What is the Etiology of Amyloid Negative Amnestic Mild Cognitive Impairment?

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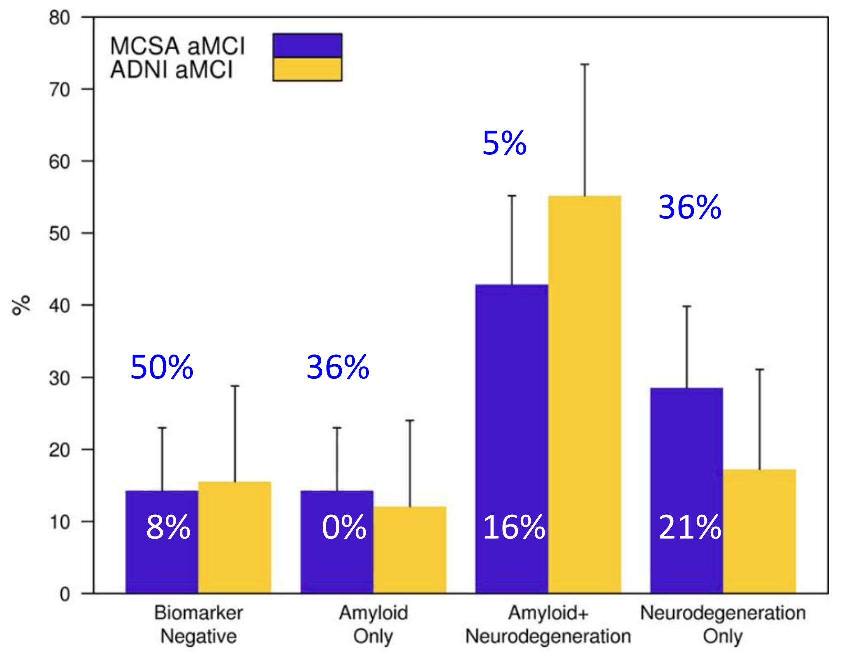
Disclosures: Nothing to disclose

Amyloid Negative Amnestic MCI

- ~50% in some studies of a-MCI
  - Variable rates of progression to dementia
    - ~10-25% over 3 years in recent studies (Rowe *et al.*, 2013; Doraiswamy *et al.*, 2014; Wolk et al., AAIC, 2014)
  - Variable association with neurodegenerative markers of AD
    - "SNAP MCI" (Jack et al., 2012)
    - Potentially modulates risk of progression
    - Likely reflects differences in underlying etiology of cognitive impairment
    - Little work examining phenotypic differences between these groups (and relative to amyloid positive individuals)

Outcomes in MCI Based on Biomarker-Defined Groups

- Petersen et al., Annals of Neurology, 2013
  - Mayo Clinic Study of Aging (n=126); ADNI (n=58)
  - PiB PET, FDG PET, and Hippocampal volume
  - Neurodegeneration = abnormal FDG PET and/or Hippocampal volume
  - Cut-offs were 10th percentile of AD distribution



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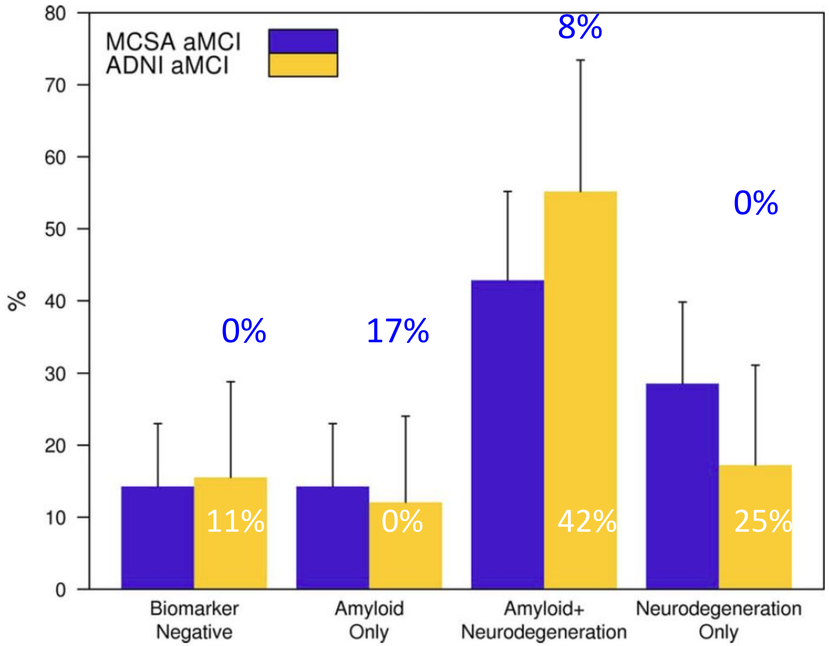
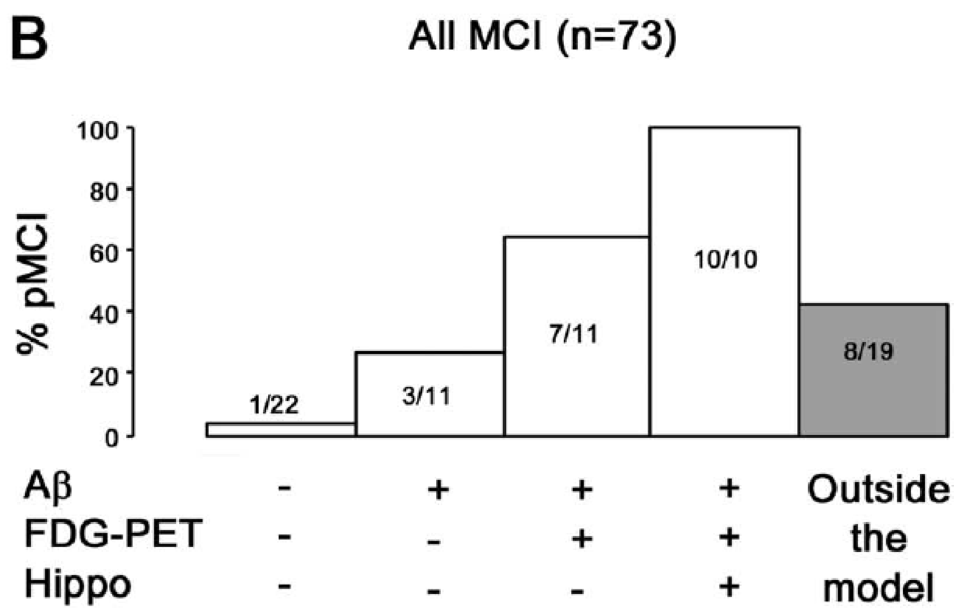


Outcomes in MCI Based on Biomarker-Defined Groups

- Prestia et al, Neurology, 2013 (n=73)
  - CSF Aβ, FDG PET, and Hippocampal volume
    - Applied standard cutoffs for center
  - Divided into groups that were proposed to fit or be "Outside the Model" (e.g. hippo atrophy, but normal amyloid)

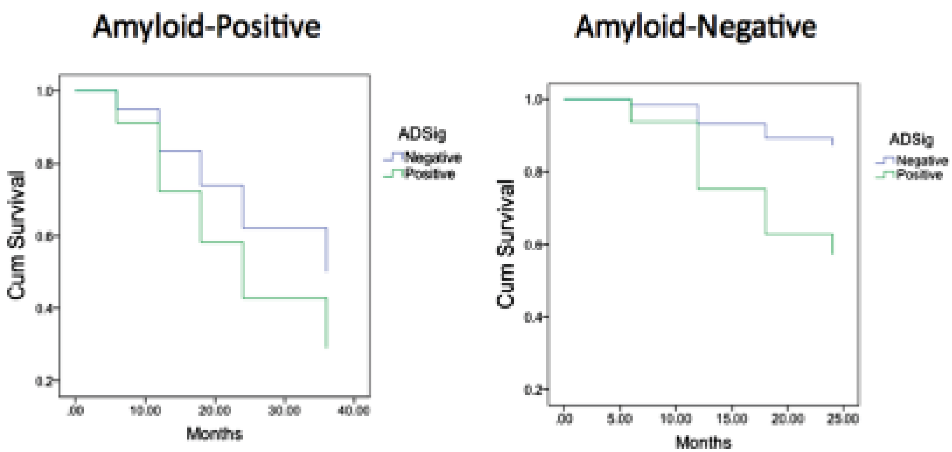


- 15 patients "Outside of the Model" had positive neurodegenerative markers, but negative amyloid
  - 7 converted to AD (47%)

Neurodegeneration Independent of Amyloid Status Predicts Progression

	X^2	HR	95% CI
AD signature	13.7 ($p < 0.001$)**	1.61	1.25–2.08
AD signature dichotomous	12.9 ($p < 0.001$)**	2.28	1.44–3.63
CSF amyloid-β dichotomous	12.2 ($p < 0.001$)**	3.66	1.68–7.99
CSF amyloid-β	7.4 ($p < 0.01$)*	1.42	1.10–1.83
CSF p-tau	9.2 ($p < 0.01$)*	1.47	1.15–1.90
CSF t-tau	5.5 ($p < 0.05$)*	1.33	1.05–1.70
Hippocampal volume	4.8 ($p < 0.05$)*	1.31	1.03–1.67
Combination of CSF dichotomous amyloid-β and AD signature	19.4 ($p < 0.0001$)**	Aβ 3.0 ADsig 1.4	1.38–6.7 1.07–1.77

*$p < 0.05$, **$p < 0.005$.



Dickerson & Wolk, *Frontiers Aging Neuroscience*, 2014

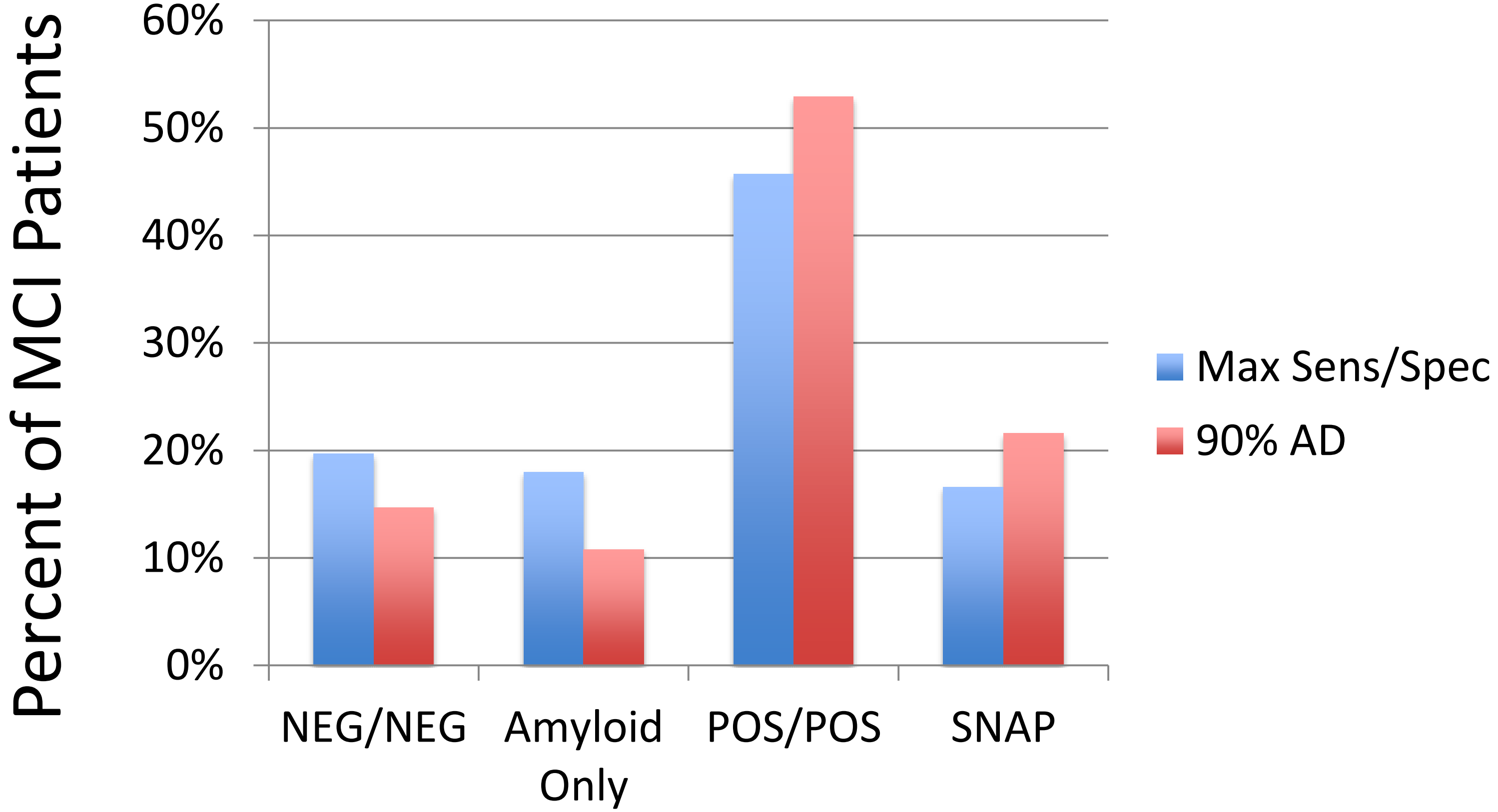
MCI Study

- ADNI GO/2 baseline a-MCI patients
- Required CSF, FDG PET, and MRI data (361 participants)
- Cutoffs
  - CSF Aβ ≤ 191 pg/ml (Shaw et al., 2009)
  - Neurodegeneration
    - Based on maximum sensitivity/specificity between amyloid negative controls and amyloid positive AD patients
    - FDG PET meta-ROI (Landau et al., 2012)
    - ICV-corrected hippocampal volume
    - Either FDG PET and/or hippocampal volume needed to be below cutoff
- Additional Imaging measures
  - White matter hyperintensity (Decarli et al., 2005)
  - Florbetapir composite ROI (Landau et al., 2012)
  - Automated Segmentation of Hippocampal Subfields (Yushkevich et al., 2014)
  - SPARE AD score (Davatzikos et al., 2009)

Amnestic MCI Subgroups

	AMY-NEU-	AMY+NEU-	AMY+NEU+	SNAP
Percent (n)	19.7% (71)	18.0% (65)	45.7% (165)	16.6% (60)
Age	67.1 (6.6)[a,b,c]	71.0 (8.0)[d]	73.8 (6.5)	73.3 (7.7)
Sex (% men)	46.5	58.5	57.6	51.7
Education	16.4 (2.3)	16.2 (2.8)	16.2 (2.6)	16.1 (2.9)
APOE 4 (%)	22.5[a,b]	60.0[e]	67.99[f]	16.7
CDR SUM	1.16 (0.5, 3.5)[b]	1.28 (0.5, 4.0)[d]	1.78 (0.5, 7)[f]	1.25 (0.5, 3.5)
MMSE	28.9 (1.1) [b,c]	28.5 (1.6) [d]	27.5 (1.8) [f]	28.1 (1.8)

MCI Biomarker Groups



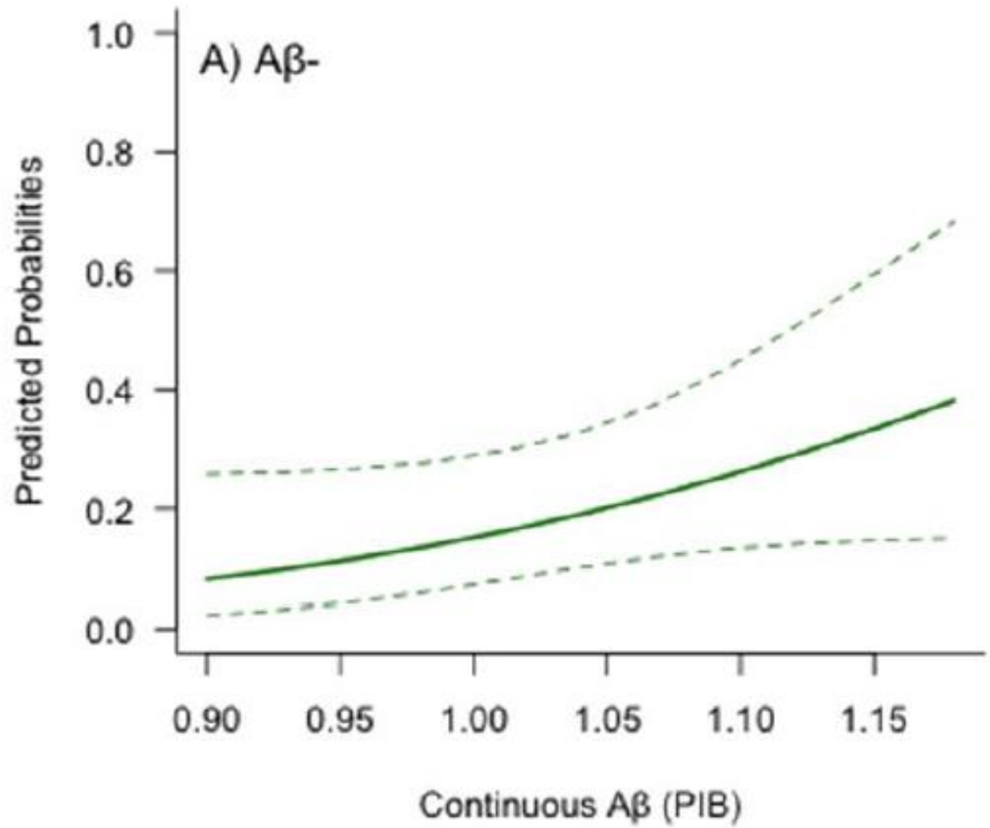
Are SNAP Cases Associated with Sub-threshold Amyloid?

	SNAP	NEG/NEG	Controls	POS/POS
CSF Abeta (pg/ml)	232.4 (28.3)	232.4 (26.3)	234.8 (26.1)	137.1 (25.5)
Amyvid (SUVR)	1.00 (0.06)	1.02 (0.07)	1.02 (0.07)	1.34 (0.20)

Logistic regression model predicting SNAP status revealed no evidence of a relationship of CSF Abeta or Amyvid uptake and group status

Are SNAP Patients Really Amyloid Negative

- Perhaps issue of A-Beta Cutoff
- In cognitively normal adults, subthreshold A-Beta, measured by PiB, associated with increased probability of neurodegeneration
- Also, associated with increased risk of decline



Mormino et al., *JAMA Neurology*, 2014

What is the Cognitive Profile of Amyloid Negative Patients

	Controls	NEG/NEG	SNAP
Immediate Memory (z-score)	.00 (.85)	-0.17 (.75)	-0.67 (0.65)
Delayed Recall (z-score)	.00 (.85)	-0.22 (.98)	-0.96 (.90)
Recognition Memory (z-score)	.00 (.84)	-0.20 (.82)	-0.78 (1.0)
LM Delay Recall (z-score)	.00 (1.0)	-1.86 (.73)	-2.05 (.82)
Trails A (z-score)	0.00 (1.0)	-0.18 (1.2)	-0.72 (1.4)
Trails B (z-score)	0.00 (1.0)	-0.17 (.84)	-0.70 (1.4)
Category Fluency (z-score)	0.00 (1.0)	-0.27 (.91)	-0.75 (.87)
BNT (z-score)	0.00 (1.0)	-0.37 (1.0)	-0.60 (1.3)
ANART Errors	7.9 (6.1)	10.9 (7.3)	13.38 (9.1)

Does SNAP Differ From Prodromal AD?

	Controls	SNAP	POS/POS	POS/POS Matched
Number	87	60	165	60
Age	72.6 (6.0)	73.3 (7.7)	73.8 (6.5)	72.7 (6.8)
Education	16.8 (2.6)	16.1 (2.9)	16.2 (2.6)	16.6 (2.5)
Hippocampal Volume (z-score)	0.0 (1.0)	-1.28 (1.0)	-1.51 (1.0)	-1.28 (1.0)
FDG PET (z-score)	0.0 (1.0)	-0.52 (1.0)	-1.28 (1.2)	-1.26 (1.3)
SPARE AD	-1.32 (.47)	-0.51 (.92)	-0.19 (.89)	-0.39 (.84)

Does SNAP Differ from Prodromal AD

	SNAP	POS/POS Matched
Immediate Memory (z-score)	-0.67 (.65)	-.79 (.57)
Delayed Recall (z-score)	-0.96 (.90)	-1.57 (.86)
Recognition Memory (z-score)	-0.78 (1.0)	-1.19 (.87)
Trails A (z-score)	-0.72 (1.4)	-1.50 (2.3)
Trails B (z-score)	-0.70 (1.4)	-1.26 (1.7)
Category Fluency (z-score)	-0.75 (.87)	-0.91 (.88)
BNT (z-score)	-0.60 (1.3)	-0.81 (1.5)

SNAP Group Mostly Associated with Hippocampal Atrophy

	HIPPO+	FDG+	HIPPO+FDG+
Number (%)	43	9	8
Age	72.5 (7.5)	73.2 (9.3)	77.5 (6.6)
APOE 4 (%)	16.3	22.2	12.5
FDG PET (z-score)	-0.05 (.80)	1.14 (.05)	-1.70 (.32)
Hippo (z-score)	-1.53 (.71)	4.07 (0.16)[c]	-1.82 (1.1)
Spare AD	-0.56 (.92)	-0.82 (.83)	0.11 (.89)
CDR Sum of Boxes	1.14 (.59)	1.33 (.66)	1.75 (1.1)
MMSE	28.3 (1.5)	29.1 (1.5)	25.9 (1.6)
Amyvid (SUVR)	1.00 (.06)	1.01 (.07)	0.98 (.06)
CSF Abeta (pg/ml)	234.0 (26.6)	240.8 (39.7)	214.4 (16.0)

Outcomes

	AMY-NEU-	AMY+NEU-	AMY+NEU+	SNAP
12 Months				
NL (%)	9.2	3.4	2.5	0
MCI (%)	87.7	94.9	77.2	96.4
AD (%)	3.1	1.7	20.3	3.6
24 Months				
NL (%)	10.3	6.7	3.2	2.3
MCI (%)	87.9	88.9	54.4	95.5
AD (%)	1.7	4.4	42.4	2.3

Potential Etiologies of SNAP

- Hippocampal greater than cortical involvement
- No biomarker evidence of amyloid pathology
- Somewhat older in age relative to amyloid-negative MCI patients without neurodegeneration
- Low APOE e4 carrier rate
- Significant memory loss, but other domains involved to variable extent

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CONSENSUS PAPER

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

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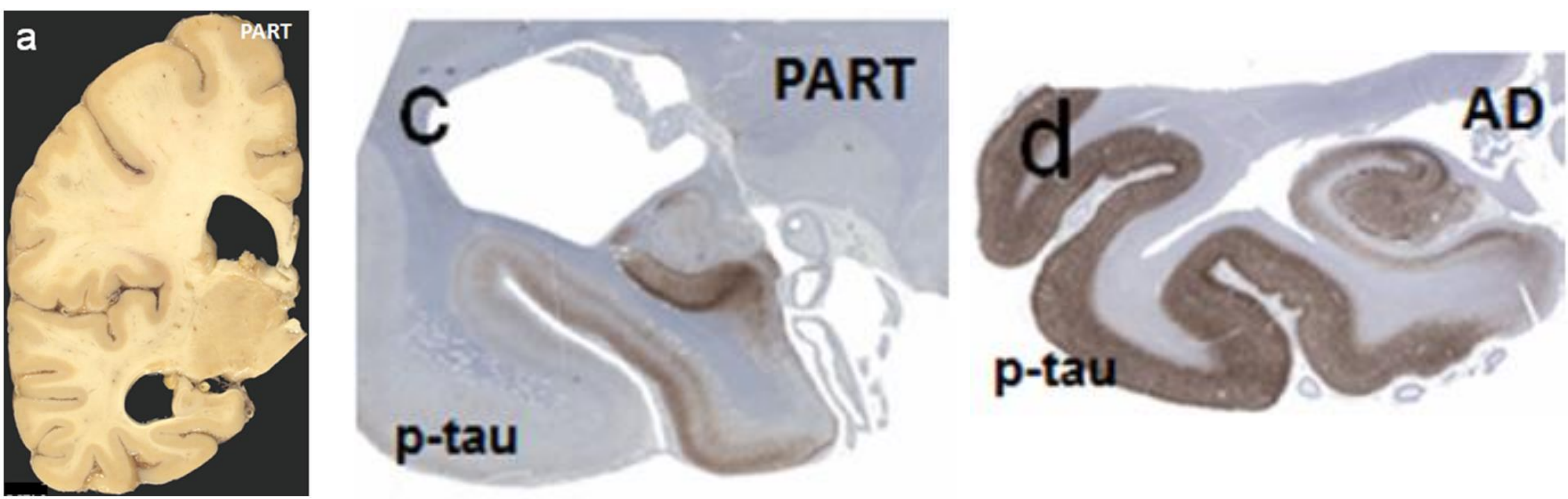


Table 2 Primary age-related tauopathy (PART): working classification

1. Requires

NFTs present with Braak stage ≤IV (usually III or lower)

2. Then subclassify as follows

Category	Thal Aβ Phase[a]	Other disease associated with NFT[b]
Definite	0	Absent
Possible	1–2	Absent

Examples

Primary age-related tauopathy (PART), Definite, Braak stage II

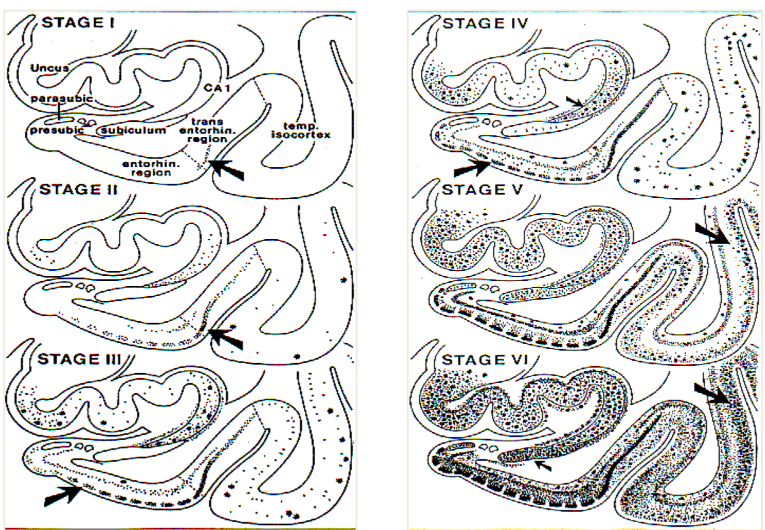
Primary age-related tauopathy (PART), Possible, Braak stage III, Thal Aβ phase 2

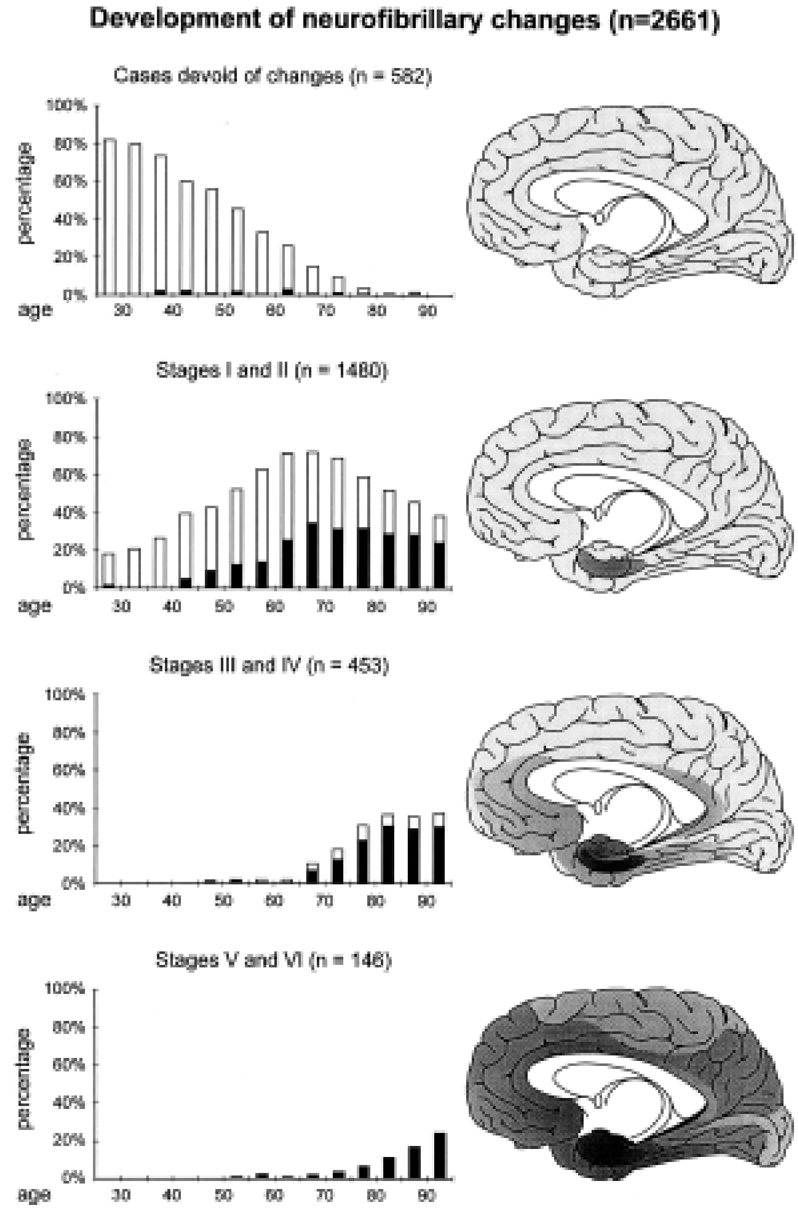
3. Ancillary studies (not required)

Immunohistochemistry: 3R and 4R tau-positive

Electron microscopy: paired helical filaments present

Genetics: absence of pathogenic FTLD-tau mutation





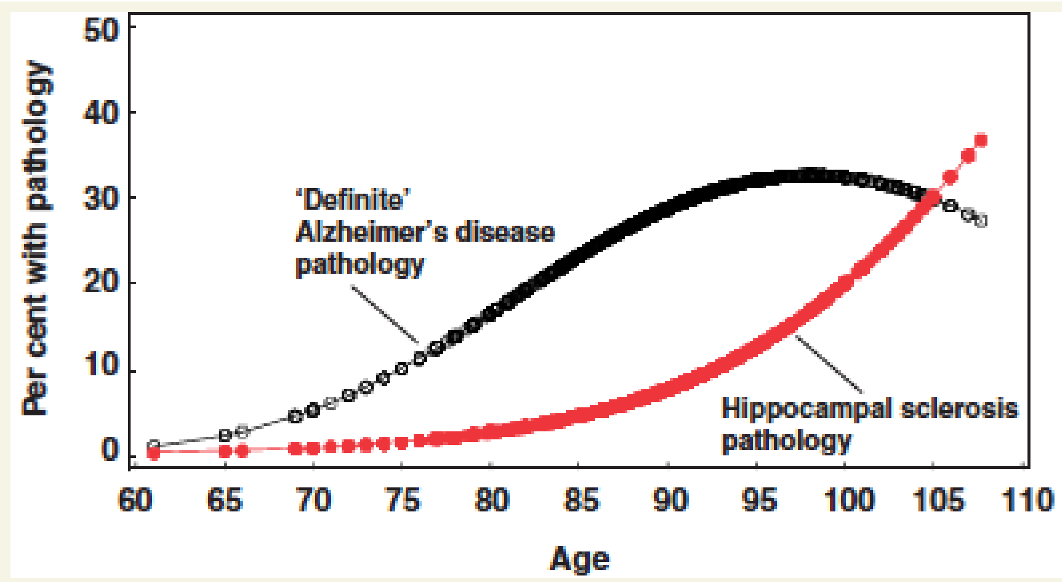
Braak & Braak, 1991; 1997

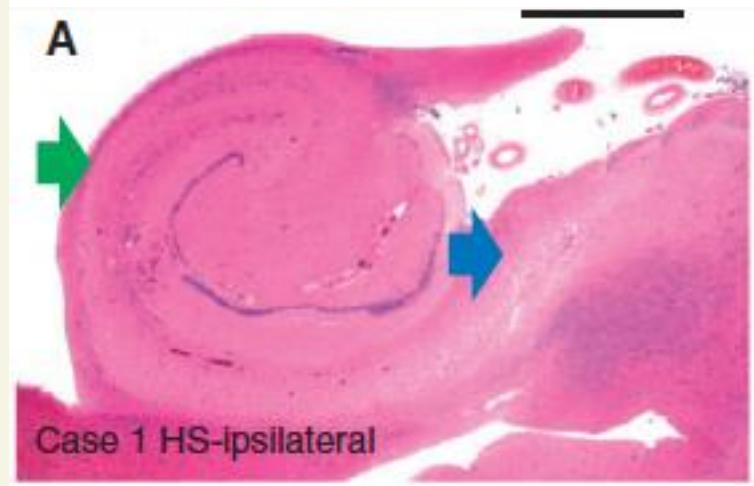
PART Associated with Older Age, Low ApoE e4 carrier Rate, and Mild Cognitive Decline

	Amyloid plaque density	Braak stage				
		0	I	II	III	IV
Number of subjects						
PART, definite	None	11	22	25	15	15
PART, possible	Low	4	16	27	16	31
–	Mod	2	11	15	32	50
–	High	3	7	10	39	83
Age at death (average)						
PART, definite	None	81.3	82.4	88.5	88.4*	92.0*,**
PART, possible	Low	88.4	80.4	84.7	89.7*	87.6*
–	Mod	89.0	80.2	87.4*	84.9	86.5
–	High	77.0	84.9	86.7	85.3	84.6
Final MMSE scores						
PART, definite	None	28.0	28.4	26.5	25.1***	24.3***
PART, possible	Low	28.5	25.8	24.4	24.6	21.9*
–	Mod	26.5	26.8	27.3	23.2*	19.8*
–	High	25.5*	24.5	27.9*	21.2*	18.8*,**
APOE ε4 positive (%)						
PART, definite	None	9.1	13.6	0.0	20.0	13.3
PART, possible	Low	25.0	12.5	14.8	37.5	35.5*
–	Mod	0.0	36.4	13.3	34.4*	50.0*
–	High	66.7*	28.6	50.0*	33.3*	56.6*,**

Crary et al., ACTA Neuropath, 2014

Hippocampal Sclerosis





Cohort	Total stained for TDP-43 (*n*)	Average age at death (years)	HS-Ageing evaluated for TDP-43 (*n*)	HS-Ageing with TDP⁺ *n* (%)	HS-NEG evaluated for TDP-43 (*N*)	HS-NEG with TDP⁺ *n* (%)
UK-Alzheimer's Disease Centre	208	84.3	23	15 (65)	185	15 (5)
Nun Study	48	92.8	48	43 (90)		
Georgia centenarians	50	102.2	8	8 (100)	42	7 (17)
Total	306	88.6	79	66 (89.9)	227	22 (9.7)

Nelson et al., Brain, 2011

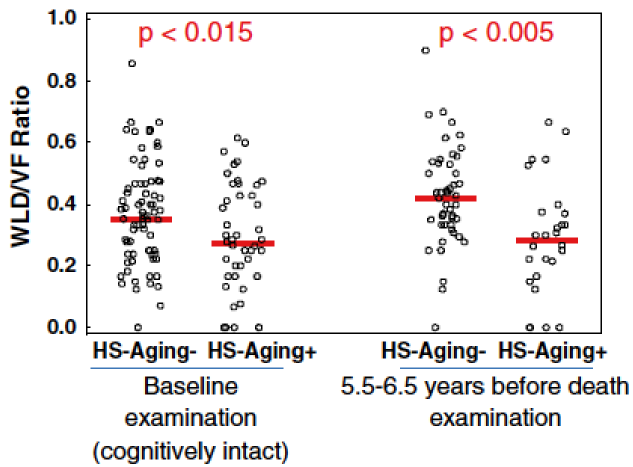
Cognitive Phenotype of HS

	HS-Ageing negative				HS-Ageing positive			
	Alzheimer's disease negative	*n*	Alzheimer's disease positive	*n*	Alzheimer's disease negative	*n*	Alzheimer's disease positive	*n*
At intake								
Test scores (average ± SEM)								
MMSE	27.8 ± 0.3	52	27.5 ± 0.4	23	27.6 ± 0.4	30	26.2 ± 0.6	13
Verbal fluency	16.7 ± 0.6	52	15.1 ± 0.9	23	16.3 ± 0.8	30	14.5 ± 1.2	13
Word list delay	5.9 ± 0.4	52	5.7 ± 0.5	23	5.1 ± 0.5	30	3.7 ± 0.7	13
Word list delay/verbal fluency	0.36 ± 0.02	52	0.39 ± 0.04	23	0.32 ± 0.03	30	0.26 ± 0.05	13
5.5–6.5 years prior to death								
Test scores (average ± SEM)								
MMSE	27.6 ± 0.9	37	25.0 ± 1.6	12	25.4 ± 1.1	25	18.7 ± 2.7	4
Verbal fluency	16.5 ± 0.9	37	12.9 ± 1.6	12	13.9 ± 1.1	25	12.0 ± 2.7	4
Word list delay	6.8 ± 0.4	37	5.7 ± 0.8	11	4.2 ± 0.5	25	2.1 ± 1.3	4
Word list delay/verbal fluency	0.42 ± 0.03	37	0.43 ± 0.05	10	0.30 ± 0.04	24	0.20 ± 0.10	3

Neurocognitive test scores in HS-Aging:

Word list delayed recall (WLD)/Verbal fluency (VF) ratio

N= 43 cases with subsequent autopsy confirmed HS-Aging pathology, and N=75 controls



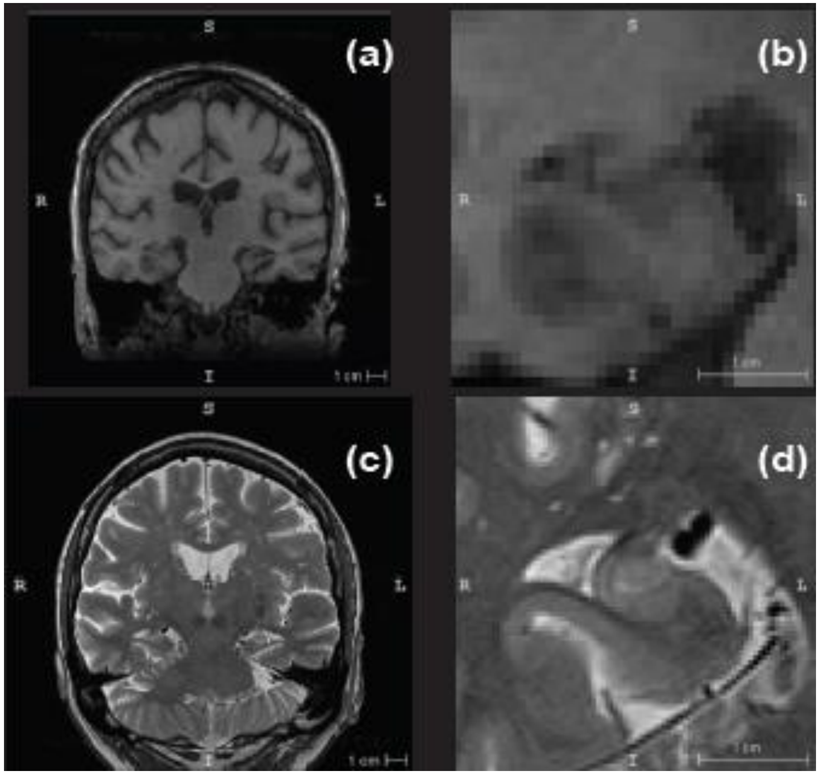
- Delayed Recall on CERAD Word-list divided by Category Fluency (animals)
- Ratio lower in HS, regardless of the presence of AD pathology
- Likely non-specific measure of hippocampal pathology

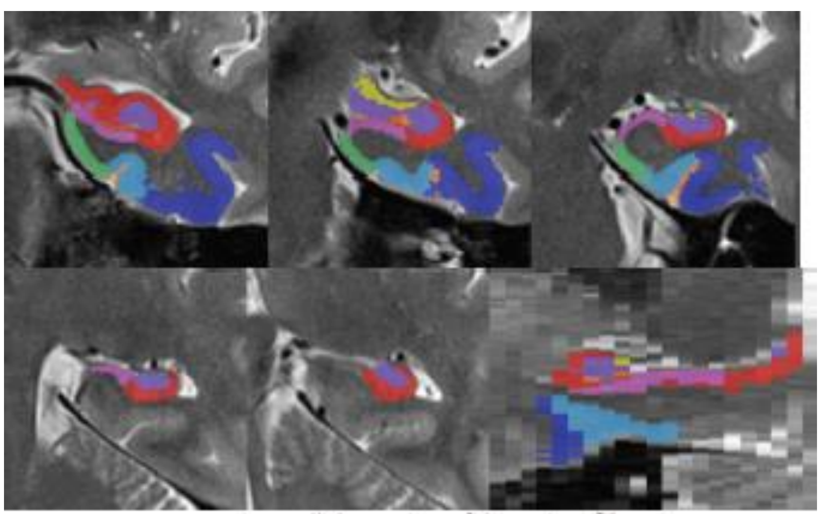
Potential Etiologies of Hippocampal Sclerosis

- Hippocampal Sclerosis of Aging
  - TDP-43 positive in ~90%
  - APOE does not alter risk
  - Not clearly related to AD pathology
- Taupathy
  - Non-AD tauopathy (agryrophilic grain disease, PSP)
- FTD, non-tauopathy
  - Associated with FTD syndrome, earlier onset
- CVD
  - HS co-exists with other CVD sequelau, less progressive

SNAP Associated with Increased White Matter Hyperintensities, but Not Elevated CSF Tau

	SNAP	Controls	NEG/NEG	POS/POS
CSF T-Tau	59.6 (27.9)	61.0 (24.9)	53.6 (26.0)	112.3 (58.3)
CSF P-Tau	27.81 (14.5)	30.5 (14.0)	27.3 (13.5)	51.3 (24.5)
WM Hyperintensity (z-score)	-0.46 (1.12)	0.00 (1.0)	0.09 (.93)	-0.71 (1.1)
Delayed Recall/Cat Fluency	0.29 (.14)	0.34 (.12)	.34 (.12)	.22 (.15)





	Controls (n=19)	SNAP (n=8)
CA1 (mm3)	1114.6 (198.1)	869.6 (187.8)
DG (mm3)	732.4 (128.0)	558.6 (154.7)
Subiculum (mm3)	268.6 (62.8)	225.3 (70.5)
ERC Thickness (mm)	2.51 (.68)	1.59 (.75)
BA35 Thickness (mm)	2.04 (.58)	1.28 (.58)
BA36 Thickness (mm)	2.71 (.50)	1.79 (.62)

- Atrophy includes hippocampus proper, but also extrahippocampal MTL structures
- Consistent with Braak tau staging in MTL

Conclusions

- Amyloid Negative Amnestic MCI in the absence of evidence of neurodegeneration in AD pattern
  - Represents about half of amyloid negative cases
  - Associated with minimal objective cognitive impairment despite designation
  - Higher rate of reversion than conversion (but mostly stable)
  - A significant proportion may not have an underlying neurodegenerative process with perhaps reduced cognitive reserve

Conclusions

- SNAP is also relatively common
  - Stable with low rate of conversion in this cohort over 2 years
  - No evidence of subthreshold amyloidosis based on current biomarkers
  - Perhaps more focused MTL/Hippocampus involvement that cortical dysfunction
  - Clear cognitive impairment with memory involved, particularly retrieval, but other domains affected
    - Less so than in prodromal AD
  - Likely somewhat heterogeneous in etiology
    - Number of features consistent with PART
    - Subcortical CVD may contribute to cognitive symptoms and hippocampal atrophy
    - Additional causes of hippocampal sclerosis
    - Less likely other non-AD neurodegenerative conditions