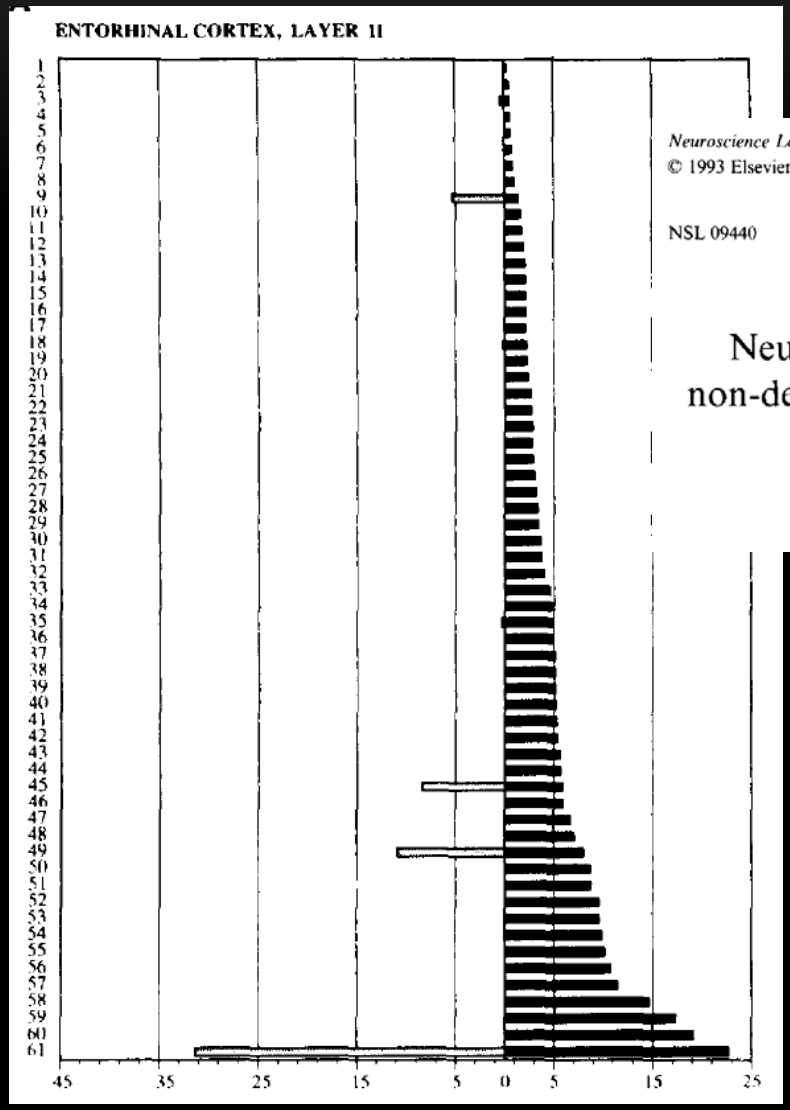
*Primary Age-Related Tauopathy*

**Pete Nelson**

UNIVERSITY OF KENTUCKY

# *WHAT DO THE DATA SHOW ?*

# Plaques Tangles




*Neuroscience Letters*, 153 (1993) 131–135



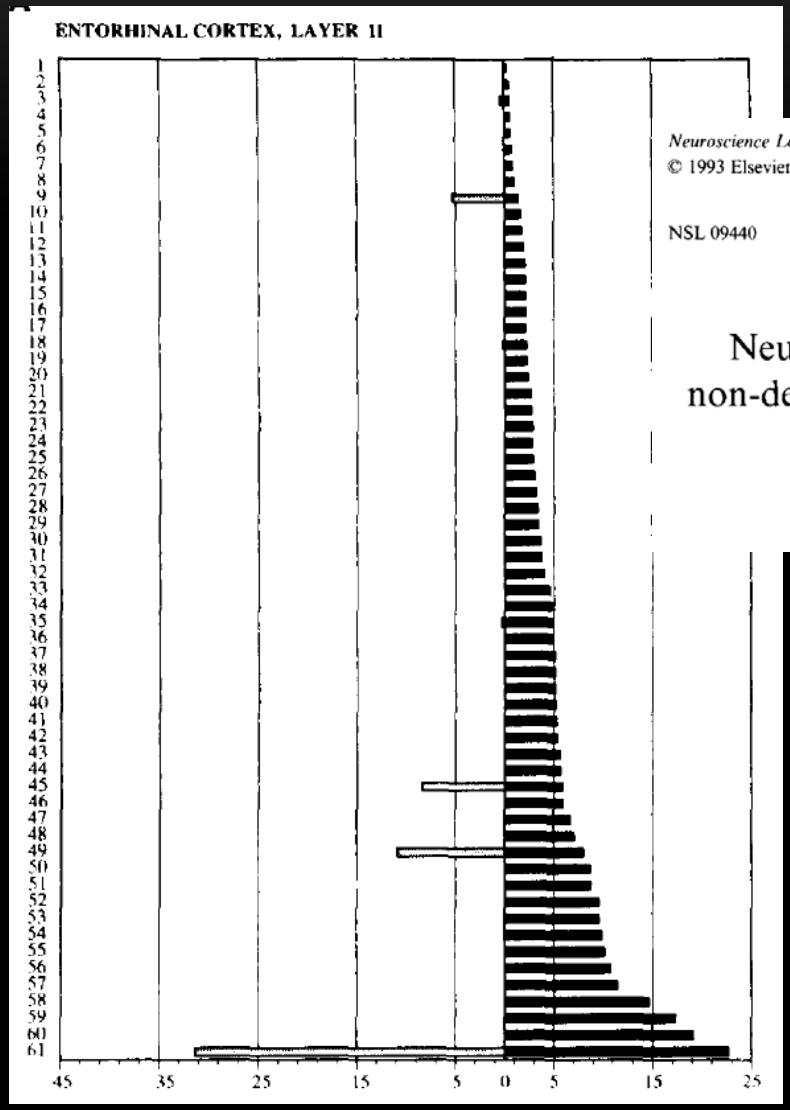
NSL 09440

Neurofibrillary tangle densities in the hippocampal formation in a non-demented population define subgroups of patients with differential early pathologic changes

Constantin Bouras[a,b], Patrick R. Hof[b,c] and John H. Morrison[b,c]

***Bouras et al*, 1993**

# Plaques Tangles

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Constantin Bouras[a,b], Patrick R. Hof[b,c] and John H. Morrison[b,c]

***As a rule, with or without AD pathology, every person in advanced old age has limbic NFTs***

J Neuropathol Exp Neurol


Vol. 68, No. 7
July 2009
pp. 774–784

ORIGINAL ARTICLE

# Brains With Medial Temporal Lobe Neurofibrillary Tangles But No Neuritic Amyloid Plaques Are a Diagnostic Dilemma But May Have Pathogenetic Aspects Distinct From Alzheimer Disease

Peter T. Nelson, MD, PhD, Erin L. Abner, MS, Frederick A. Schmitt, PhD, Richard J. Kryscio, PhD, Gregory A. Jicha, MD, PhD, Karen Santacruz, MD, Charles D. Smith, MD, Ela Patel, HT, and William R. Markesbery, MD

NFT and Amyloid plaque counts:

*Neocortical:*
Frontal, parietal, temporal, occipital

*Medial limbic:*
CA1, subiculum, amygdala, ERC

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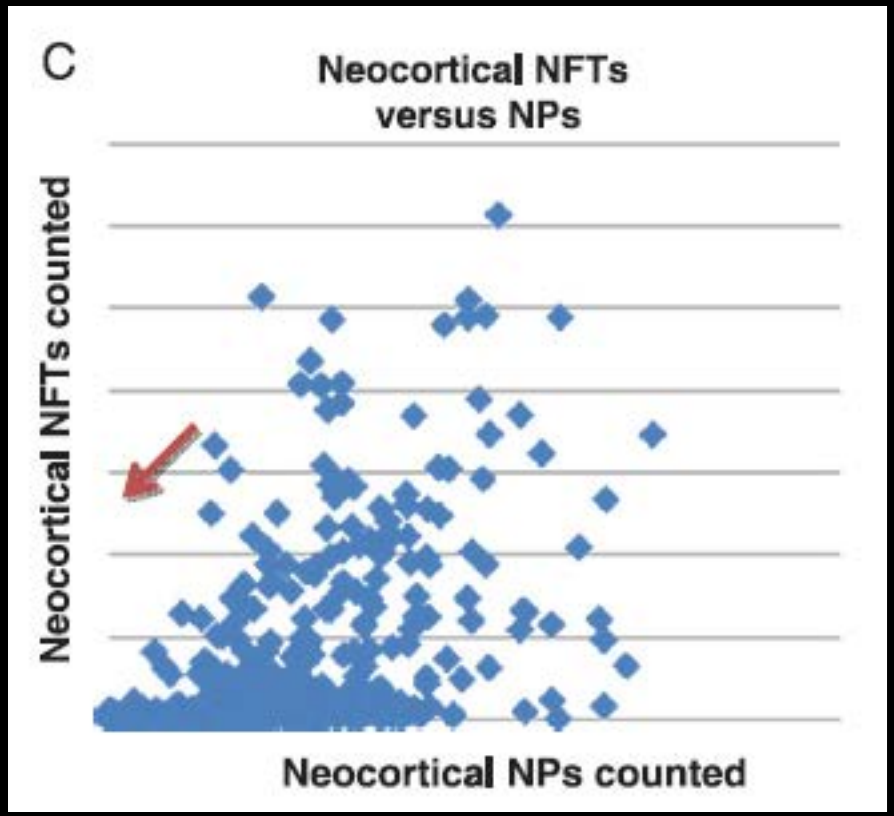


**>1,000 case autopsy series (many not impaired)**

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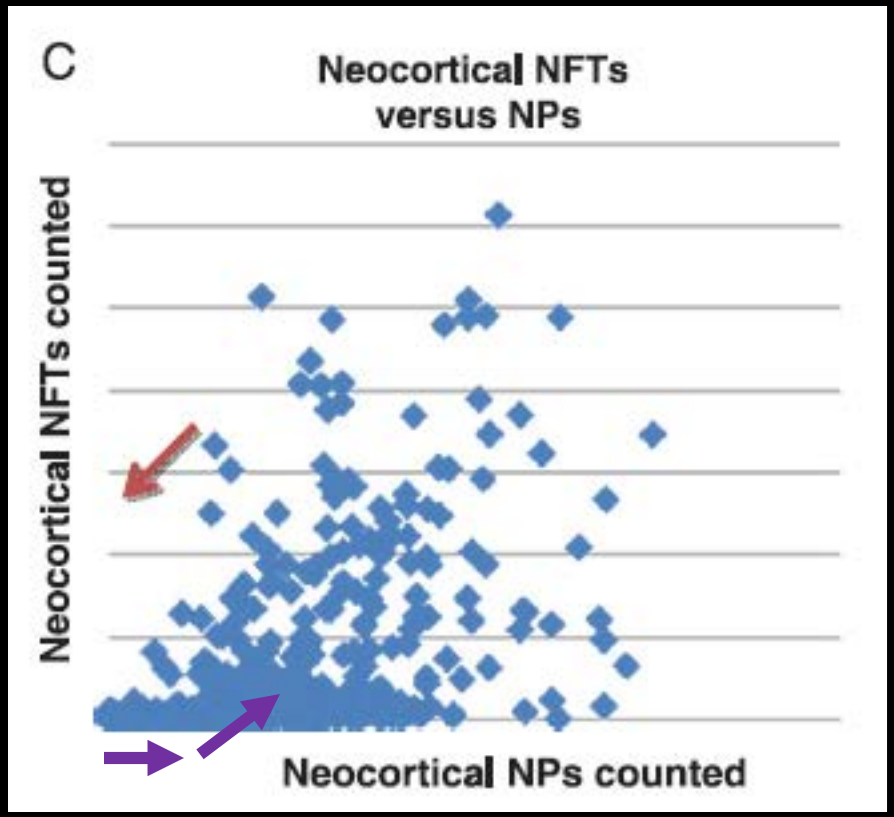


Plaques, THEN neocortical tangles

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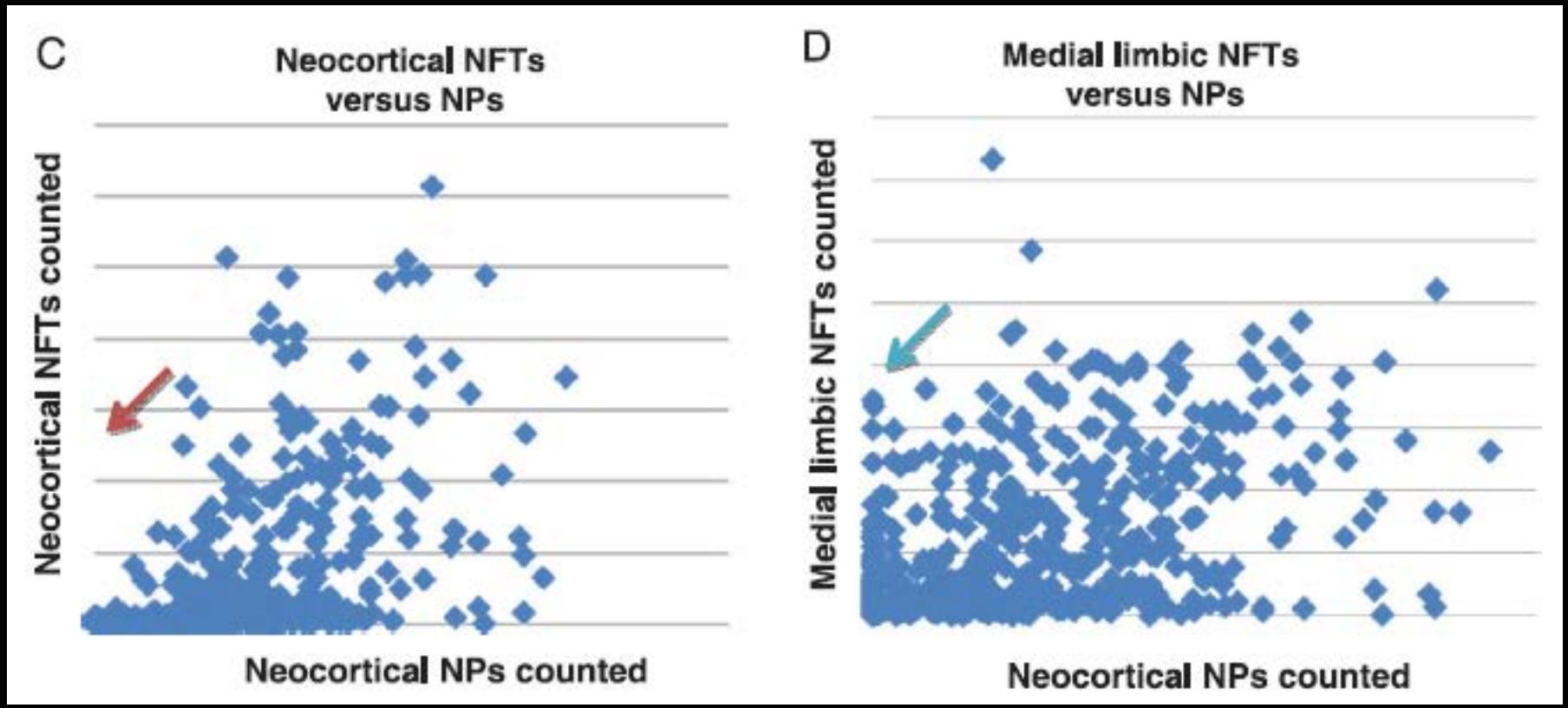


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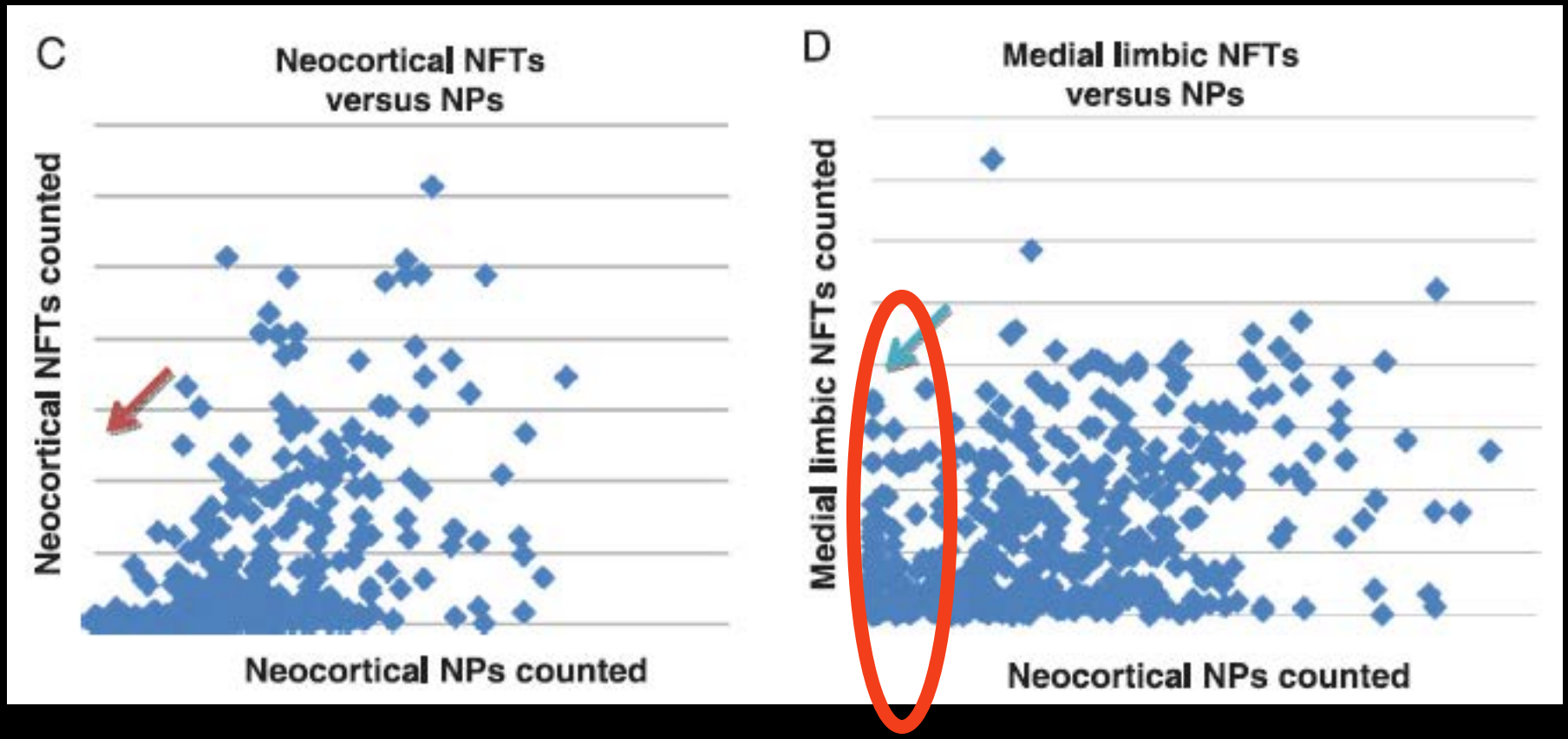

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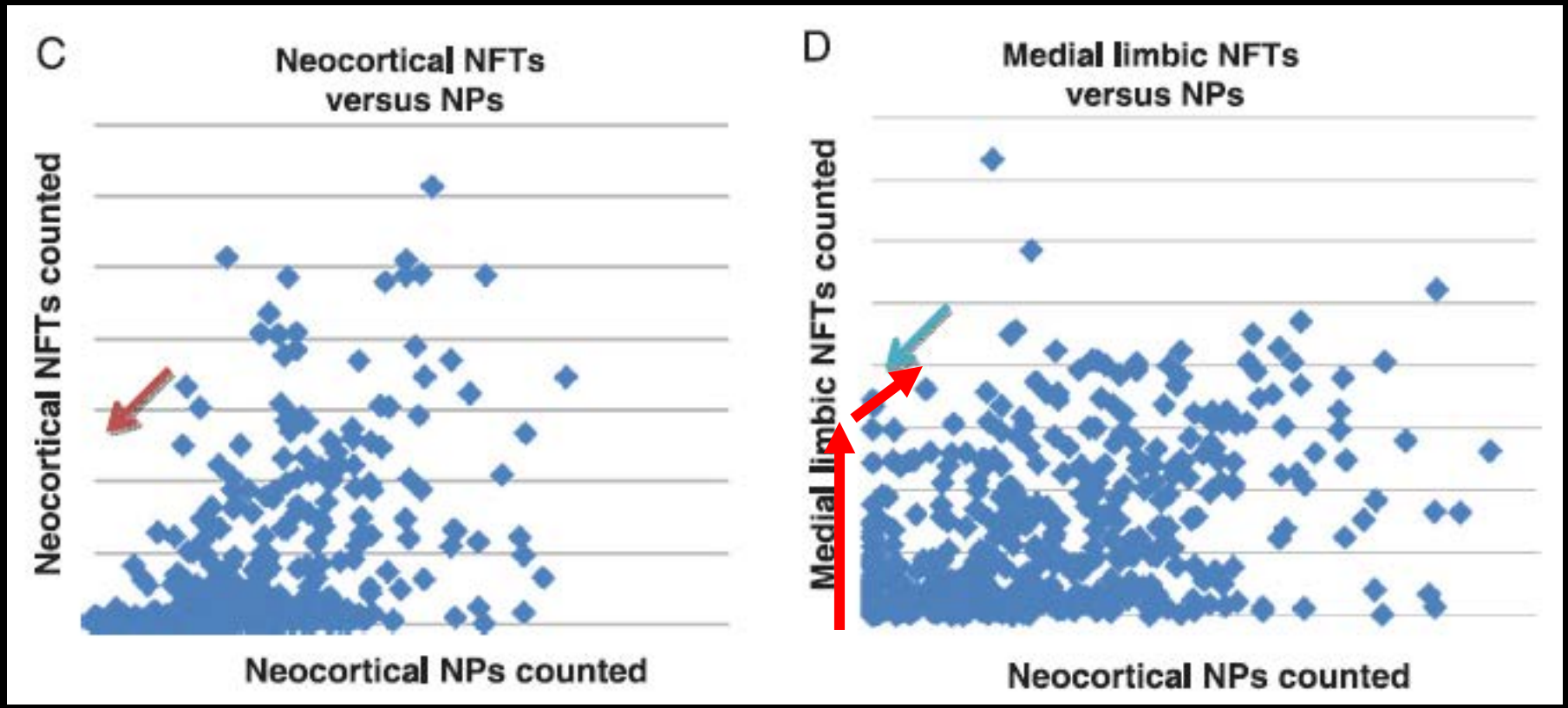


Hippocampal NFTs, ***without*** amyloid plaques

TABLE 1. Demographics of Neurofibrillary Tangle–Positive/Neuritic Plaque–Negative Cases From the University of Kentucky Alzheimer's Disease Center

| Case No. | Age, Years | Sex | Braak Stage | CERAD Score | ApoE Genotype Status | Last MMSE Score | Years Since Last MMSE | Clinical Diagnosis |
|---|---|---|---|---|---|---|---|---|
| 1 | 98 | M | IV | Negative | 3/3 | 25 | 0.7 | Normal |
| 2 | 90 | M | IV | Negative | 3/3 | 27 | 0.2 | Normal |
| 3 | 86 | M | IV | Negative | 3/3 | 30 | 0.6 | Normal |
| 4 | 86 | M | IV | Negative | 3/3 | 28 | 1.1 | Normal |
| 5 | 105 | M | IV | Negative | 3/3 | 26 | 1.0 | Normal |
| 6 | 90 | F | IV | Negative | 3/3 | 29 | 1.2 | Normal |
| 7 | 78 | M | IV | Negative | 3/3 | 27 | 0.7 | Normal |
| 8 | 89 | F | IV | Negative | 2/4 | 28 | 0.9 | Normal |
| 9 | 95 | F | IV | Negative | 3/4 | 14 | 1.5 | AD |
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| 12 | 88 | F | IV | Negative | 2/3 | 29 | 0.9 | Normal |
| 13 | 84 | F | IV | Negative | 3/3 | 30 | 1.8 | Normal |
| 14 | 80 | F | IV | Negative | | 20 | 4.8 | AD |
| 15 | 95 | M | IV | Negative | 3/4 | 26 | 0.9 | Normal |
| 16 | 95 | M | III | Negative | 2/3 | 30 | 0.7 | Normal |
| 17 | 87 | M | III | Negative | 3/3 | 27 | 0.9 | Normal |
| 18 | 96 | F | III | Negative | 3/3 | 27 | 0.6 | MCI |
| 19 | 86 | F | III | Negative | 2/3 | 28 | 0.4 | Normal |
| 20 | 88 | F | III | Negative | 2/3 | 21 | 0.3 | AD |
| 21 | 77 | M | III | Negative | 3/4 | 30 | 0.6 | Normal |
| 22 | 80 | M | III | Negative | 3/4 | 27 | 1.2 | Normal |
| 23 | 83 | M | III | Negative | | 26 | 0.1 | Normal |
| 24 | 89 | M | III | Negative | 3/3 | 28 | 0.9 | Normal |
| 25 | 87 | F | III | Negative | 3/3 | 29 | 0.8 | Normal |
| 26 | 85 | F | III | Negative | 3/4 | 23 | 0.8 | AD |

AD, Alzheimer disease; M, male; F, female; MMSE, Mini-Mental State Examination; CERAD, Consortium to Establish a Registry for Alzheimer Disease; ApoE, apolipoprotein E; MCI, mild cognitive impairment.

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AD, Alzheimer disease; M, male; F, female; MMSE, Mini-Mental State Examination; CERAD, Consortium to Establish a Registry for Alzheimer Disease; ApoE, apolipoprotein E; MCI, mild cognitive impairment.

Braak III and IV PART:

- ***Mostly clinically "normal"***
- ***Mostly (85%) not MMSE=30***
- ***Mostly (77%) >= age 85***

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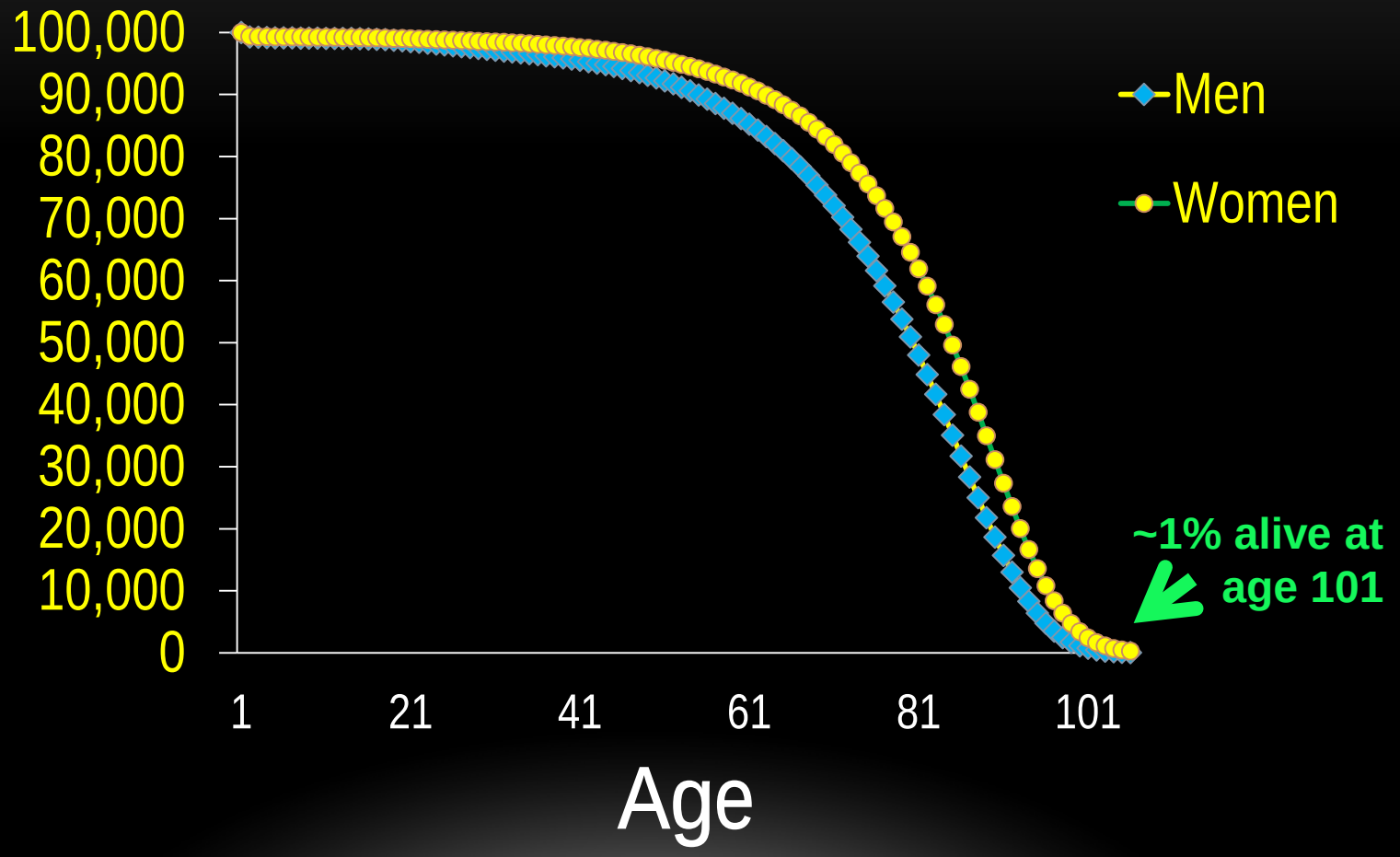
Braak III and IV PART:

Would they go on to get full-blown Alzheimer's disease?

AD, Alzheimer disease; M, male; F, female; MMSE, Mini-Mental State Examination; CERAD, Consortium to Establish a Registry for Alzheimer Disease; ApoE, apolipoprotein E; MCI, mild cognitive impairment.

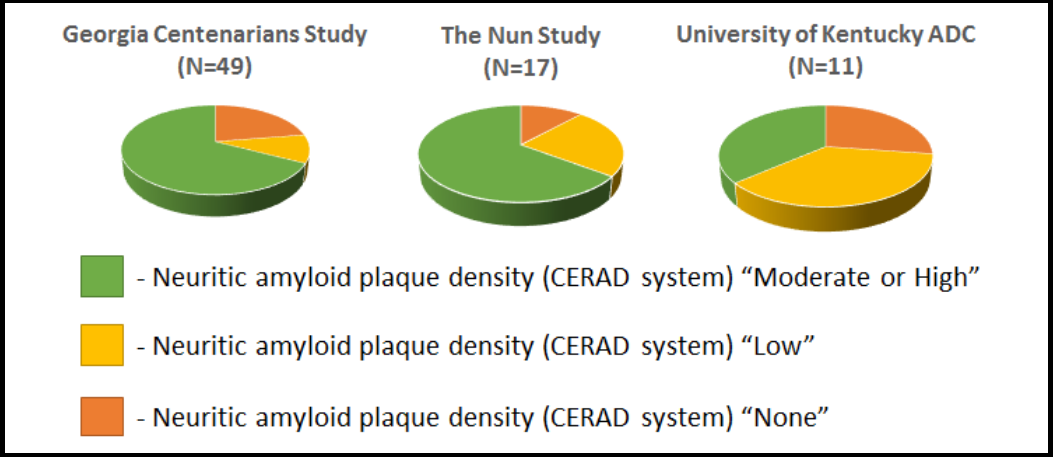
# # Alive per 100,000 population, U.S.

*Source: 2007 Actuarial Tables*



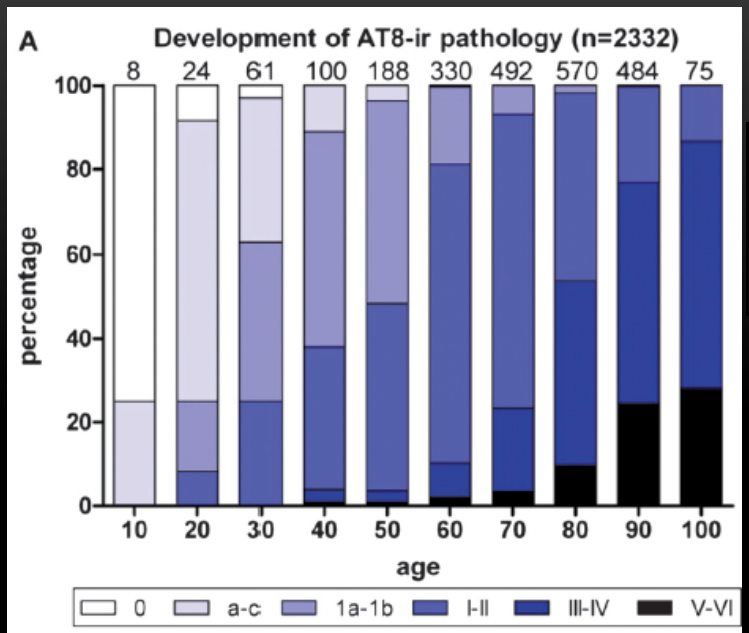
# Centenarians

## Mean Age at death: 102.0 years N=77

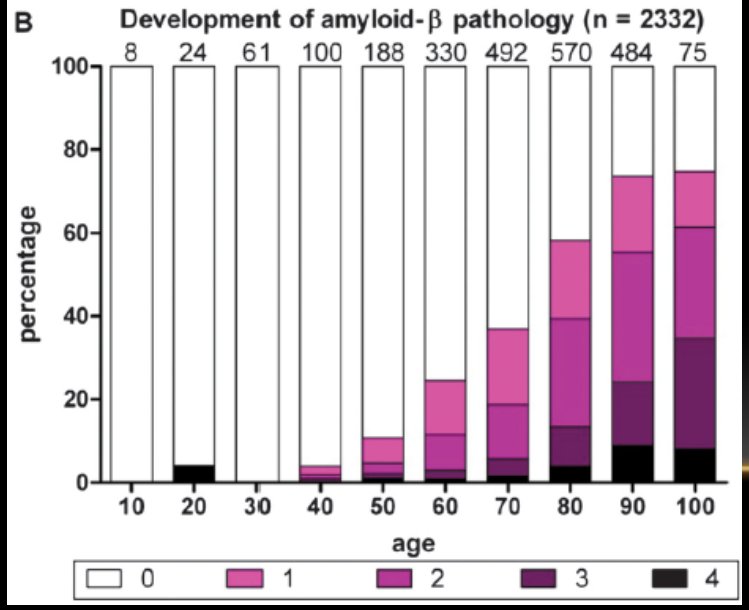



*NBI Aging, In Revisions*

**(Everyone gets PART but…)**
**not everyone**
**gets AD**




← Tangles




← Plaques

*Braak H, et al,*
*J Neuropathol Exp Neurol. 2011*

Biomarkers!

doi:10.1093/brain/awv199 BRAIN 2015: 138; 2701–2715 | 2701

BRAIN
A JOURNAL OF NEUROLOGY

# Alzheimer's disease cerebrospinal fluid biomarker in cognitively normal subjects

Jon B. Toledo,[1] Henrik Zetterberg,[2,3] Argonde C. van Harten,[4] Lidia Glodzik,[5] Pablo Martinez-Lage,[6] Luisella Bocchio-Chiavetto,[7,8] Lorena Rami,[9] Oskar Hansson,[10,11] Reisa Sperling,[12] Sebastiaan Engelborghs,[13,14] Ricardo S. Osorio,[5] Hugo Vanderstichele,[15] Manu Vandijck,[16] Harald Hampel,[17,18] Stefan Teipl,[19,20] Abhay Moghekar,[21] Marilyn Albert,[21] William T. Hu,[22] Jose A. Monge Argilés,[23] Ana Gorostidi,[24] Charlotte E. Teunissen,[25] Peter P. De Deyn,[13,14] Bradley T. Hyman,[12] Jose L. Molinuevo,[9] Giovanni B. Frisoni,[7,26] Gurutz Linazasoro,[6] Mony J. de Leon,[5] Wiesje M. van der Flier,[4,27] Philip Scheltens,[4] Kaj Blennow,[2,28] Leslie M. Shaw[1] and John Q. Trojanowski[1] on behalf of the Alzheimer's Disease Neuroimaging Initiative

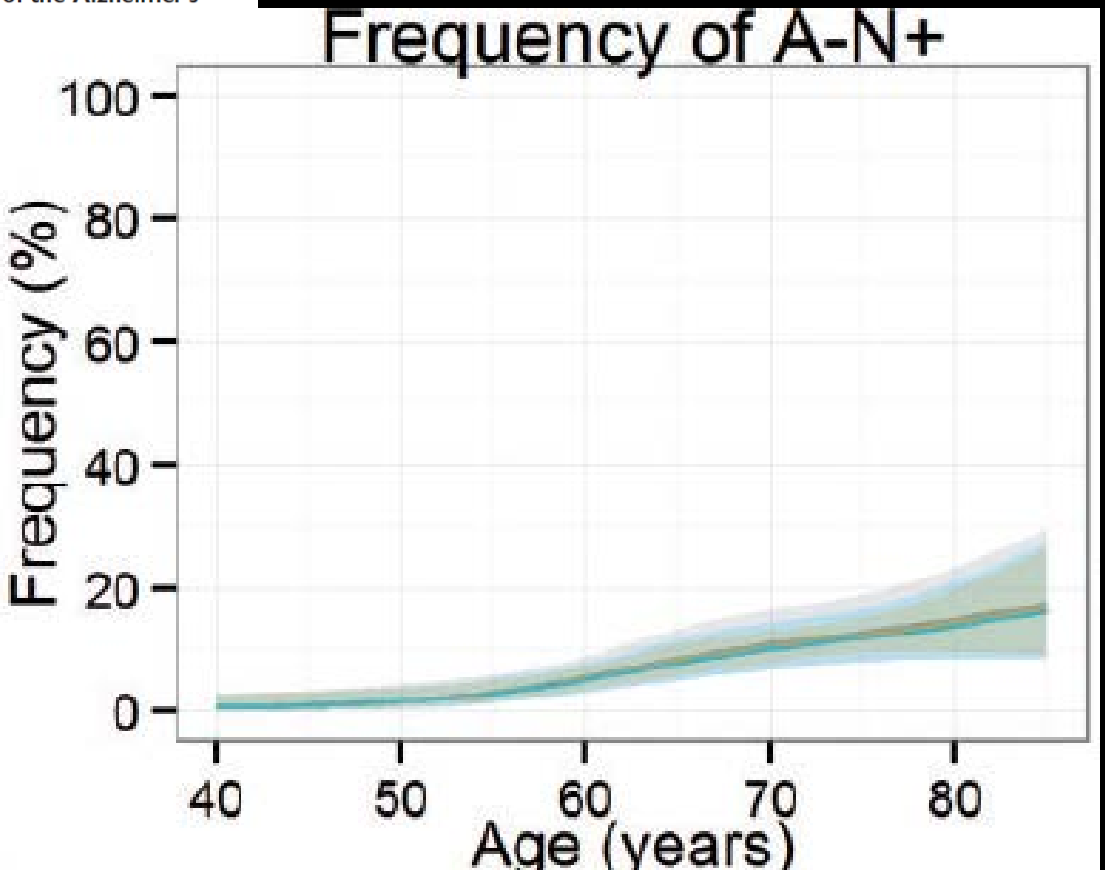
**Toledo et al, 2015**

Biomarkers!

CSF signature:

Aβ negative

Tau positive



# *WHAT DO THE DATA SHOW ?*

# *2 PATHWAYS*

# 2 PATHWAYS

1 ? → Aβ → MTL NFTs → Neocortical NFTs → Dementia

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2 ? → MTL NFTs → Impairment often
but usually not dementia

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but usually not dementia

~20 % of “oldest-old”
-(those that lack Aβ plaques)

~5 % relatively severe
(Braak NFT stages III/IV)

# Terminology: used previously…

- Tangle only dementia
- Tangle/NFT predominant dementia
- Tangle-predominant senile dementia
- Preferential development of NFT without senile plaques
- Senile dementia of the NFT type
- Limbic neurofibrillary tangle dementia

# Why not use existing terminology

*“Tangle only dementia”…? (&c.)*

# Why not
# *“Tangle only dementia”…? (&c.)*

- Terms date from when autopsy series included FTLD-MAPT
- Multiplicity of terminology requires clarification anyway
- Impetus to dissociate pathologic from clinical diagnoses
- Clinicians would probably avoid prior terminology
  - *(nor would pathologists without detailed clinical info)*
  - *Biomarker-based investigators would find a better term*
- Often/usually no “dementia” in pure PART
- Words “only” or “predominant” are too restrictive (comorbid pathologies are the norm)
- Solid precedence of use of “age related” in nomenclature
- People who are the “parents” of “TOD” and other like terms have signed on to “PART”

Acta Neuropathol
DOI 10.1007/s00401-014-1349-0

CONSENSUS PAPER

# Primary age-related tauopathy (PART): a common pathology associated with human aging

John F. Crary · John Q. Trojanowski · Julie A. Schneider · Jose F. Abisambra · Erin L. Abner · Irina Alafuzoff · Steven E. Arnold · Johannes Attems · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Marla Gearing · Lea T. Grinberg · Patrick R. Hof · Bradley T. Hyman · Kurt Jellinger · Gregory A. Jicha · Gabor G. Kovacs · David S. Knopman · Julia Kofler · Walter A. Kukull · Ian R. Mackenzie · Eliezer Masliah · Ann McKee · Thomas J. Montine · Melissa E. Murray · Janna H. Neltner · Ismael Santa-Maria · William W. Seeley · Alberto Serrano-Pozo · Michael L. Shelanski · Thor Stein · Masaki Takao · Dietmar R. Thal · Jonathan B. Toledo · Juan C. Troncoso · Jean Paul Vonsattel · Charles L. White 3rd · Thomas Wisniewski · Randall L. Woltjer · Masahito Yamada · Peter T. Nelson

Acta Neuropathol (2014) 128:767–772
DOI 10.1007/s00401-014-1356-1

COMMENTARY

# Are cases with tau pathology occurring in the absence of Aβ deposits part of the AD-related pathological process?

Heiko Braak · Kelly Del Tredici

Acta Neuropathol (2014) 128:773–776
DOI 10.1007/s00401-014-1362-3

COMMENTARY

# PART and SNAP

Clifford R. Jack Jr.

Acta Neuropathol
DOI 10.1007/s00401-015-1390-7

POSITION PAPER

# PART is part of Alzheimer disease

Charles Duyckaerts · Heiko Braak · Jean-Pierre Brion · Luc Buée · Kelly Del Tredici · Michel Goedert · Glenda Halliday · Manuela Neumann · Maria Grazia Spillantini · Markus Tolnay · Toshiki Uchihara

Acta Neuropathol
DOI 10.1007/s00401-015-1407-2

CORRESPONDENCE

# PART, a distinct tauopathy, different from classical sporadic Alzheimer disease

Kurt A. Jellinger[1] · Irina Alafuzoff[2] · Johannes Attems[3] · Thomas G. Beach[4] · Nigel J. Cairns[5] · John F. Crary[6] · Dennis W. Dickson[7] · Patrick R. Hof[8] · Bradley T. Hyman[9] · Clifford R. Jack Jr.[10] · Gregory A. Jicha[11] · David S. Knopman[12] · Gabor G. Kovacs[13] · Ian R. Mackenzie[14] · Eliezer Masliah[15,16] · Thomas J. Montine[17] · Peter T. Nelson[18] · Frederick Schmitt[11] · Julie A. Schneider[19,20] · Albert Serrano-Pozo[21] · Dietmar R. Thal[22] · Jonathan B. Toledo[23] · John Q. Trojanowski[23] · Juan C. Troncoso[24] · Jean Paul Vonsattel[6] · Thomas Wisniewski[25,26,27]

Received: 11 February 2015 / Revised: 4 March 2015 / Accepted: 4 March 2015

# *IS THIS TERM USEFUL?*

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*WHO CARES ABOUT A "DISEASE" NOT NECESSSARILY a/w "DEMENTIA"?*

*“Self-reported/subjective memory complaint”:*

“perceived changes in memory”…not meeting clinical criteria for either MCI or dementia.

*“Self-reported memory complaint”:*

“perceived changes in memory”…not meeting clinical criteria for either MCI or dementia.

*(Still troubling and potentially troublesome!)*

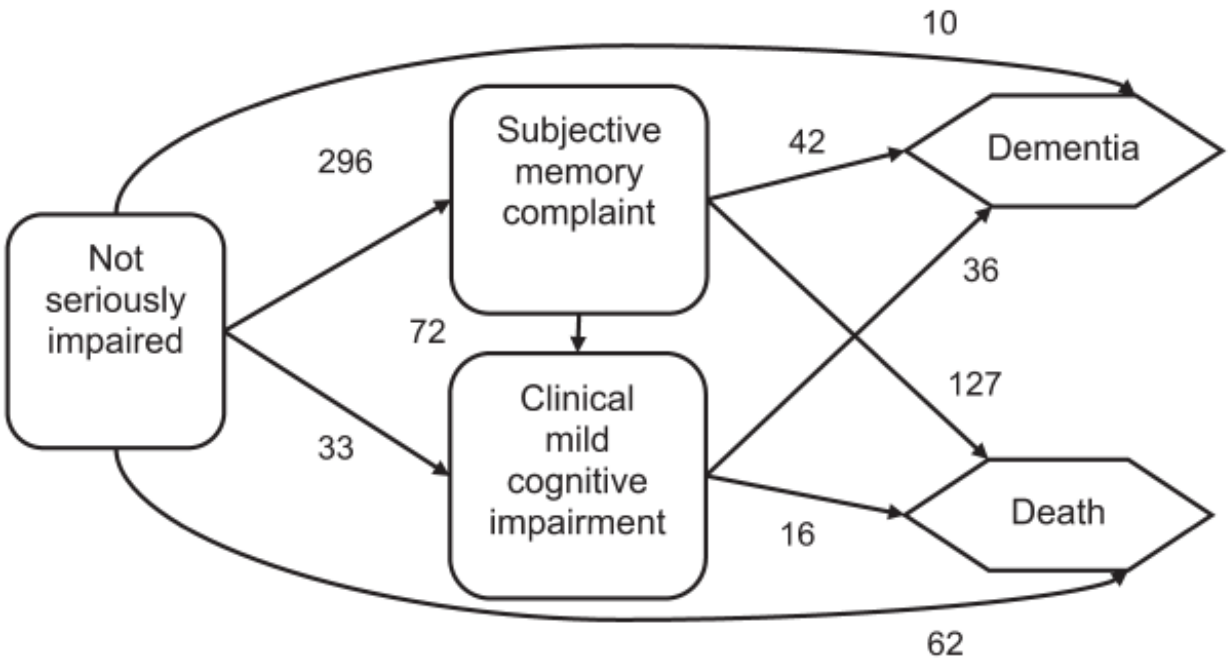
# Self-reported memory complaints

## Implications from a longitudinal cohort with autopsies


Richard J. Kryscio, PhD
Erin L. Abner, PhD
Gregory E. Cooper, MD, PhD
David W. Fardo, PhD
Gregory A. Jicha, MD, PhD
Peter T. Nelson, MD, PhD
Charles D. Smith, MD
Linda J. Van Eldik, PhD
Lijie Wan
Frederick A. Schmitt, PhD

Correspondence to Dr. Kryscio: kryscio@email.uky.edu


**Figure 1** Flow diagram and frequency of transitions among states



# Patients followed longitudinally for avg > 10 years!

## Self-reported memory complaints

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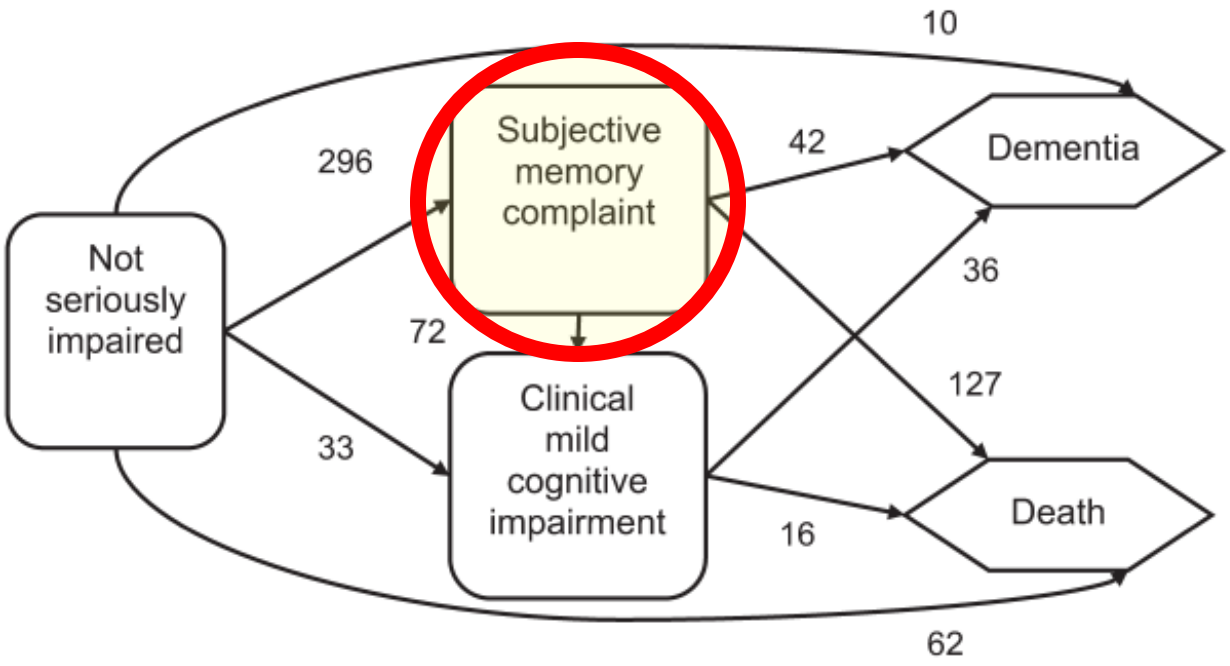
Correspondence to Dr. Kryscio: kryscio@email.uky.edu

**Figure 1** Flow diagram and frequency of transitions among states



*The Journal of Prevention of Alzheimer's Disease - JPAD©*

# Self-Reported Memory Complaints: A Comparison of Demented and Unimpaired Outcomes

*R.J. Kryscio[1,2,3,4], E.L. Abner[1,2,5], G.A. Jicha[1,2,6], P.T. Nelson[1,2,7], C.D. Smith[1,2,6], L.J. Van Eldik[1,2,8], W. Lou[1,4], D.W. Fardo[2,3], G.E. Cooper[1,2,9], F.A. Schmitt[1,2,6]*

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J Prev Alz Dis 2015;in press

Comparison of autopsy findings by SMC outcome group

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## Comparison of autopsy findings by SMC outcome group

AD and HS-Aging:

SMC-> Dementia



**Table 4.** Comparison of autopsy findings by SMC outcome group

| Percent with pathology | Dementia | Death w/o impairment | P value** |
|---|---|---|---|
| AD pathology | | | < 0.0001 |
| None | 2.8 | 25.4 | |
| Low | 19.4 | 37.5 | |
| Intermediate | 61.1 | 35.6 | |
| High | 16.7 | 1.7 | |
| Hippocampal Sclerosis | 22.2 | 1.7 | 0.0037 |
| Intermediate Diffuse Lewy Body Disease | 11.1 | 5.9 | 0.40 |
| Cerebral Amyloid Angiopathy | 55.6 | 52.5 | 0.98 |
| Vascular Pathologic Diagnosis | 38.9 | 19.5 | 0.055 |
| Large artery cerebral infarcts | 80.6 | 83.0 | 0.81 |
| Cortical microinfarcts | 75.0 | 72.0 | 0.70 |
| PART | 11.1 | 41.5 | 0.0030 |

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## Comparison of autopsy findings by SMC outcome group

PART:

SMC-> No Dementia



**Table 4.** Comparison of autopsy findings by SMC outcome group

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## Comparison of autopsy findings by SMC outcome group

| Percent with pathology | Dementia | Death | P value** |
|---|---|---|---|
| HS-Aging | 22.2 | 1.7 | 0.0037 |
| PART | 11.1 | 41.5 | 0.003 |

Unlike other pathologies, PART pathology is seen often in persons with SMC that never led to dementia

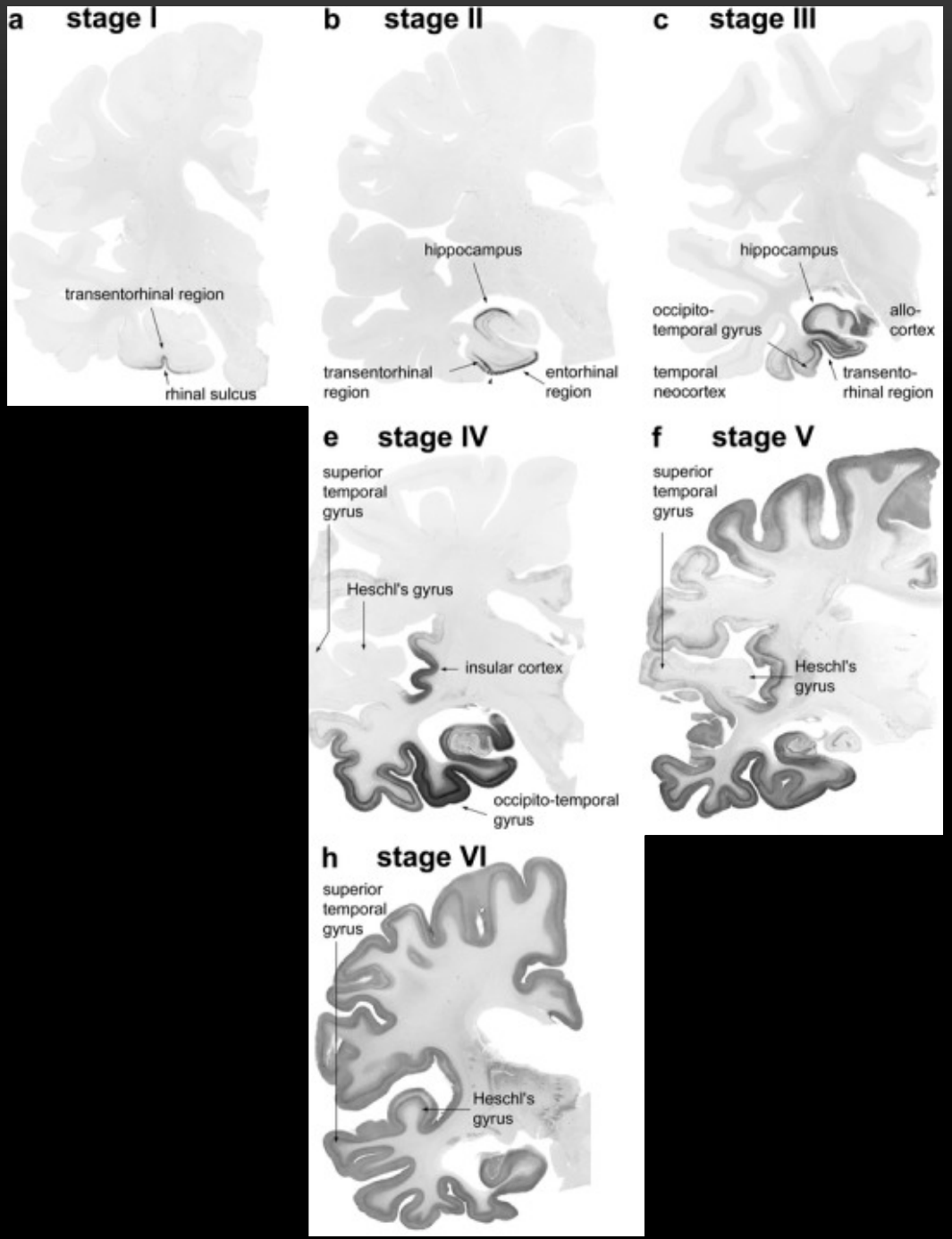
# PART:

- A newly-defined pathologic condition
- Symptoms overlap imperfectly with AD:
  - "Pure" PART LESS impactful on cognition than AD ("Self-reported Memory Complaints")
- Process may be MORE common than AD
- PART is probably often obscured by AD pathology
- Important to identify for individual patients, clinical trials, other future research efforts, etc

# Braak staging:

very non-linear/ordinal

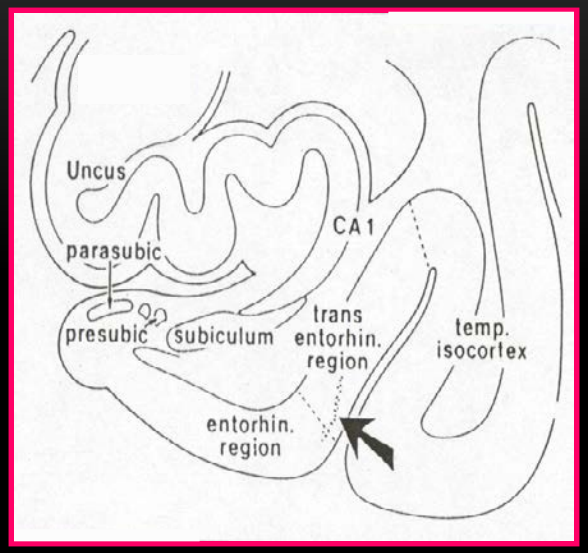
(stained here with anti-phospho-Tau)




H Braak et al,
*Acta Neuropathol.*
2006; 112(4): 389–404.

# Braak Stages

## Stage I

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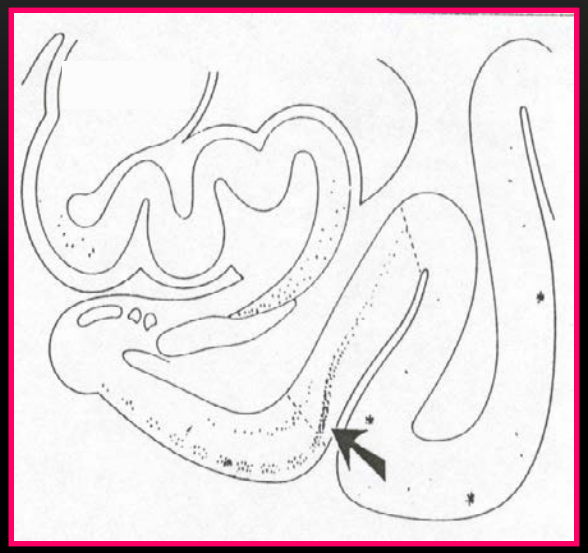
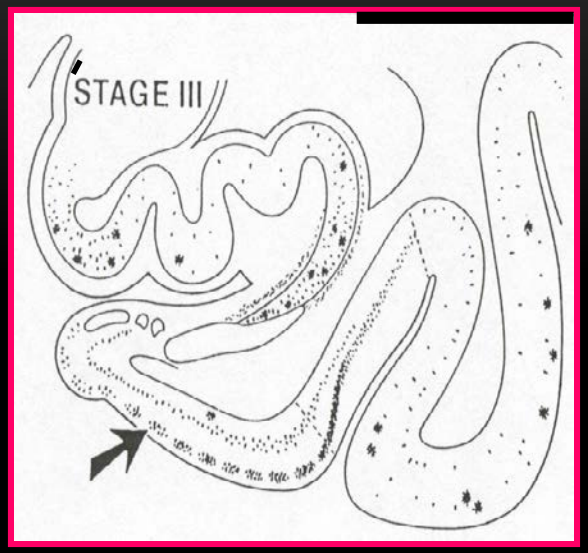
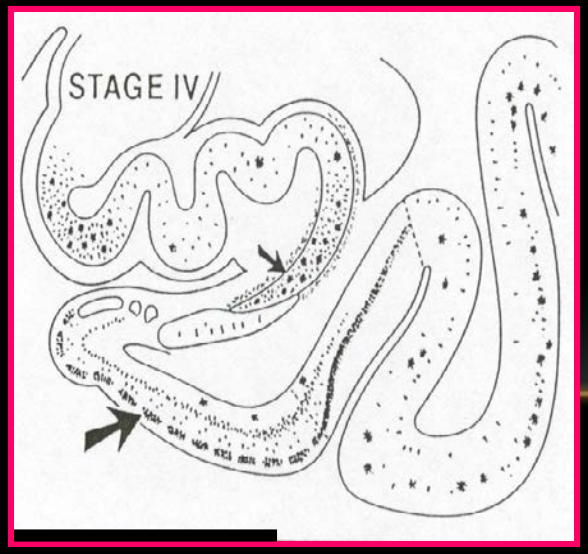


## Stage III

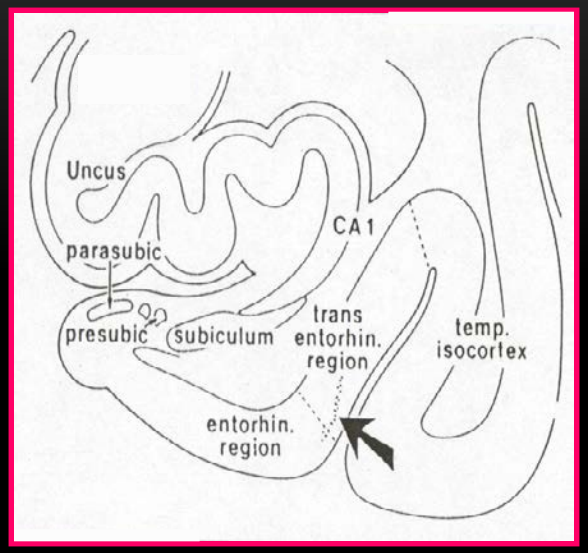



## Stage IV




# Braak Stages

## Stage I

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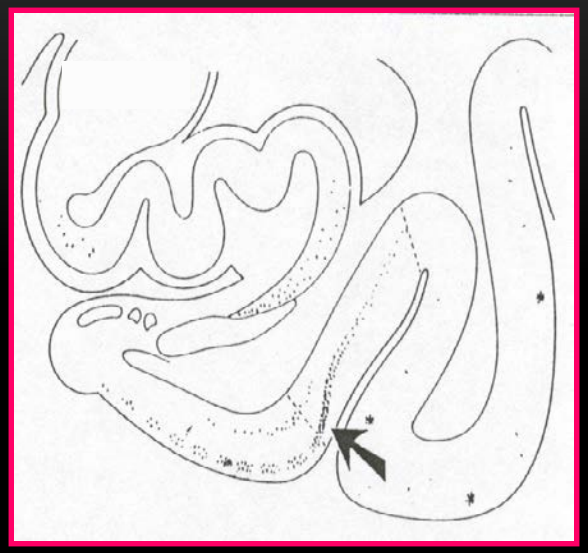

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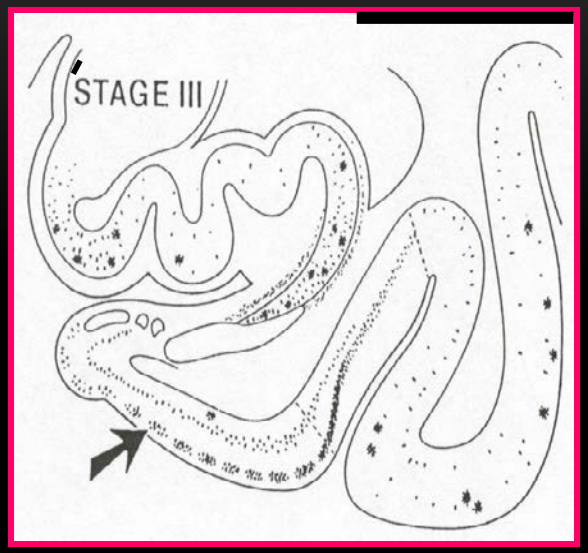
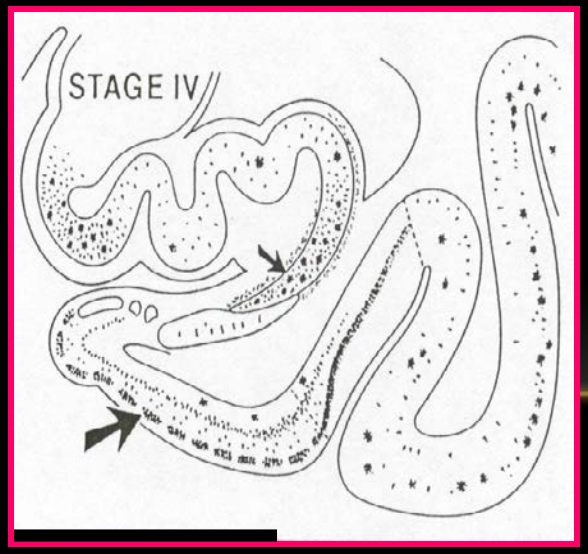
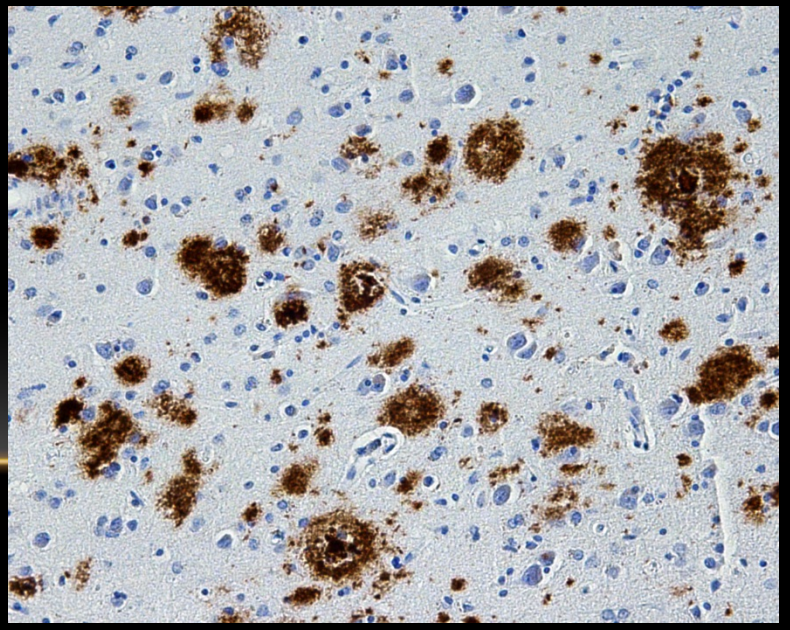



## Stage IV



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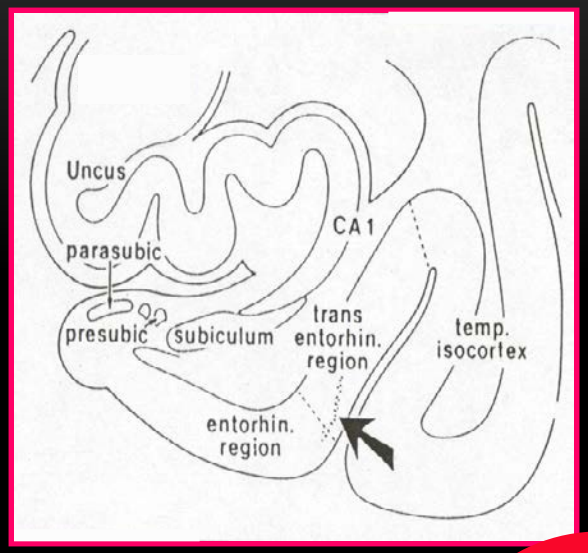


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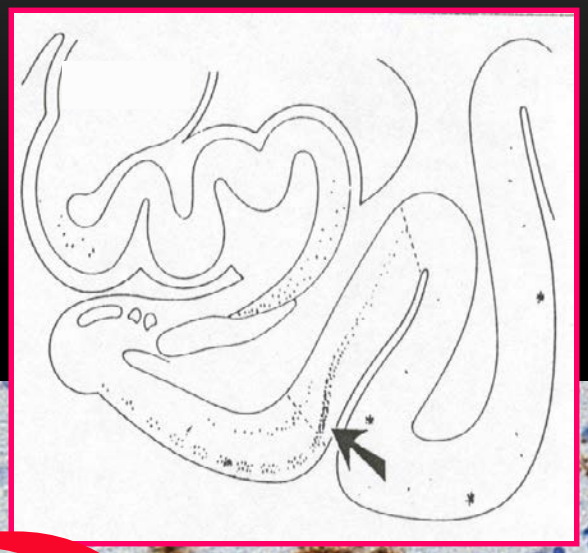
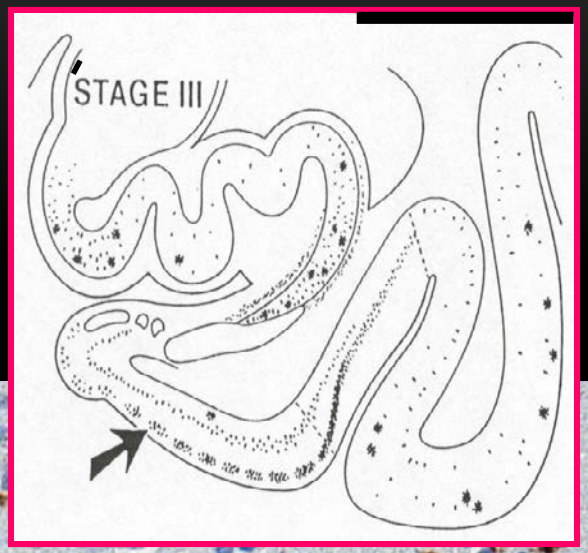
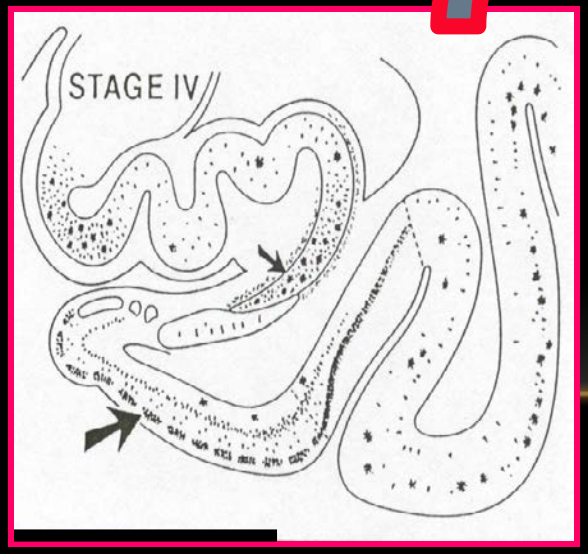


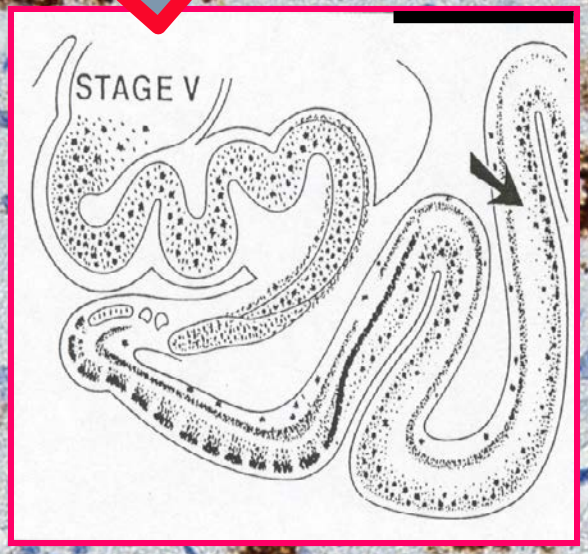
## Stage III



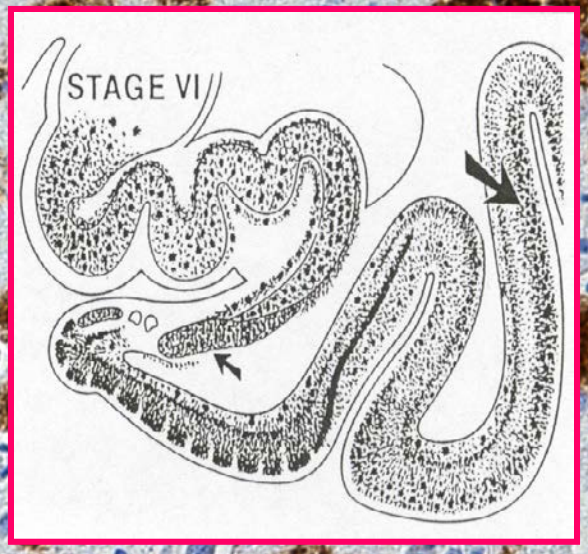

## Stage IV




## Stage V



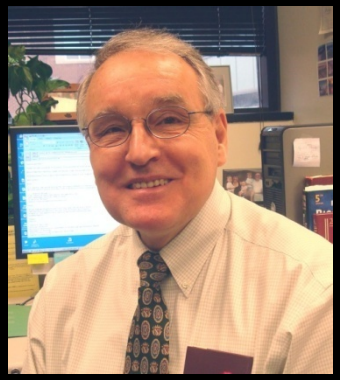

## Stage VI



Erin Abner, MPH

Greg Jicha, MD PhD

Dick Kryscio, PhD

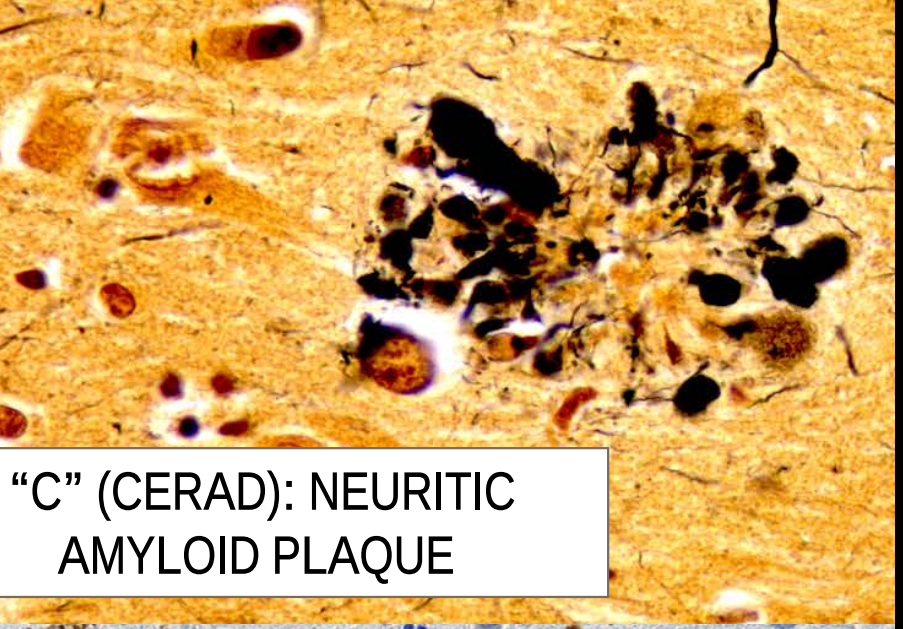


Fred Schmitt, PhD

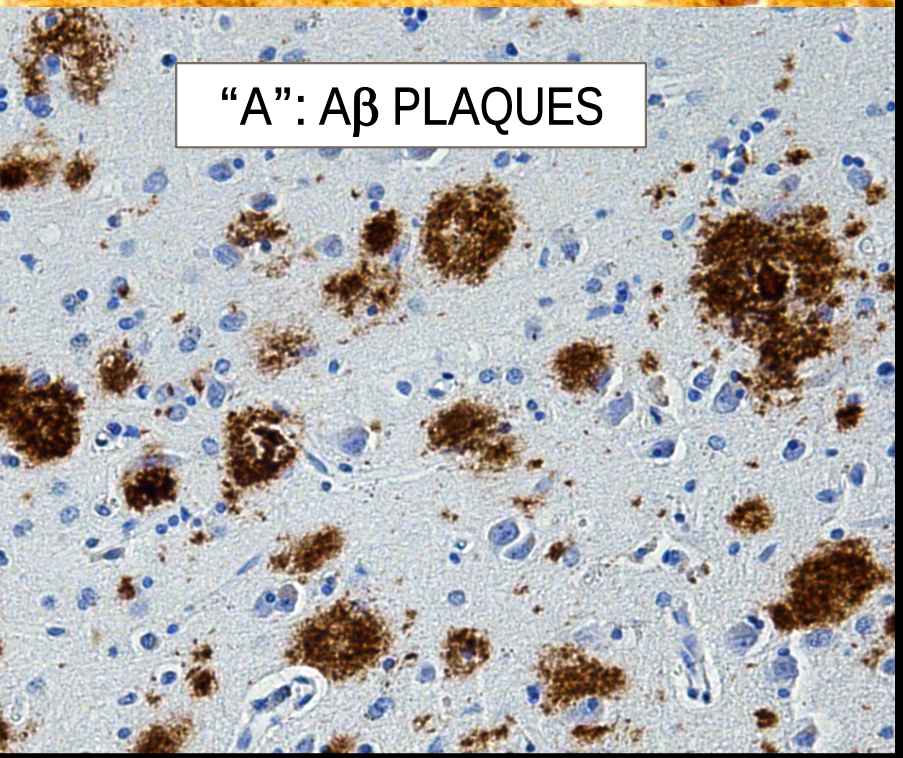
Linda Van Eldik, PhD

# Thanks

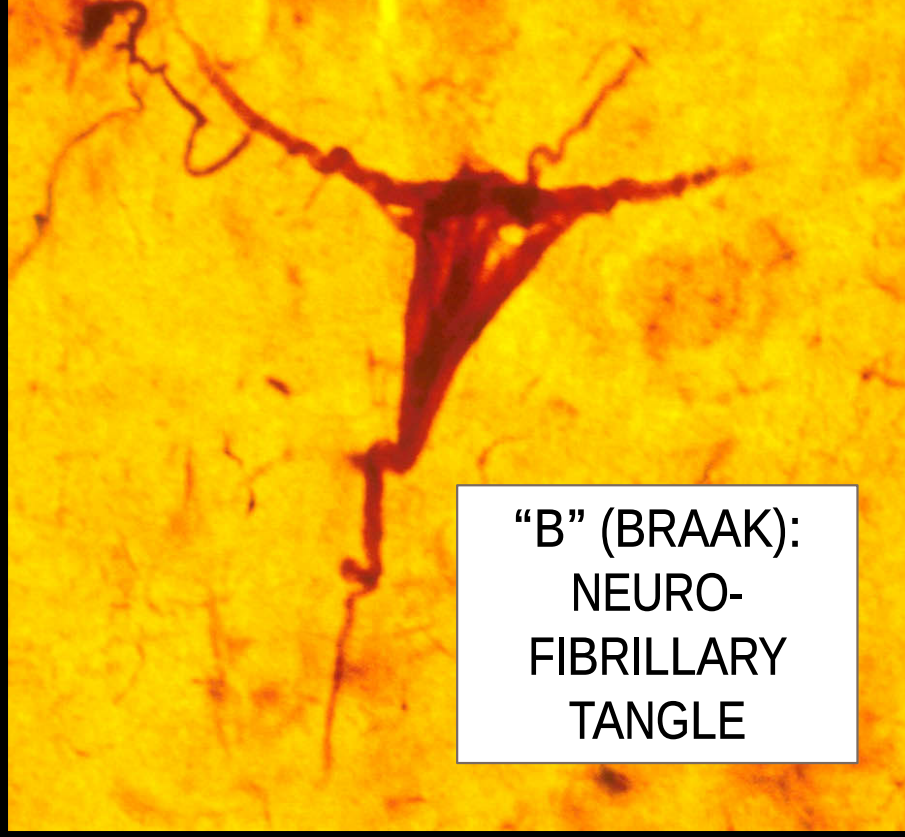
NIH/NIA  ADC Neuropathology Core



"C" (CERAD): NEURITIC AMYLOID PLAQUE



"A": Aβ PLAQUES



"B" (BRAAK): NEURO-FIBRILLARY TANGLE

# AD neuropathologic hallmarks

# 2012 NIA-AA consensus recommendation for AD diagnosis

Acta Neuropathol
DOI 10.1007/s00401-011-0910-3

CONSENSUS PAPER

## National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach

Thomas J. Montine · Creighton H. Phelps · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Charles Duyckaerts · Matthew P. Frosch · Eliezer Masliah · Suzanne S. Mirra · Peter T. Nelson · Julie A. Schneider · Dietmar Rudolf Thal · John Q. Trojanowski · Harry V. Vinters · Bradley T. Hyman

Cases with NFTs

Cases with no amyloid plaques

**Table 3** "ABC" score for level of AD neuropathologic change

| AD neuropathologic change | | B[a] | | |
|---|---|---|---|---|
| A[b] | C[c] | 0 or 1 | 2 | 3 |
| 0 | 0 | Not[d] | Not[d] | Not[d] |
| 1 | 0 or 1 | Low | Low | Low[e] |
| | 2 or 3[f] | Low | Intermediate | Intermediate[e] |
| 2 | Any C | Low[g] | Intermediate | Intermediate[e] |
| 3 | 0 or 1 | Low[g] | Intermediate | Intermediate[e] |
| | 2 or 3 | Low[g] | Intermediate | High |

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