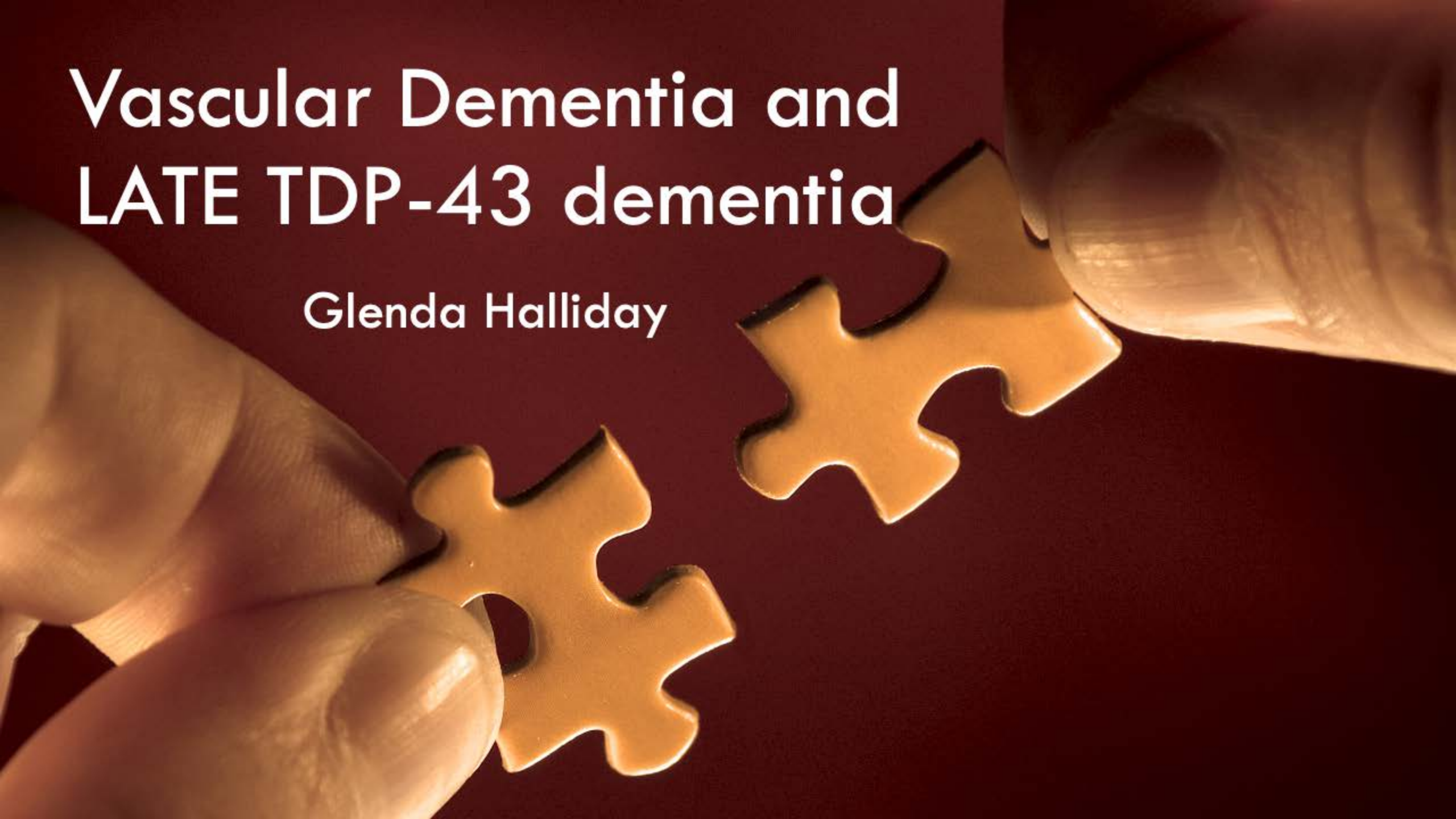
Vascular Dementia and LATE TDP-43 dementia

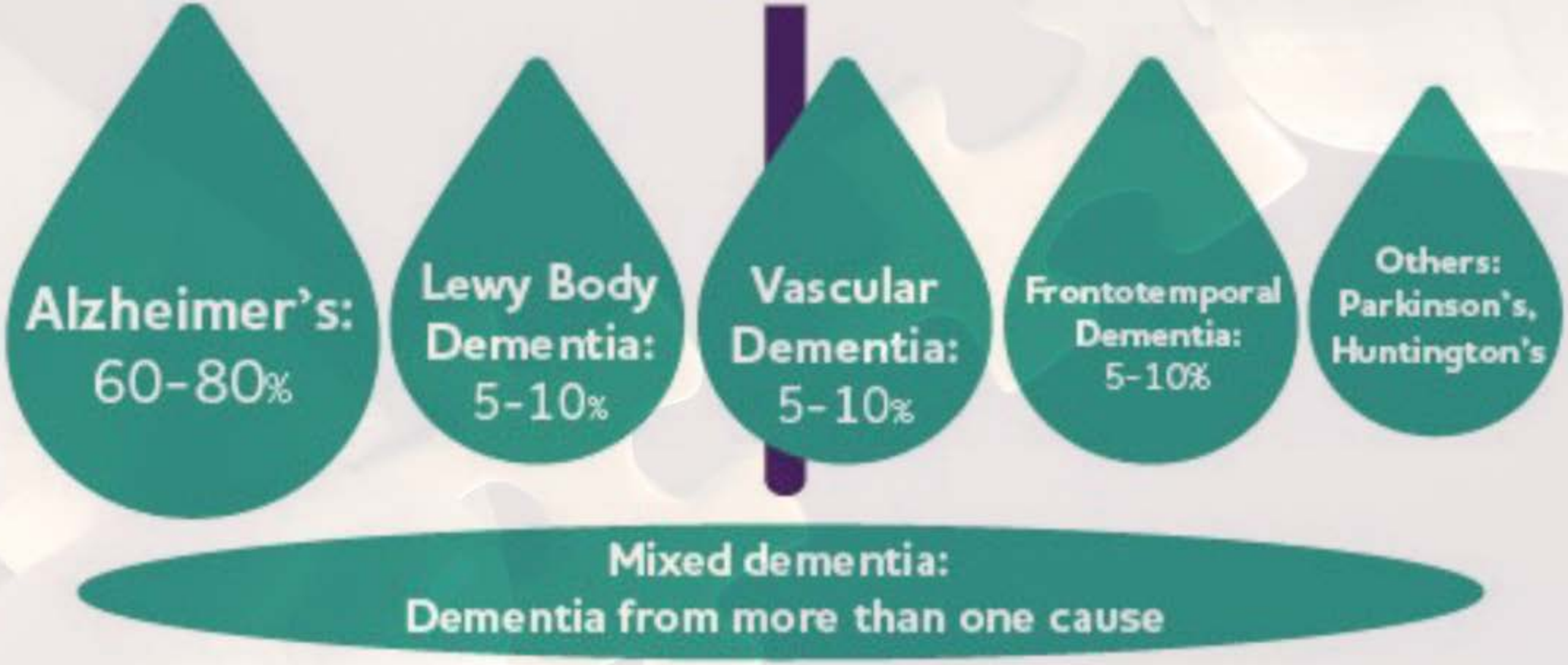
Glenda Halliday



Outline

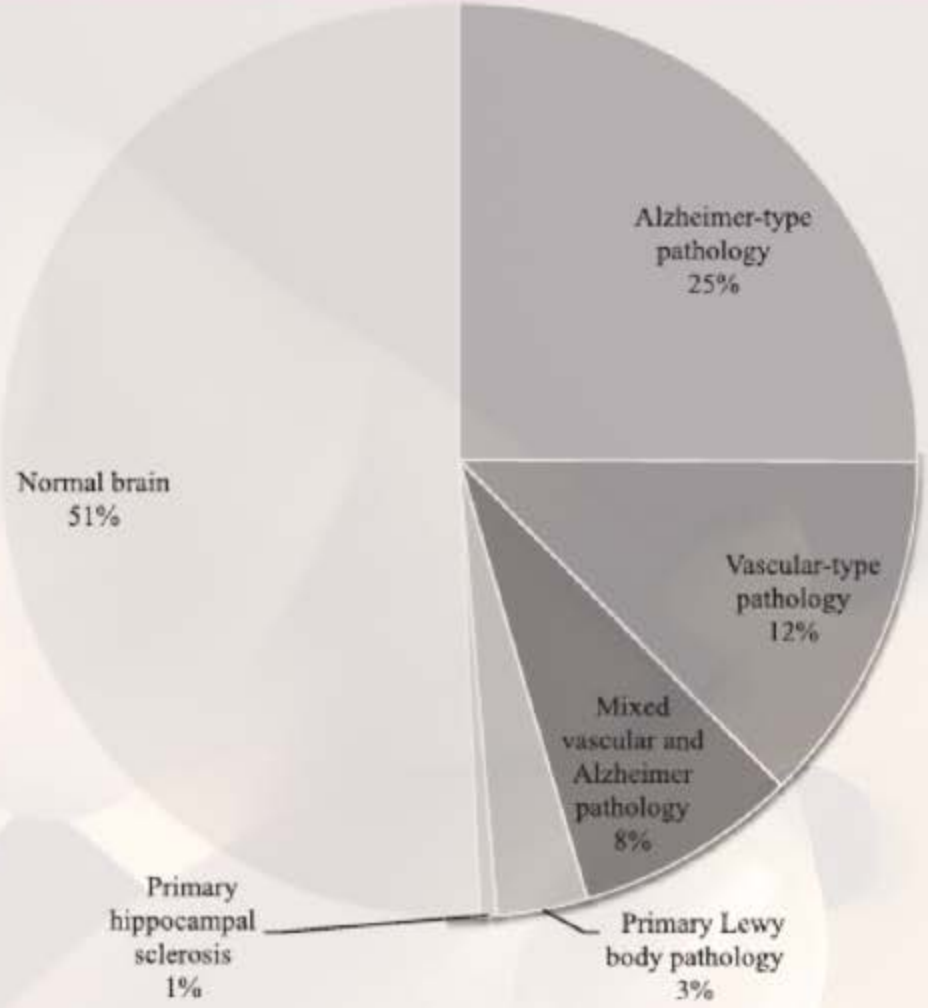
- General comments
  - Types of dementia – where do vascular and LATE TDP-43 fit in
  - Dementia pathologies – where do vascular and LATE TDP-43 fit in
  - Mixed pathologies and their impact
- LATE TDP-43 dementia
  - Typical characteristics
  - Relationship to frontotemporal dementia (FTD) and Alzheimer's
- Vascular dementia
  - Typical characteristics
  - Relationship to Alzheimer's
- Overlap between LATE and vascular pathologies
- Summary

Prevalence of dementia syndromes

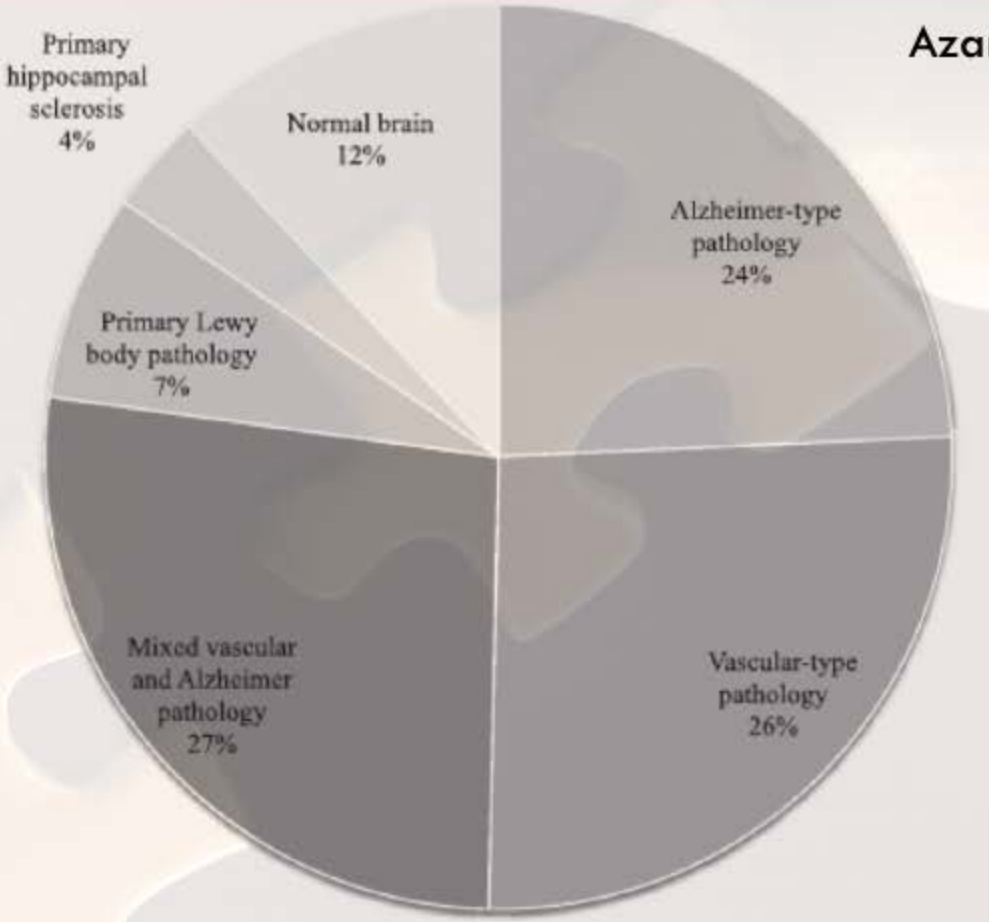


American Alzheimer's Association

Dementia pathologies are common



Nondemented subjects (55%, n=343/627)



Demented subjects (45%, n=284/627)

Azarpazhooh *et al.* Alzheimer Dement 2018;14:148

Prevalence of pathologies in dementia subtypes

Thomas *et al.* Sci Rep 2020;10:14579

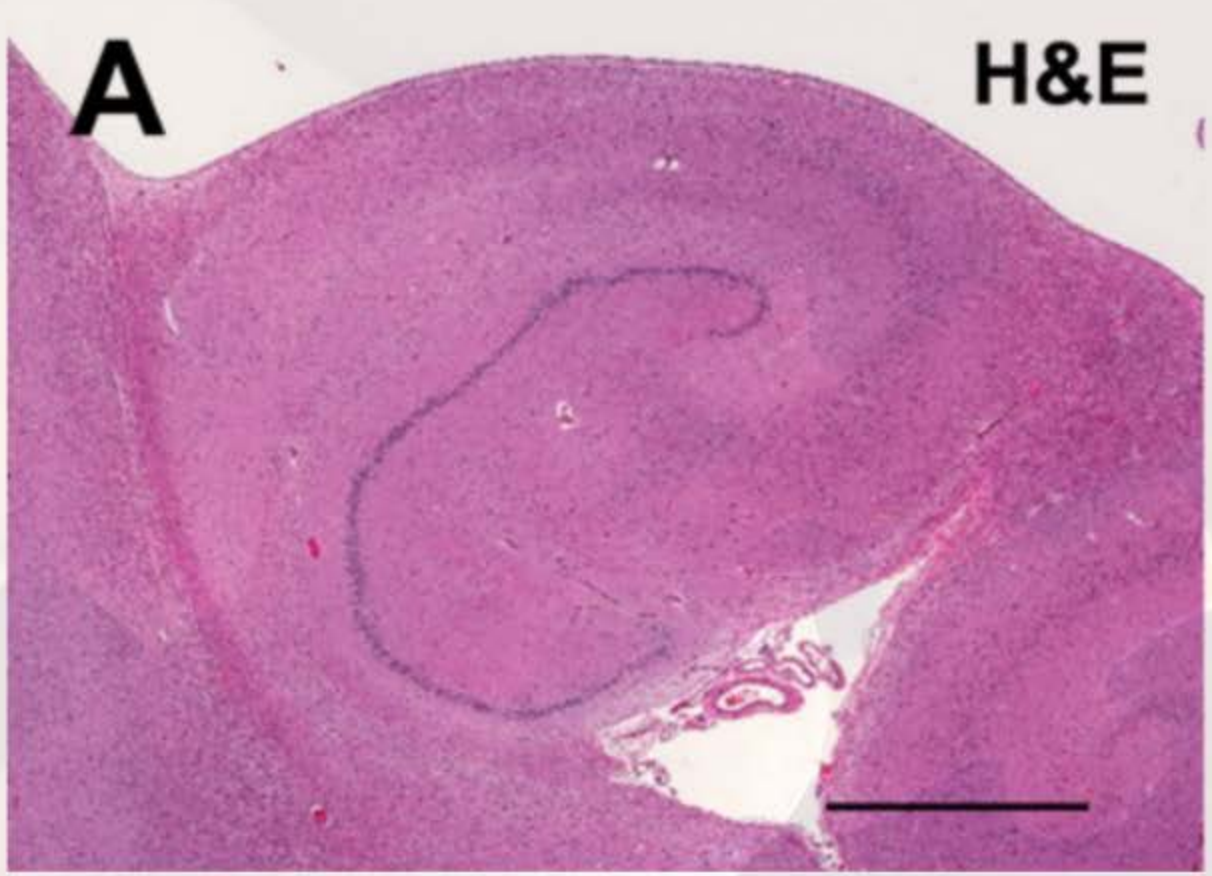
Neuropathology	Intermediate/high Alzheimer's (76%)	Zero/ low Alzheimer's (24%)
• Pure/mixed pathologies	• 22/78%	• 42/58%
• Dementia patients with co-pathologies have a steeper rate of decline		
• Lewy bodies	• 45%	• 25%
• Cerebral amyloid angiopathy	• 42%	• 10%
• TDP-43	• 34%	• 34%
• FTLD (Neocortical)	• 6% (92%)	• 65% (92%)
• LATE (Neocortical)	• 94% (12%)	• 35% (12%)
• One additional co-pathology increases risk of dementia 20-fold		

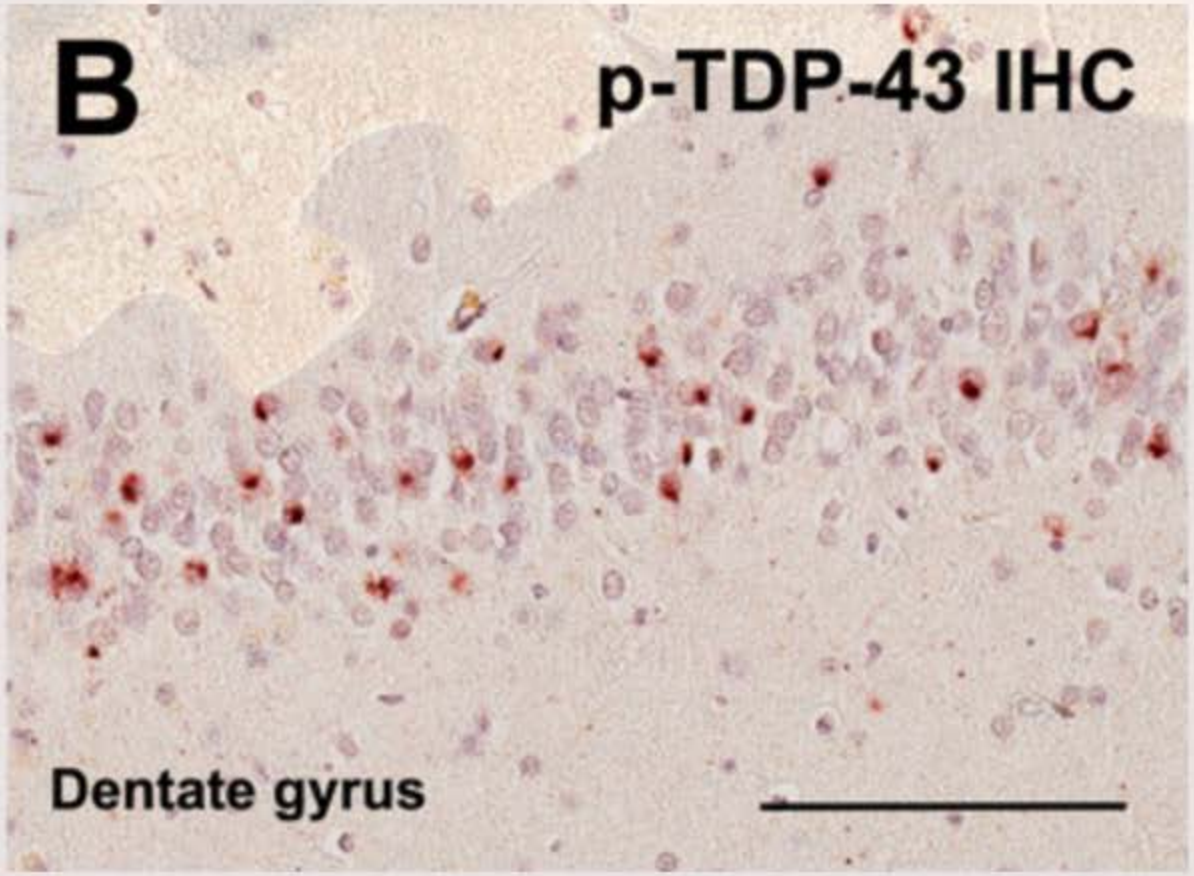
McAleese *et al.* Alzheimer Dement 2021;17:1121

LATE: limbic-predominant age-related TDP-43 encephalopathy

Nelson *et al.* Brain 2019;142:1503

- Stereotypical TDP-43 proteinopathy ± hippocampal sclerosis





LATE: limbic-predominant age-related TDP-43 encephalopathy

- Associated with an amnestic dementia syndrome that mimics Alzheimer's disease (AD)
- Distinguishable for frontotemporal dementia by age of onset and the relatively restricted neuroanatomical distribution
- ~25% of community-based autopsies
- Consensus working group findings

Nelson *et al.* Brain 2019;142:1503

Limbic predominant age-related TDP-43 encephalopathy (LATE)

(Brain 2019;142:1503-1527)

Consensus working group report

- Common TDP-43 proteinopathy (50% of dementia with onset >80y)
- Often has comorbid arteriolosclerosis, capillary CAA, amyloid plaques and tauopathy
- Associated with an Alzheimer-type amnesia, but not congestive heart failure or motor problems
- Genetic risk genes are *GRN*, *TMEM106B*, *ABCC9*, *KCNMB2*, and *APOE*

Simplified staging of TDP-43 proteinopathy* for routine LATE-NC diagnosis (consensus recommendation)	
0	None
1	Amygdala
2	Hippocampus
3	Middle frontal gyrus (MFG)

Cluster analysis of TDP-43 proteinopathies

Katsumata *et al*. Acta Neuropathol 2020;140:659

- Cluster 1
- 74±10y at death
- FTLD-TDP
- Neocortical
- Eating problems
- Disinhibition
- Primary progressive aphasia

- Cluster 2
- 89±10y at death
- LATE
- Neocortical
- Amnestic
- Apathetic
- Slow cognitive decline

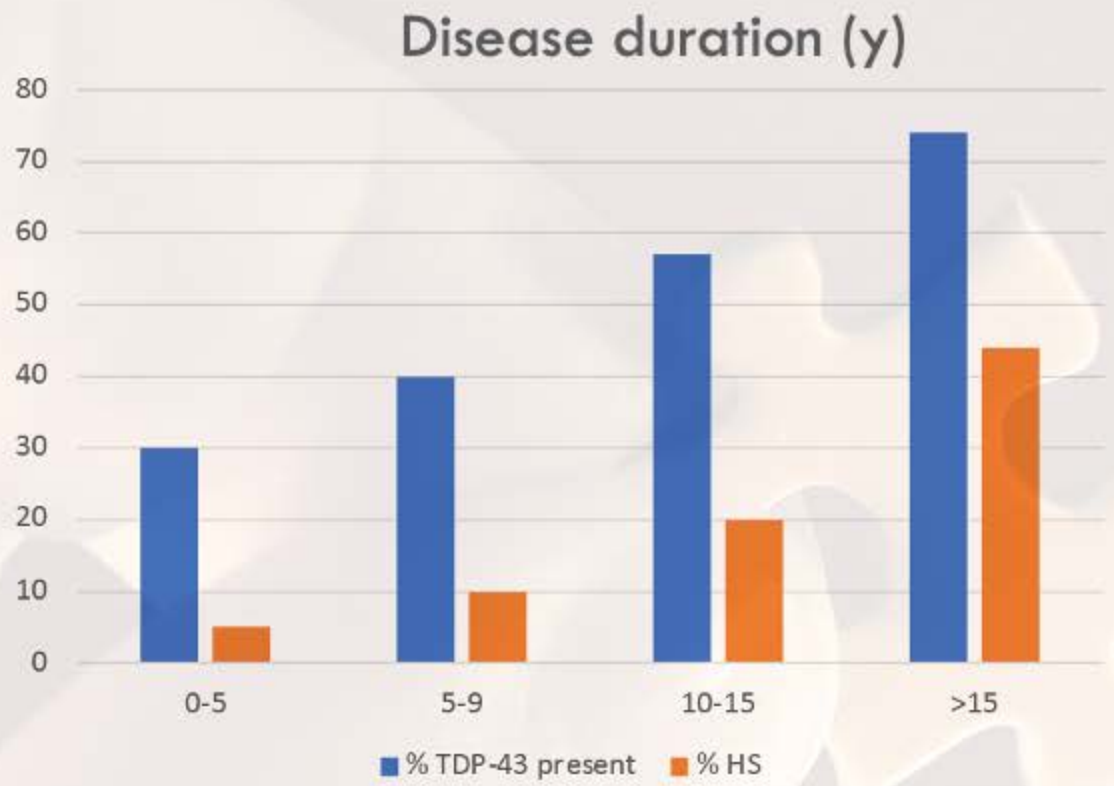
- Cluster 3
- 89±5y at death
- Alzheimer's + LATE
- Limbic
- Amnestic
- Apathetic

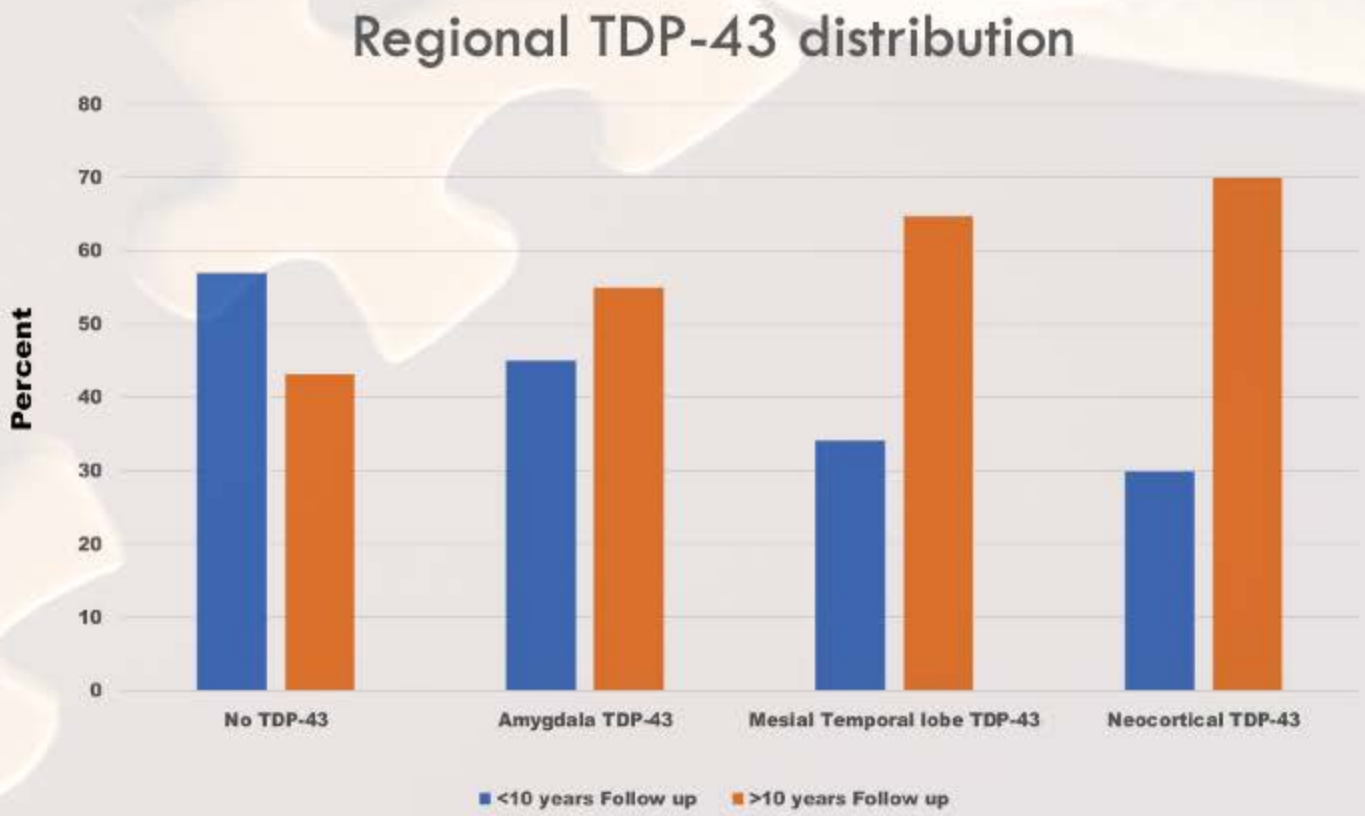
- Cluster 4
- 77±6y at death
- Alzheimer's + LATE
- Limbic
- Lewy bodies
- Amnestic
- Faster decline

Patients with Alzheimer's disease & LATE

Lopez *et al.* Ann Clin Transl Neurol 2020;7:1546

LATE occurs later in those with Alzheimer's pathology





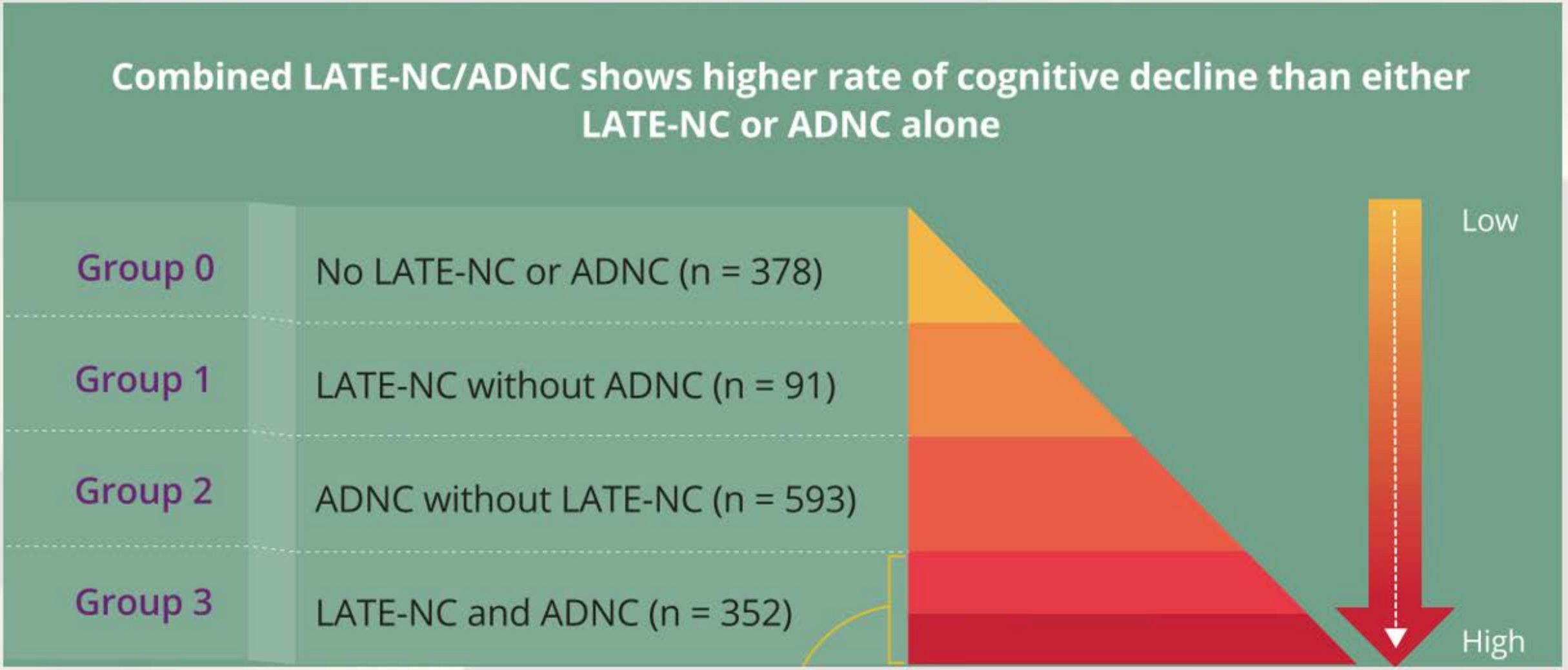
Two distinct profiles of LATE patients

Yu *et al.* Alzhiemer Dis Assoc Disord 2020;34:299

Characteristic	Group 1 – high performers (44%)	Group 2 – low performers (56%)
• Baseline literacy	• 10% over norm	• 6% under norm
• Age at baseline (y)	• 85±6	• 87±5
• Age at death (y)	• 90±6	• 92±6
• Years of education	• 16±2.5	• 14±3
• Rate of decline	• Slow (1%/y)	• Fast (>2%/y)
• % female	• 51	• 81
• % with Alzheimer's	• 13	• 49

Comparison between AD & LATE

Kapasi *et al.* Neurology 2020;95:e1951



LATE is an insidious neurodegenerative pathology causing cognitive decline in the elderly

Vascular dementia

Scrobot *et al.* Brain 2016;139:2957

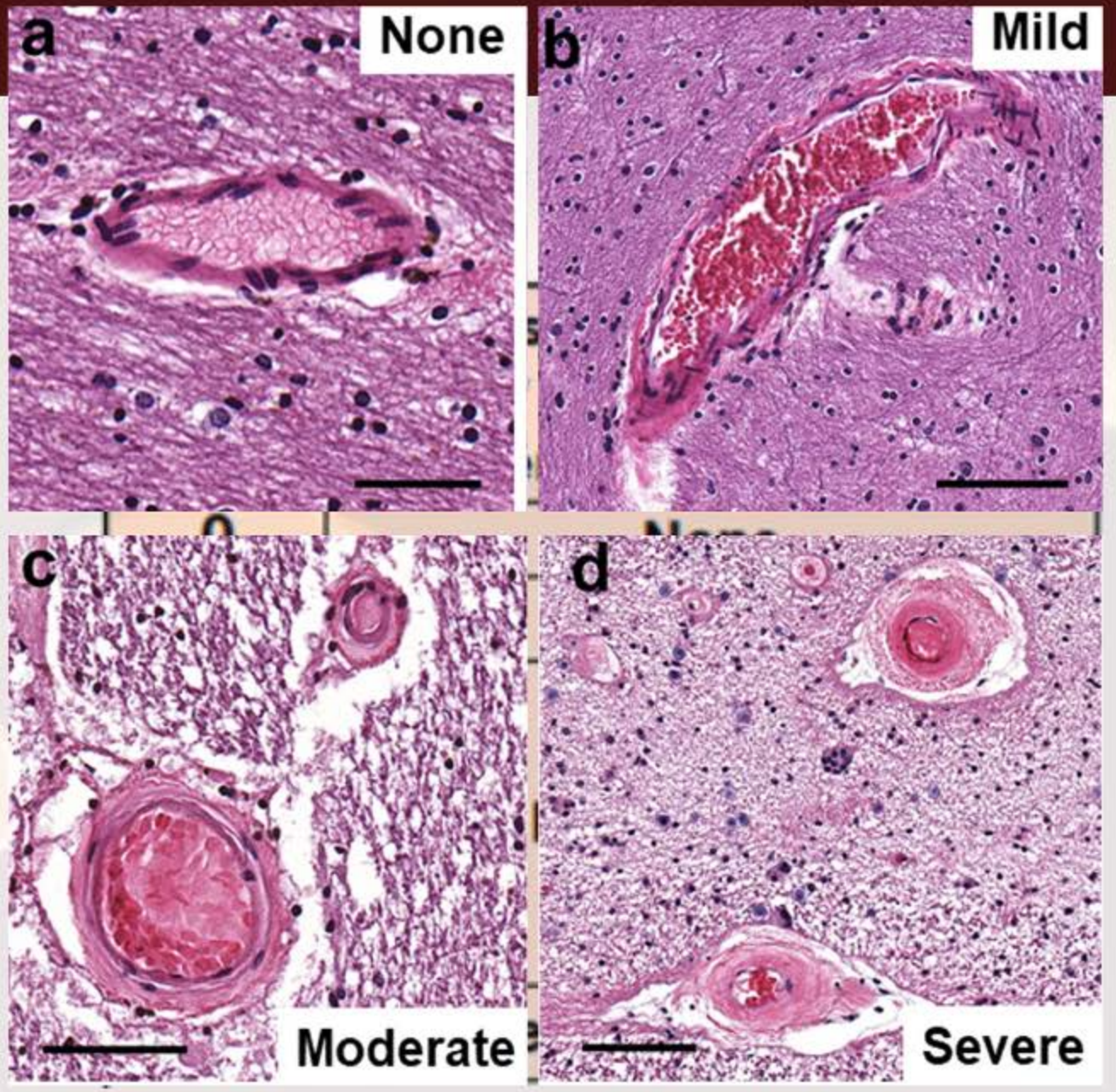
- Neuropathological guidelines published in late 2016
- 7 vascular pathologies predict cognitive impairment
  - Moderate to severe cerebral amyloid angiopathy (CAA)
  - Moderate to severe arteriolosclerosis
  - At least one large infarct

  77%
  - And others
    - Lacunar infarcts
    - Microinfarcts / microbleeds
    - Perivascular space dilation
    - Myelin loss
- Increasing probability of cognitive decline with one (43%), two (73%) or three (95%) pathologies

Brain arteriolosclerosis

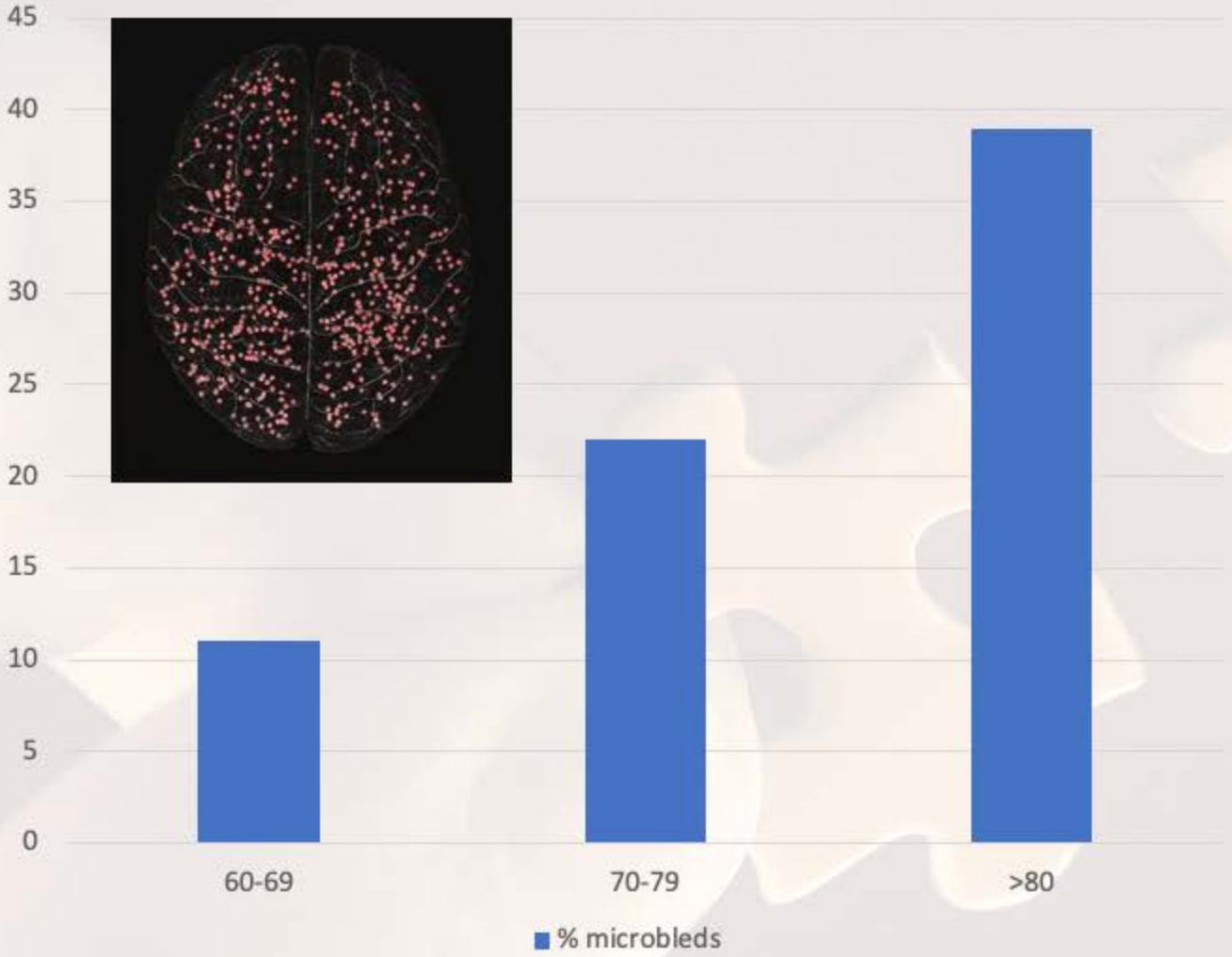
(Acta Neuropathologica 2021;141:1-24)

- Common >80y (80% of autopsies)
- Risk factors include hypertension and diabetes
- Linked to autonomic dysfunction and motor symptoms including parkinsonism
- Independently associated with impairments of global cognition, episodic memory, working memory, and perceptual speed



Cerebral microbleeds & amyloid burden

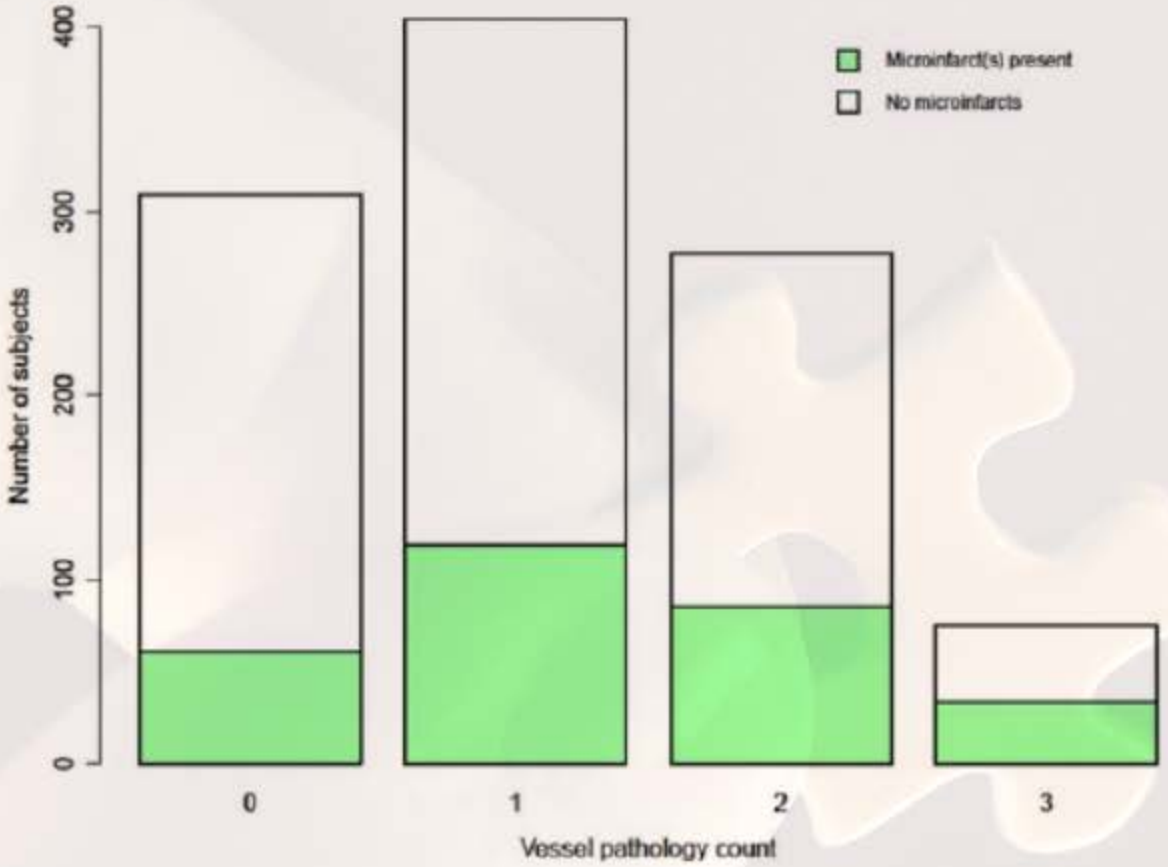
Graff-Radford *et al.* Neurology 2019;92:e253



- The odds of cerebral microbleeds increasing with age, hypertension and β-amyloid burden
- The relationship is to lobar and not deep microbleeds - β-amyloid burden correlates with microbleeds in all lobar regions
- Microbleed density is greatest in parietal and occipital lobes

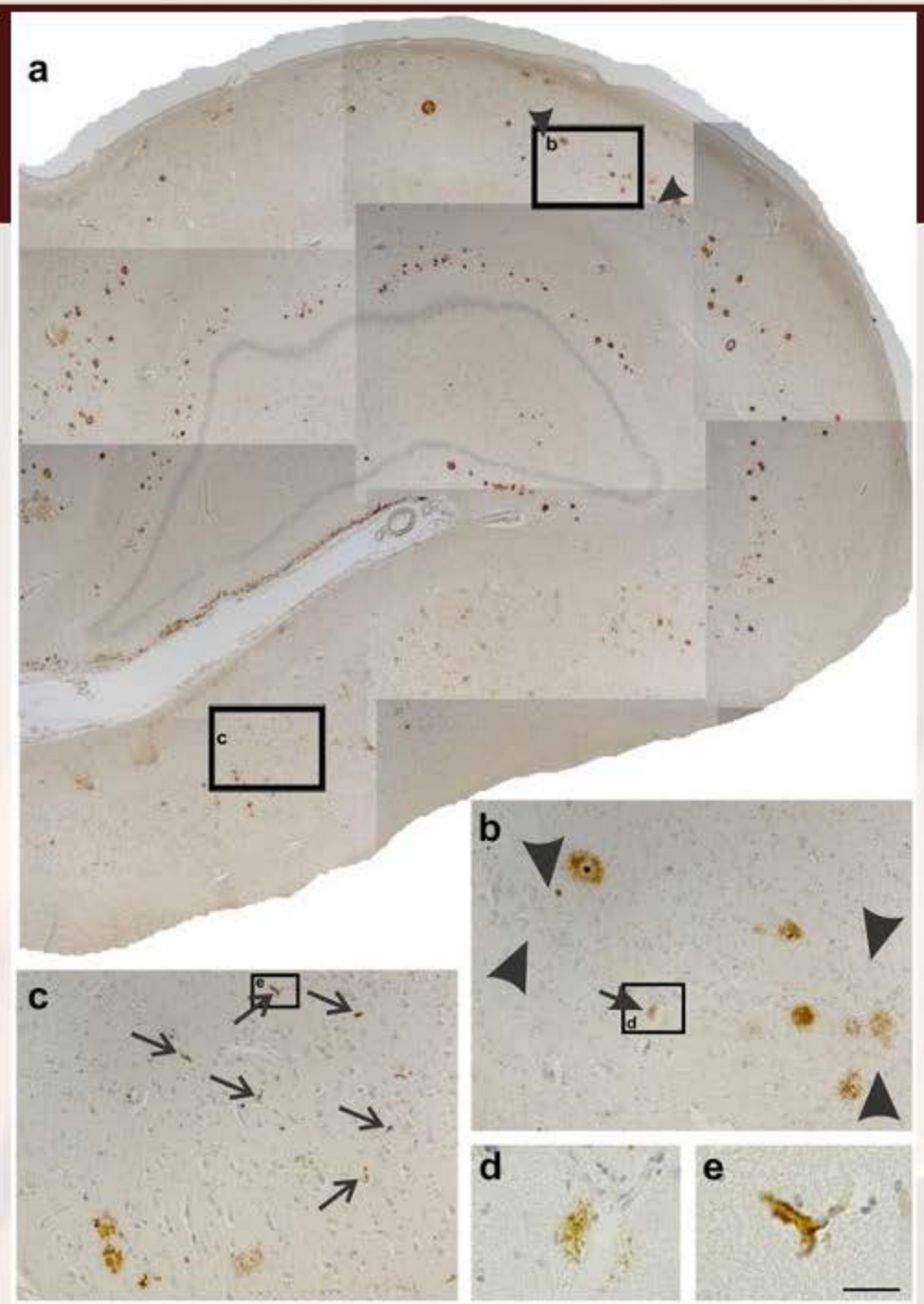
Cerebral vessel pathology and microinfarcts

Arvanitakis *et al.* Brain Pathol 2017;27:77



- Odds of subcortical microinfarcts increases with more severe arteriolosclerosis (OR=1.49)
- Odds of cortical microinfarcts increases with CAA (OR=1.26)
- Overall, the odds of one or multiple microinfarcts increases with more severe arteriolosclerosis (OR=1.22) and CAA (OR=1.13)

CAA & hippocampal microinfarcts

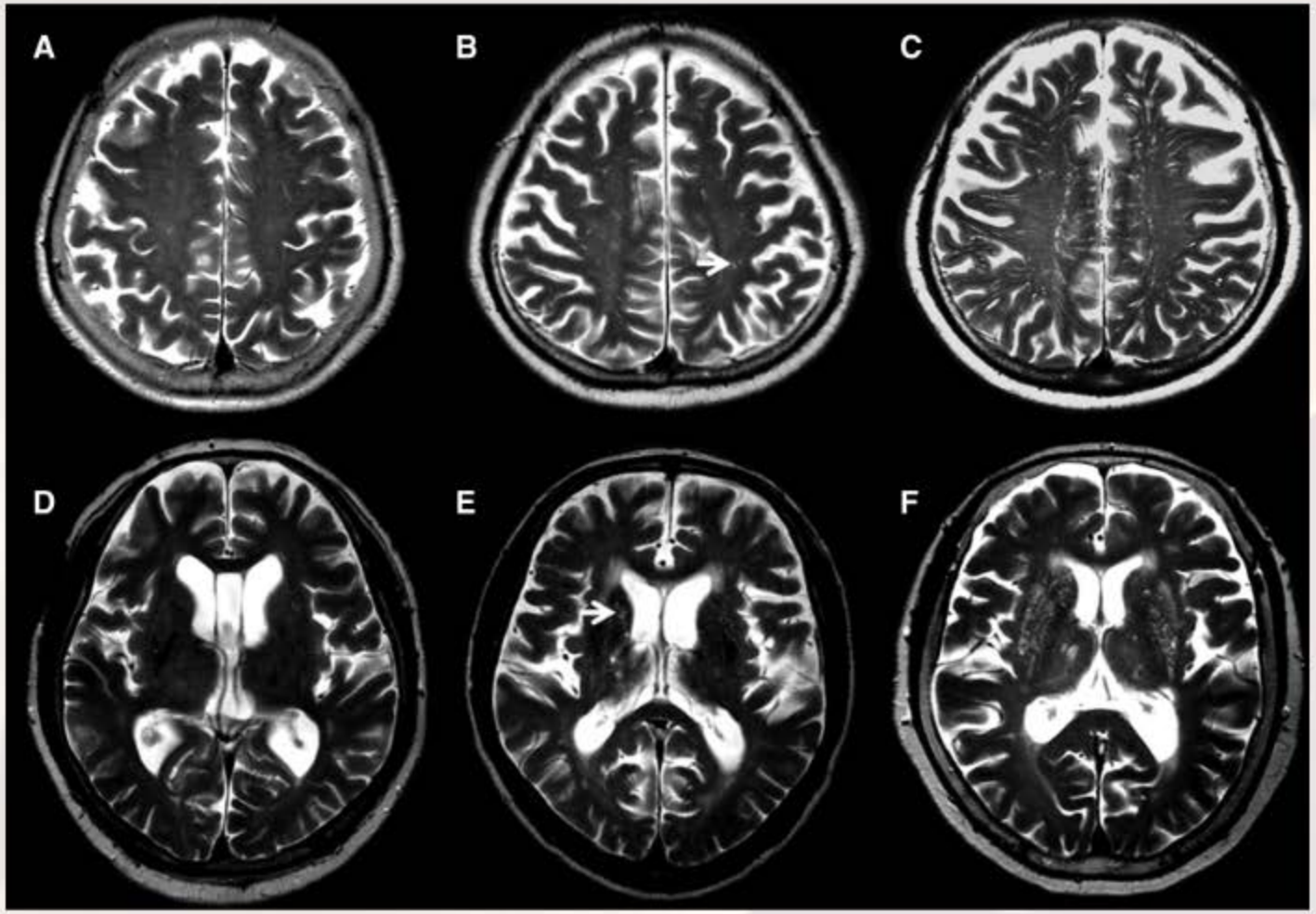


Hecht *et al.* Acta Neuropathol 2018;135:681

- Presence of capillary CAA and CAA severity relates to hippocampal microinfarcts
- Alzheimer cases with capillary CAA develop dementia due to hippocampal microinfarcts and not amyloid and tau deposition

Perivascular dilation and AD

Banerjee *et al.* Brain 2017;140:1107



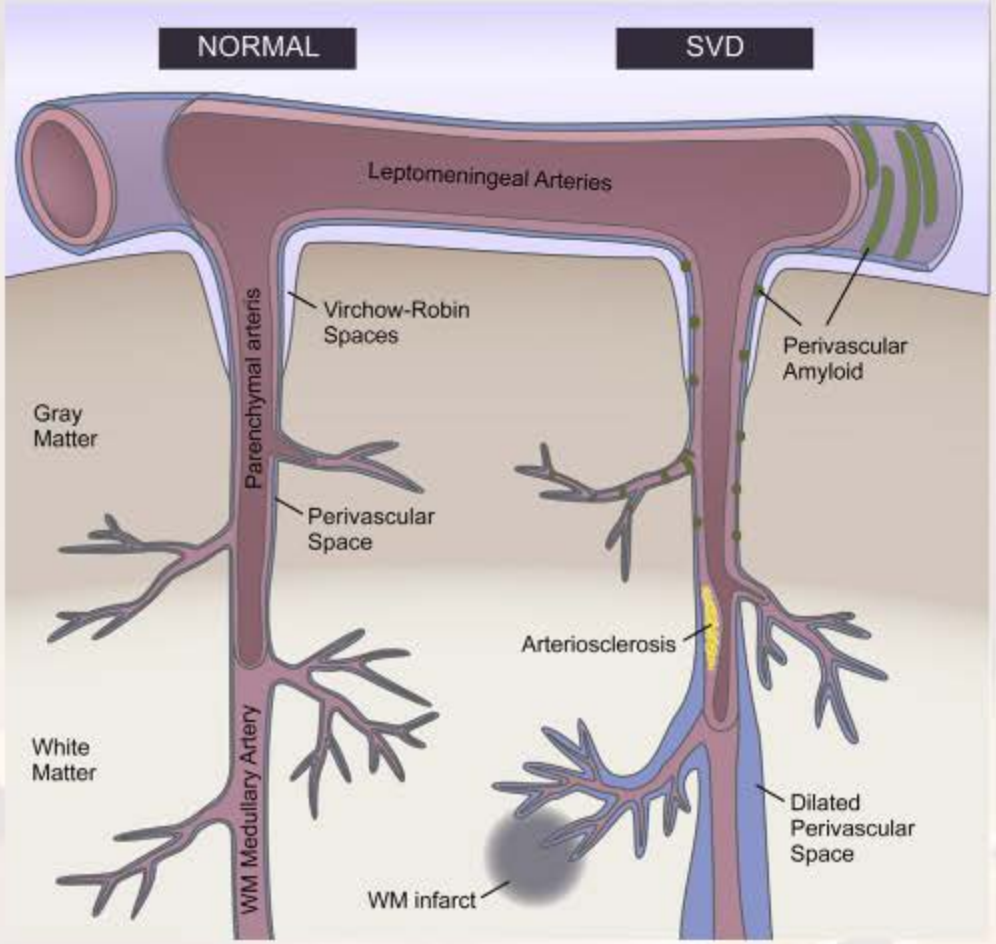
- Severity of subcortical perivascular dilation associates with clinical Alzheimer's (OR=6.25)
- Severity of basal ganglia perivascular dilation associates with vascular dementia and predicts an absence of Alzheimer's (OR=0.03)

Cerebrovascular neuropathology & AD

Liu *et al*. Curr Alzheimer Res 2020;17:1167

- Alzheimer's dementia relates to
  - Arteriolosclerosis severity
  - Presence of infarcts/lacunes
  - Presence of old microinfarcts
  - Number of cortical microinfarcts
- Progression of Alzheimer's dementia relates to
  - Arteriolosclerosis severity
- Impairment in processing speed and executive function relate to
  - Arteriolosclerosis severity
- Language and global cognitive deficits relate to
  - Arteriolosclerosis severity
- Cerebrovascular pathology has an additive effect in the development and progression of Alzheimer's disease

Cerebrovascular pathology in the elderly



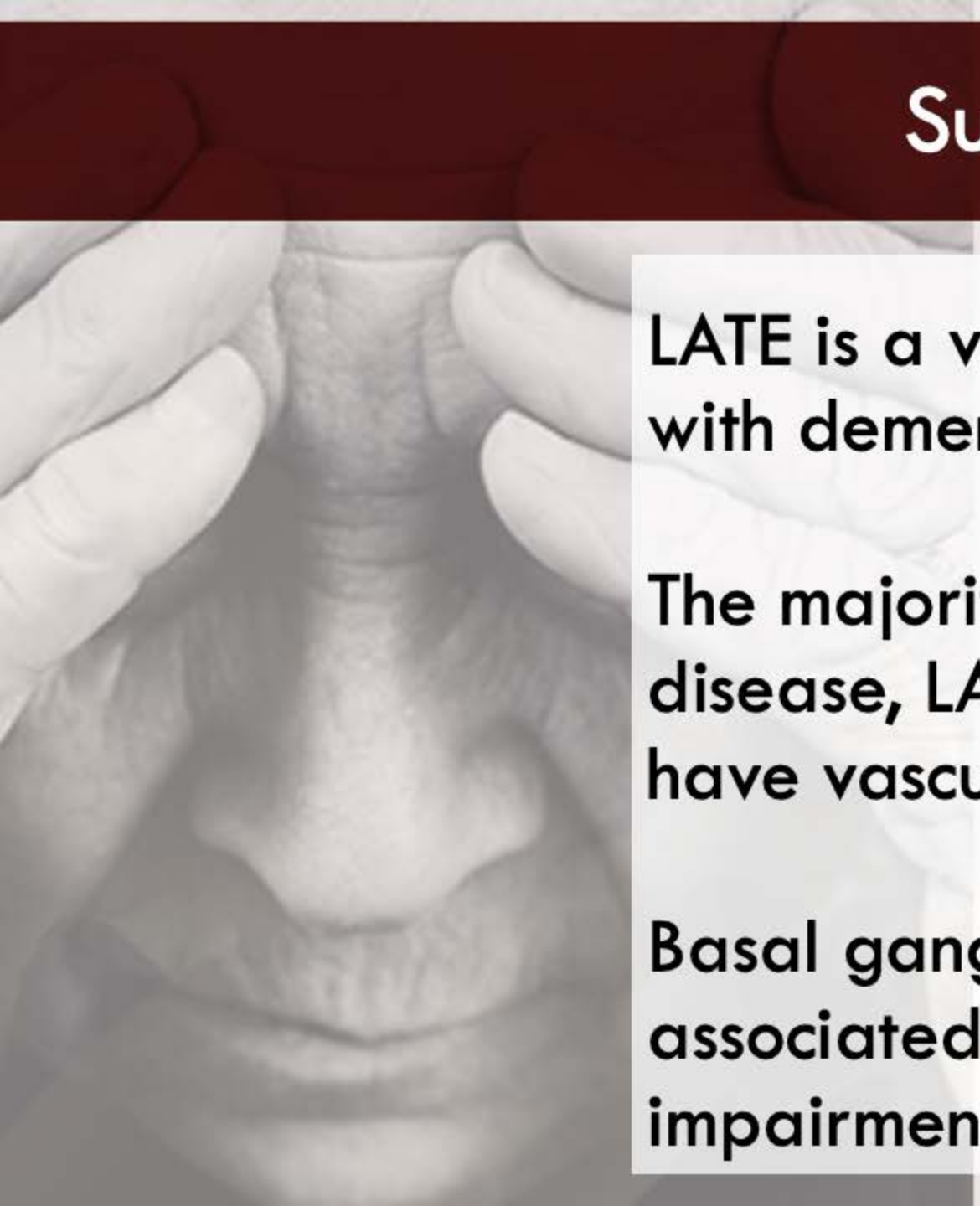
- Arteriolosclerosis is very common in the elderly in general (>80% in those over 80y)
- CAA is very common in Alzheimer's (>80%) with the regional distribution (hippocampal and cortical) impacting on clinical severity and progression and increasing risk of microbleeds and subcortical perivascular dilation
- Basal ganglia perivascular dilation associates with vascular dementia

LATE and arteriolosclerosis

Agrawal *et al.* Brain Pathol 2021;31:e12939

- LATE with microvascular pathology is very common
- 87% of LATE have one or multiple microvascular pathologies
  - Arteriolosclerosis in basal ganglia (32%), in anterior watershed (48%), in posterior watershed (35%)
  - 42% with CAA
  - 37% with microinfarcts
- more advanced LATE pathology associates with
  - posterior watershed arteriolosclerosis (Odds Ratio = 1.12)
  - CAA (Odds Ratio = 1.71)

Summary



LATE is a very common pathology associated with dementia in the very elderly

The majority of patients with Alzheimer's disease, LATE, and Alzheimer's with LATE also have vascular disease

Basal ganglia vascular pathologies are associated with vascular cognitive impairment