#### PATHOLOGIC HETEROGENEITY OF CLINICALLY DEFINED AD

Embracing heterogeneity:

Apprehending an increasingly complex disease in the age of biomarkers

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Julie A. Schneider, M.D. M.S. The Deborah R. And Edgar D. Jannotta Presidential Professor of Pathology and Neurological Sciences Associate Director, Rush Alzheimer's Disease Center Rush University Medical Center

## PATHOLOGIC HETEROGENEITY OF CLINICALLY DEFINED AD

- Older data on mixed pathology
- Pathologies; additive effect/impact
- Updated data with additional pathologies.
- Special considerations

#### Mixed brain pathologies common in MCI and probable AD



Fig. Pathology by clinical status proximate to death. (Blue shades) Pathologic diagnosis of Alzheimer disease (AD). Clockwise: light blue = pathologic diagnosis of AD only; dark blue = pathologic diagnosis of AD and neocortical Lewy bodies (LB); medium blue = pathologic diagnosis of AD and cerebral infarcts (I); aqua = pathologic diagnosis of AD, I, and LB. (Red shades) I and/or LB (with no pathologic diagnosis of AD). Clockwise: pink = I or LB; red = I and LB. (White) No pathologic diagnosis of AD, no I, no LB.

#### Schneider JA et al. Ann Neurol 2009;66:200-208.

\* Estimates do not include vascular path other than gross infarcts

**\*\*** Estimates do not include milder amounts of AD pathology

## The pathologies of the aging brain

- <u>NEURODEGENERATIVE</u>
- Alzheimer's disease
- Lewy body disease
- TDP-43 pathology
- Hippocampal sclerosis

- <u>VASCULAR</u>
- Macroinfarcts

- Microinfarcts
- CAA
- Atherosclerosis
- Arteriolosclerosis







**Arvanitakis** Z et al., Lancet Neurol. 2016. Aug;15(9):934-943.



infarcts, microinfarcts and neocortical Lewy bodies.

#### Schneider JA et al. Brain 2012;135:3005-3014

#### HS - higher odds of dementia and AD dementia

#### Interaction with TDP such that HS with TDP had higher odds



Nag S, et al. Ann Neurol. 2015 Feb 23. doi: 10.1002/ana.24388.

#### Figure 2. Odds ratios for clinical Alzheimer's-type dementia

Odds ratios compared to not having pathologic diagnosis of AD or TDP-43 pathology, from a model adjusted for age, sex, education, cerebral infarcts, Lewy bodies, and Hippocamapal



James BD et al., Brain. 2016 Sep 30. pii: aww224. [Epub ahead of print]

### Updated data on mixed pathologies

- N= 1078 deceased autopsied from Religious Orders Study, Rush Memory and Aging Project and Minority Aging Research Study with final diagnosis proximate to death (~7 months) of NCI, MCI, or probable AD
- Age at death, 89 years, SD=6.5;
- 32% men;
- Mean education, 16 years

	Clinical Diagnosis			
Pathology	No Cognitive	Mild Cognitive	Probable AD	
	Impairment	Impairment	(n=447)	
	(n=360)	(n=271)		
No Vascular or	50 (13.89%)	12 (4.43%)	4 (0.89%)	
Neurodegenerative				
Vascular only	102 (28.33%)	57 (21.03%)	22 (4.92%)	
Other Degenerative	14 (3.89%)	8 (2.95%)	6 (1.34%)	
only				
Other Degenerative	41 (11.39%)	28 (10.33%)	35 (7.83%)	
+ Vascular (no AD)				
AD only	30 (8.33%)	20 (7.38%)	<b>14 (3.13%)</b>	
AD + Vascular	75 (20.83%)	65 <mark>(23.99%)</mark>	122 (27.29%)	
AD + Other	6 (1.67%)	17 (6.27%)	<b>34 (7.61%)</b>	
Degenerative				
AD + other	42 (11.67%)	64 (23.62%)	210 (46.98%)	
Degenerative +				
Vascular				



#### Figure 1 – Prevalence of Mixed Pathologies in ROS/MAP cohort

Prevalence of mixed pathologies in ROS/MAP subjects with a clinical diagnosis of no cognitive impairment, mild cognitive impairment, and probable Alzheimer's disease. Key: v – vascular; d – degenerative; dv – degenerative vascular; AD – Alzheimer's disease; 0 – no vascular or neurodegenerative pathology.



Figure 2 – Prevalence of Mixed AD with Vascular/Neurodegenerative Pathologies in the ROS/MAP cohort.

Pathology and dementia in the oldest old (age 90+ vs. <90)

James BD et al., JAMA. 2012 May 2;307(17):1798-800.

Characteristic	Total (n=804)	Age 65-89	Age 90 +	P value
		(n=503)	(n = 301)	
Age at death, yrs(SD)	87.7 (6.7)	83.8 (4.8)	94.3 (3.3)	<0.001
Dementiaª, no. (%)	304 (37.8%)	143 (28.4%)	161 (53.5%)	<0.001
AD <sup>c</sup>	493 (61.3%)	279 (55.5%)	214 (71.1%)	< 0.001
Infarcts <sup>d</sup>	272 (33.8%)	147 (29.2%)	125 (41.5%)	< 0.001
Single path	374 (46.5%)	238 (47.3%)	136 (45.2%)	0.56
Mixed path	225 (28.0%)	113 (22.5%)	112 (37.2%)	<0.001
AD + LB	41 (5.1%)	25 (5.0%)	16 (5.3%)	0.83
AD + Infarcts	162 (20.2%	79 (15.7%)	83 (27.6%)	<0.001

# Other special populationsClinic vs. Community...

## Single vs. Mixed Neuropathology (all clinical dementias)



Schneider JA et al., J. Alz. Disease 2009



Barnes LL et al. Neurology 2015 in press.

Does not include atherosclerosis, arteriolosclerosis, CAA, TDP, HS...



Boyle PA, Wilson RS, Yu L, Barr AM, Honer WG, Schneider JA, Bennett DA. Ann Neurol. 2013 Sep;74(3):478-89.

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