Hippocampal sclerosis of aging (HS-Aging)

Pete Nelson

UNIVERSITY OF KENTUCKY

HS-Aging literature:

Part of fast expanding research derived from ADC and related series

Better data → better conclusions

ADCs and related series:

a new standard

- **Longitudinal assessment**
- **Improving clinical & neurocognitive evaluation**
- **More variables, more quantitative correlation**

…linked to a key asset: neuropathologic data

NACC data:
Pitfalls:

-Dementia clinics have strong bias in recruitment:

MORE AD, FTLD, “zebras”

LESS Vascular disease, “normals”

-(yes, there are some other potential pitfalls)

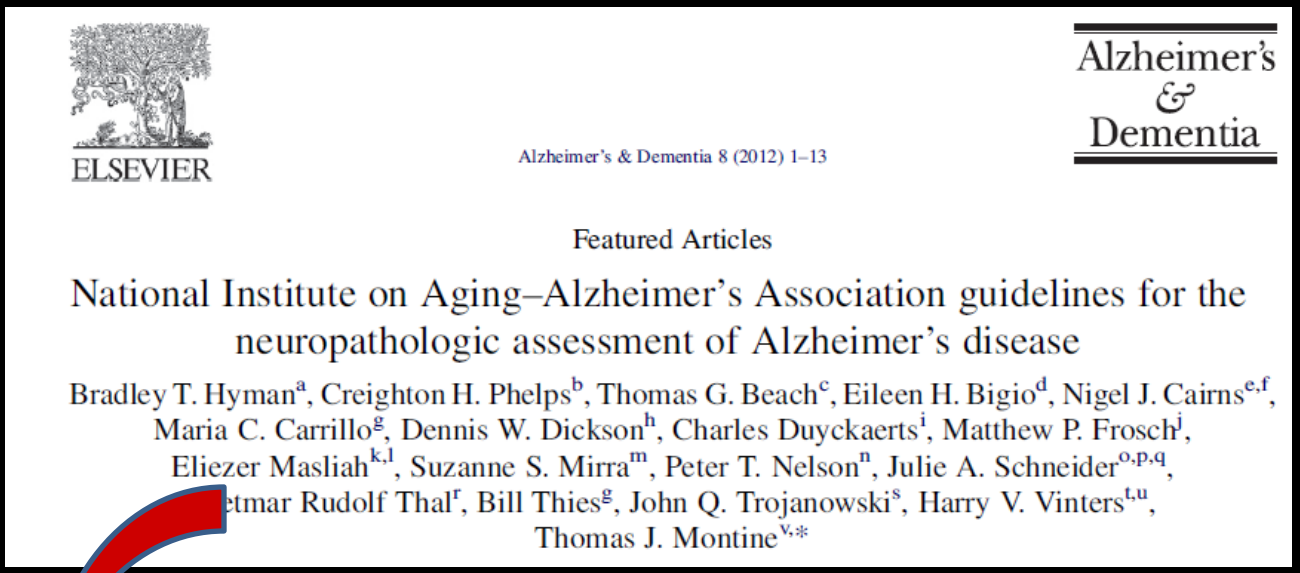
NACC data:
Opportunities:

-Increasingly well-audited, high-quality data
-Detailed clinical and pathologic data
-Very large number of cases and controls
-If desired, more recent = better
-Sampling multiple centers is a strength
-A great resource to track correlations and diagnostic trends at state-of-the-art U.S. research centers

HS-Aging

- *What is it?*
  Neuropathology
- Clinical impact
- Public health impact
- Border zone issues
- New stuff

Diagnosis and definition rest completely on neuropathology



ELSEVIER

Alzheimer's & Dementia 8 (2012) 1–13

Alzheimer's & Dementia

Featured Articles

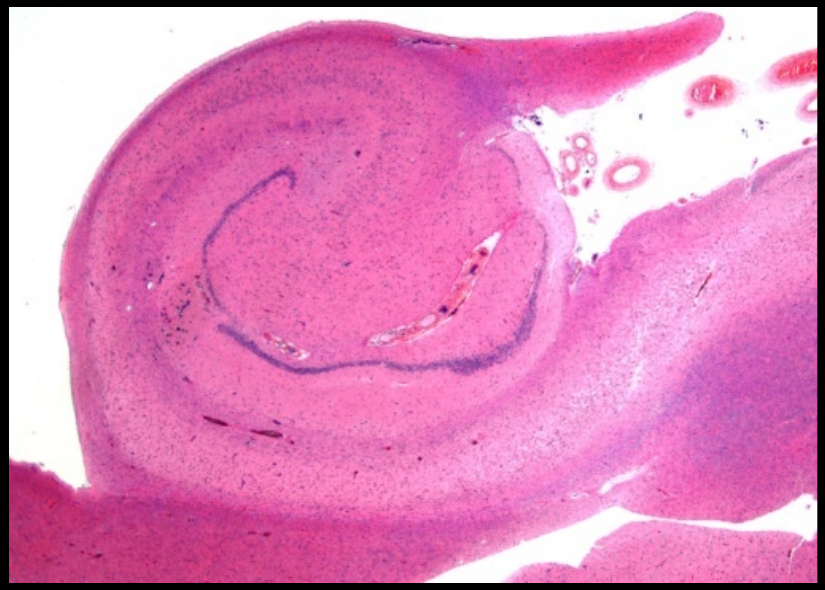
National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease

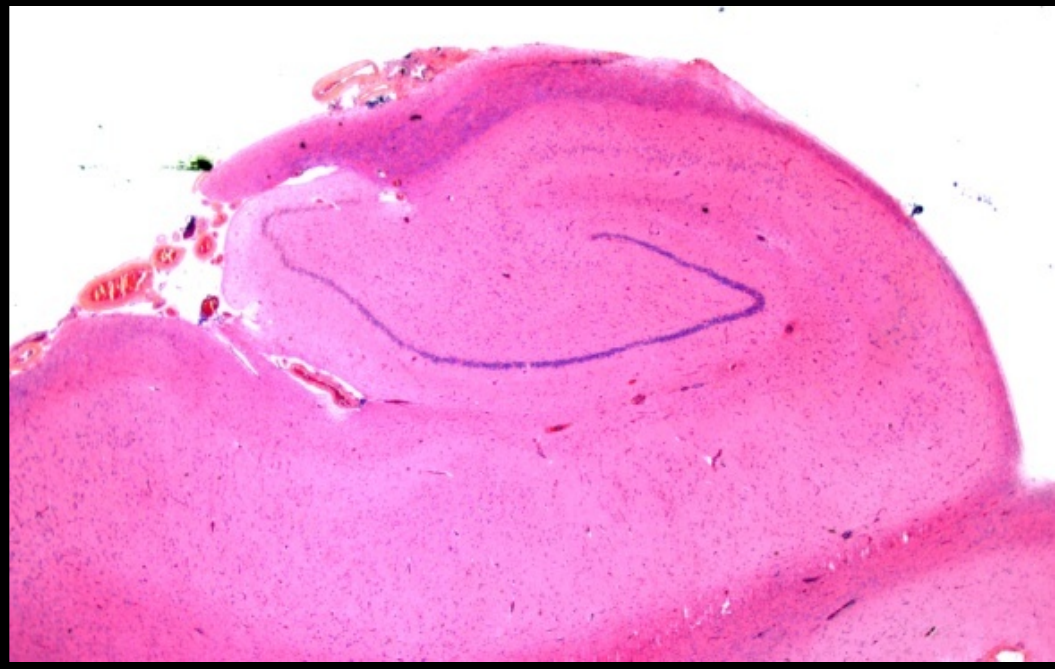
Bradley T. Hyman[a], Creighton H. Phelps[b], Thomas G. Beach[c], Eileen H. Bigio[d], Nigel J. Cairns[e,f], Maria C. Carrillo[g], Dennis W. Dickson[h], Charles Duyckaerts[i], Matthew P. Frosch[j], Eliezer Masliah[k,l], Suzanne S. Mirra[m], Peter T. Nelson[n], Julie A. Schneider[o,p,q], tmar Rudolf Thal[r], Bill Thies[g], John Q. Trojanowski[s], Harry V. Vinters[t,u], Thomas J. Montine[v,*]

Diagnosis and definition rest completely on neuropathology:

"Hippocampal sclerosis (HS) is defined by pyramidal cell loss and gliosis in CA1 and subiculum of the hippocampal formation that is out of proportion to AD neuropathologic change in the same structures ."

Hippocampal Sclerosis





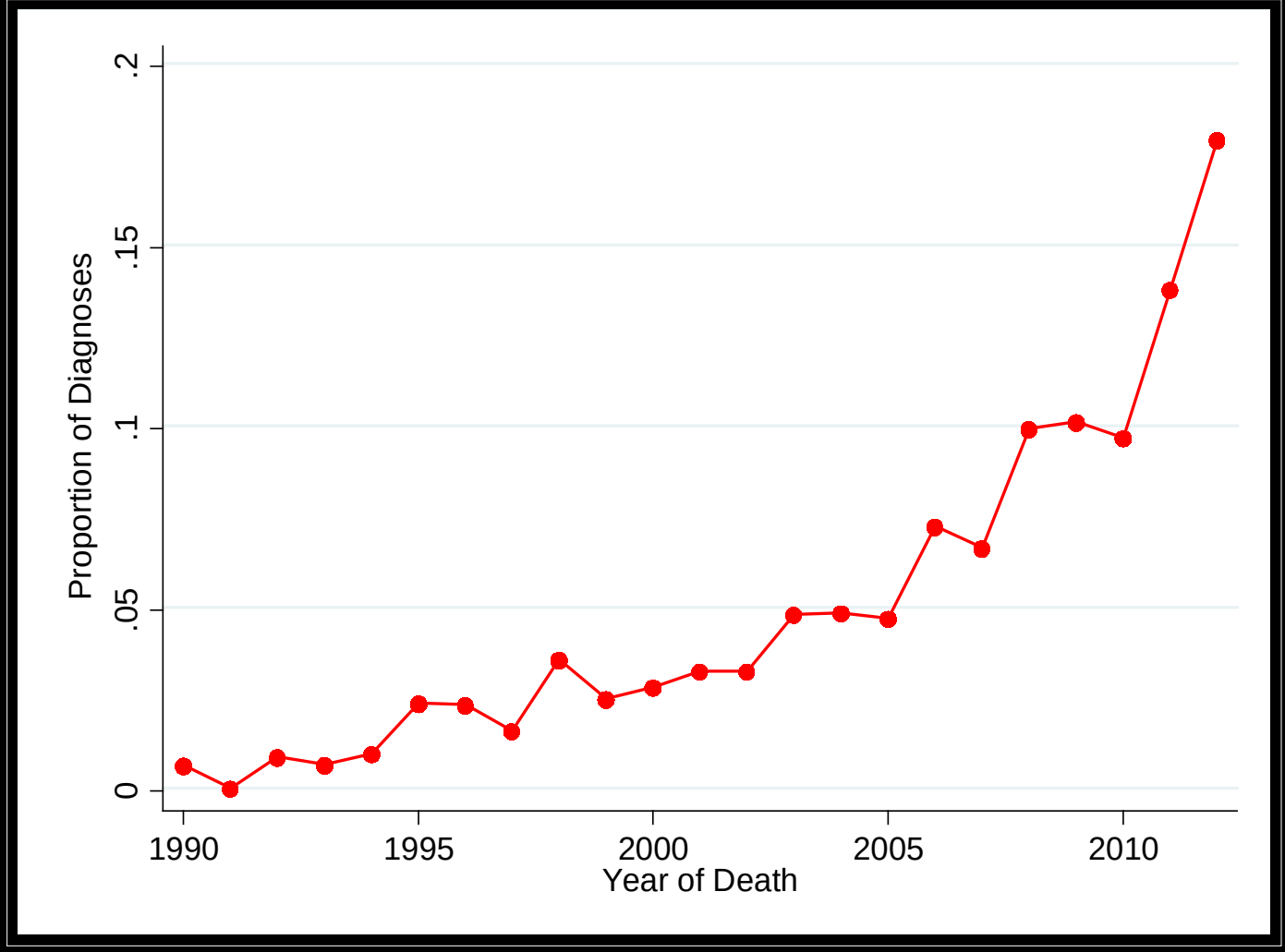
- **Autopsy diagnosis required**
- **No clinical biomarker**
- **Aberrant TDP-43 usually**

(Neumann et al, 2006)

(Amador-Ortiz et al, 2007)

Hippocampal Sclerosis – Neuropathology

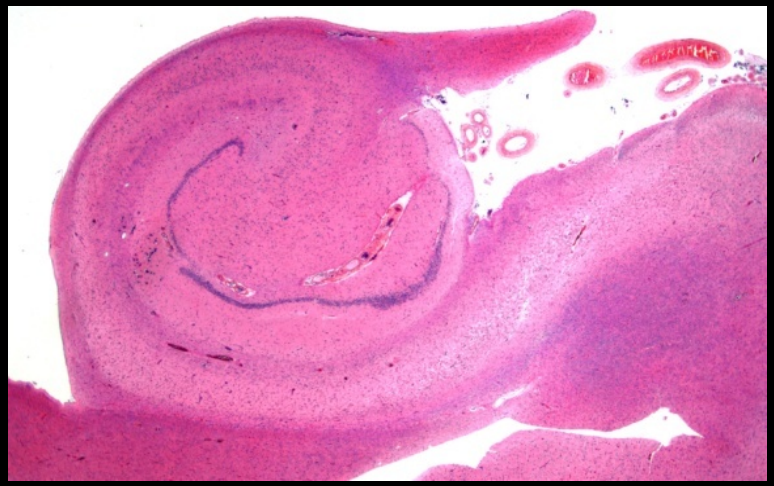
- **Rapidly changing field**
- **Laterality**
- **“Whole brain disease”**
- **(New stuff later)**

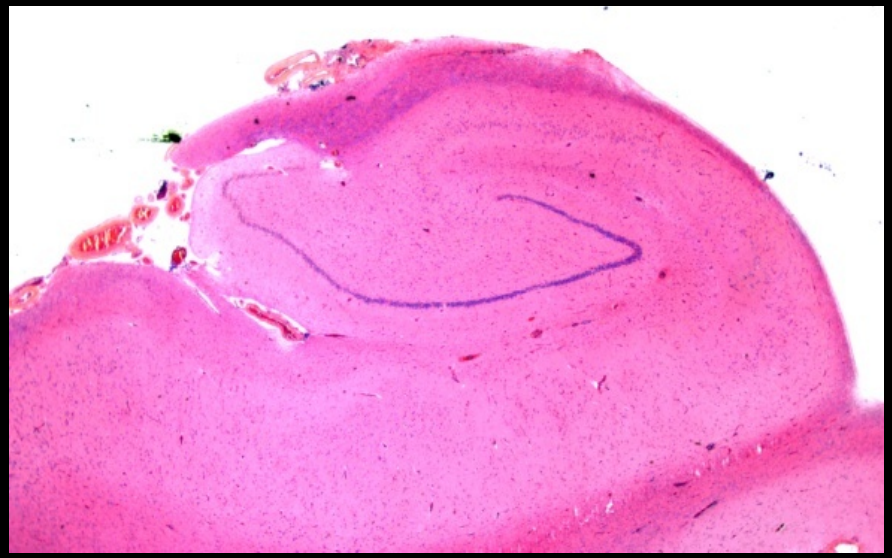


← 20%!

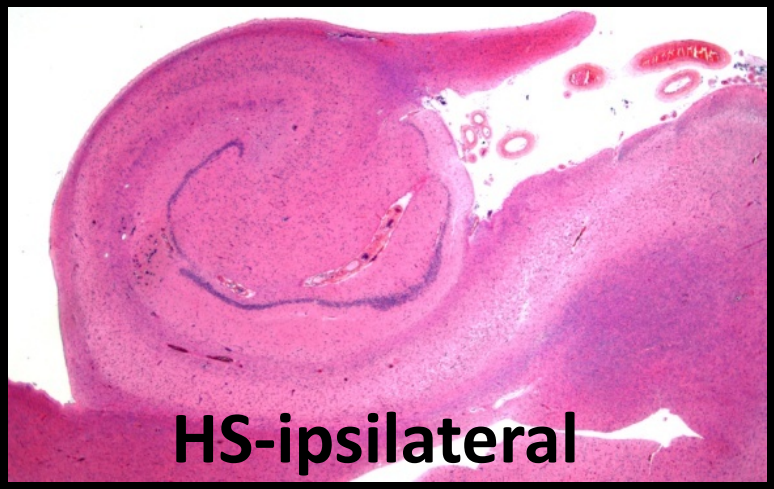
Proportion of Hippocampal Sclerosis pathological diagnoses (primary and contributing) among autopsied participants in the NACC Neuropathology Data Set, by year of death, 1990-2012 (N=9,187).

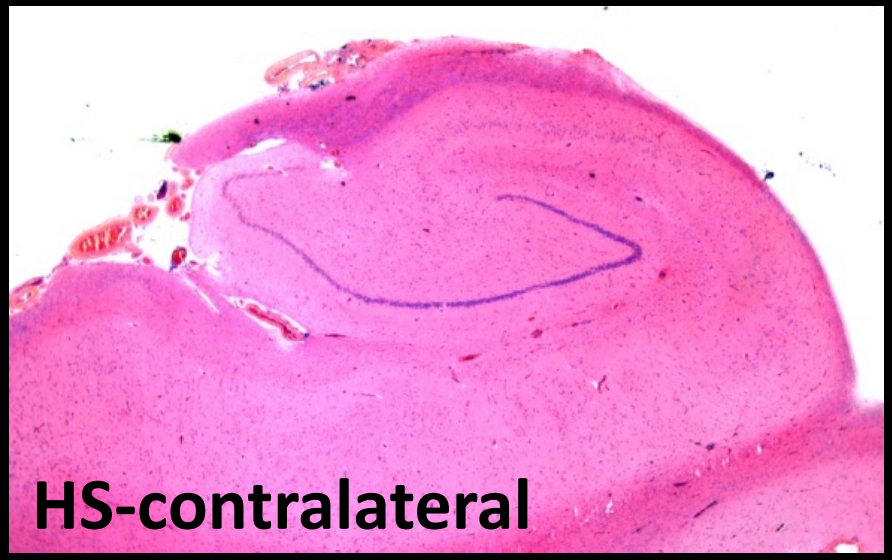
Brenowitz et al, *JAD, In Press*

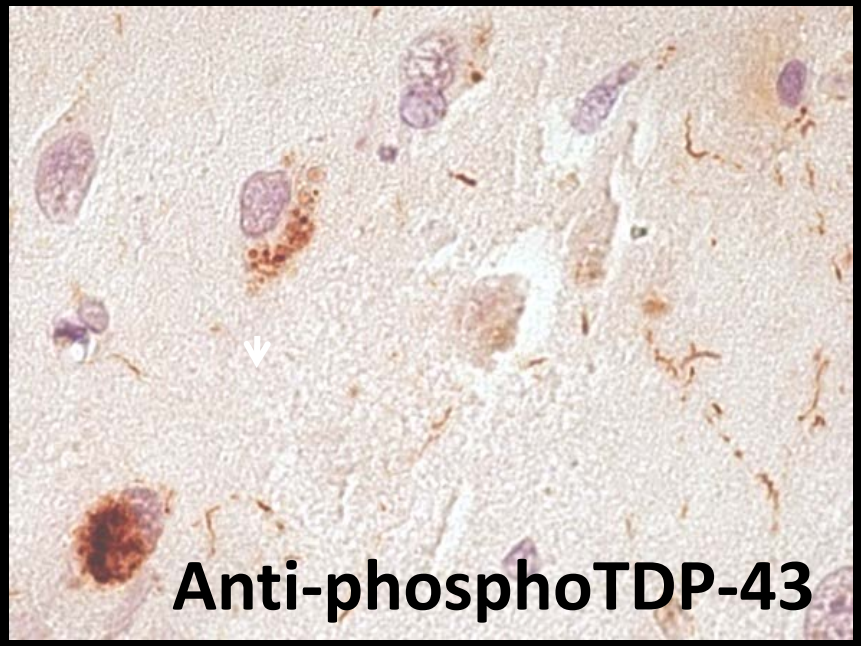




Laterality – 40-50% of cases







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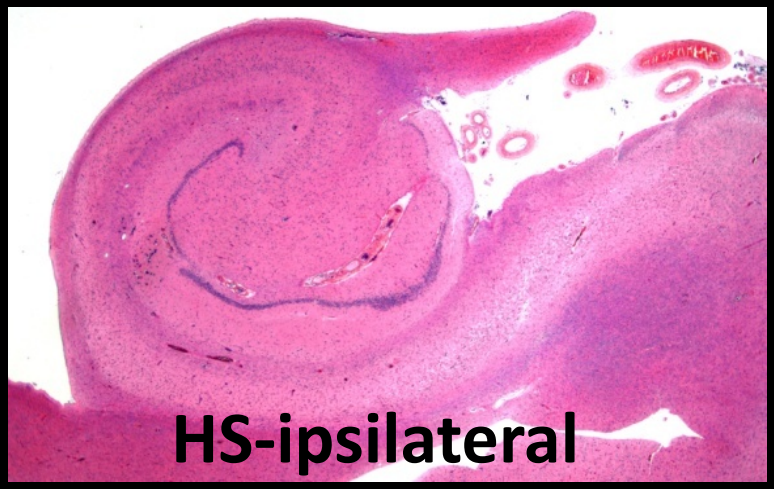

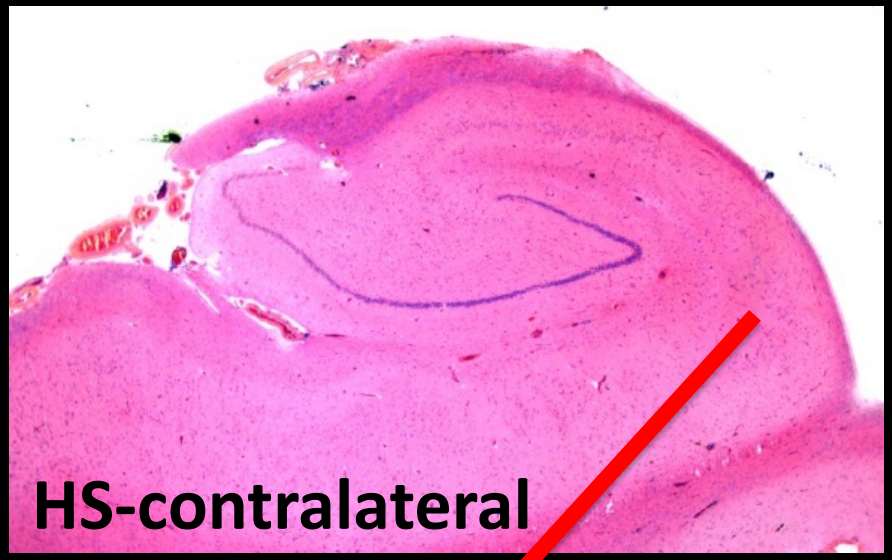

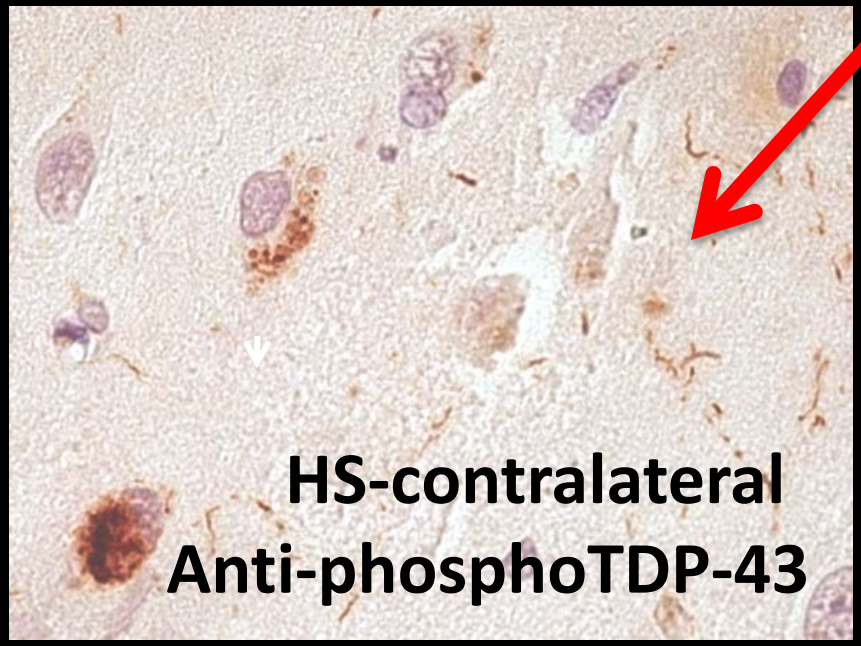

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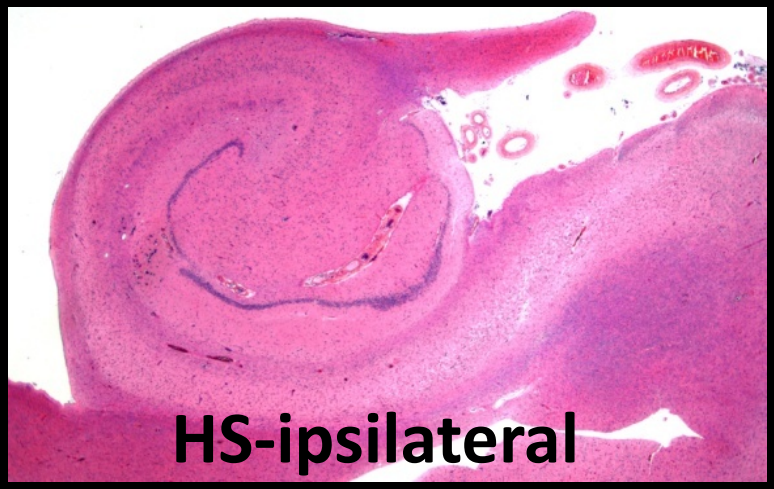
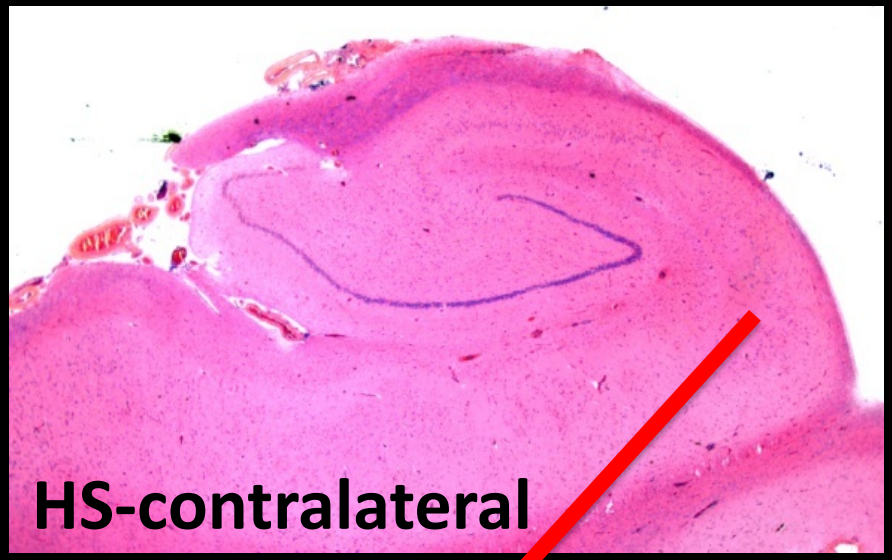
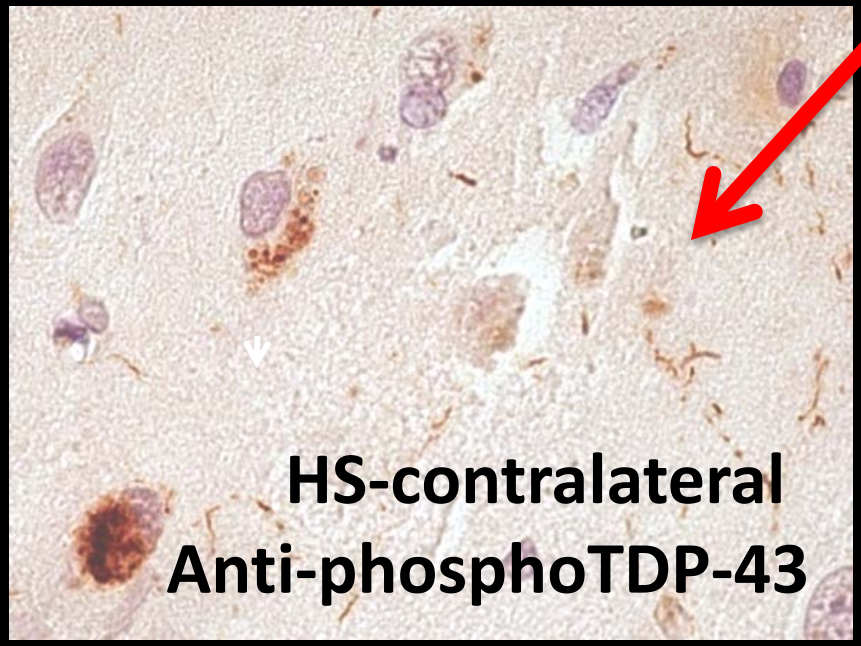
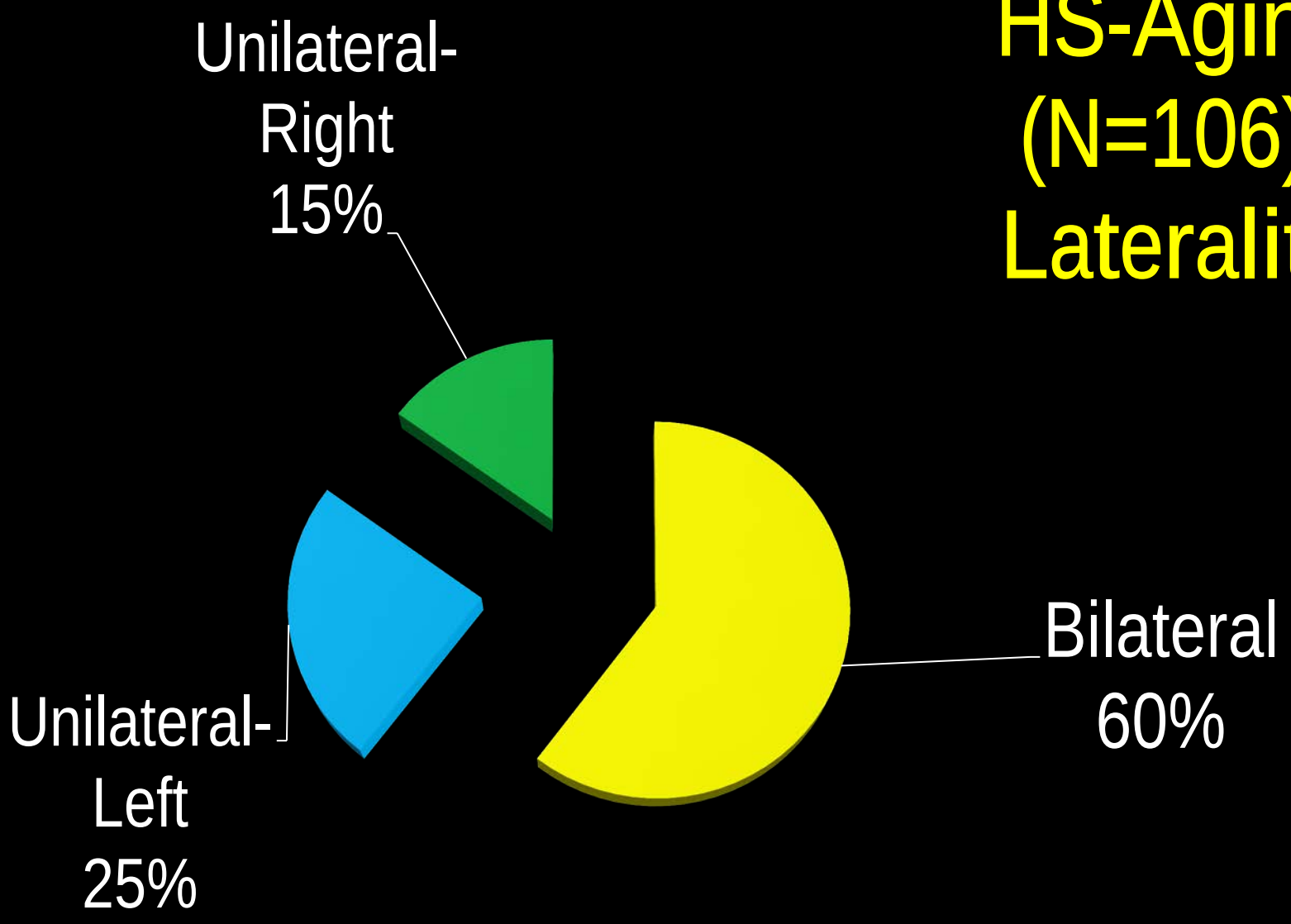






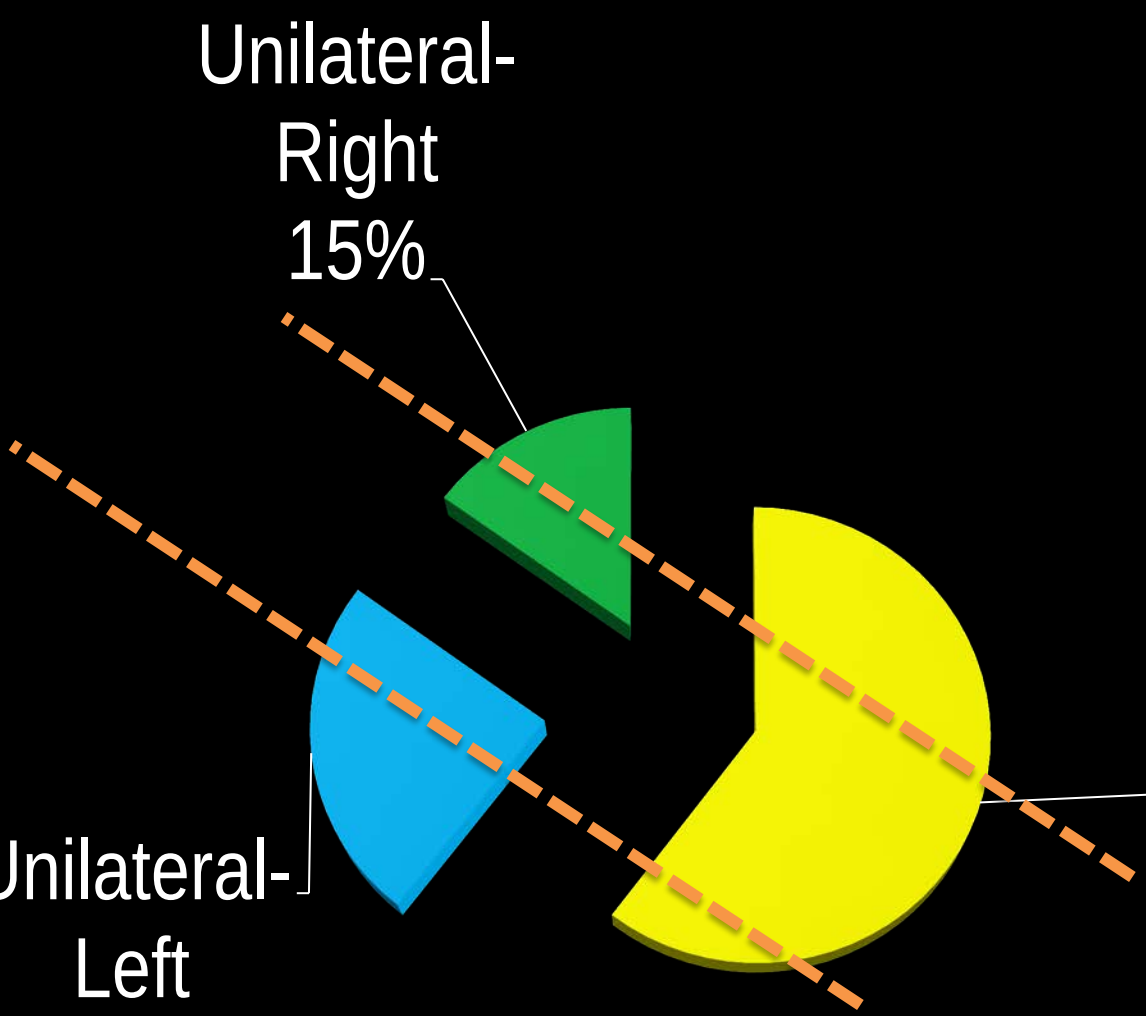
Whole brain disease

HS-Aging (N=106): Laterality



Nelson PT et al, *Brain,* 2011

HS-Aging (N=106): Laterality



Unilateral sampling→~20% false negative

Nelson PT et al, *Brain*, 2011

HS-Aging

- What is it?
  Neuropathology
- *Clinical impact*
- Public health impact
- Border zone issues
- New stuff

RESEARCH ARTICLE

Modeling the Association between 43 Different Clinical and Pathological Variables and the Severity of Cognitive Impairment in a Large Autopsy Cohort of Elderly Persons

Peter T. Nelson; Erin L. Abner; Frederick A. Schmitt; Richard J. Kryscio; Gregory A. Jicha; Charles D. Smith; Daron G. Davis*; John W. Poduska; Ela Patel; Marta S. Mendiondo; William R. Markesbery

of Kentucky Medical Center, Sanders-Brown Center on Aging and Alzheimer's

Clinical indices	Pathological indices
Age at death	
Sex	Macroinfarct(s)—cortical
Education	Cerebral amyloid angiopathy
ApoE alleles	Arteriolosclerosis
AFib/other cardiac arrhythmia*	Number of microinfarcts
Hypertension*	Number of pale infarcts
Body mass index	Number of hemorrhagic infarcts
Transient ischemic attack(s)*	Number of lacunar infarcts
Head trauma*	Subcortical non-lacunar infarcts
Diabetes/takes insulin*	Argyrophilic grains
Seizures/epilepsy*	Lewy bodies—isocortical
Smoking*	Lewy bodies—brainstem
Peripheral vascular disease*	Lewy bodies—medial temporal lobe
Advanced coronary artery disease*	Lewy bodies—amygdala only*
Cancer*	Isocortical neurofibrillary tangles (NFTs)
Anxiety*	Isocortical neuritic plaques (NPs)
Depression/antidepressant meds*	Isocortical diffuse plaques (DPs)
Number of documented drugs	Mesial temporal lobe NFTs
Opiates*	Mesial temporal lobe NPs
Antipsychotics*	Mesial temporal lobe DPs
Barbiturates*	Hippocampal sclerosis (HS) unilateral*
Benzodiazepenes*	HS bilateral*

*Dichotomous (1 or 0).

Multiple variable regression model:

Testing the impact of many different potential causes of global cognitive impairment (most cases with multiple comorbid pathologies)

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Department of Pathology and Division of Neuropathology, University of Kentucky Medical Center, Sanders-Brown Center on Aging and Alzheimer's Disease Center, University of Kentucky, Lexington, Ky.

All significant parameters combined			P value
Intercept	24.32	1.07	<0.0001
NFTs, isocortex	−19.66	2.27	<0.0001
LBs, isocortex	−12.47	1.67	<0.0001
HS—unilateral	−8.58	1.82	<0.0001
NFTs, mesial temporal	−12.44	1.87	<0.0001
HS—bilateral	−7.84	2.04	0.0001

Hippocampal sclerosis, either bilateral or unilateral on H&E, was associated with additional global cognitive impairment

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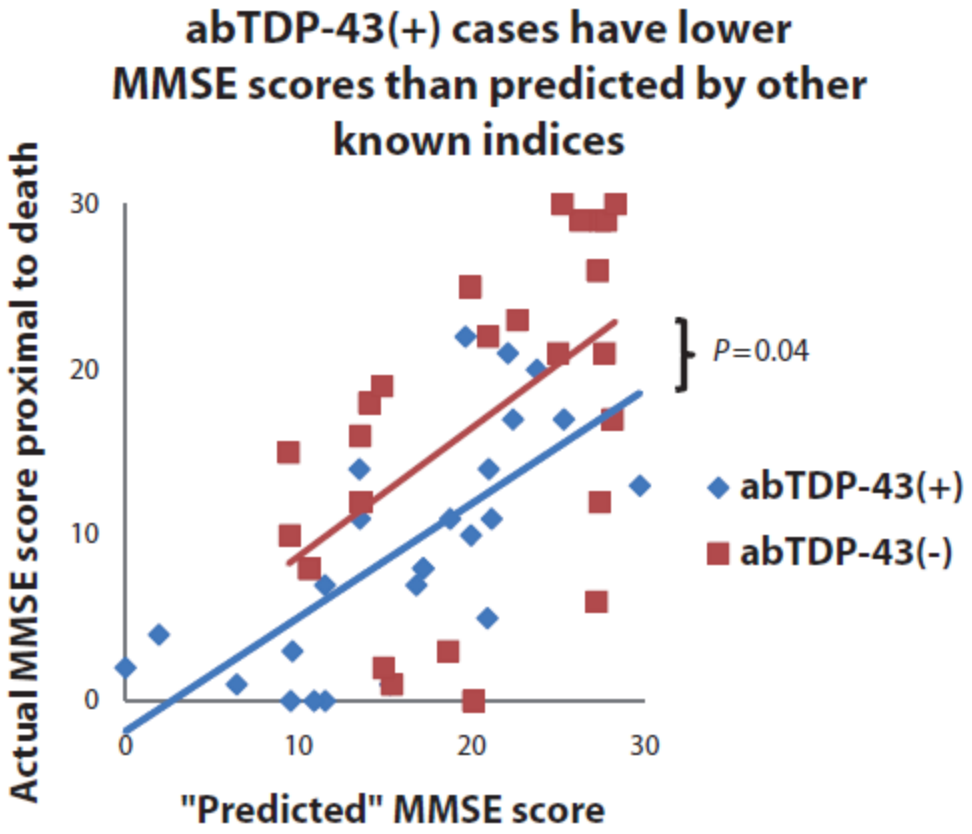
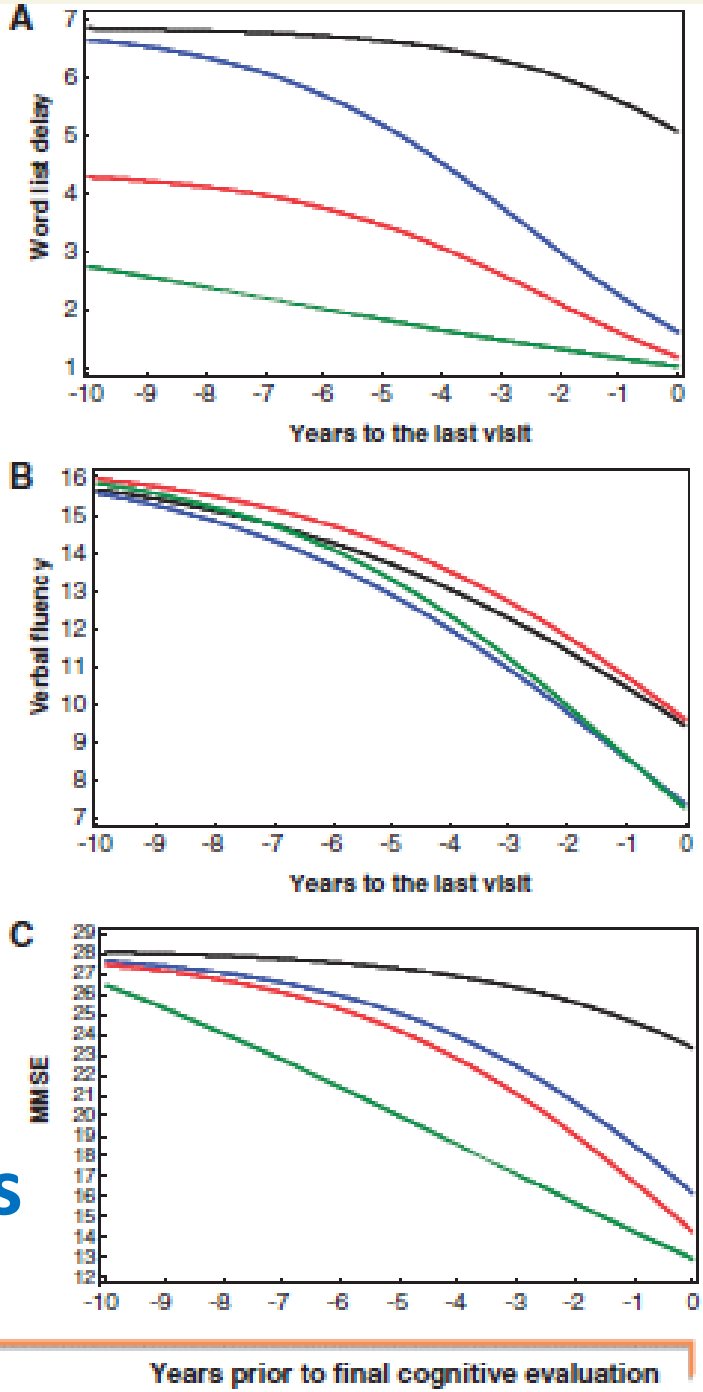


Independent of all other known factors, hippocampal TDP-43 pathology was associated with additional global cognitive impairment

What about particular cognitive domains?



Cognitive decline in groups stratified by eventual pathology:

Non-linear mixed model trajectory of cognitive scores tracking backward from final cognitive evaluation (mean 8.2 evaluations/patient):

- No AD, yes HS
- Yes AD, no HS
- Yes AD, yes HS
- No AD, no HS

N=118

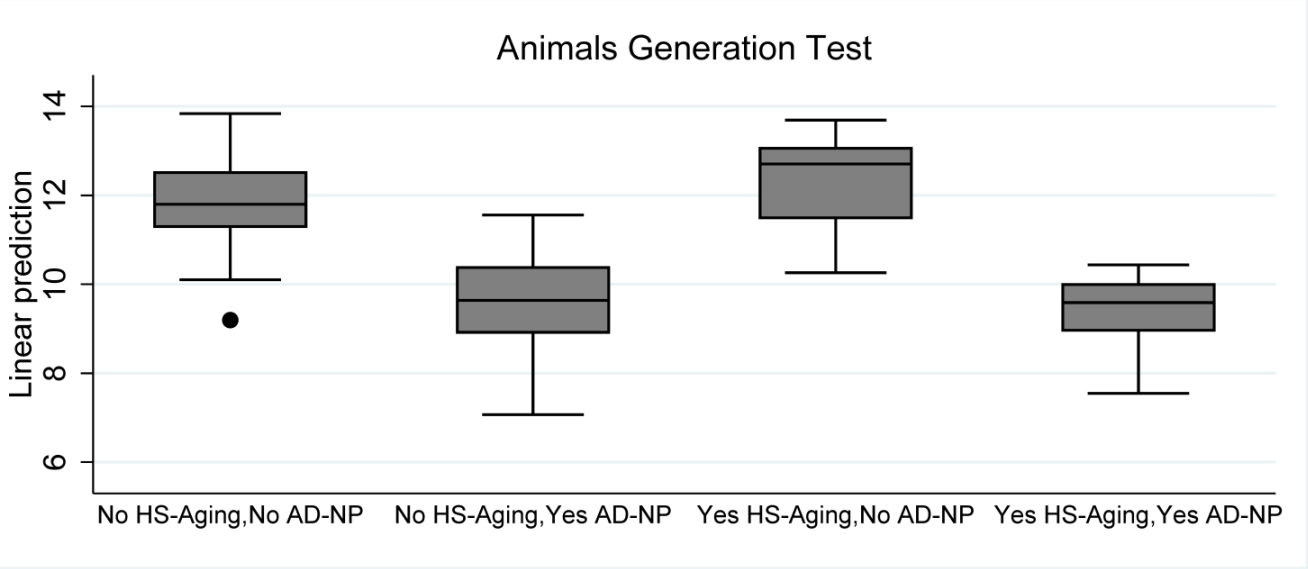
Avg 8.2 evals

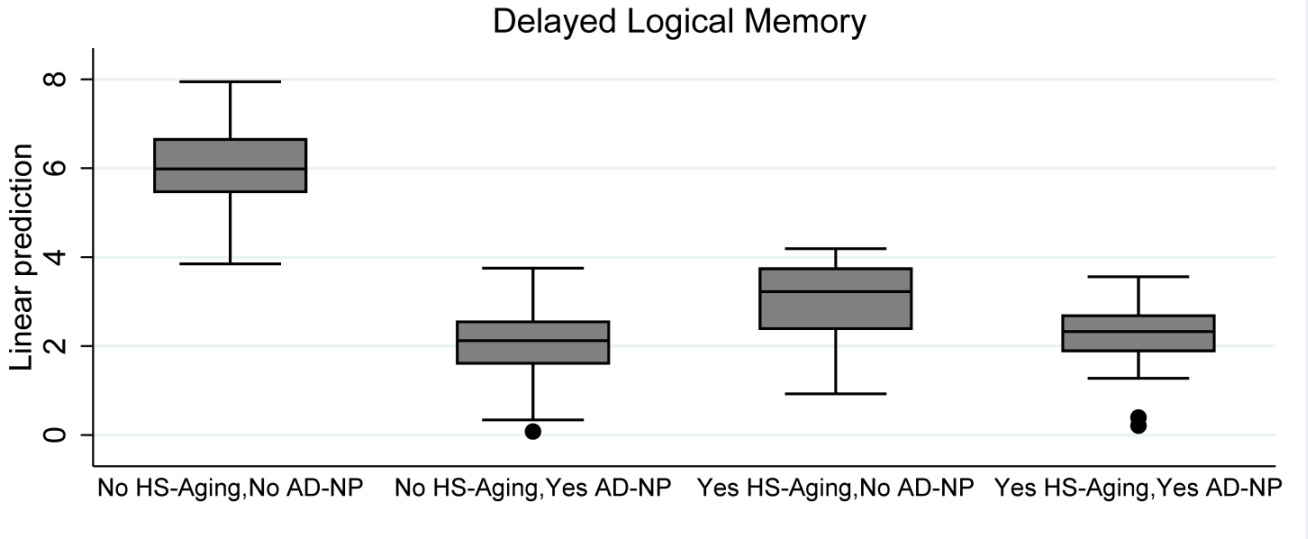
Word List Delay ↓

Verbal Fluency ↑

MMSE ↔

Brain, 2011





Brenowitz et al, *JAD, In Press—*

Group level differences: HS-Aging, AD, FTLD

Neurocognitive profile: NACC

Bottom line:

HS-Aging pathology is associated with appreciable added cognitive impairment including in cases with multiple comorbidities

HS-Aging

- What is it?
  Neuropathology
- Clinical impact
- *Public health impact*
- Border zone issues
- New stuff

doi:10.1093/brain/awr053 Brain 2011: 134; 1506–1518 | 1506

BRAIN
A JOURNAL OF NEUROLOGY

Hippocampal sclerosis in advanced age: clinical and pathological features

Peter T. Nelson,[1,2] Frederick A. Schmitt,[2,3] Yushun Lin,[4] Erin L. Abner,[2] Gregory A. Jicha,[2,3] Ela Patel,[2] Paula C. Thomason,[2] Janna H. Neltner,[1] Charles D. Smith,[2,3] Karen S. Santacruz,[5] Joshua A. Sonnen,[6] Leonard W. Poon,[7] Marla Gearing,[8] Robert C. Green,[9] John L. Woodard,[10] Linda J. Van Eldik[2,11] and Richard J. Kryscio[2,4]

106 autopsy-confirmed HS-Aging cases
1,004 controls (all with autopsy data)

doi:10.1093/brain/awr053 Brain 2011: 134; 1506–1518 | 1506

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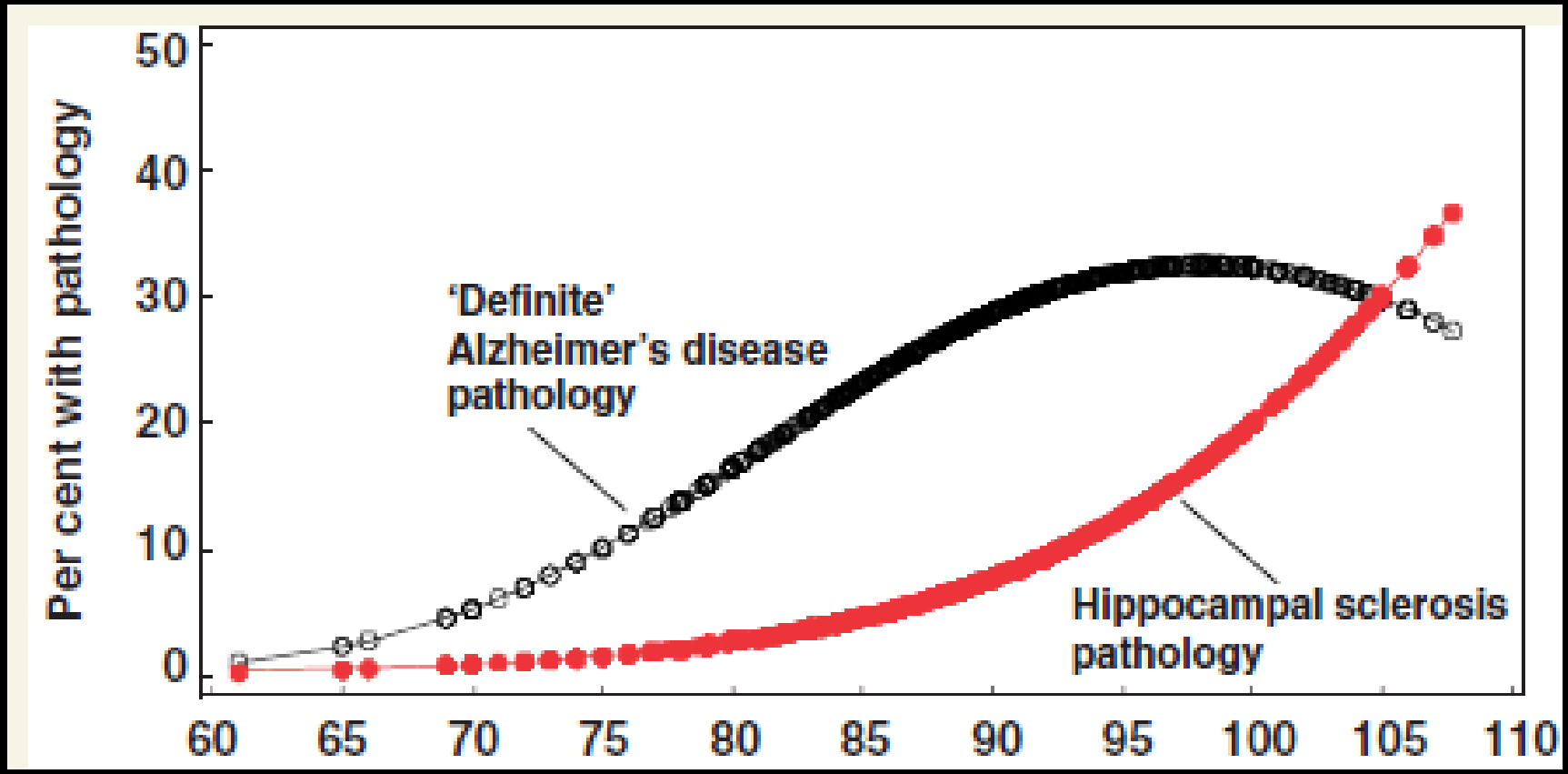
Acknowledgements

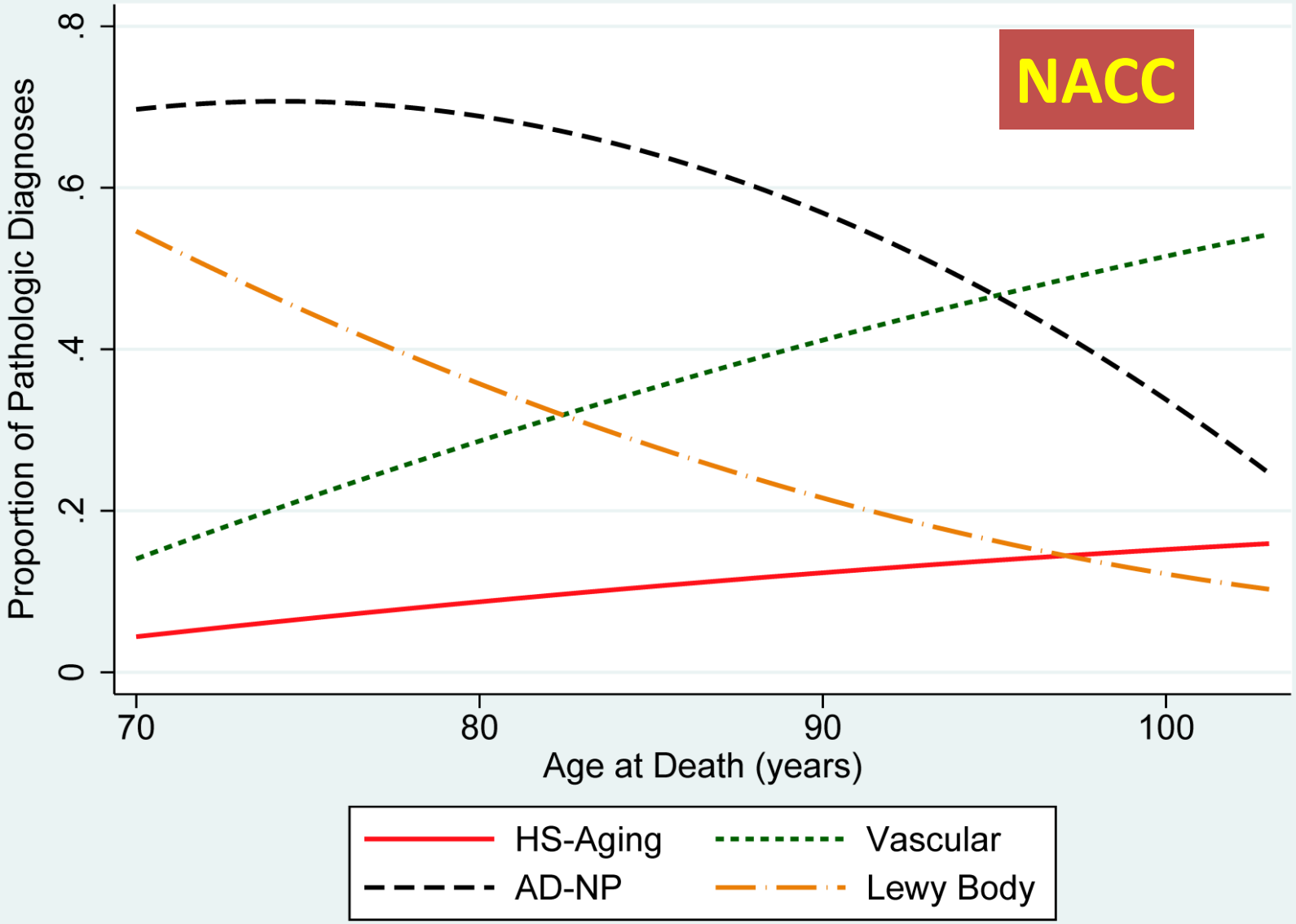
Dr William R. Markesbery performed the neuropathological evaluations for the great majority of cases and controls before his death in January 2010.



In extreme old age, AD pathology becomes LESS prevalent

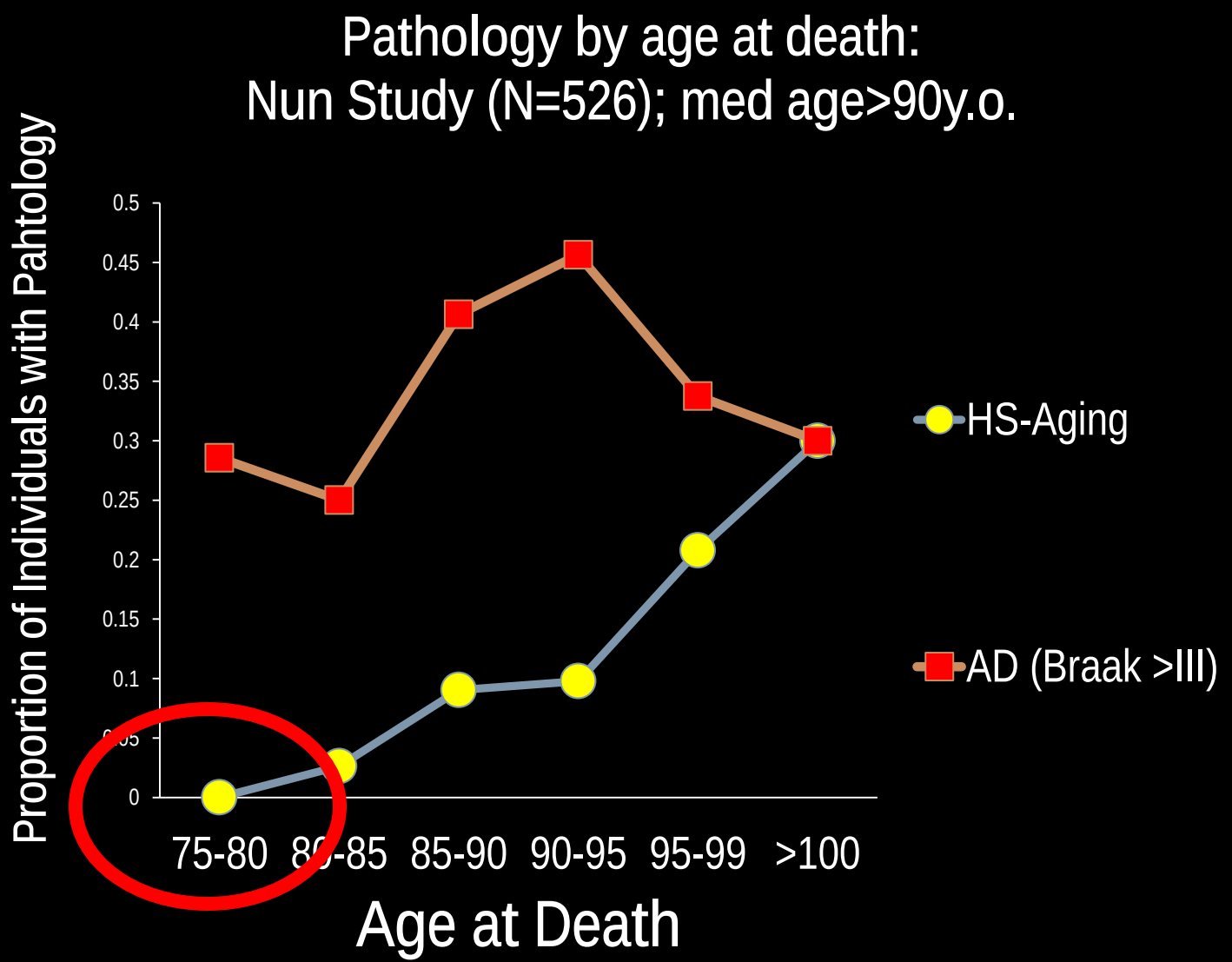
Hippocampal sclerosis pathology becomes MORE prevalent

Brain, 2011



Trends by age at death for pathological diagnoses in individuals with dementia. (N=1,061).

Brenowitz et al, *JAD, In Press*


Pathology by age at death:
Nun Study (N=526); med age>90y.o.
Proportion of Individuals with Pahtology
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0
75-80
85-90
90-95
95-99
>100
Age at Death
HS-Aging
AD (Braak >III)

("Epi- cohort"!!!)

J Neuropathol Exp Neurol

Vol. 72, No. 6
June 2013
pp. 452–461

ORIGINAL ARTICLE

Consensus Recommendations on Pathologic Changes in the Hippocampus: A Postmortem Multicenter Inter-Rater Study

Tuomas Rauramaa, MD, Maria Pikkarainen, PhD, Elisabet Englund, MD, PhD, Paul G. Ince, MD, FRCPath, Kurt Jellinger, MD, PhD, Anders Paetau, MD, PhD, and Irina Alafuzoff, MD, PhD

TABLE 2. Cases Studied

Type Given by the Coordinating Group*	n	Percent of Total	Mean Age ± SE, years	Sex (male/female)	Clinical Manifestations, %			Brain Weight, Mean ± SE, g	Rapidity of Death as Defined by Johnston et al†, %					Postmortem Delay, Mean ± SE, hours
					CI	Seizures	NA		2	3	4	5	NA	
No lesions	9	4	77 ± 3	3/6	33	10		1,318 ± 77	33	44		22		94 ± 10
+	9	4	69 ± 6	2/7	33	10		1,299 ± 57	33		44	11	11	57 ± 11
1	143	55	77 ± 1	67/76	26	4	4	1,343 ± 12	27	10	54	6	3	67 ± 4
2	13	5	76 ± 3	7/6	31	23	8	1,329 ± 59	8	38	38	8	8	74 ± 11
3	59	23	77 ± 1	18/41	71	7	3	1,260 ± 24	29	7	61		3	72 ± 8
4	27	10	78 ± 4	10/17	74	11		1,137 ± 51	22	7	67		4	48 ± 11
Σ	260	77 ± 1	107/153	42	7	4	1,300 ± 12		27	11	54	4	69 ± 3	

*Type of lesion as described in Materials and Methods and Figure 2: Type +, recent diffuse hypoxic/ischemic degeneration of cornu Ammonis (CA) neurons; Type 1, small focal infarcts (single or multiple); Type 2, extensive infarction of CA1; Type 3, patchy diffuse neuronal degeneration in CA sectors associated with or without neuronal lesions of neurodegenerative origin; Type 4, complete neuronal loss from CA1 caused by neurodegeneration, most frequently associated with neurofibrillary tangle formation but sometimes without degenerative pathology.

†Johnston et al (17).

CI, cognitive impairment; NA, not available.

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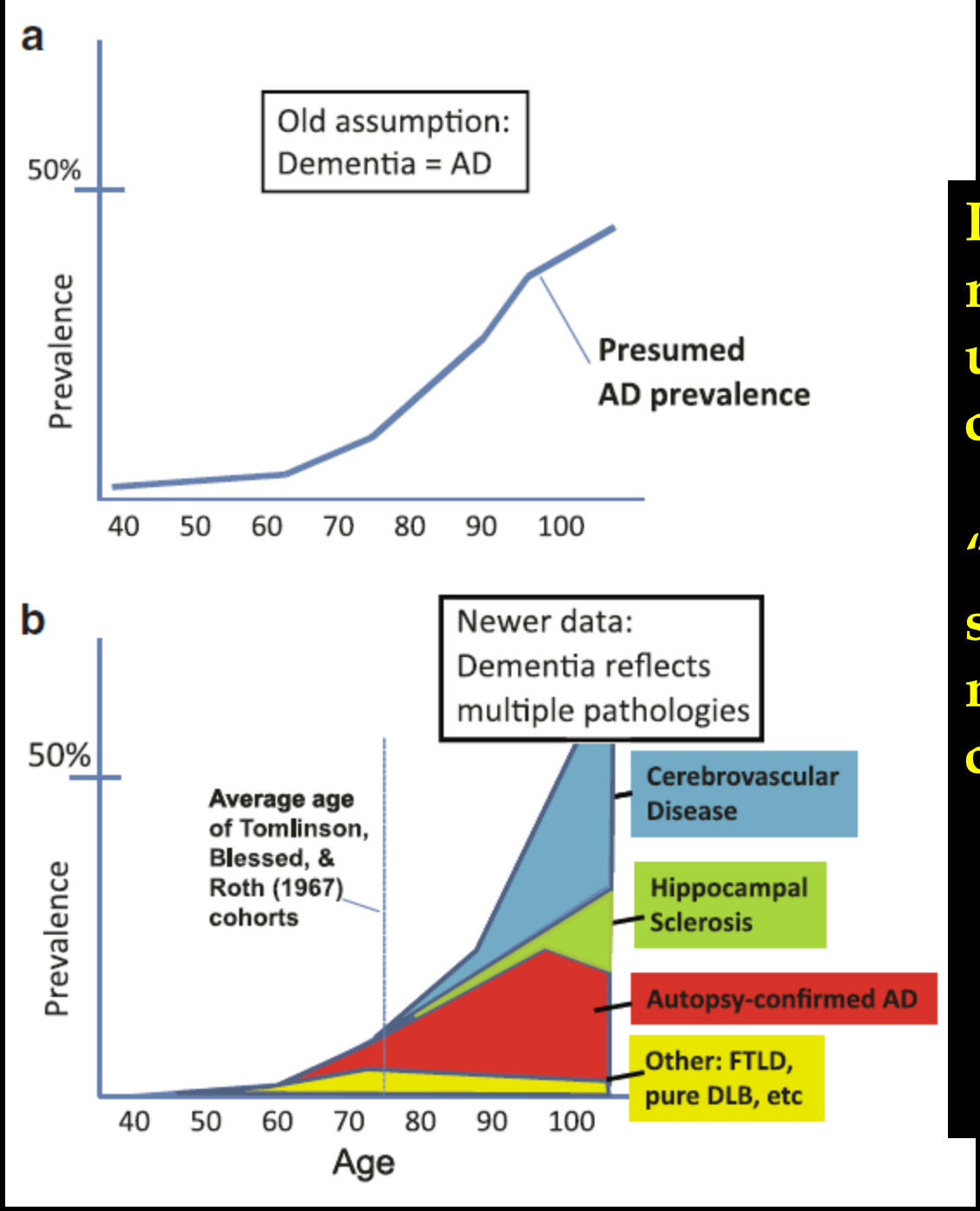
+	9	4	69 ± 6
1	143	55	77 ± 1
2	13	5	76 ± 3
3	59	23	77 ± 1
4	27	10	78 ± 4
Σ	260	77 ± 1	107/153

HS-Aging

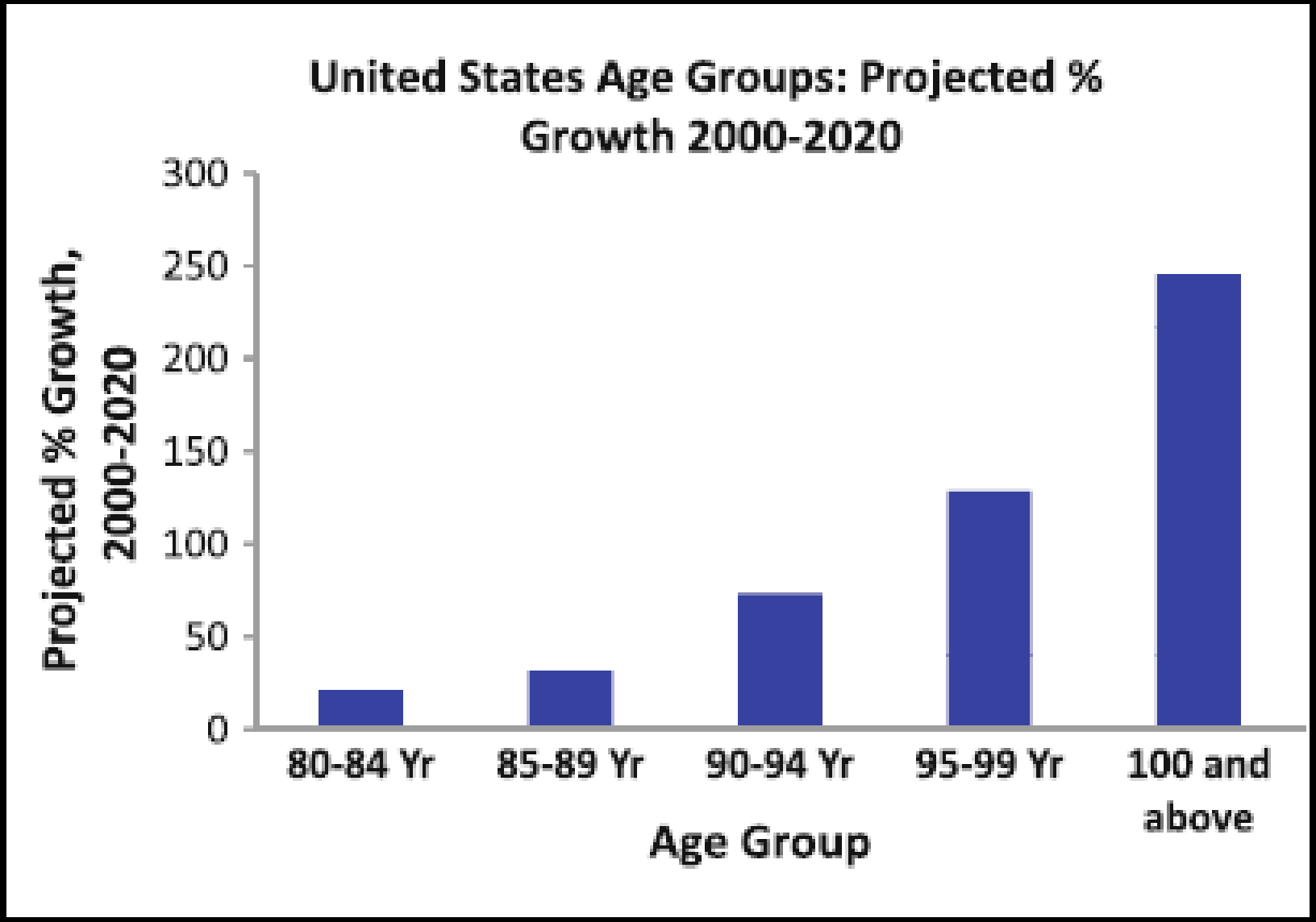
HS-Aging



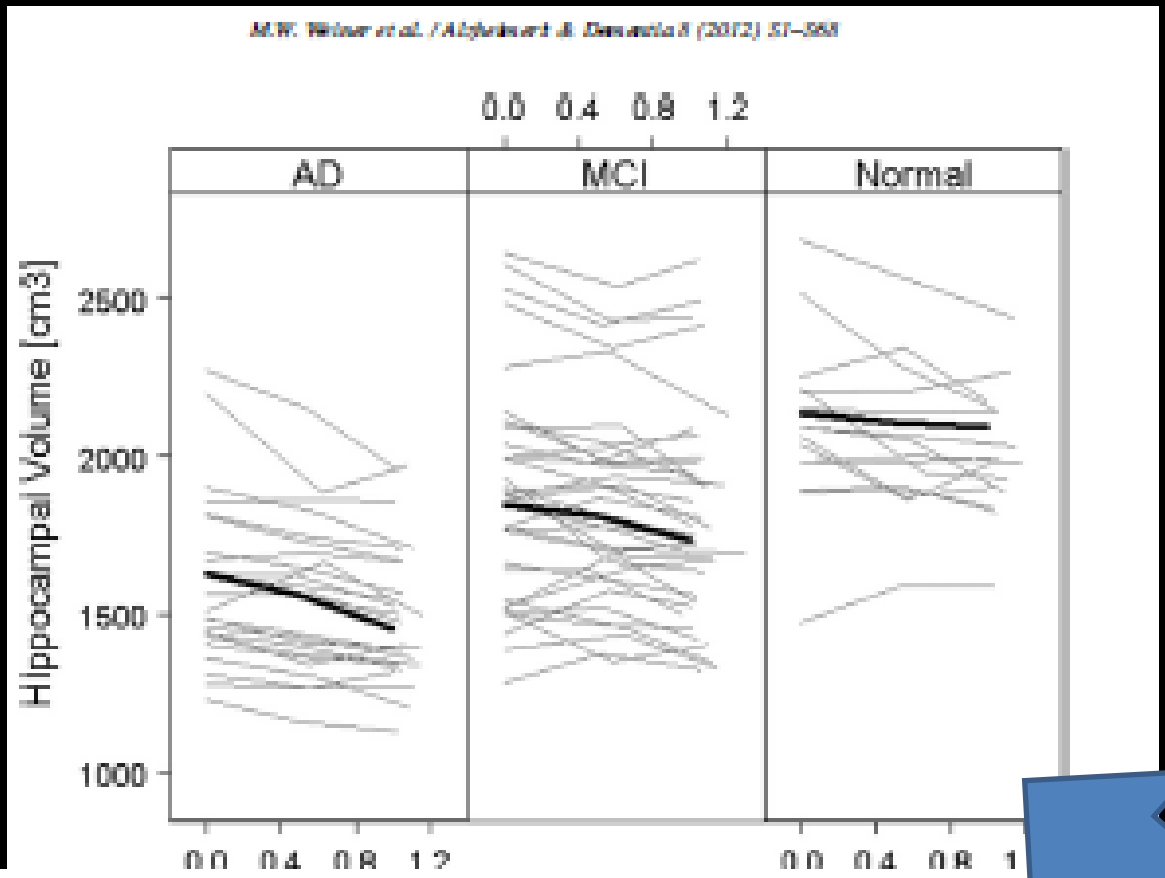
In advanced old age, non-AD diseases underlie much of clinical dementia

"Classic" clin-path studies addressed much younger cohorts.

Nelson et al
Acta Neuropathologica, 2011



Source: U.S. Census Bureau
Acta Neuropathologica, 2011



ELSEVIER

Alzheimer's & Dementia 8 (2012) S1–S68

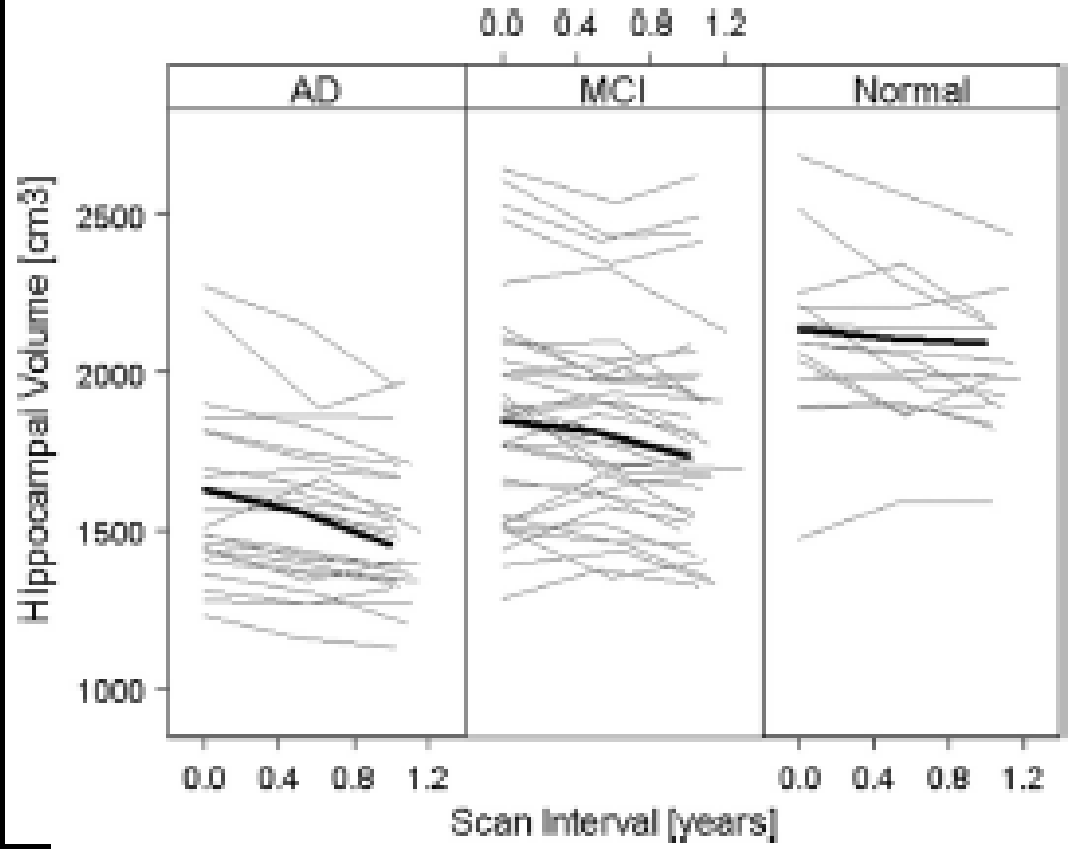
Alzheimer's & Dementia

Review Article

The Alzheimer's Disease Neuroimaging Initiative: A review of papers published since its inception

Michael W. Weiner[a,b,c,d,e,*], Dallas P. Veitch[a], Paul S. Aisen[f], Laurel A. Beckett[g], Nigel J. Cairns[h,i], Robert C. Green[j], Danielle Harvey[g], Clifford R. Jack[k], William Jagust[l], Enchi Liu[m], John C. Morris[f], Ronald C. Petersen[n], Andrew J. Saykin[o,p], Mark E. Schmidt[q], Leslie Shaw[r], Judith A. Siuciak[s], Holly Soares[t], Arthur W. Toga[u], John Q. Trojanowski[v,w,x,y], Alzheimer's Disease Neuroimaging Initiative

Hippocampal MRI structural changes as an AD biomarker



A large proportion of MRI-visualized hippocampal atrophy is NOT AD!

ELSEVIER

Alzheimer's & Dementia

Alzheimer's & Dementia 8 (2012) S1–S68

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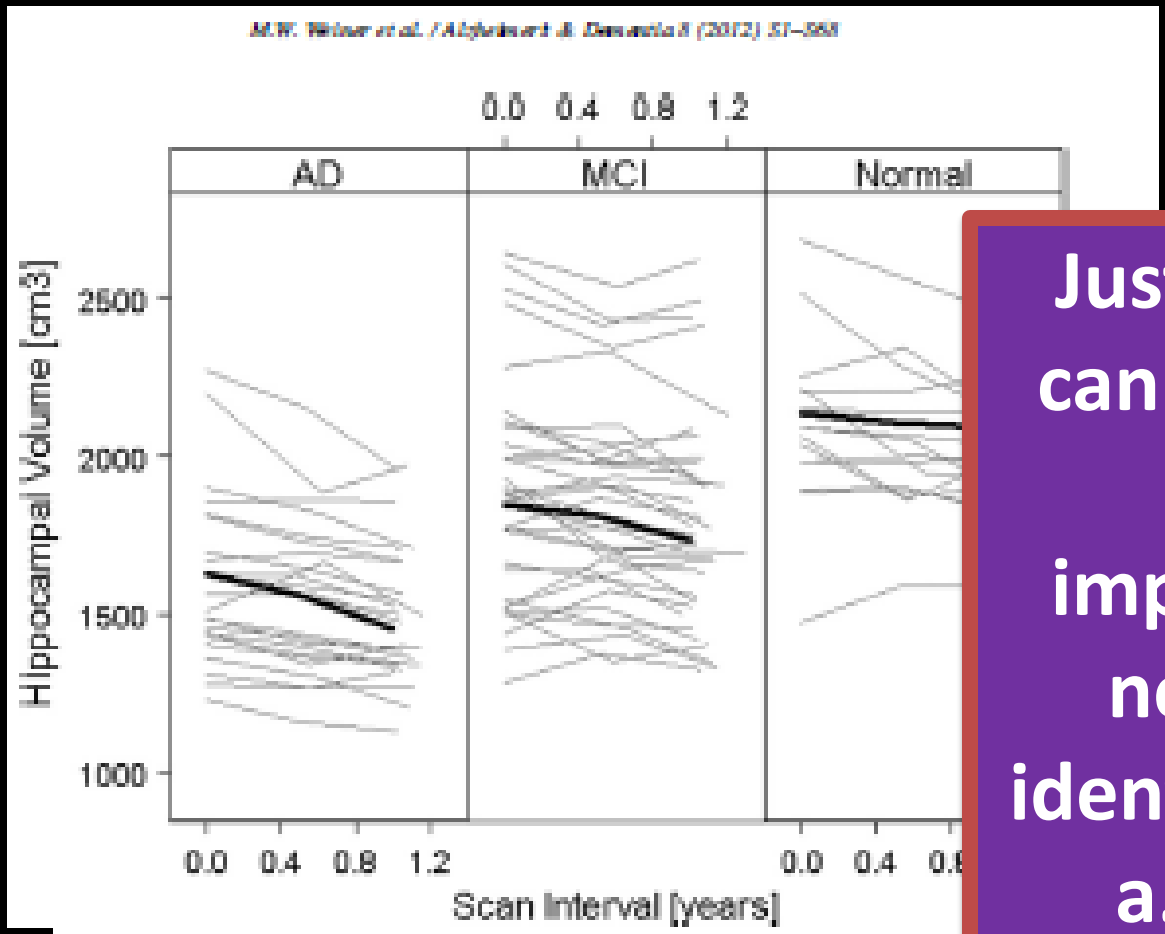

Just because you can predict future cognitive impairment does not mean you identified its cause, a.k.a. disease (directly relevant to clinical trials)

ELSEVIER

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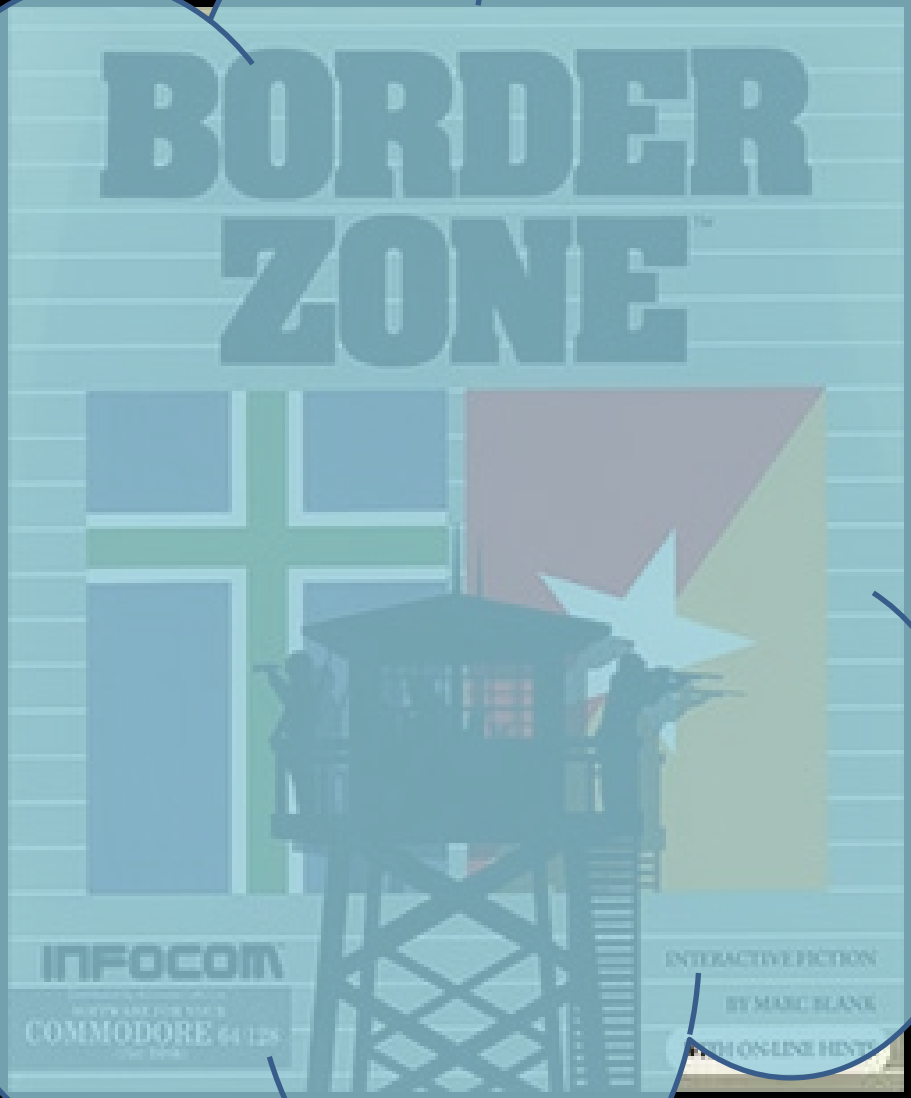
HS-Aging

- What is it?
  Neuropathology
- Clinical impact
- Public health impact
- *Border zone issues*
- New stuff


BORDER
ZONE
INFOCOM
COMMODORE 64/128
INTERACTIVE FICTION
BY MARC BLANC

AD

NACC: Subject characteristics at last visit by Hippocampal Sclerosis of aging and Alzheimer's disease neuropathology (N=1,422)

Primary Clinical Diagnosis
Probable AD
Possible AD
Normal
Other

Subject characteristics at last visit by Hippocampal Sclerosis of aging and Alzheimer's disease neuropathology (N=1,422)

	No HS-Aging Pathology	
	No AD-NP (n=675)	AD-NP (n=629)
Primary Clinical Diagnosis		
Probable AD	209 (31.0)	471 (74.9)
Possible AD	75 (11.1)	59 (9.4)
Normal	204 (30.2)	8 (1.3)
Other	187 (27.7)	91 (14.5)
	Mean (SD)	

AD Neuropathology positively identified

When no HS path present, AD-NP predicted correctly ~85% of the time

Subject characteristics at last visit by Hippocampal Sclerosis of aging and Alzheimer's disease neuropathology (N=1,422)

NO AD Neuropathology positively identified

83% of the time

	HS-Aging Pathology Present	
	No AD-NP (n=47)	AD-NP (n=71)
Primary Clinical Diagnosis		
Probable AD	32 (68.1)	66 (93.0)
Possible AD	7 (14.9)	2 (2.8)
Normal	2 (4.3)	1 (1.4)
Other	6 (12.8)	2 (2.8)
	Mean (SD)	

What about the association between HS-Aging pathology and Alzheimer's disease pathology (plaques and tangles)

?

There is

NO

association between

APOE genotype

and HS-Aging risk

Troncoso JC et al, *Neurosci Lett*. 1996

Leverenz JB et al, *Arch Neurol*. 2002

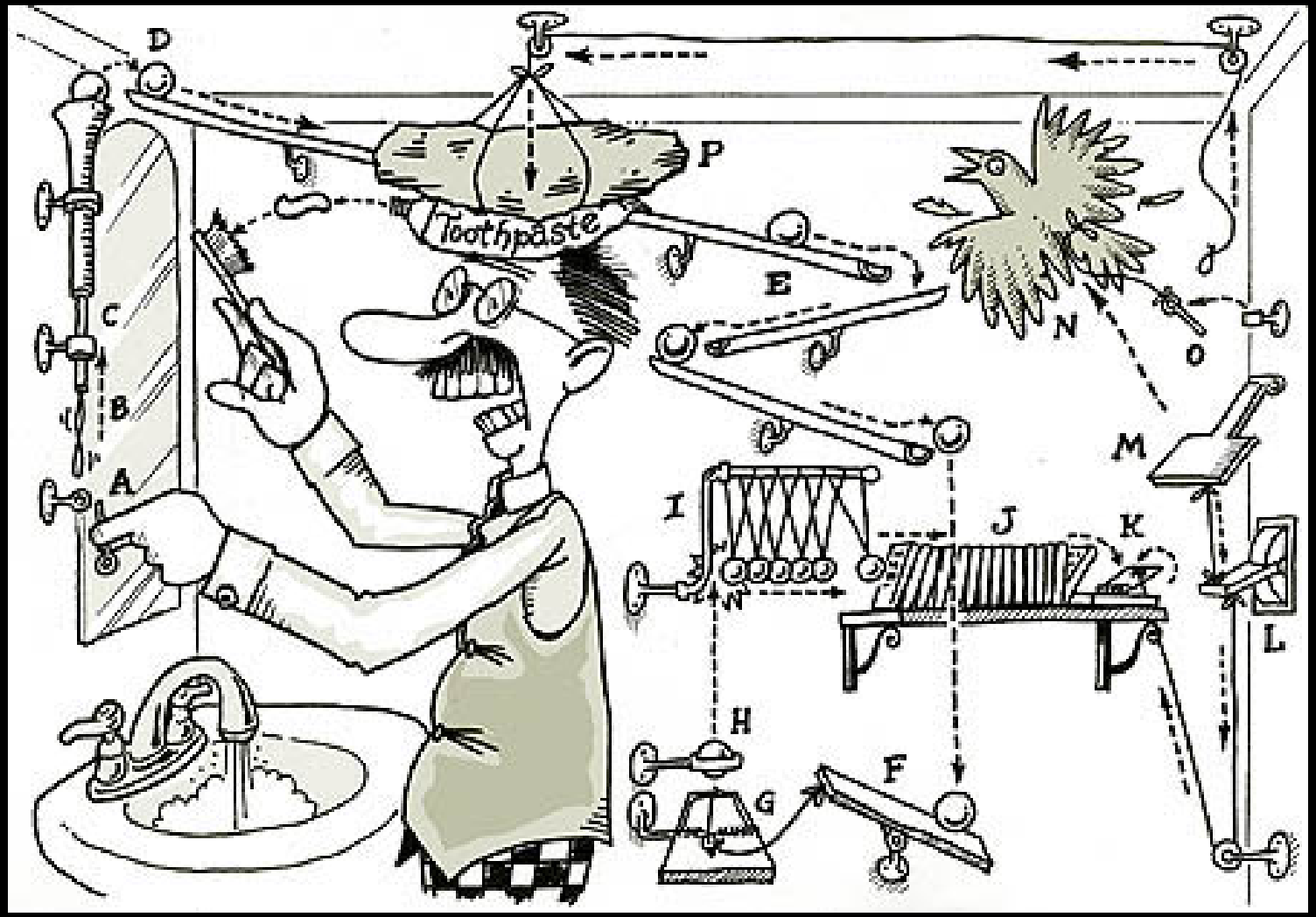
Nelson PT et al, *Brain*. 2011

Pao WC et al, *Alzheimer Dis Assoc Disord*. 2011

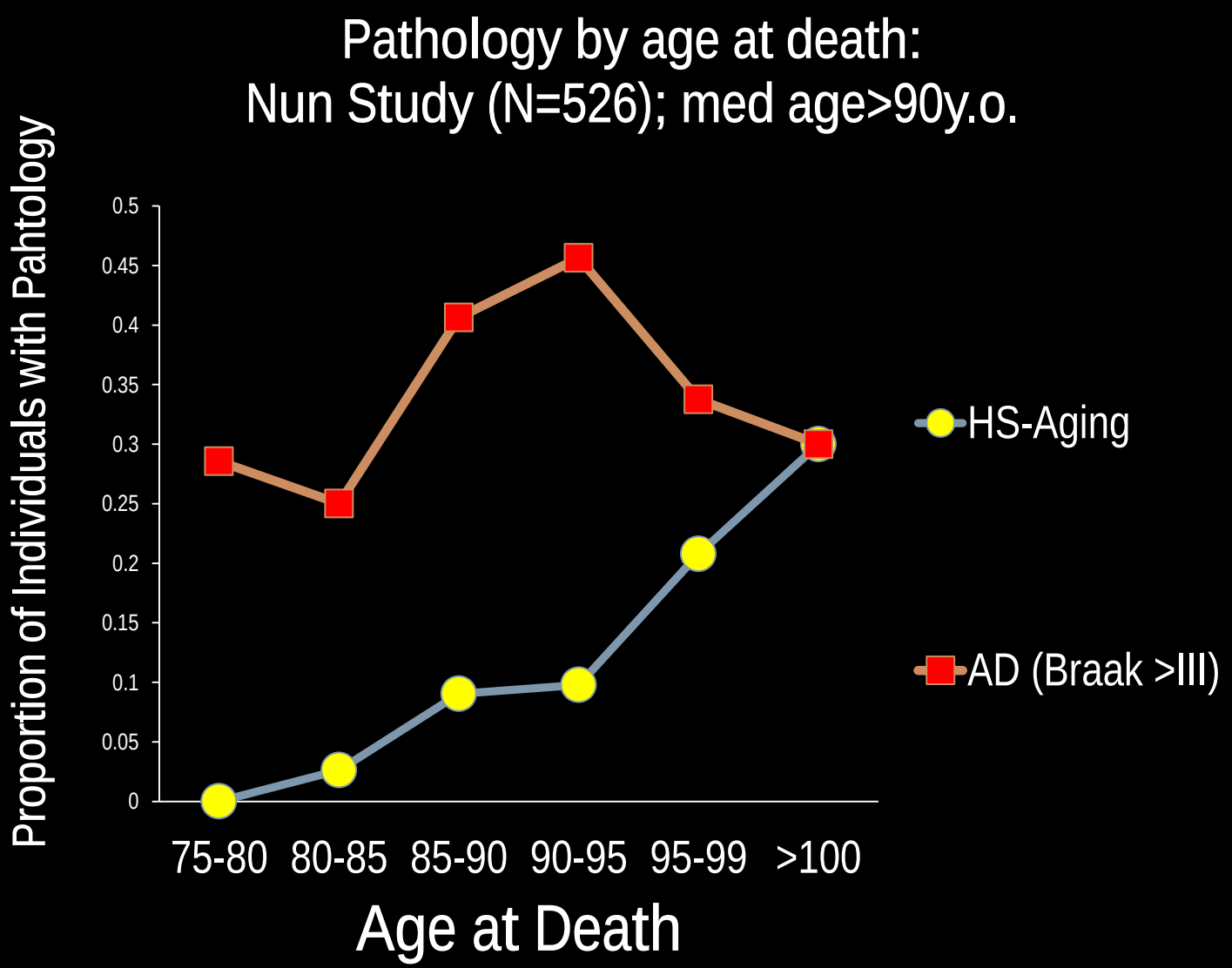
Brenowitz W et al, *JAD*, In Press

Testing the association between HS-Aging pathology and Alzheimer's disease pathology (plaques and tangles)

No fancy statistical models !!!



Rube Goldberg


Pathology by age at death:
Nun Study (N=526); med age>90y.o.
Proportion of Individuals with Pahtology
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
75-80
80-85
85-90
90-95
95-99
>100
Age at Death
HS-Aging
AD (Braak >III)

All participants (n=1,422)

CERAD Neuritic amyloid plaque densities	Braak Stage (Neurofibrillary tangles)						
	0	I	II	III	IV	V	VI
None							
Sparse							
Moderate							
Severe							

More severe AD pathology

Pathologically confirmed **HS pathology**
N=1,455 cases (NACC dataset)

% of cases with cortical HS pathology, by Braak and CERAD stages

Percent of participants with HS-Aging pathology

CERAD Neuritic amyloid plaque densities	Braak Stage (Neurofibrillary tangles)						
	0	I	II	III	IV	V	VI
None	9.5	8.2	1.5	12.5	3		
Sparse		14.3	6.1	4.9	7.4		
Moderate		14.3	2.6	1.6	6.3	11.5	9.8
Severe			7.1	7.3	10.6	10.4	7.8

More severe AD pathology

Brenowitz et al, *JAD, In Press*

Both
HS-Aging and AD pathology
are very prevalent,
and frequently co-occur.
However,
in old patients with
minimal AD pathology
one frequently sees
HS-Aging pathology

BORDER ZONE™

INFOCOM

COMMODORE 64/128

INTERACTIVE FICTION

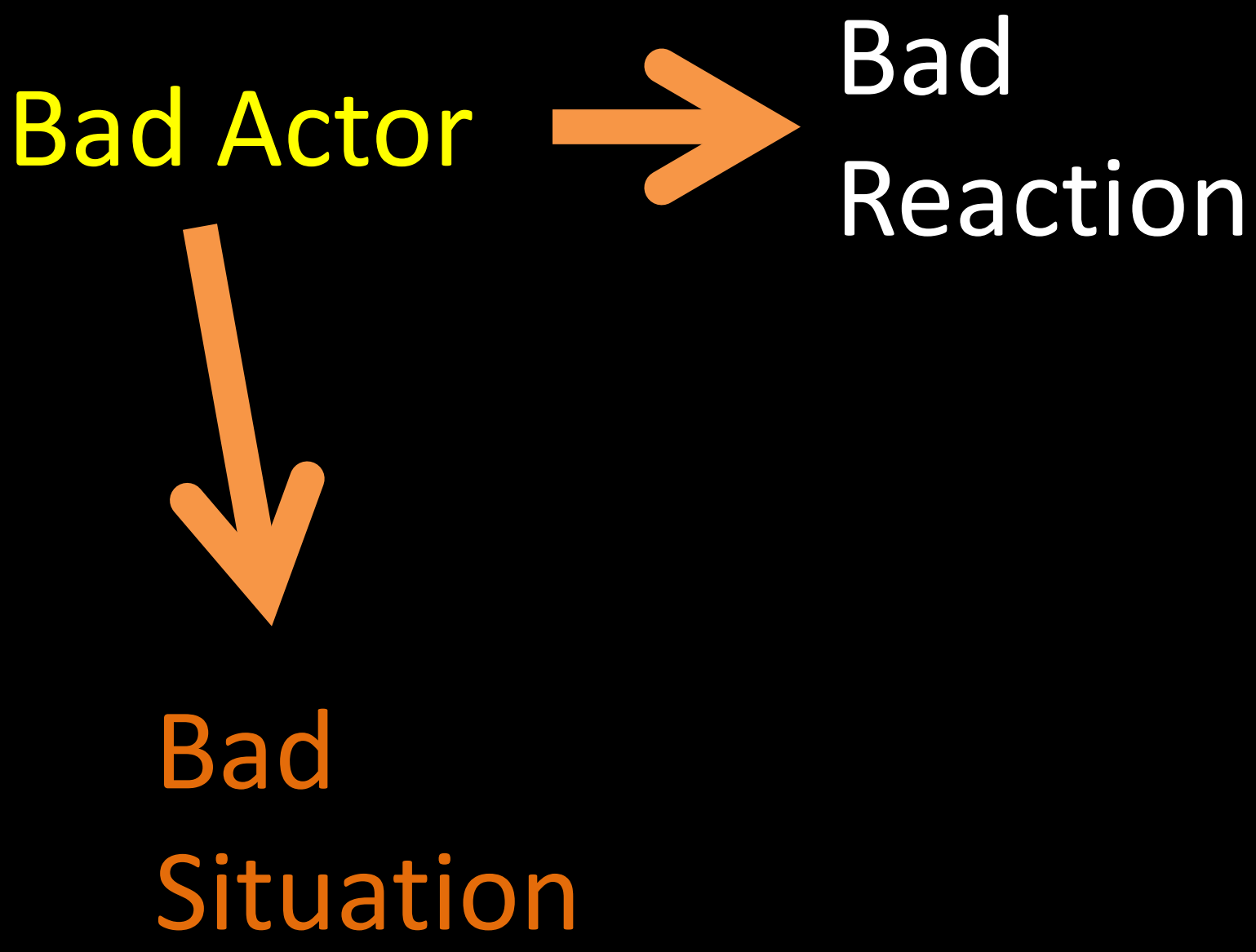
BY MARC BLANC

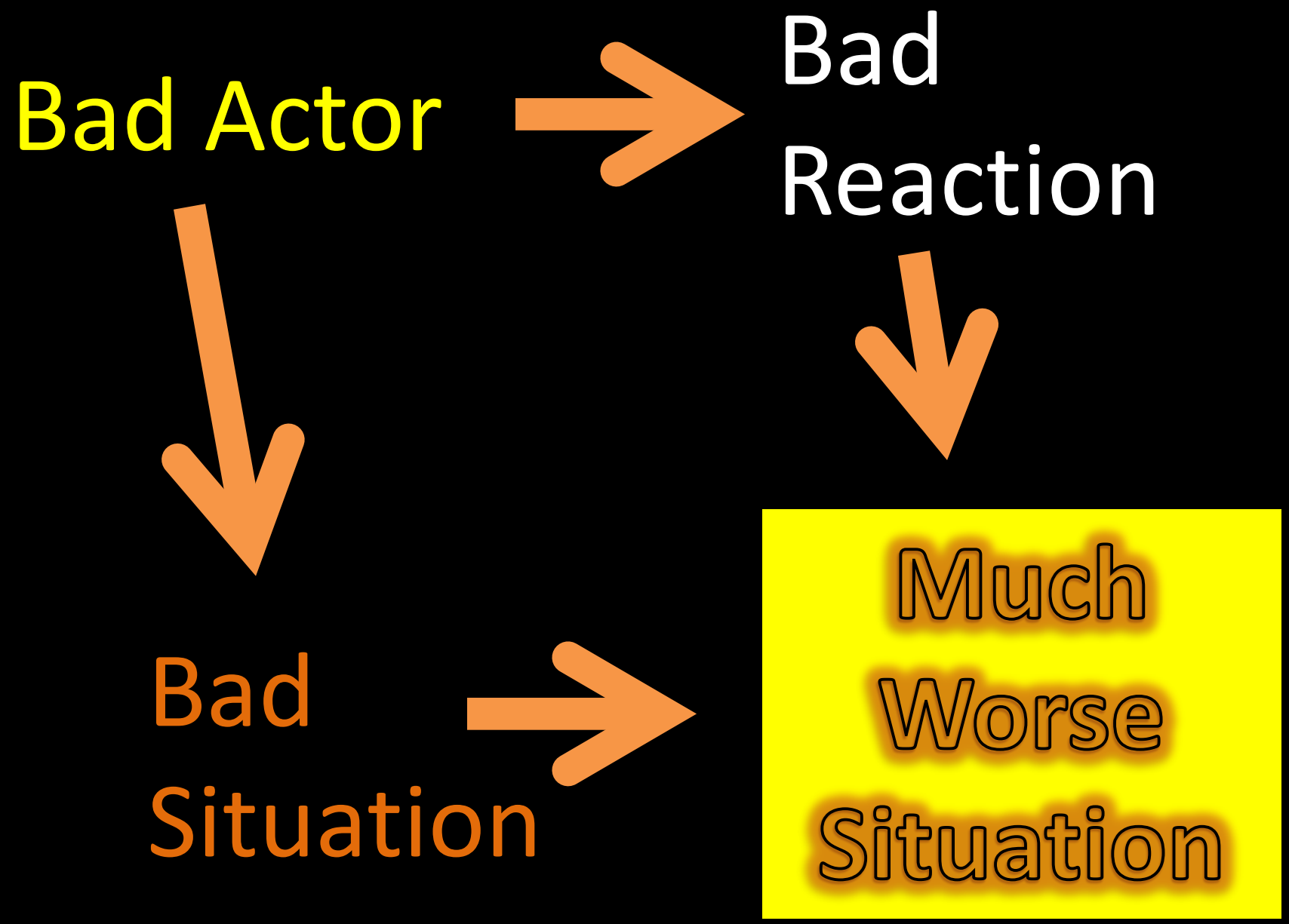
WITH ON-LINE HINTS

FTLD

Bad Actor

Bad Situation

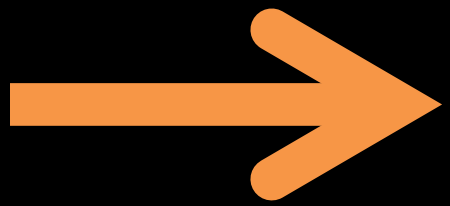

Bad Actor
Bad Reaction
Bad Situation


Bad Actor
Bad Reaction
Bad Situation
Much Worse Situation

Amyloid Plaques

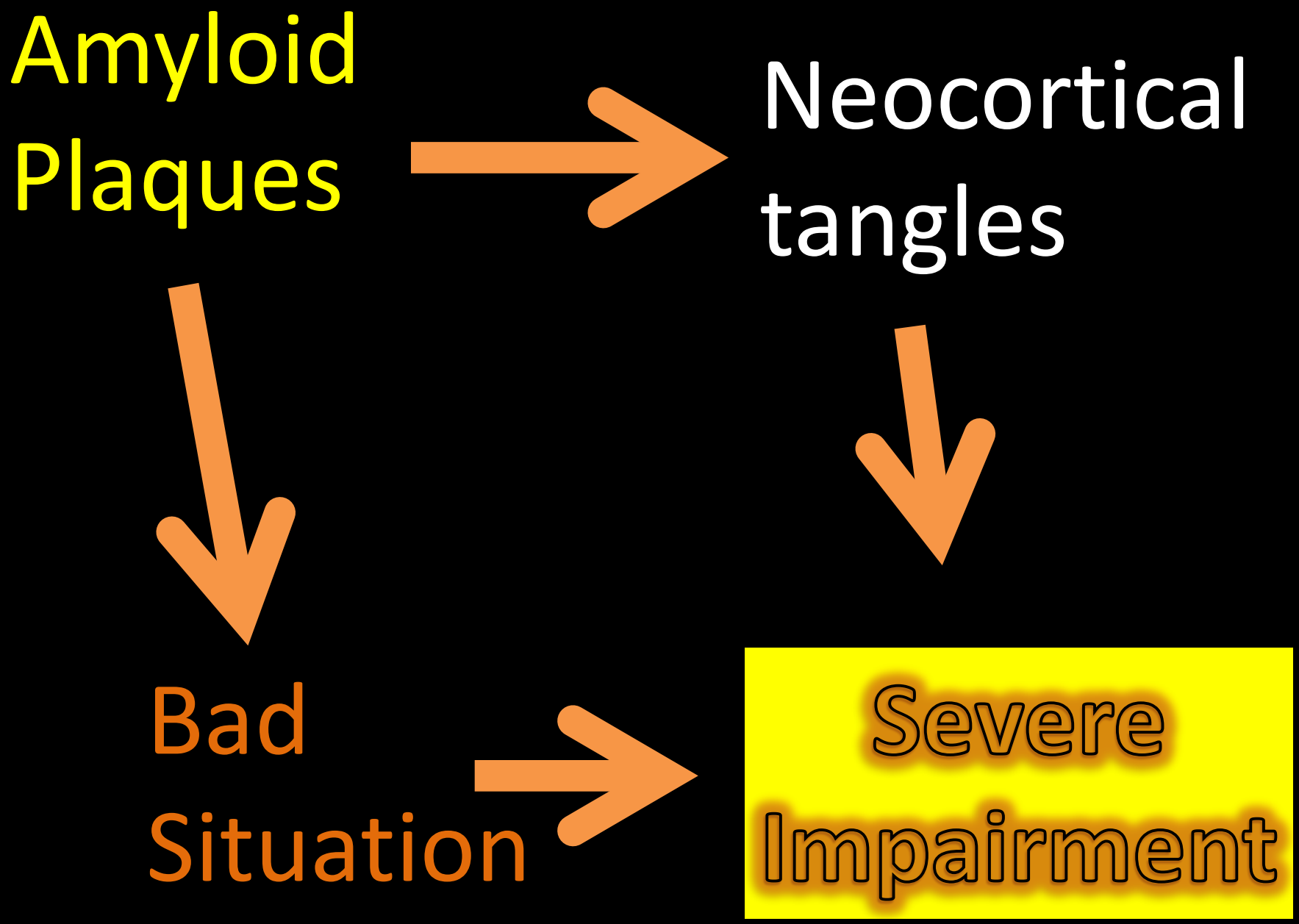
Bad Situation

Amyloid Plaques

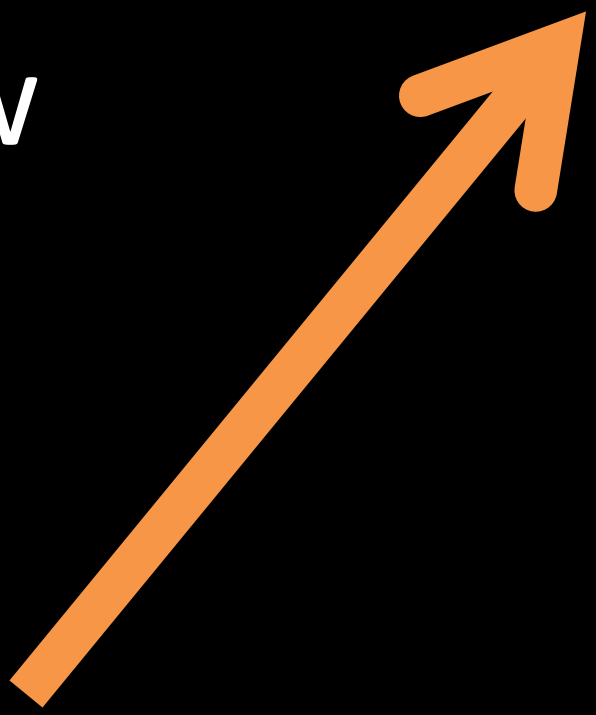


Neocortical tangles

Bad Situation


Amyloid Plaques
Neocortical tangles
Bad Situation
Severe Impairment

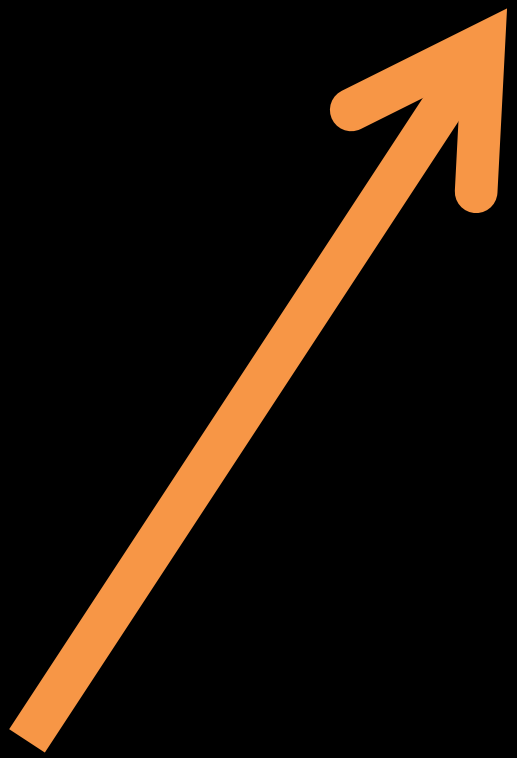
Credible—we now know lots of other stimuli/diseases



Neocortical tangles

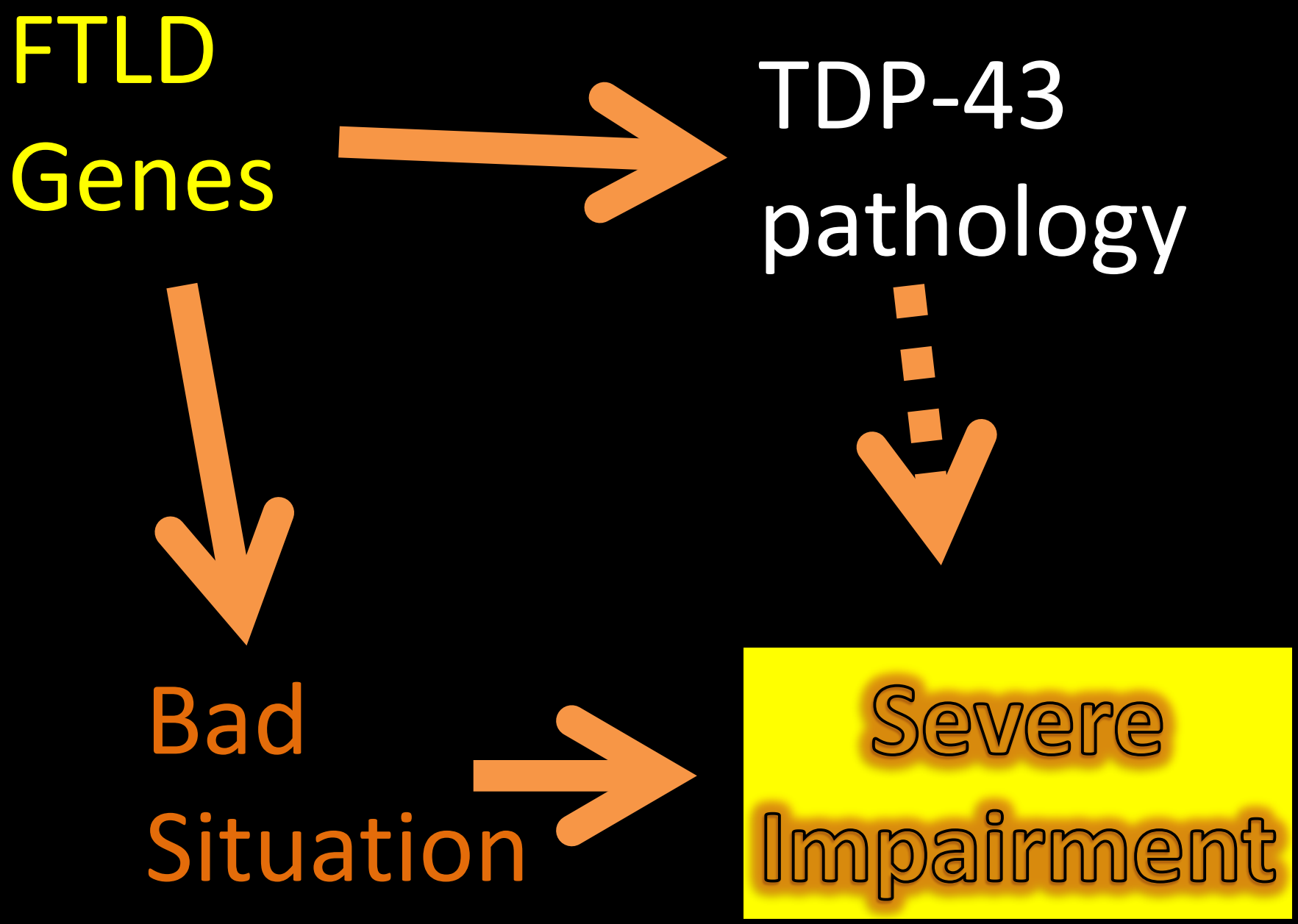
Impairment

We now know lots of other diseases including C.T.E.



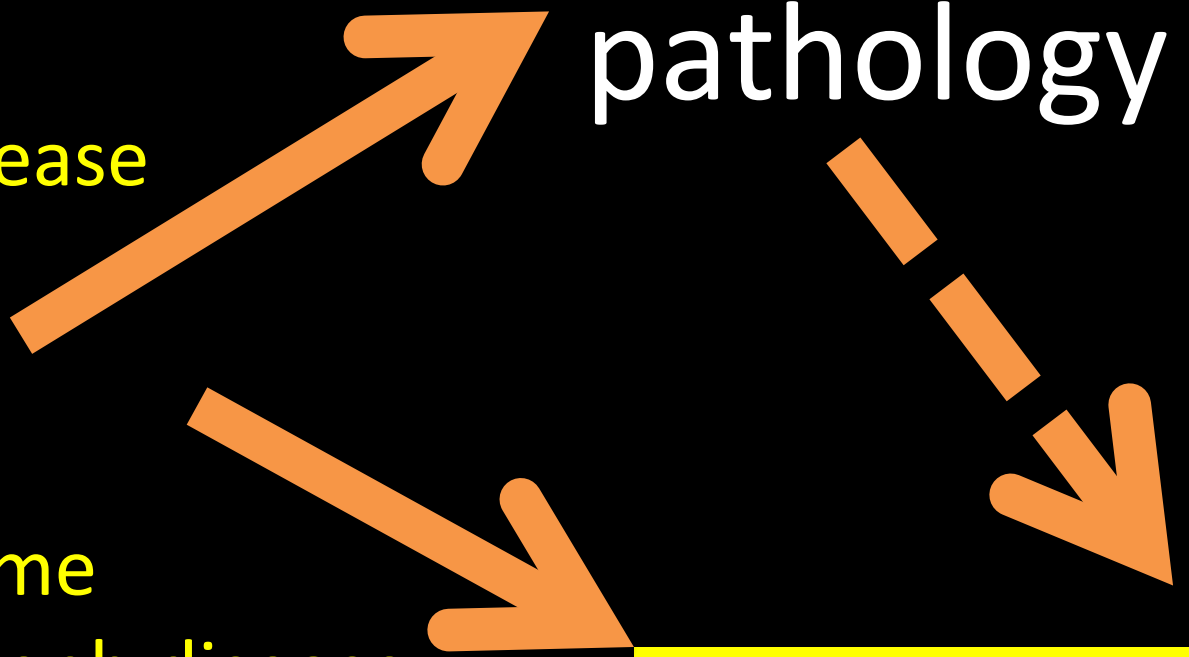
Neocortical tangles

Impairment


FTLD
Genes
TDP-43
pathology
Bad
Situation
Severe
Impairment

We now know

Cockayne disease
LRRK2 PD
SNCA PD
FAD
Perry Syndrome
Machado-Joseph disease
NBIA-1



We now know

Cockayne disease

LRRK2 PD

SNCA PD

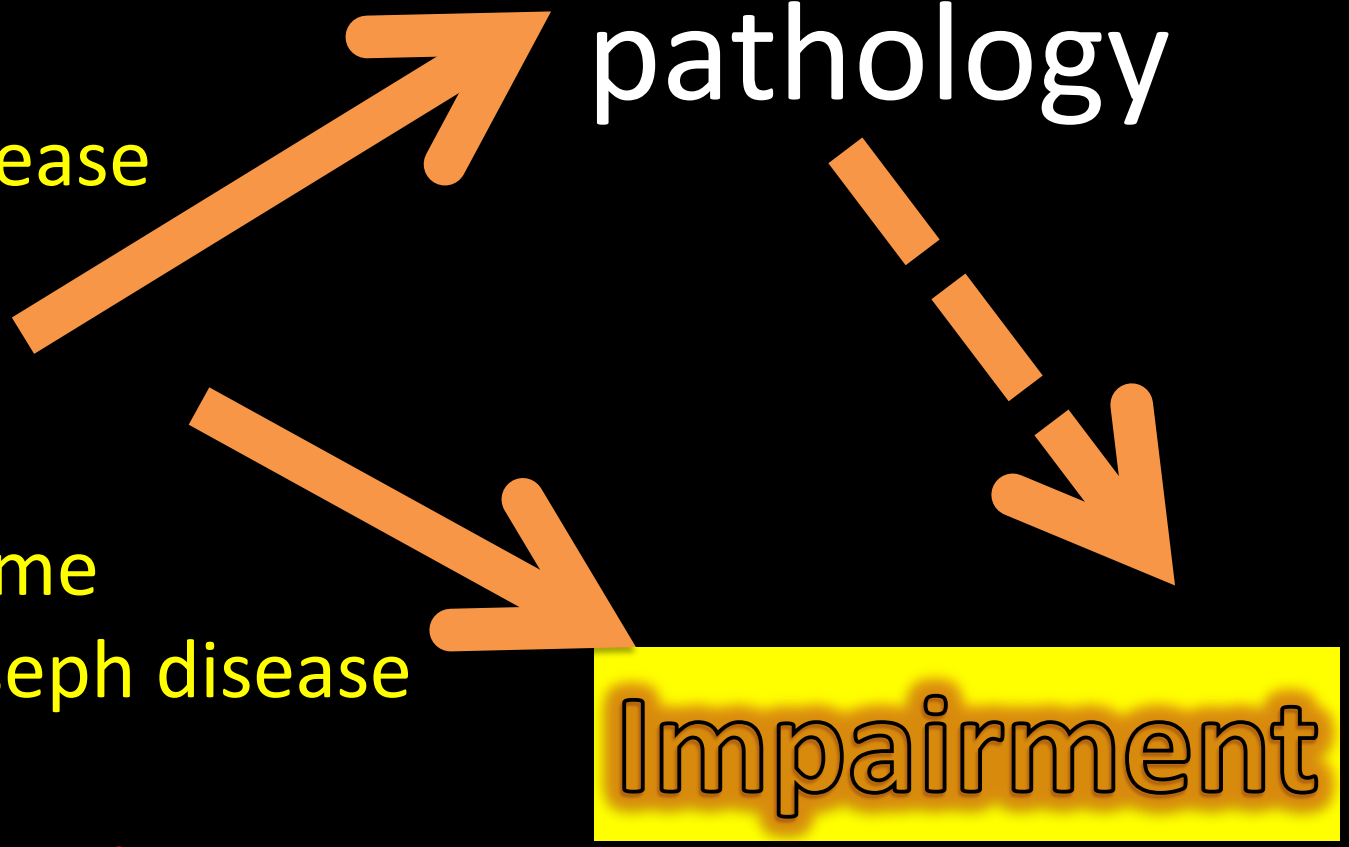
FAD

Perry Syndrome

Machado-Joseph disease

NBIA-1

Chronic traumatic encephalopathy



Age, symptoms, & neuroanatomy: HS-Aging differs ***appreciably*** from FTLD

Table 3 Comparison of mean age at death and percentage hippocampal sclerosis positive, frontotemporal dementia positive, progressive non-fluent aphasia positive, and semantic dementia positive, between the current case series (bold) and prior case series with frontotemporal lobar dementia with aberrant TDP-43 (FTLD-TDP)

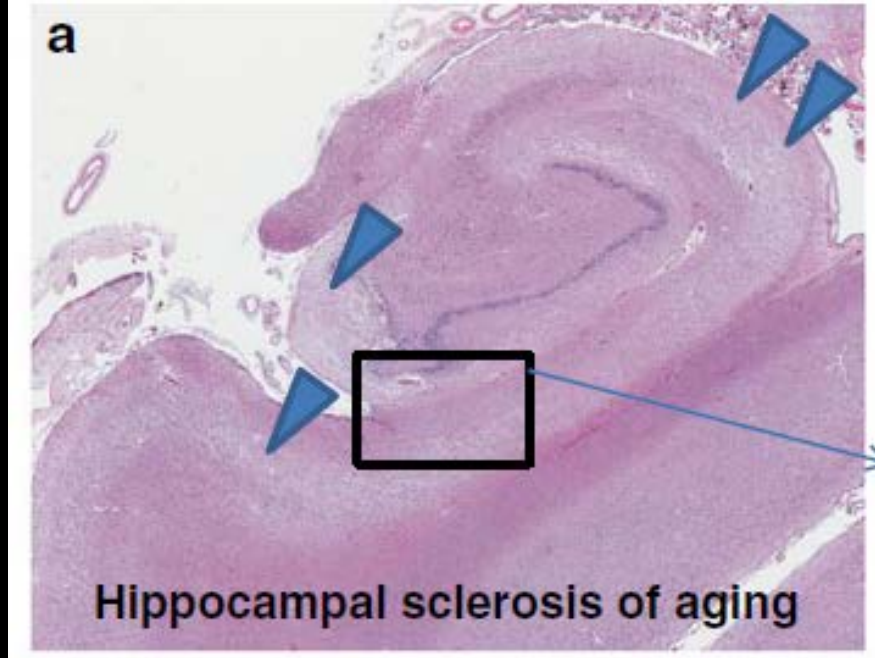
	n	Mean death age in years (SD)	Hippocampal sclerosis pathology (%)	FTD or PNFA clinically (%)	Semantic dementia clinically (%)
Current study					
HS-Ageing (all)	**106**	**92 (7)**	**100**[b]	**0**	**0**
HS-Ageing–TDP[a]	**71**	**94 (7)**	**100**[b]	**0**	**0**
Rohrer *et al.* (2010)					
FTLD–TDP type 1[c]	9	59 (8)	0	0	100
FTLD–TDP type 2[c]	5	59 (11)	20	100	0
FTLD–TDP type 3[c]	10	57 (8)	10	80	0
Josephs *et al.* (2009)					
FTLD–TDP type 1[d]	24	76 (10)	75	100	0
FTLD–TDP type 2[d]	9	74 (10)	56	29	71
FTLD–TDP type 3[d]	6	70 (8)	67	100	0
Mackenzie *et al.* (2006)[e]					
FTLD–TDP type 1[d]	15	69 (5)	93	93	7
FTLD–TDP type 2[d]	9	70 (4)	67	22	77
FTLD–TDP type 3[d]	13	59 (11)	100	100	0
Armstrong *et al.* (2009)[f]					
FTLD–TDP sporadic	52	71 (11)	6		
FTLD–TDP not sporadic	42	70 (9)	7		

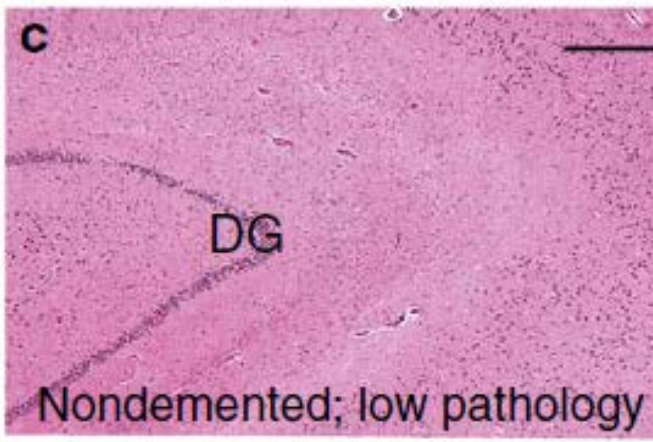
AD ≠ HS-Aging ≠ FTLD

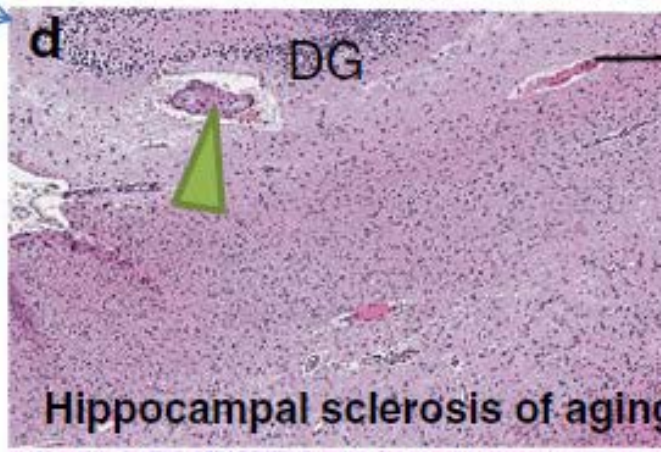
However, common biochemical pathways and genetic factors are involved

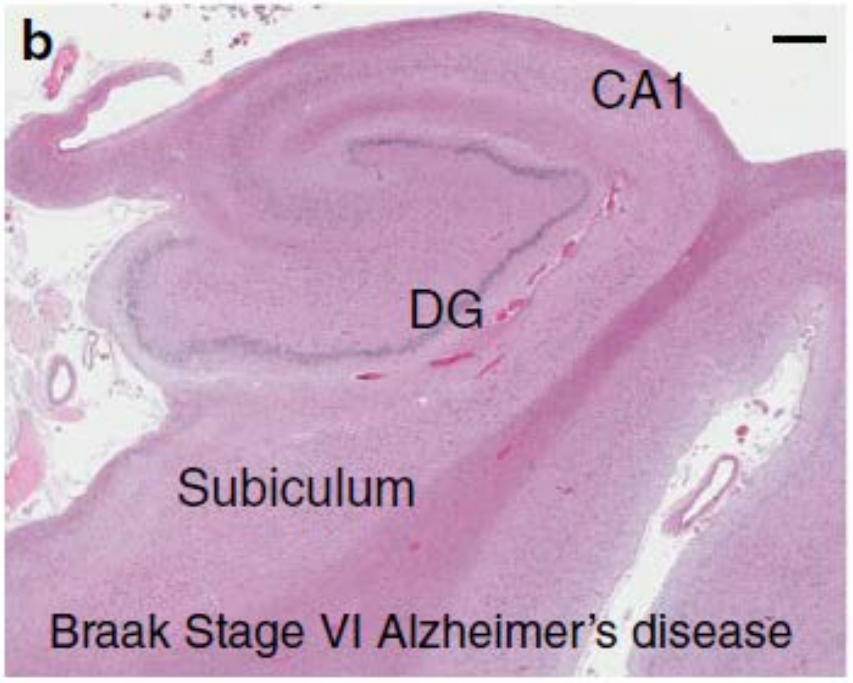
HS-Aging

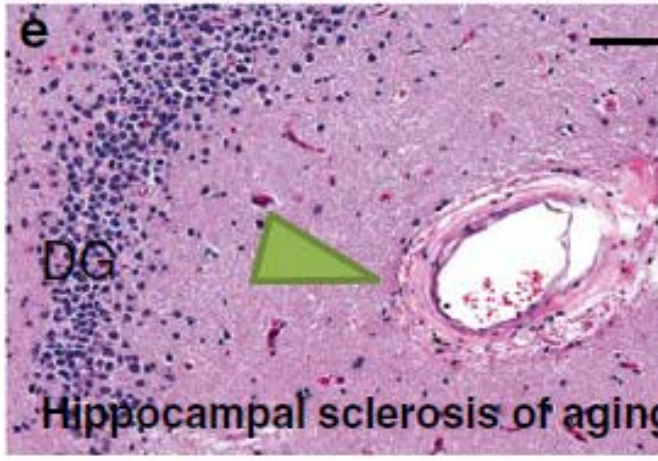
- What is it?
  Neuropathology
- Clinical impact
- Public health impact
- Border zone issues
- *New stuff*











Nelson et al,
Acta NP 2013

Acta Neuropathol (1994) 88 : 212–221

REGULAR PAPER

D. W. Dickson · P. Davies · C. Bevona
K. H. Van Hoeven · S. M. Factor · E. Grober
M. K. Aronson · H. A. Crystal

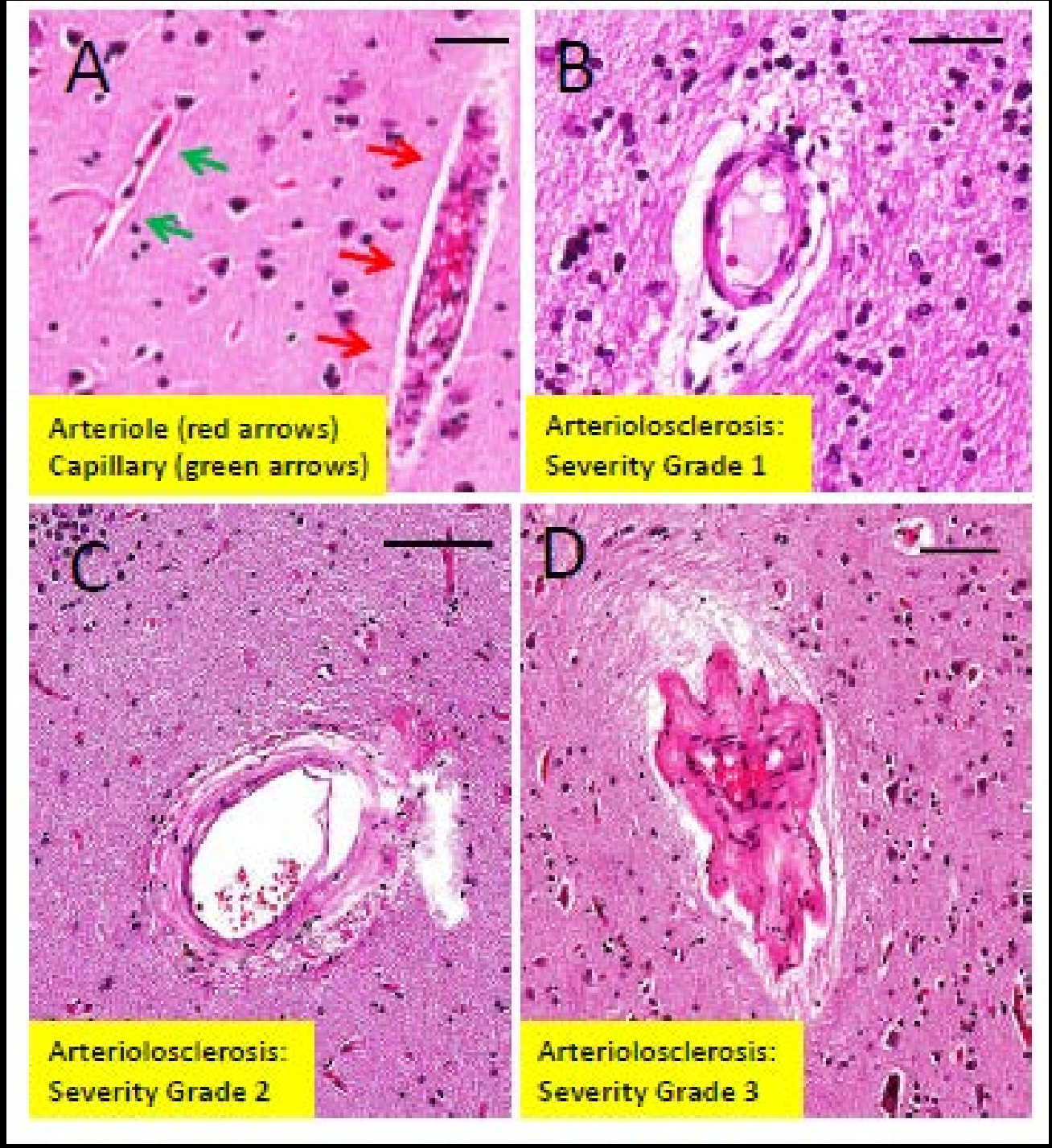
Hippocampal sclerosis: a common pathological feature of dementia in very old (≥80 years of age) humans

of people of 80 years of age or older, HpScl was detected in 13 cases (16%), including 9 women and 4 men. The latter group is the subject of this report. The average age for the 13 cases with HpScl (89.2±4.1

Cerebrovascular disease was detected in all 13 cases with HpScl. Microvascular pathology was prominent in all cases and took the form of arteriosclerosis (12 cases) or amyloid angiopathy (6 cases) or both (5 cases).

According to Wikipedia
(and Dorland's Medical Dictionary*)*—

"The following terms are similar, yet distinct, in both spelling and meaning…*Arteriosclerosis* is a general term describing any hardening (and loss of elasticity) of medium or large arteries (from the Greek *arteria*, meaning *artery*, and *sclerosis*, meaning *hardening*); *arteriolosclerosis* is any hardening (and loss of elasticity) of arterioles (small arteries)."



Neltner et al,
Brain, In Press

Summary	UK-ADC	Nun Study	NACC
Total cases included, N	327	247	1444
With HS-Aging pathology, N	39	30	157
Age at death (years), mean ± SD	88.0 ± 5.1	90.3 ± 4.8	88.3 ± 5.7
HS-Aging	90.2 ± 4.6	92.9 ± 5.1	89.1 ± 5.6
No HS-Aging	87.8± 5.1	89.9 ± 4.6	88.2 ± 5.7
% HS-Aging (no AD)	4.6	6.5	4.2
% AD (no HS)	45.3	19.8	41.9
% HS-Aging + AD	7.3	5.7	6.4

Neltner et al,
Brain, In Press

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We tested presence/severity of multiple parameters for correlation with HS-Aging pathology

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Neltner et al, *Brain, In Press*

Arteriolosclerosis severity correlated with HS-Aging pathology in all 3 datasets

None of these (presence or severity) correlated with HS-Aging pathology:

- Total infarcts
  - Micro-infarcts
  - Pale infarcts
  - Lacunar infarcts
  - Hemorrhagic infarcts
  - Hemorrhages
  - Macro-infarcts
- Cortical Laminar Necrosis
- Atherosclerosis (Circle of Willis)
- Amyloid Angiopathy

Neltner et al,
Brain, In Press

HS-Aging pathology correlated with presence of regional arteriolosclerosis in age-matched UK-ADC participants

(P value determined by logistic regression controlling for age at death via covariate adjustment; the Bonferroni-Holm method was used to correct for multiple comparisons.)

HS-Aging vs. controls: presence of regional arteriolosclerosis in age-matched UK-ADC participants

Area	p	Significant
Frontal cortex (BA 9)	0.0001	Y
Occipital cortex	0.0018	Y
Posterior Cingulate	0.0014	Y
Anterior Cingulate	0.0016	Y
Thalamus	0.0023	Y
Caudate	<0.0001	Y
Putamen	<0.0001	Y
Insular cortex (BA13)	0.0005	Y
Globus Pallidus	<0.0001	Y
Temporal cortex (BA 21/22)	0.0032	N
Parietal cortex (BA 39/40)	0.022	N
Internal Capsule	0.0767	N

Neltner et al, *Brain, In Press*

According to Wikipedia
(and Dorland's Medical Dictionary*)*—

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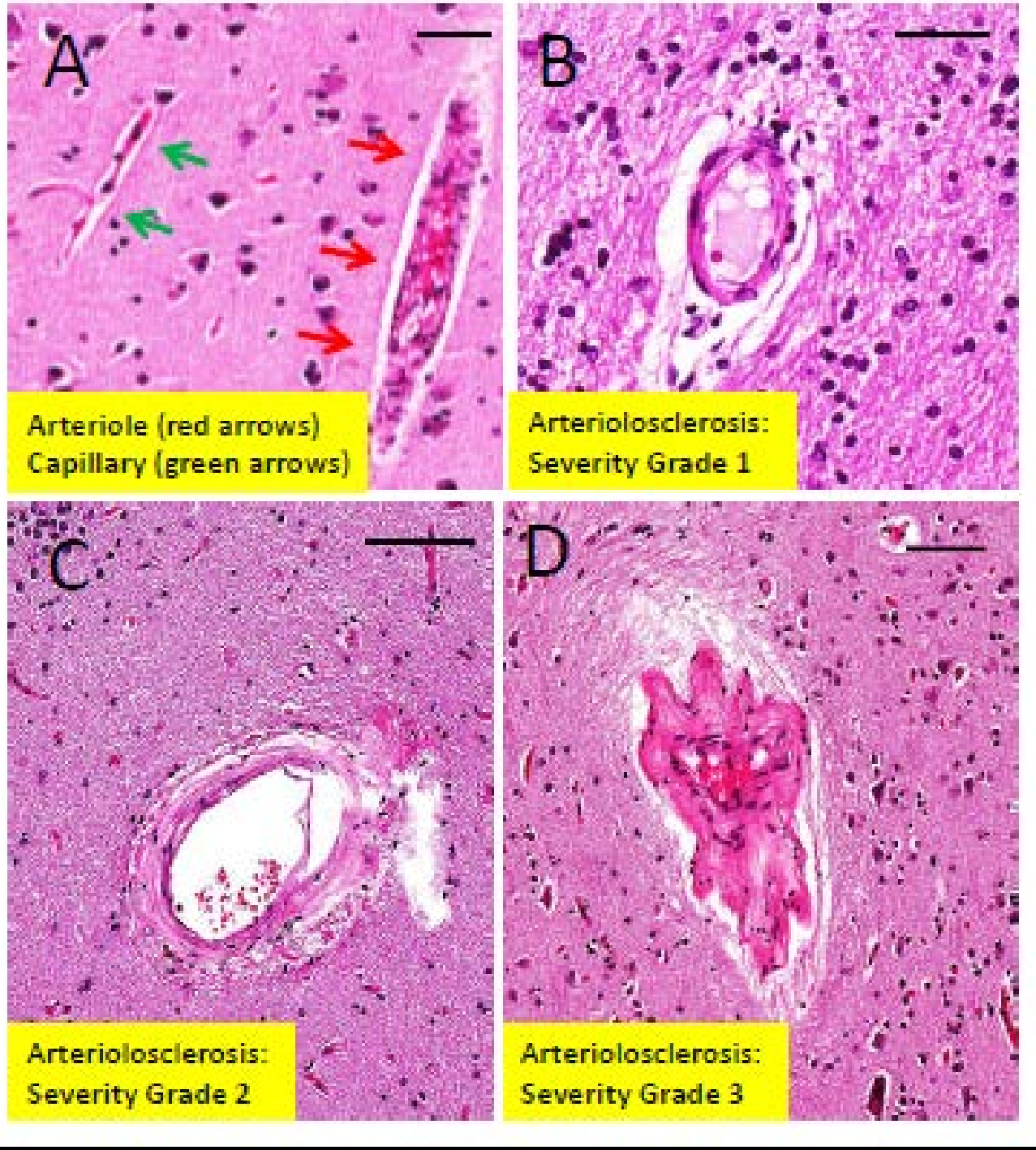
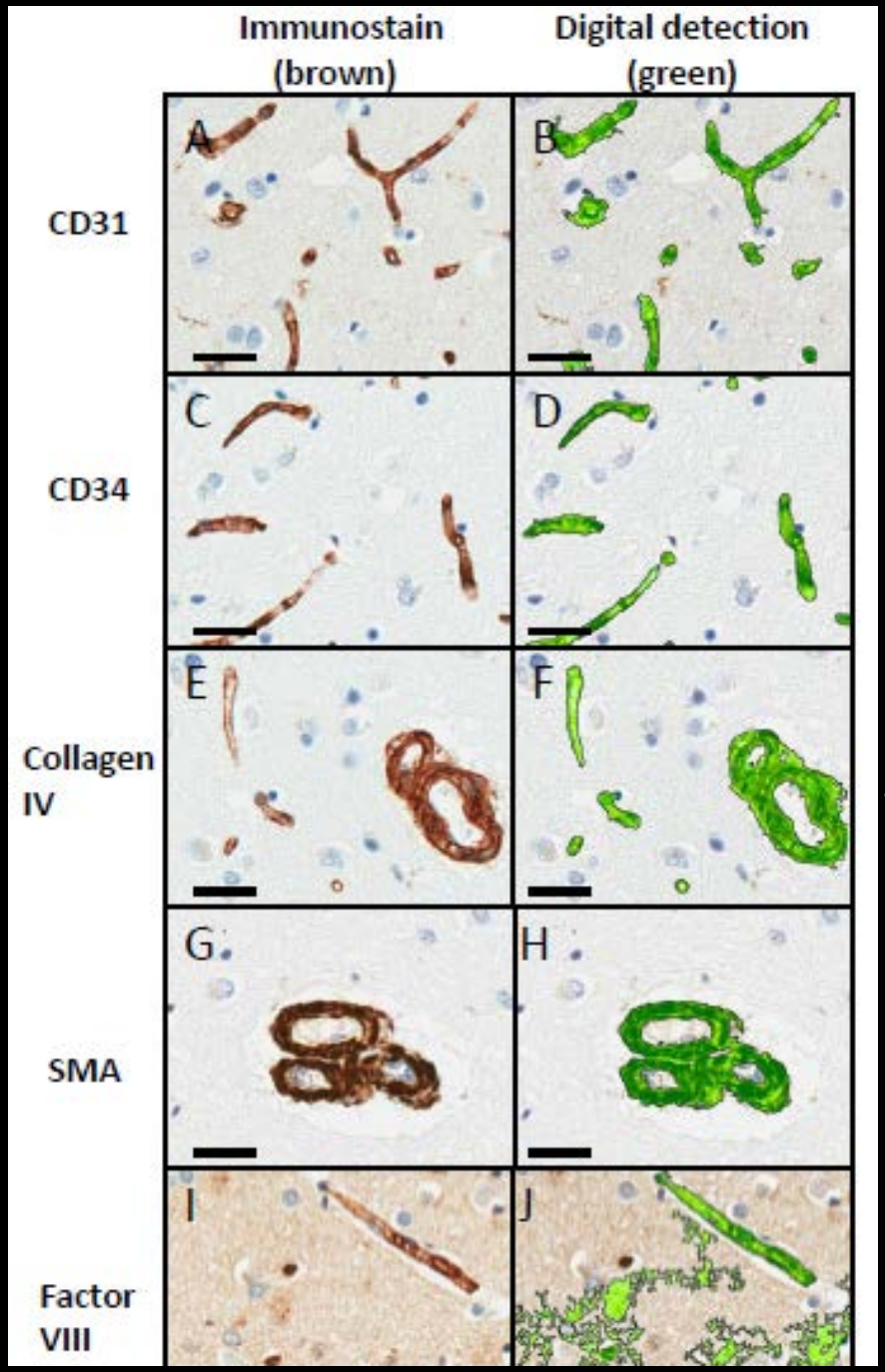
We sought a method that was more rigorous than semiquantitative scoring



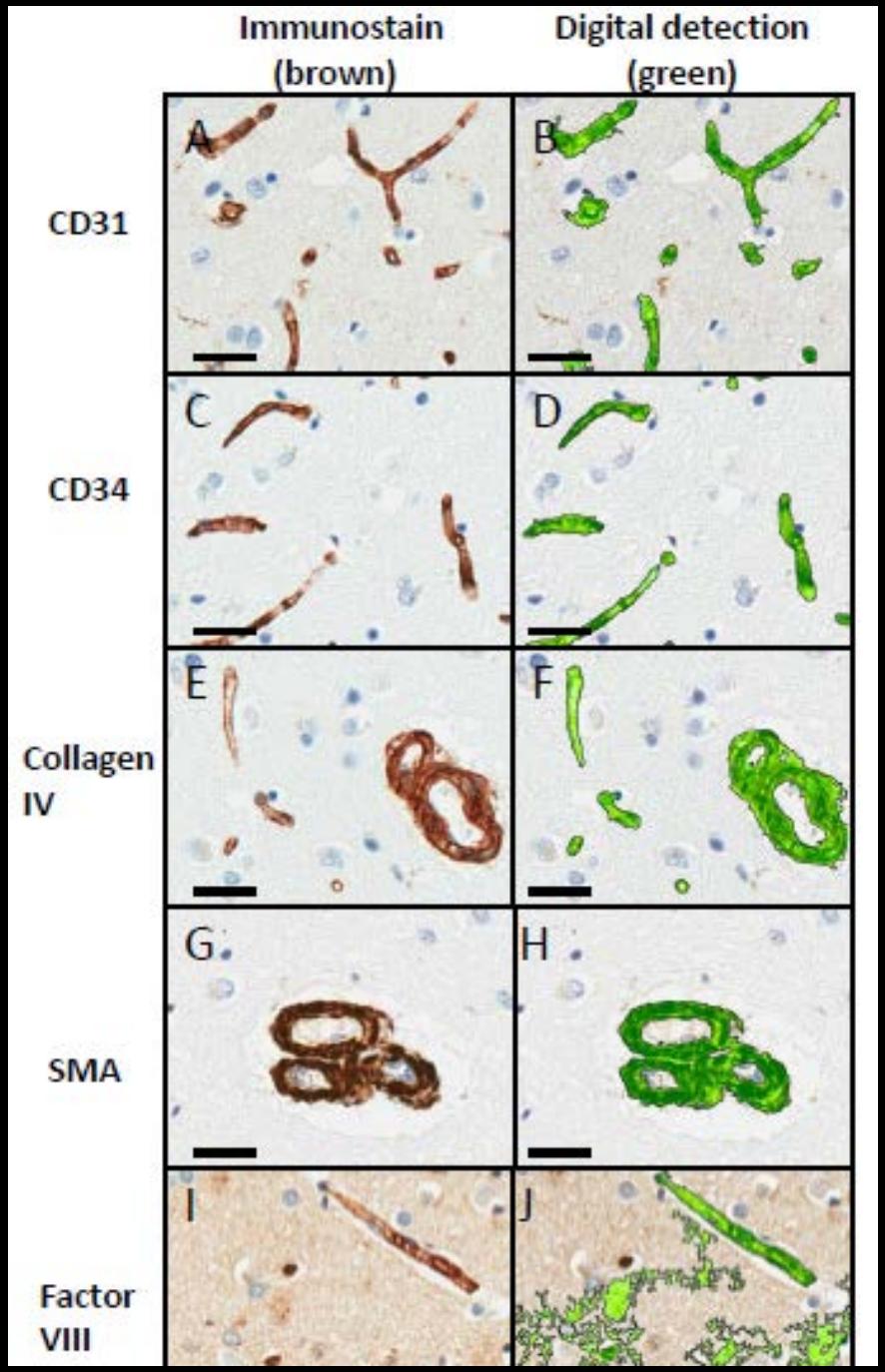
Neltner et al,
Brain, In Press

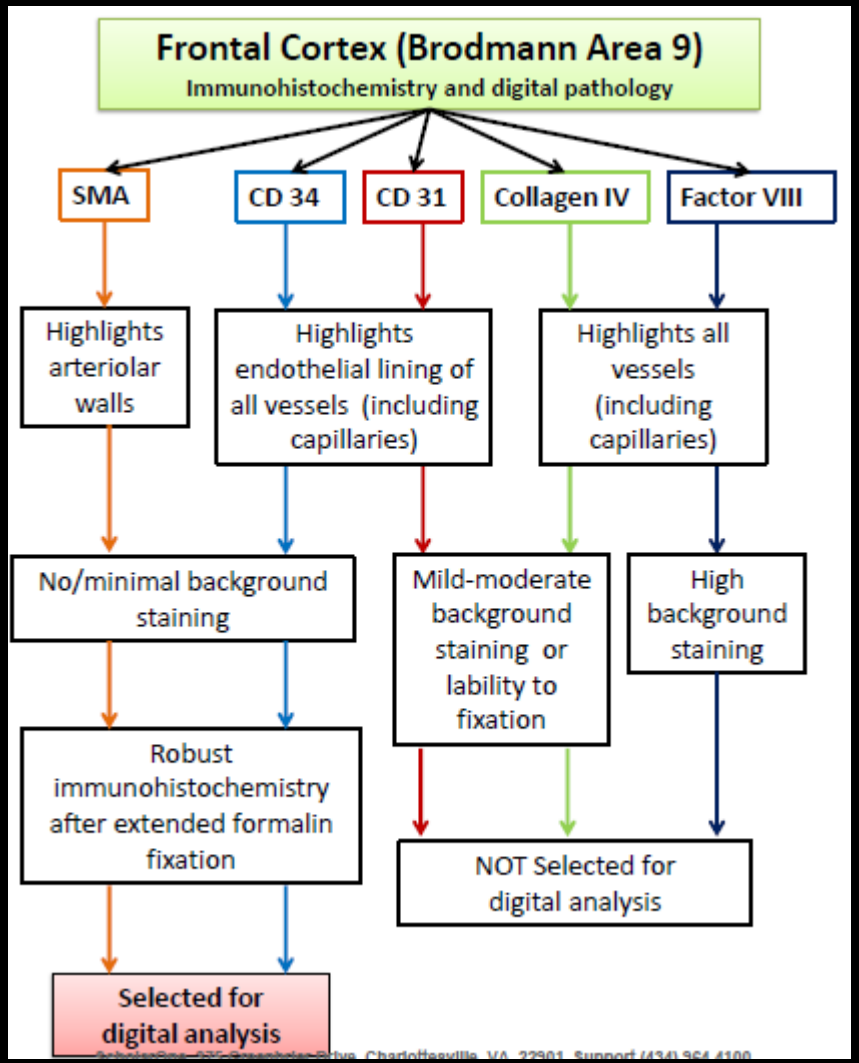


Digital pathology:

Relatively unbiased high-throughput morphometry

Neltner et al,
Brain, In Press



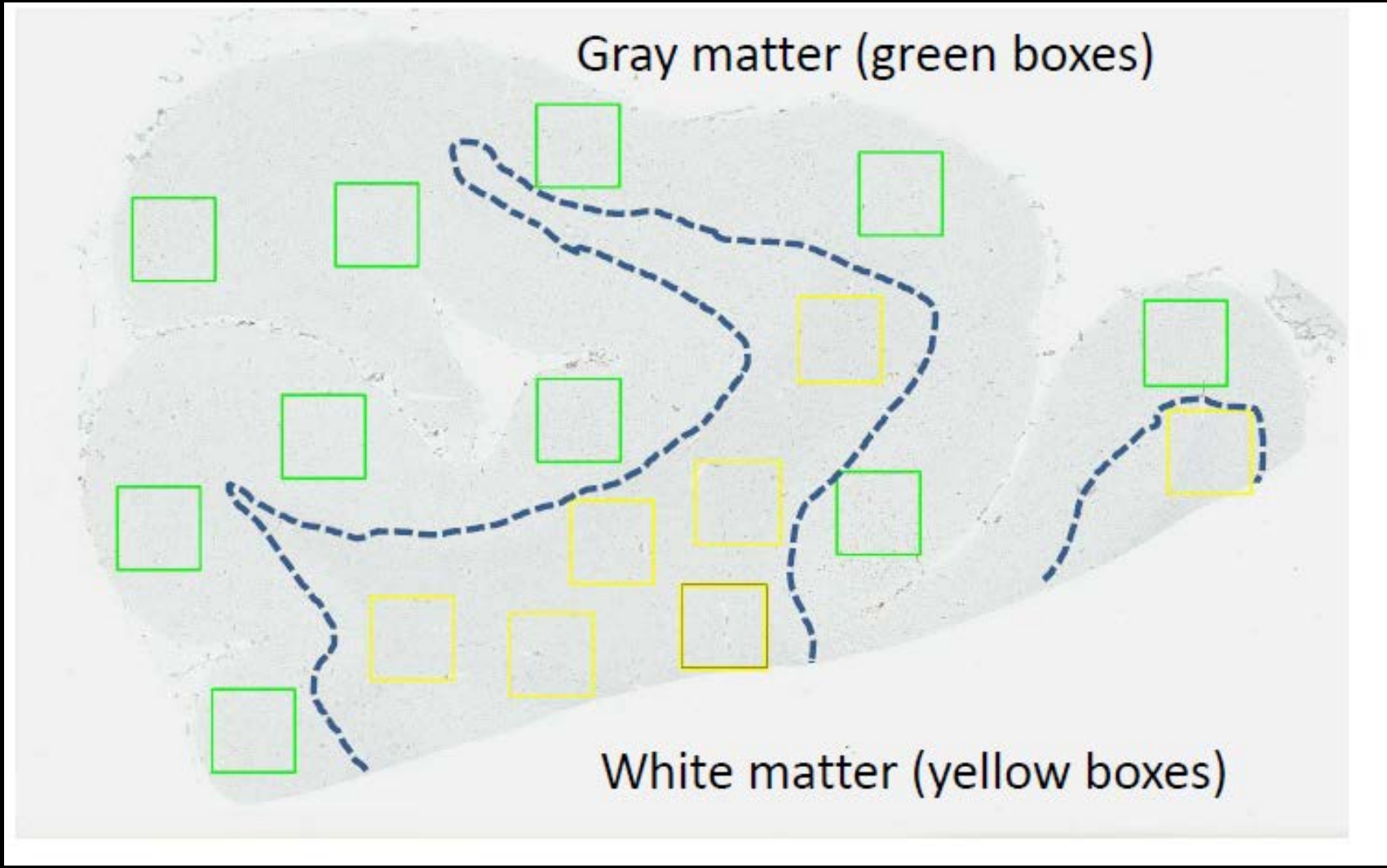


Neltner et al,
Brain, In Press

We applied digital pathologic (Aperio ScanScope) methods on a convenience subsample of frontal cortex sections from HS-Aging (N=15) and control (N=42) cases.

We applied digital pathologic (Aperio ScanScope) methods on a convenience subsample of frontal cortex sections from HS-Aging (N=15) and control (N=42) cases.

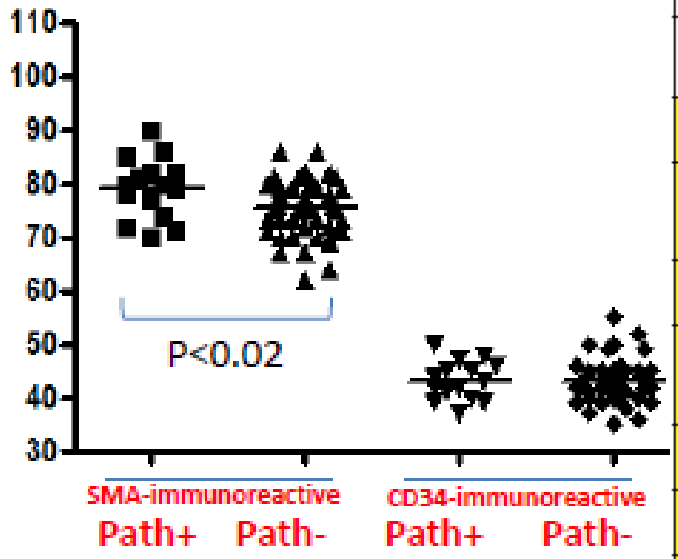
43,834 α-SMA-positive vascular profiles and 603,798 CD34-positive vascular profiles were evaluated.



Frontal cortex, Brodmann Area 9

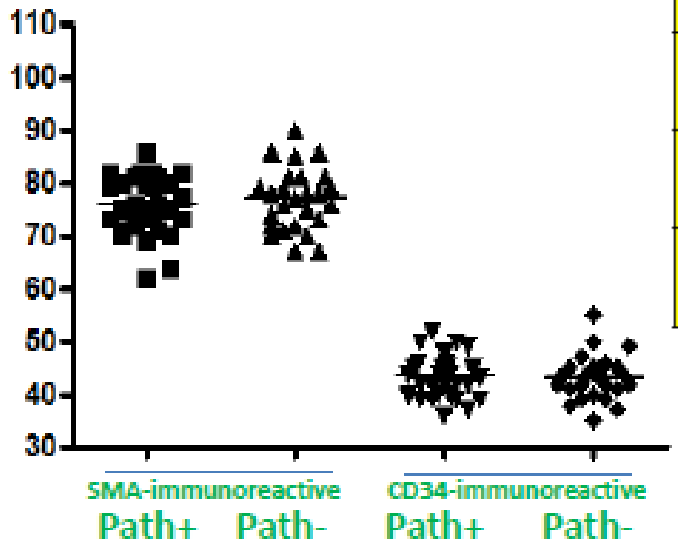
A

Gray matter: HS-Aging pathology versus Non-HS-Aging pathology



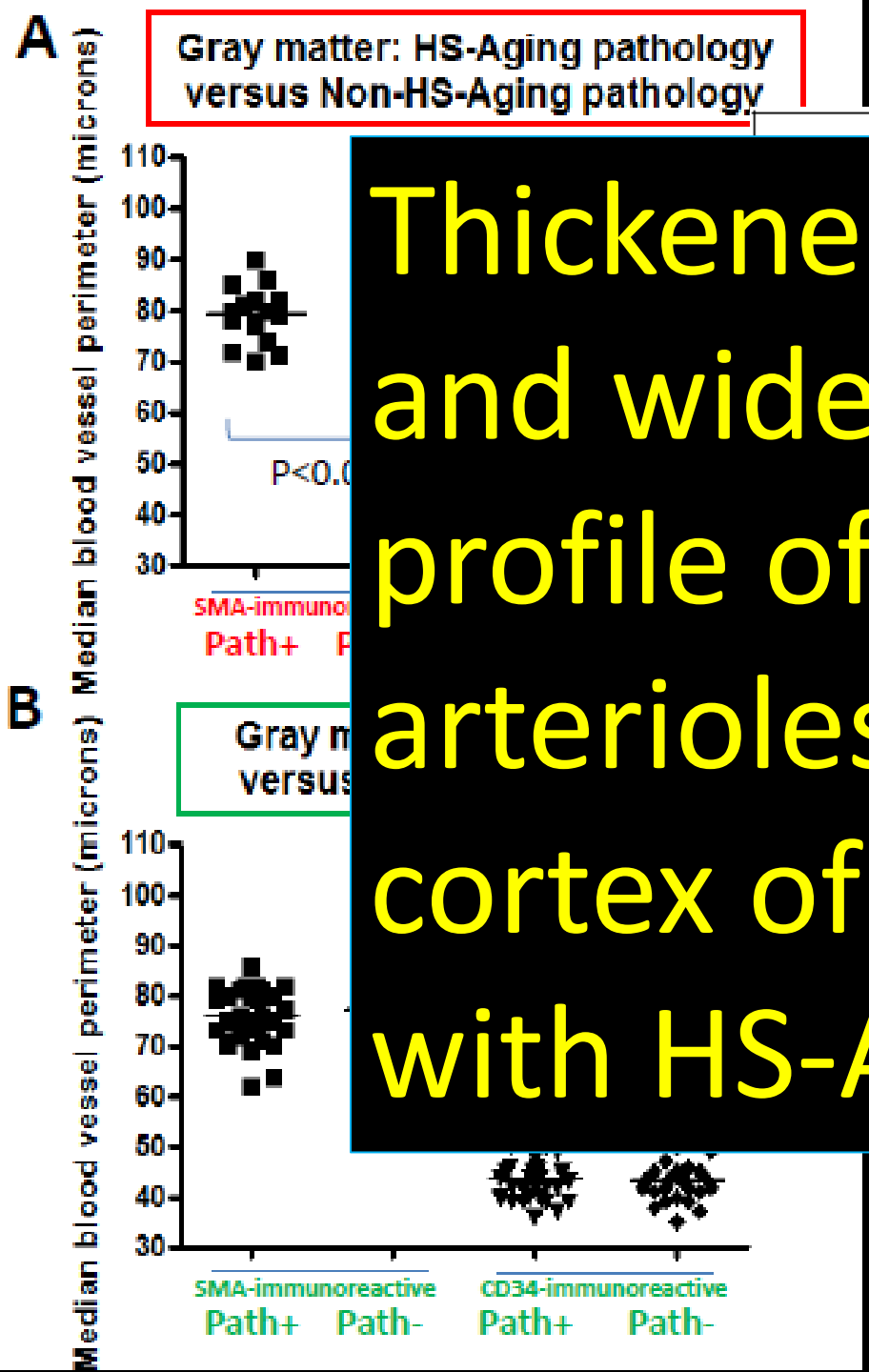
B

Gray matter:AD pathology versus non-AD pathology



	SMA-GM*		SMA-WM*		CD34-GM*		CD34-WM*	
Parameter	HS	non-HS	HS	non-HS	HS	non-HS	HS	non-HS
Number of Vessels	409.2	423.8	347.5	349.7	7751.2	7920.7	2715.6	2717.3
Total Analysis Area (μm^2)/10^7	4.03	3.97	4.02	3.69	4.02	3.92	3.96	3.68
Average Stain Intensity	101.4	101.0	104.2	103.3	140.7	141.1	135.0	135.5
Microvessel Density # /(μm^2)*10^6	1.02	1.07	0.86	0.96	19.27	20.23	6.87	7.57
Mean Vessel Area (μm^2)	352.5	324.7	327.3	315.6	123.1	120.8	201.5	195.1
Median Vessel Area (μm^2)	151.3	141.5	137.4	124.7	72.1	72.3	115.4	110.9
Mean Vessel Perimeter (µm)	122.3	116.6	140.3	133.9	61.9	60.7	82.3	81.0
Median Vessel Perimeter (µm)	79.1	75.3	79.0	74.3	43.2	43.2	55.1	54.3
Mean Vascular Area (μm^2)	280.8	256.3	263.7	250.5	118.1	115.6	193.8	187.4
Median Vascular Area (μm^2)	113.5	104.6	102.9	94.1	71.7	71.8	113.9	109.7
Mean Vessel Wall Thickness (µm)	1.817	1.731	1.471	1.480	1.694	1.694	2.069	2.024
Median Vessel Wall Thickness (µm)	1.405	1.353	1.211	1.233	1.631	1.635	2.023	1.983

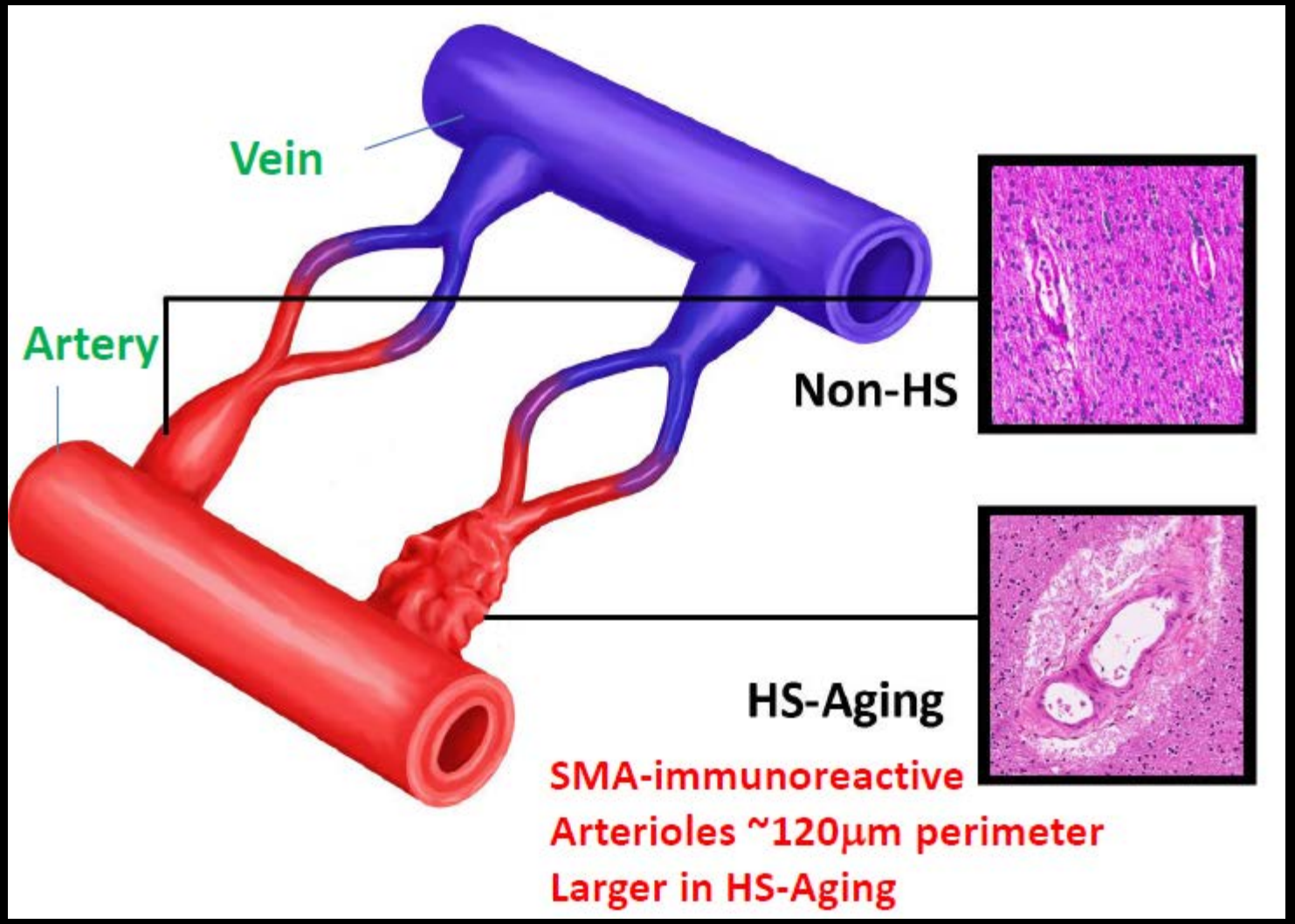
Neltner et al,
Brain, In Press



	SMA-GM*		SMA-WM*		CD34-GM*		CD34-WM*	
	HS	non-HS	HS	non-HS	HS	non-HS	HS	non-HS
	7920.7		2715.6		2717.3			
	3.92		3.96		3.68			
	141.1		135.0		135.5			
	20.23		6.87		7.57			
	120.8		201.5		195.1			
	72.3		115.4		110.9			
	60.7		82.3		81.0			
	43.2		55.1		54.3			
	115.6		193.8		187.4			
	71.8		113.9		109.7			
	1.694		2.069		2.024			
	1.635		2.023		1.983			

Thickened walls and wider vascular profile of SMA+ arterioles in frontal cortex of brains with HS-Aging

Neltner et al,
Brain, In Press



Neltner et al,
Brain, In Press

Conclusions

HS-Aging:

Distinct “whole brain” disease entity

- High prevalence
- High morbidity
- Neuropathology
  - HS in “oldest-old”
  - TDP-43 pathology
  - Arteriolosclerosis

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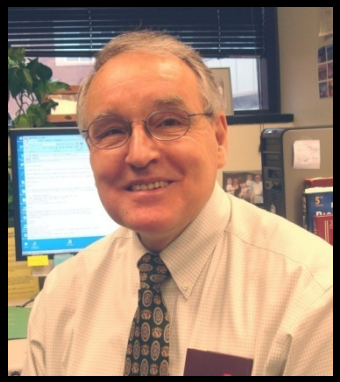

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NIH/NIA NACC (U01 AG016976)

Thickening and widening of arterioles in frontal cortex of brains with HS-Aging