Harmonized Clinical Diagnostic Criteria for the Incipient Symptomatic Stages of AD

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Knight ADRC Faculty and Staff

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Knight ADRC View of AD

- "Alzheimer disease" (AD) refers to the neurodegenerative brain disorder, regardless of clinical status, representing a continuous process of synaptic and neuronal deterioration
- AD has two major stages:
  - Preclinical (presymptomatic; asymptomatic), undetectable by current clinical methods
  - Symptomatic (clinical)
- Symptomatic AD is defined by intraindividual cognitive decline, from subtle to severe, that interfers with daily function, and can be subclassified on symptom severity:
  - Incipient (prodromal; mild cognitive impairment)
  - Dementia

Morris JC, Arch Neurol 2012; 69: 700-708.

What's in a Name?

- Semantics: relationship between words and what they mean
- Syndrome: associated clinical features occurring together
- Nosology: disease classification based on etiology, pathogenesis, or a set of symptoms (syndrome)
  - Alois Alzheimer correlated syndrome and pathology (1907)
  - Syndromic classifications lack specificity ("animals that fly" include distinct species such as bats and birds) and are insensitive to preclinical disease states
  - Future: base classifications on molecular pathology

Evolution of MCI Criteria

- Determining the degree of functional impairment that distinguishes MCI from dementia is "problematic" (Petersen, 2004)
- Revised criteria for "MCI due to AD" (Albert et al, Alzheimer's & Dementia, 2011)
  - Change in cognition, self-reported or noted by observer
  - Objective impairment in 1 or more cognitive domains
  - Independence in functional activities
  - Not demented
- However, definition of "functional independence" expanded
  - Permit "mild problems" in instrumental activities of daily living (IADLs), including shopping, cooking, and finances
  - Permit the need for aids and assistance in performing IADLs

What's in the "MCI due to AD" Name?

- Semantically imprecise: "independent function" does not mean independent function
- Syndromic classifications of MCI and very mild AD dementia now overlap
- Imposing dichotomous labels, "MCI due to AD" vs "AD dementia", on a continuous disease process produces nosological confusion
- As with the dementia syndrome, MCI has many possible causes but, also like dementia, the leading etiology for MCI is AD. When AD is the etiology, MCI represents the initial symptomatic stage of AD.

Key Symposium Work Group Consensus Recommendations to Harmonize Clinical Diagnostic Criteria for AD

Concept	"Alzheimer disease" refers to the brain disorder regardless of clinical status
Terminology	"Symptomatic AD" refers to the clinically expressed disorder, from very mild (encompassing "MCI due to AD" and "prodromal AD") to severe dementia
Biomarkers	On the successful completion of standardization efforts, molecular and degeneration biomarkers can be incorporated into the clinical diagnostic algorithm, particularly to help characterize atypical presentations
Memory	Amnestic presentations are the "typical" clinical phenotype for AD, but the diagnosis can also be made with non-amnestic presentations (especially with biomarker support)

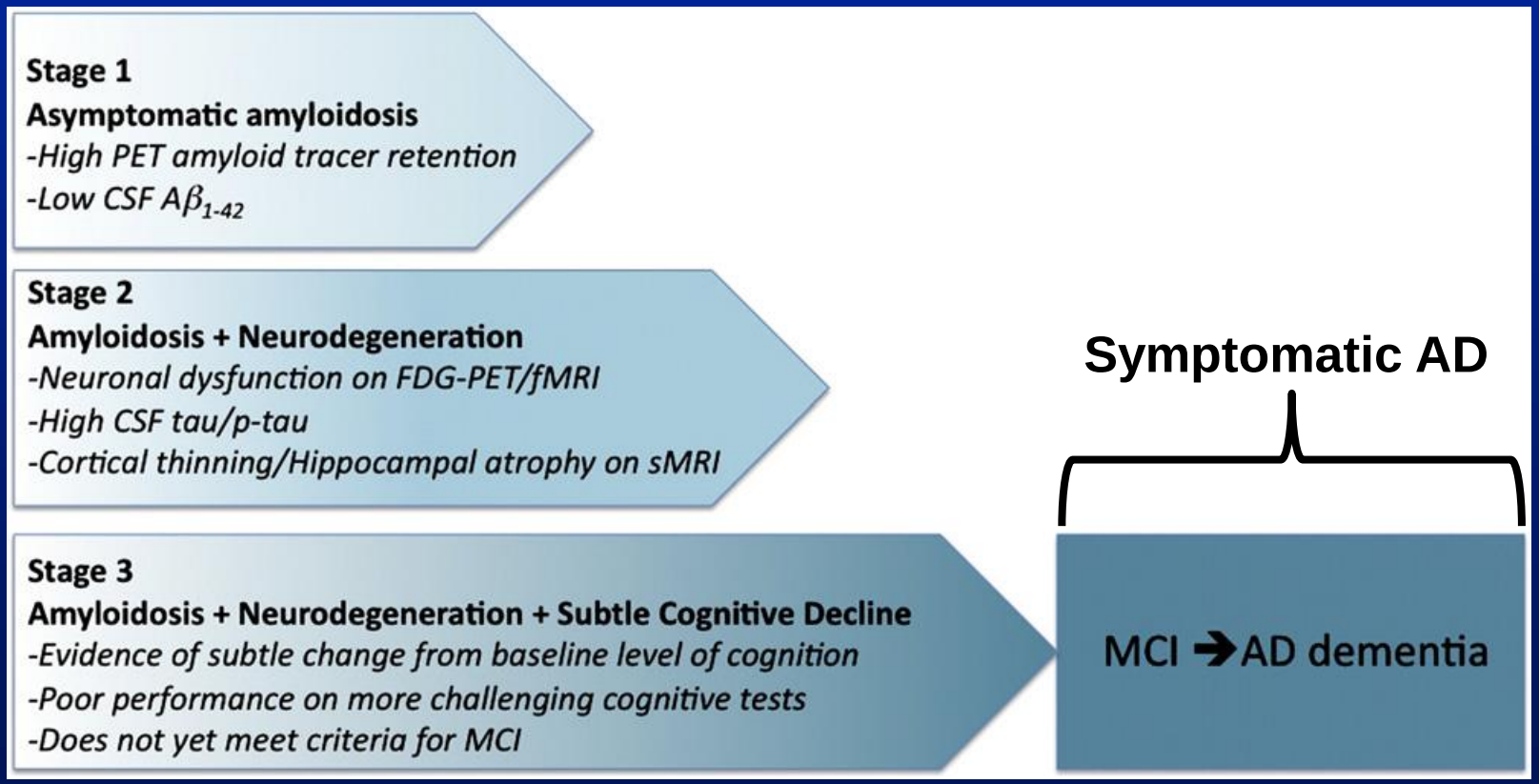
Morris JC, Blennow K, Froelich L, Nordberg A, Soininen H, Waldemar G, Wahlund L-O, Dubois B. J Int Med 2014; 275: 204-213.

Hypothetical Relationships of Aging, Preclinical AD, and Symptomatic AD

	Aging	Preclinical AD	Very Mild AD
Plaques in neocortex	None or a few diffuse plaques	Many neuritic & diffuse plaques	Many neuritic & diffuse plaques
Tangles in entorhinal cortex & hippocampus/CA1	Few to many (increases w/age)	Many	Many
Cell loss in entorhinal cortex & hippocampus/CA1	None	Little to none	Substantial (30%-60%)
Clinical diagnosis	Normal, CDR 0	Normal, CDR 0	Very mild dementia or MCI, CDR 0.5
Pathological diagnosis	Normal	AD	AD

Price and Morris, Ann Neurol 1999;45:358-368; Price JL et al, Arch Neurol 2001;58:1395-1402; Morris and Price, J Mol Neurosci 2001;17:101-118

Staging Framework for Preclinical AD



Sperling RA et al., Alzheimer's & Dementia 2011; 7:280-292

Characterizing the Transition from Cognitive Normality to Impairment: A Case Study

Baseline

- 82y; prostate cancer at age 52; current good health (simvastatin only prescrip med); neuro exam unremarkable
- 9y of education (GED later); oil distributor, retired at age 72; no known fam hx of dementia
- Built current home after retirement; chairs board for local bank; church deacon; exercises daily
- Dgtr notes “very slight” decline in memory and temporal disorientation in past year, but it is not a “problem”
- P: “lost” credit card, c/o difficulty recalling names

Characterizing the Transition from Cognitive Normality to Impairment: A Case Study

1 Year F/U

- Recurrent prostate cancer, completed radiation therapy; now has hearing aid
- Dgtr notes decline in his judgment & problem solving (e.g., mistakes making a shelf)

2 Year F/U

- 84y; dgtr notes P has difficulty with time relationships x 3 y, is less “efficient” and has “trouble processing”, makes repeat trips to store, and had several “fender benders”; still chairs bank board, active in church
- P notes “slower STM” x 5y

Clinical Assessment

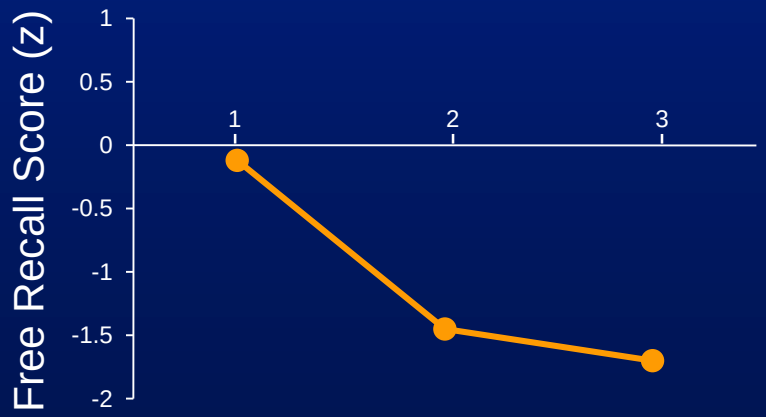
	Baseline	1 Y F/U	2Y F/U
MMSE	24 (complained "could not hear" questions)	27	30
GDS (15 item) - Item 10 ("more memory problem than most")	0 N	2 N	2 N
FAQ	0	0	0
CDR - global - CDR-SB	 0 0	 0 0	 0 0

Subsequent Course

- Worsening metastatic prostate cancer
- Died in hospice at age 86
- Retrospective interview with dgtr: any cognitive problems from age 84 to death were not clearly independent from analgesic meds and terminal medical condition

Psychometric Performance

- No change from T1 to T3
  - Logical Memory-I, Logical Memory-D, Associate Learning, Boston Naming, Fluency for “S” and “P”, Digit Symbol, WAIS Information, Letter-Number Sequencing
- Worse performance at T3 compared with T1
  - Selective Reminding Test Free Recall
  - Trailmaking B
  - Animal Fluency



Brief Measures of "Subtle Cognitive Decline"

Subjective Cognitive Decline	+/–: P c/o "poor STM", but did not officially endorse a "problem" at any assessment
Brief Objective Screening Test (MMSE)	–: P improved from 24 to 30 over 2y
Brief Informant Report (AD8) at age 84	+: "Yes" to "poor judgment", "yes" to temporal disorientation; 2 or more "yes" answers indicate abnormal AD8

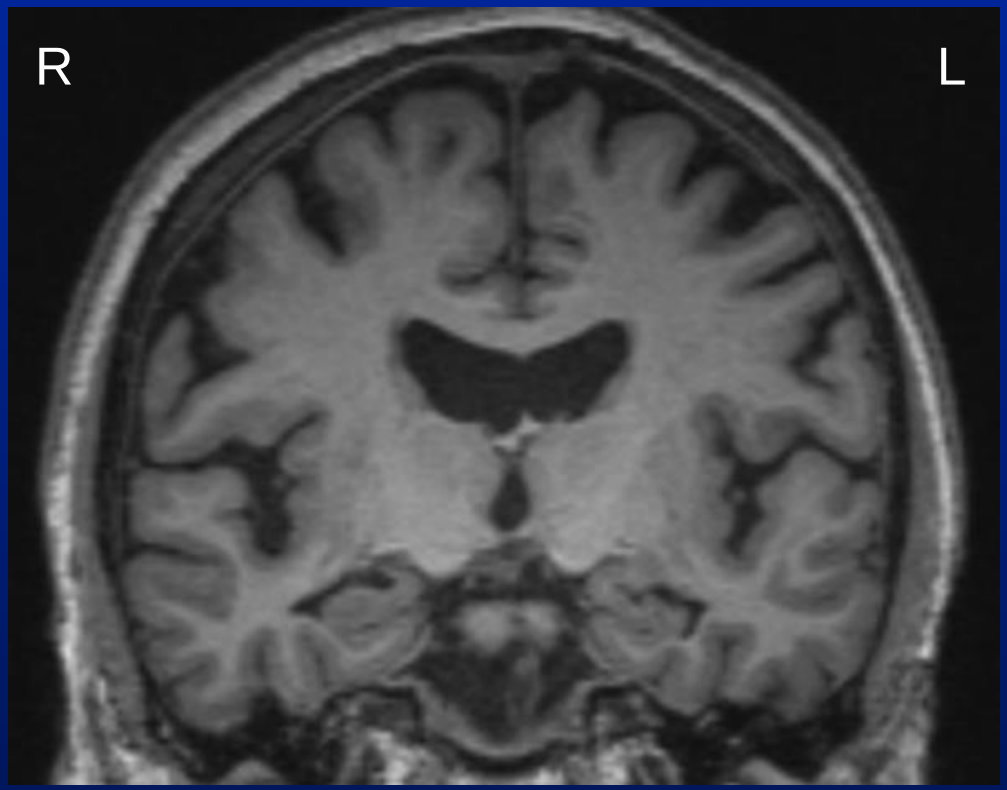
Biomarker Evidence of Preclinical AD

- CSF (age 82)

Aβ42	323.6	(cutoff: <608 pg/ml)
Tau	784.7	(cutoff: >339 pg/ml)
P-tau	122.2	(cutoff: >67 pg/ml)

- APOE 3/4

MRI (Age 82y)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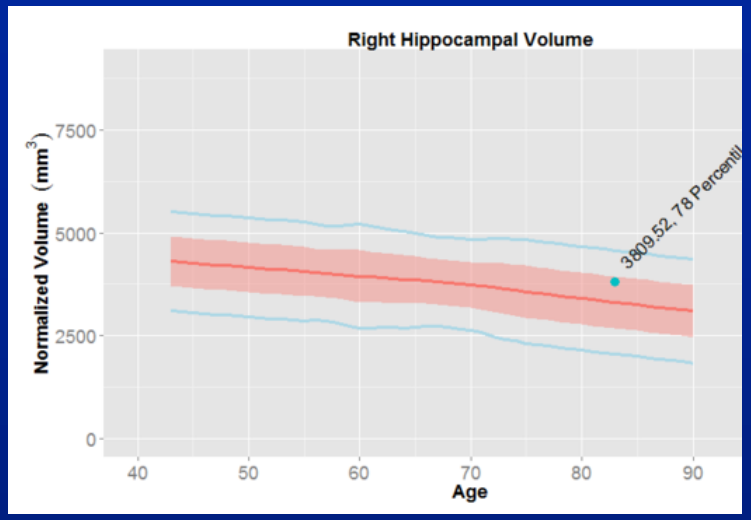
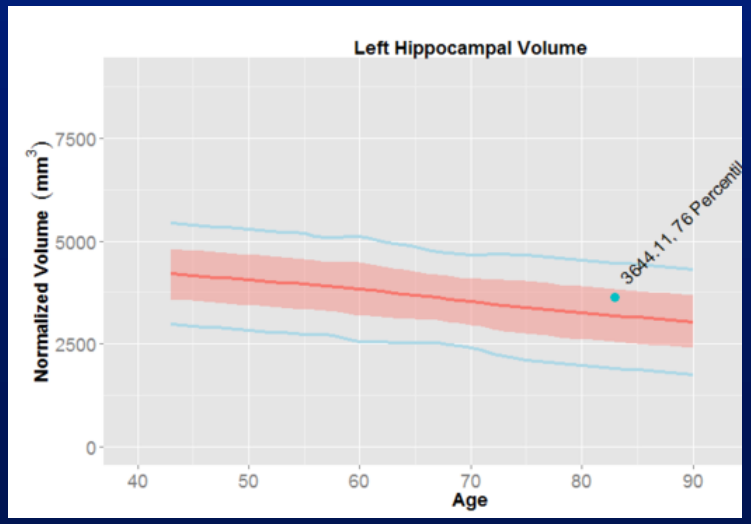
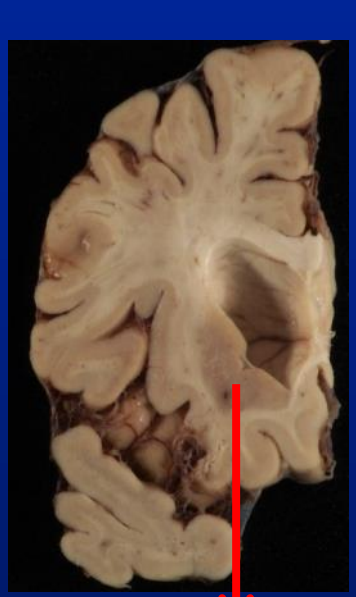
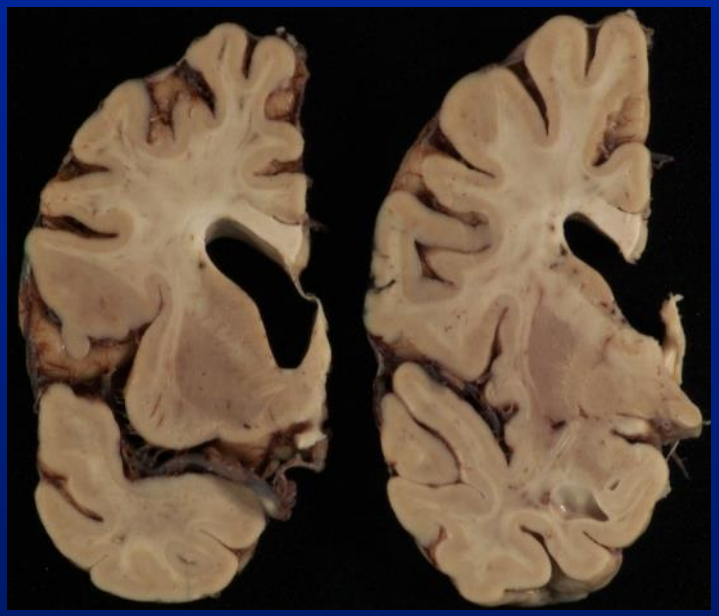

Right Hippocampal Volume
Normalized Volume (mm3)
7500
5000
2500
0
40
50
60
70
80
90
Age
3809.52, 78 Percentil

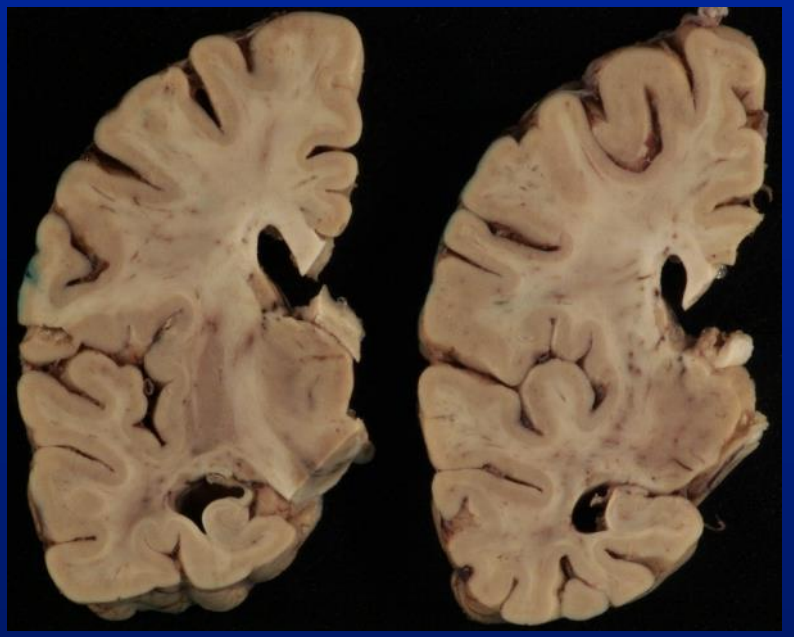

Left Hippocampal Volume
Normalized Volume (mm3)
7500
5000
2500
0
40
50
60
70
80
90
Age
3644.11, 76 Percentil

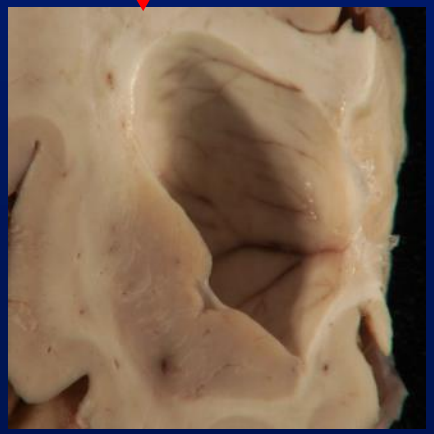
Macroscopy *(PMI: 7 h; fresh brain weight: 1,237 g)*

- Mild atrophy of the frontal, temporal, and parietal lobes and of the hippocampus

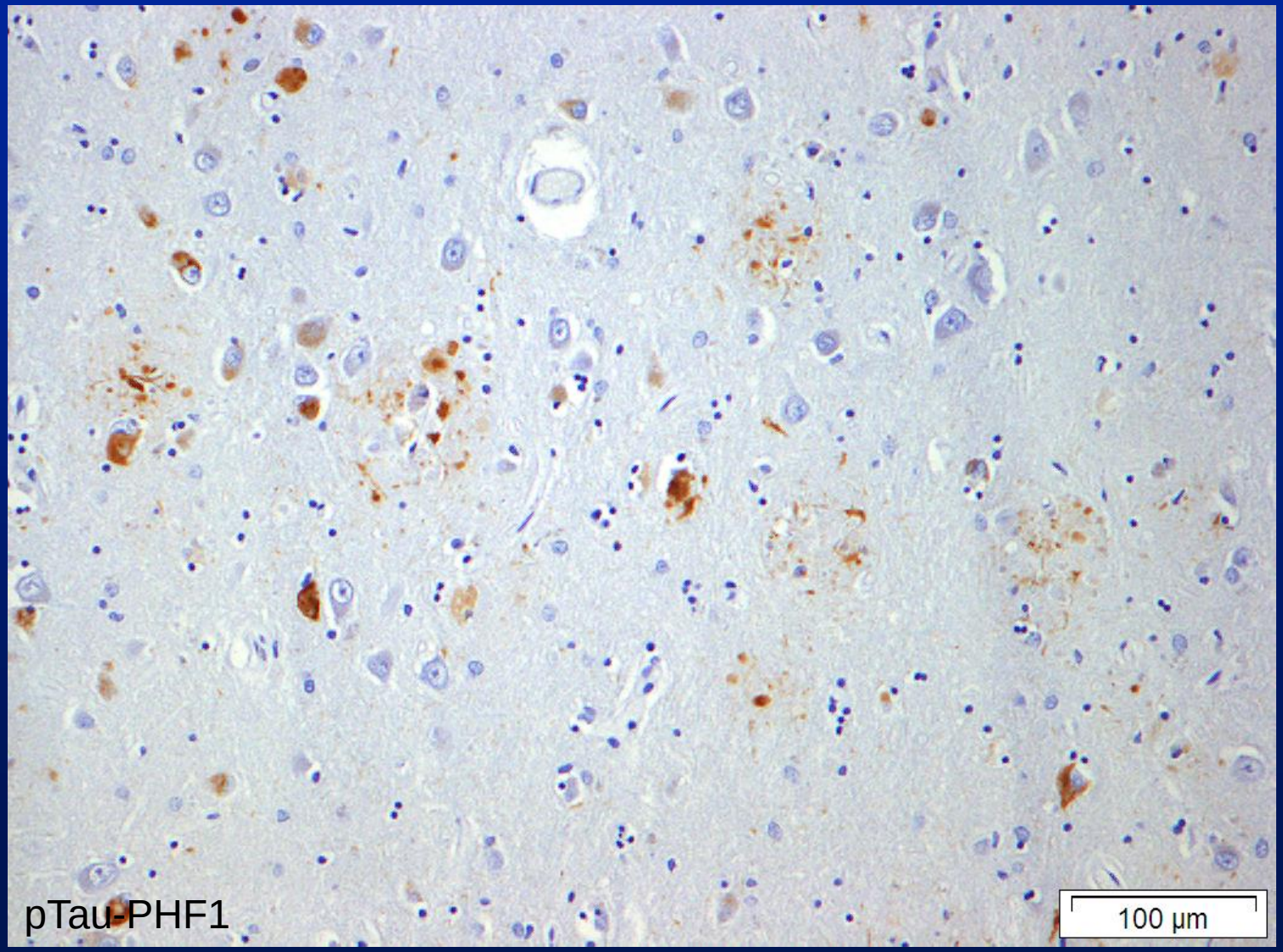




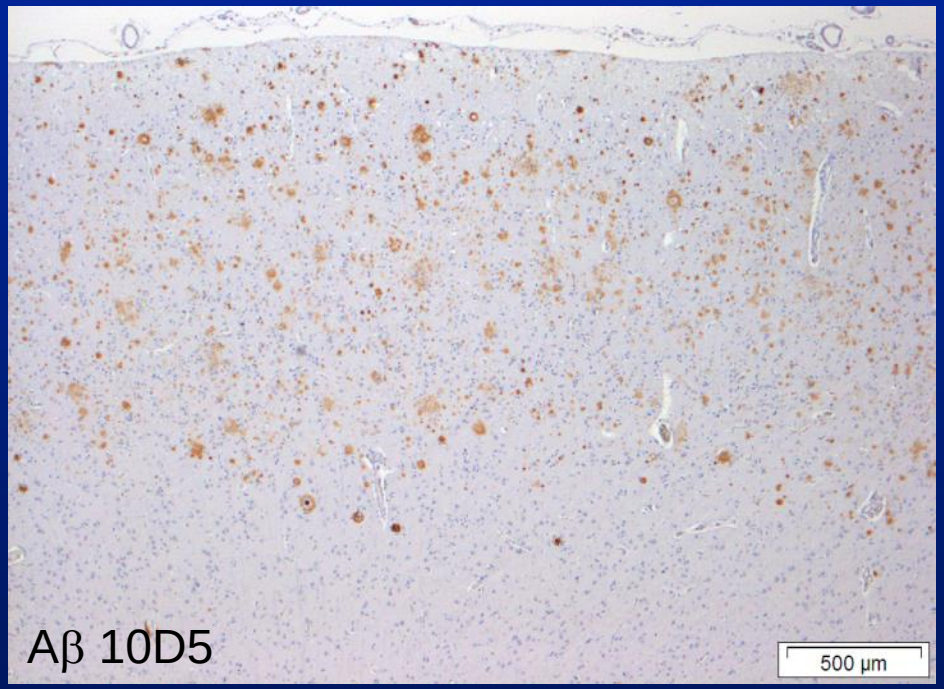


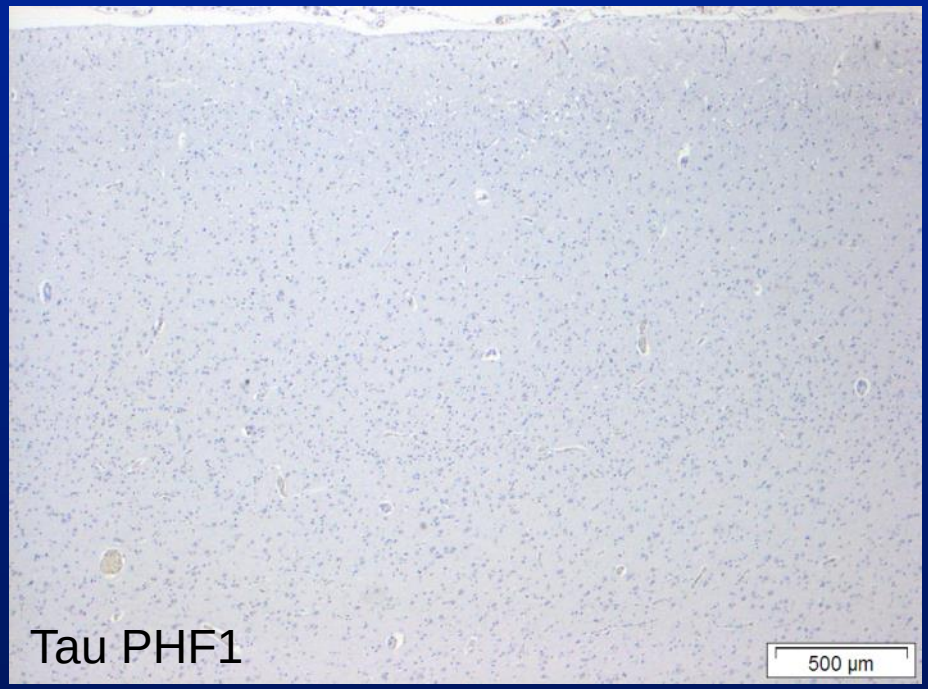


Neuritic Plaques and Neurofibrillary Tangles in Entorhinal Cortex



Aβ Plaques but no Neuritic Plaques or Neurofibrillary Tangles in Frontal Lobe





ABC Score (NIA-AA ADNC): A3 (Thal plaque stage 4/5); B2 (Braak stage III/IV; C1 (neuritic plaques sparse) – Intermediate

Hypotheses

- At baseline, P had preclinical AD with amyloidosis and neurodegeneration (CSF)
- From baseline, P was experiencing the “subtle cognitive decline” that is postulated for Stage 3 of preclinical AD
- The duration of Stage 3 can be ≥4 y (CDR 0 at baseline and at expiration 4y later)
- The pathological correlate of “subtle cognitive decline” is the breach of synaptic/neuronal integrity