Investigating spatial characteristics of brain atrophy in Alzheimer's and LATE neuropathology

Saifullah K[1], Ridwan AR[2], Bennett DA[2],

Schneider JA[2], Arfanakis K[1,2]

[1]Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL, USA

[2]Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA

Declaration of Financial Interests or Relationships

Speaker Name: Khalid Saifullah

I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

Introduction

- AD and LATE are common in older adults
- Both associated with brain atrophy, cognitive decline and dementia

Boyle et. al., Brain. 2017

- AD and LATE often coexist, increasing the risk of dementia

James et. al., Brain. 2016

Robinson et. al., Brain. 2018

- LATE can only be detected at autopsy, posing challenges for diagnosis.
- Differential effects of AD and LATE on brain morphometry remain unclear

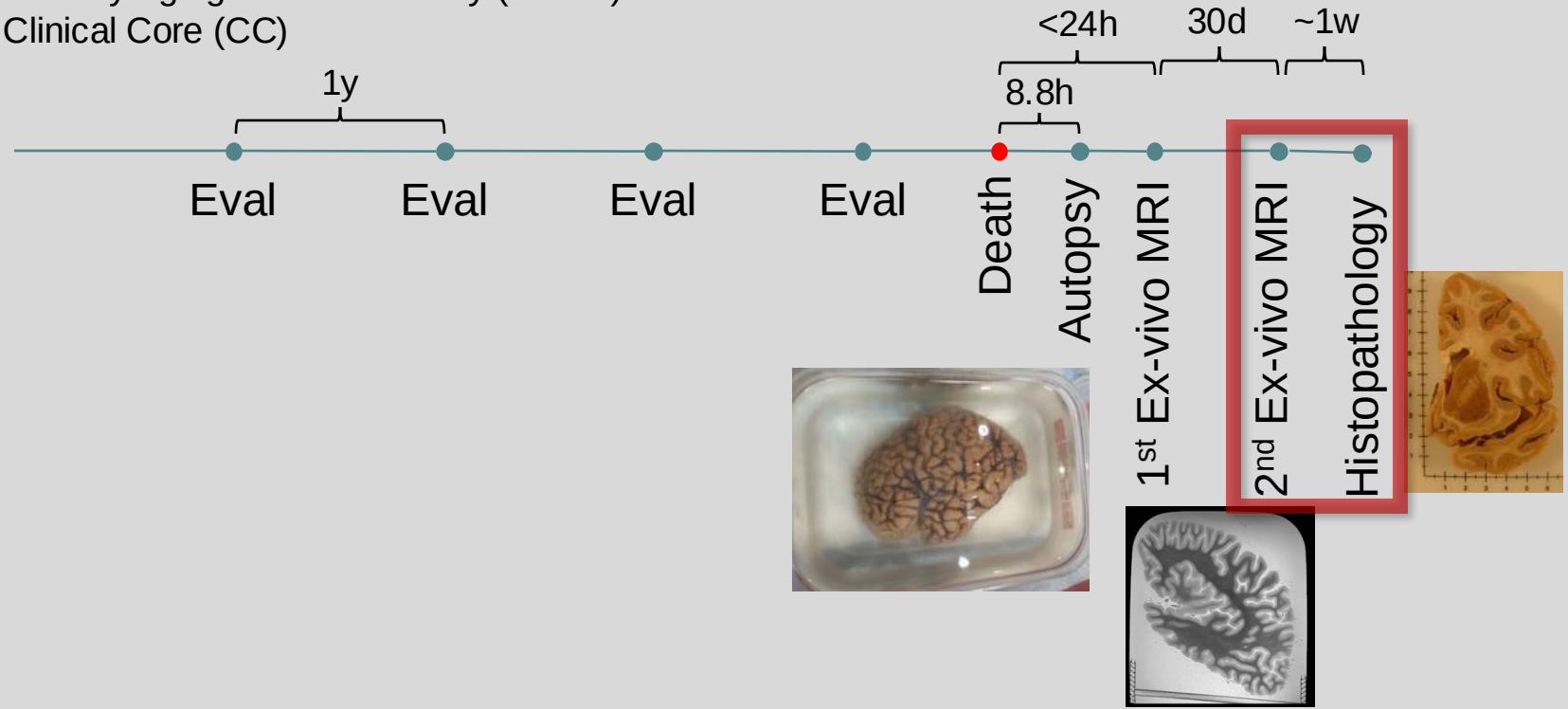
Purpose: To investigate brain atrophy patterns associated with AD, LATE, AD+LATE and AD vs LATE

- Combined DBM on ex-vivo MRI and neuropathology in a large number of community-based older adults

Data collection

Study cohort consists of 912 participants from

- Rush Memory and Aging Project (MAP) Bennett et al. J Alzheimer's Disease 2018
- Religious Orders Study (ROS) Bennett et al. J Alzheimer's Disease 2018
- Minority Aging Research Study (MARS) Barnes et al. Curr Alzheimer Res 2012
- Clinical Core (CC)



Demographic, clinical, neuropathologic characteristics

N	912
Age at death, y (SD)	90.6 (6.4)
Male, n (%)	256 (28.0)
Education, y (SD)	15.7 (3.5)
MMSE, mean (SD)	19.9 (9.6)
Antemortem clinical diagnosis, n (%)	
NCI	294 (32.2)
MCI	210 (23.0)
Dementia	397 (43.5)

AD, n (%)	
No AD	110 (12.0)
Low AD	173 (19.0)
Intermediate	395 (43.3)
High	234 (25.7)

LATE, n (%)	
Stage 0	402 (44.1)
Stage 1	159 (17.4)
Stage 2	102 (11.2)
Stage 3	249 (27.3)

Gross infarcts, n (%)	370 (40.6)
Microscopic infarcts, n (%)	355 (38.9)
Lewy Bodies, n (%)	259 (28.4)
CAA, n (%)	
None	187 (20.5)
Mild	387 (42.4)
Moderate	226 (24.8)
Severe	112 (12.3)
Atherosclerosis, n (%)	
None	200 (21.9)
Mild	484 (53.1)
Moderate	184 (20.2)
Severe	44 (4.8)
Arteriolosclerosis, n (%)	
None	324 (35.5)
Mild	339 (37.2)
Moderate	187 (20.5)
Severe	62 (6.8)

Methodology

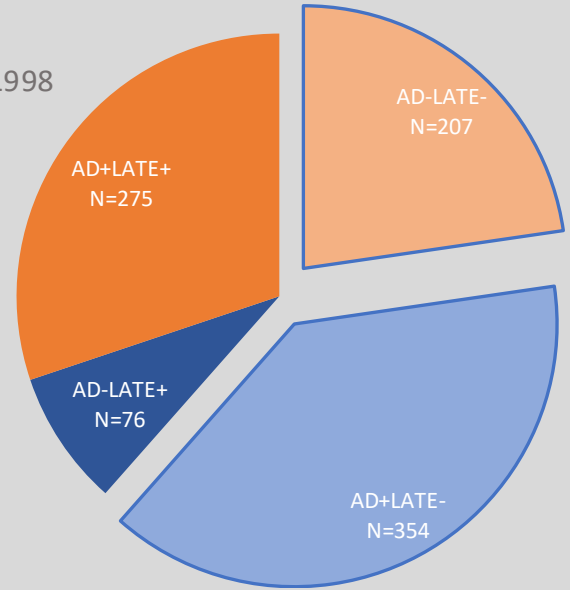
AD, n (%)	
No AD	110 (12.0)
Low AD	173 (19.0)
Intermediate	395 (43.3)
High	234 (25.7)

LATE, n (%)	
Stage 0	402 (44.1)
Stage 1	159 (17.4)
Stage 2	102 (11.2)
Stage 3	249 (27.3)

- Deformation-Based Morphometry

Ashburner et. al., Hum Brain Mapp. 1998
Gaser et. al., Neuroimage. 2001
Hua et. al., Neuroimage. 2008
Sarro et. al., Brain. 2016

- **Volume of AD+LATE- < Volume of AD-LATE-**



Methodology

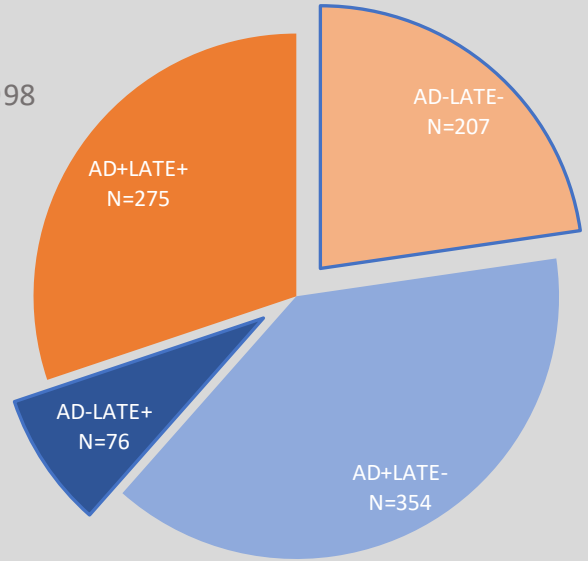
AD, n (%)	
No AD	110 (12.0)
Low AD	173 (19.0)
Intermediate	395 (43.3)
High	234 (25.7)

LATE, n (%)	
Stage 0	402 (44.1)
Stage 1	159 (17.4)
Stage 2	102 (11.2)
Stage 3	249 (27.3)

- Deformation-Based Morphometry

Ashburner et. al., Hum Brain Mapp. 1998
Gaser et. al., Neuroimage. 2001
Hua et. al., Neuroimage. 2008
Sarro et. al., Brain. 2016

- Volume of AD+LATE- < Volume of AD-LATE-
- **Volume of AD-LATE+ < Volume of AD-LATE-**



Methodology

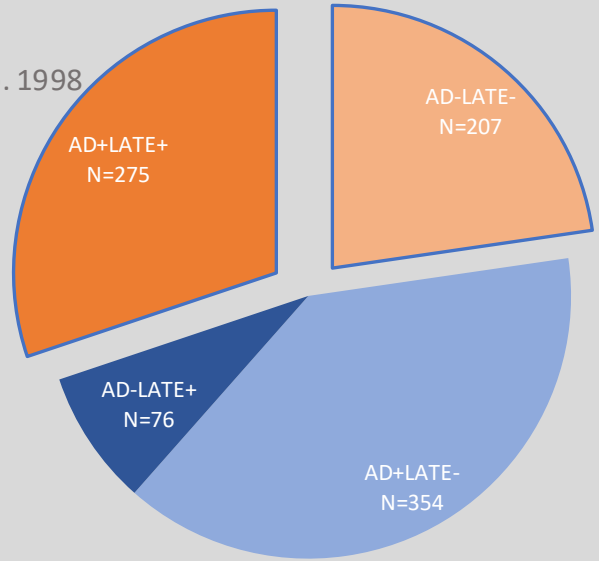
AD, n (%)	
No AD	110 (12.0)
Low AD	173 (19.0)
Intermediate	395 (43.3)
High	234 (25.7)

LATE, n (%)	
Stage 0	402 (44.1)
Stage 1	159 (17.4)
Stage 2	102 (11.2)
Stage 3	249 (27.3)

- Deformation-Based Morphometry

Ashburner et. al., Hum Brain Mapp. 1998
Gaser et. al., Neuroimage. 2001
Hua et. al., Neuroimage. 2008
Sarro et. al., Brain. 2016

- Volume of AD+LATE- < Volume of AD-LATE-
- Volume of AD-LATE+ < Volume of AD-LATE-
- **Volume of AD+LATE+ < Volume of AD-LATE-**



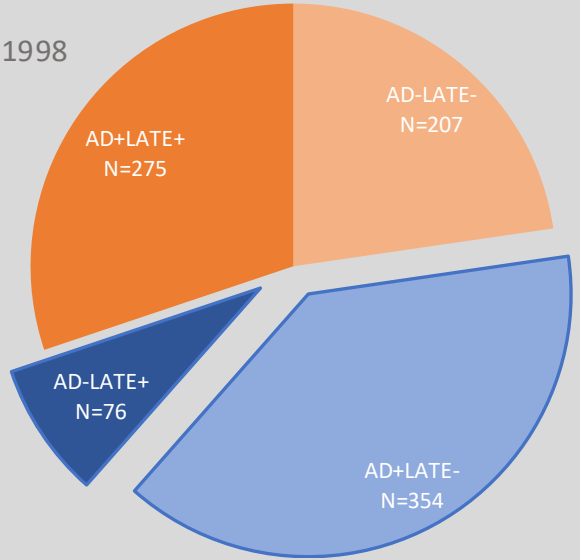
Methodology

AD, n (%)	
No AD	110 (12.0)
Low AD	173 (19.0)
Intermediate	395 (43.3)
High	234 (25.7)

LATE, n (%)	
Stage 0	402 (44.1)
Stage 1	159 (17.4)
Stage 2	102 (11.2)
Stage 3	249 (27.3)

- Deformation-Based Morphometry

Ashburner et. al., Hum Brain Mapp. 1998
Gaser et. al., Neuroimage. 2001
Hua et. al., Neuroimage. 2008
Sarro et. al., Brain. 2016



- Volume of AD+LATE- < Volume of AD-LATE-
- Volume of AD-LATE+ < Volume of AD-LATE-
- Volume of AD+LATE+ < Volume of AD-LATE-
- **Volume of AD-LATE+ < Volume of AD+LATE-**

Methodology

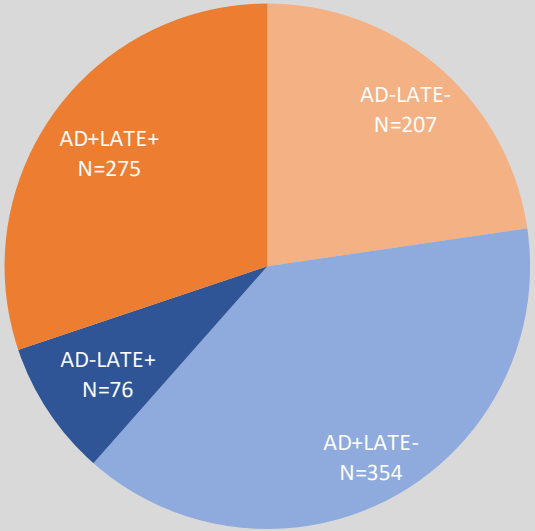
AD, n (%)	
No AD	110 (12.0)
Low AD	173 (19.0)
Intermediate	395 (43.3)
High	234 (25.7)

LATE, n (%)	
Stage 0	402 (44.1)
Stage 1	159 (17.4)
Stage 2	102 (11.2)
Stage 3	249 (27.3)

- Deformation-Based Morphometry

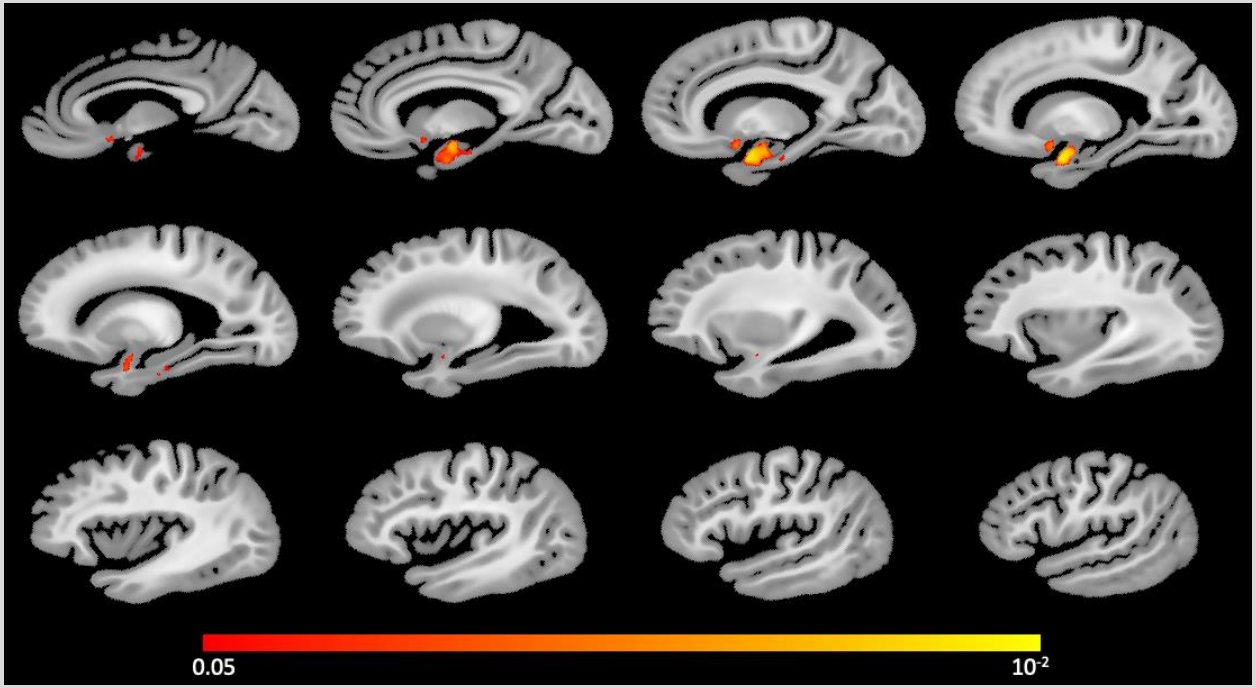
Ashburner et. al., Hum Brain Mapp. 1998
Gaser et. al., Neuroimage. 2001
Hua et. al., Neuroimage. 2008
Sarro et. al., Brain. 2016

- Volume of AD+LATE- < Volume of AD-LATE-
- Volume of AD-LATE+ < Volume of AD-LATE-
- Volume of AD+LATE+ < Volume of AD-LATE-
- Volume of AD-LATE+ < Volume of AD+LATE-



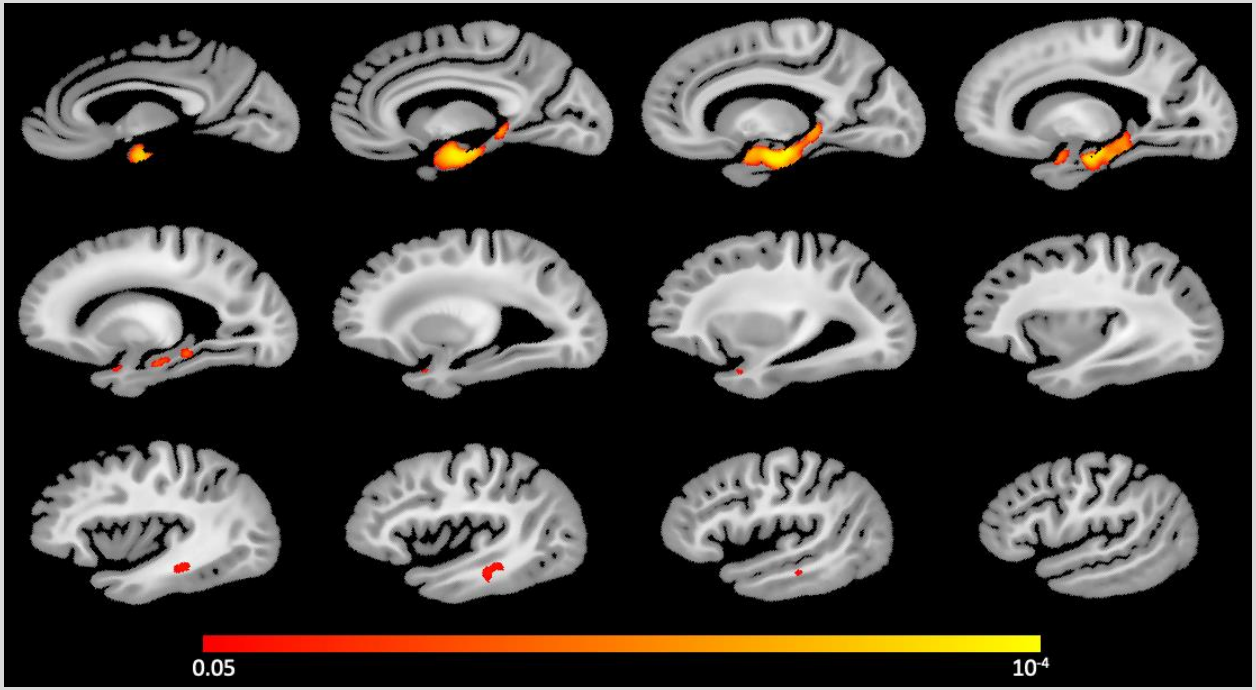
- PALM, 5000 permutations, $p<0.05$, FWER
- Controlled for: other neuropathologies, demographics (age at death, sex, education), PMI_f, PMI_i, and scanners

Volume of AD+LATE- < Volume of AD-LATE-



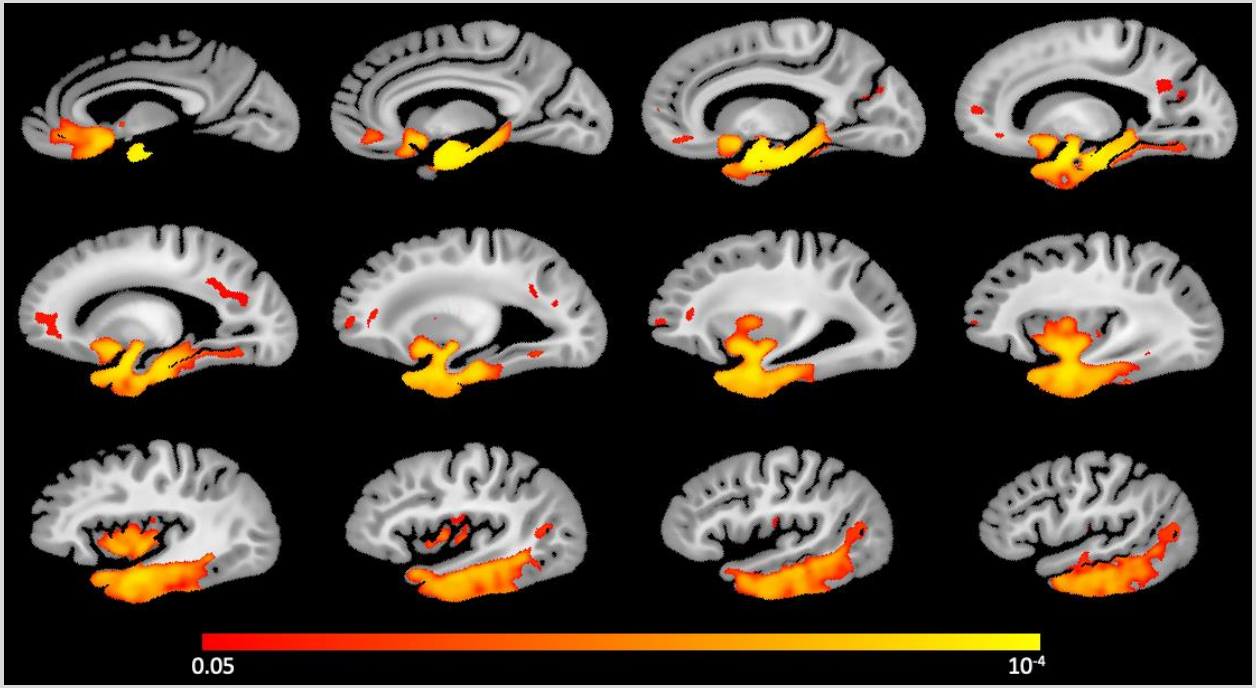
Controlling for other neuropathologies, demographics and covariates

Volume of AD-LATE+ < Volume of AD-LATE-



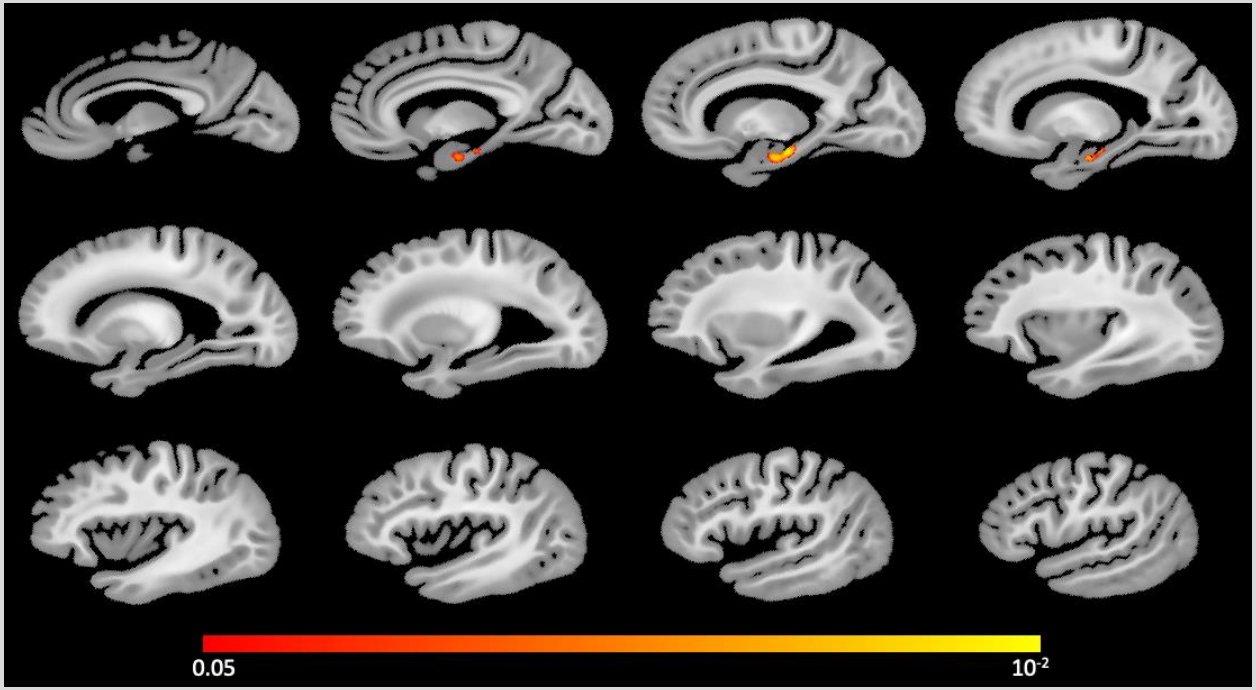
Controlling for other neuropathologies, demographics and covariates

Volume of AD+LATE+ < Volume of AD-LATE-



Controlling for other neuropathologies, demographics and covariates

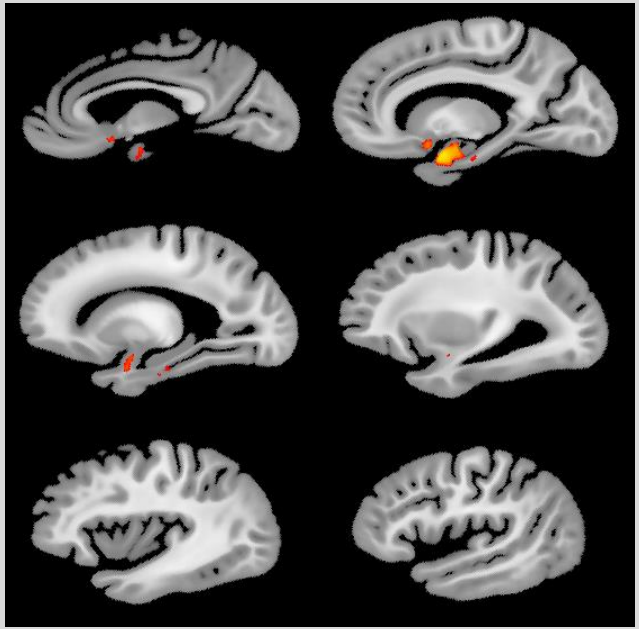
Volume of AD-LATE+ < Volume of AD+LATE-



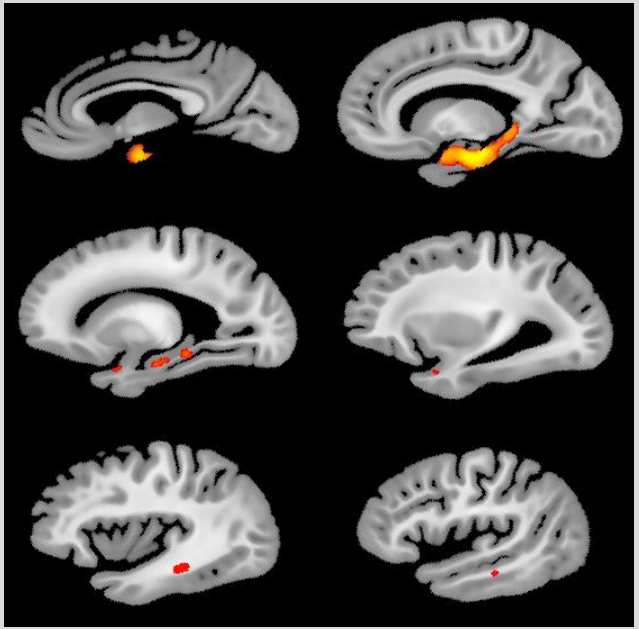
Controlling for other neuropathologies, demographics and covariates

Dawe et. al., PloS One. 2011

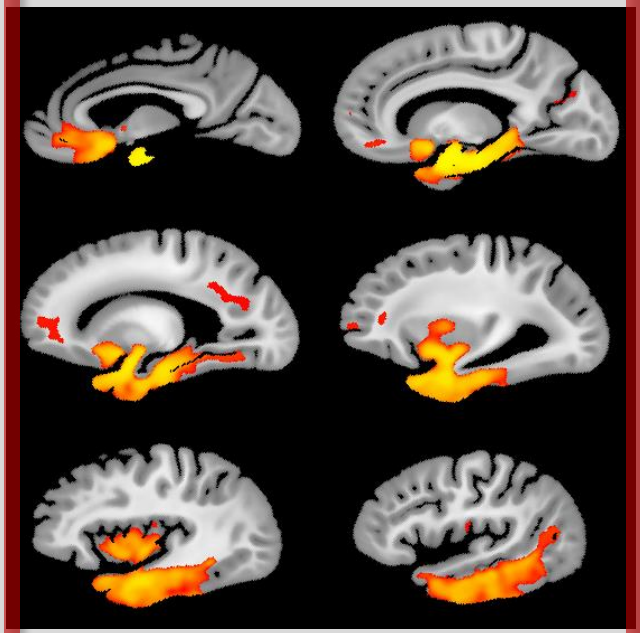
Results



AD+LATE-



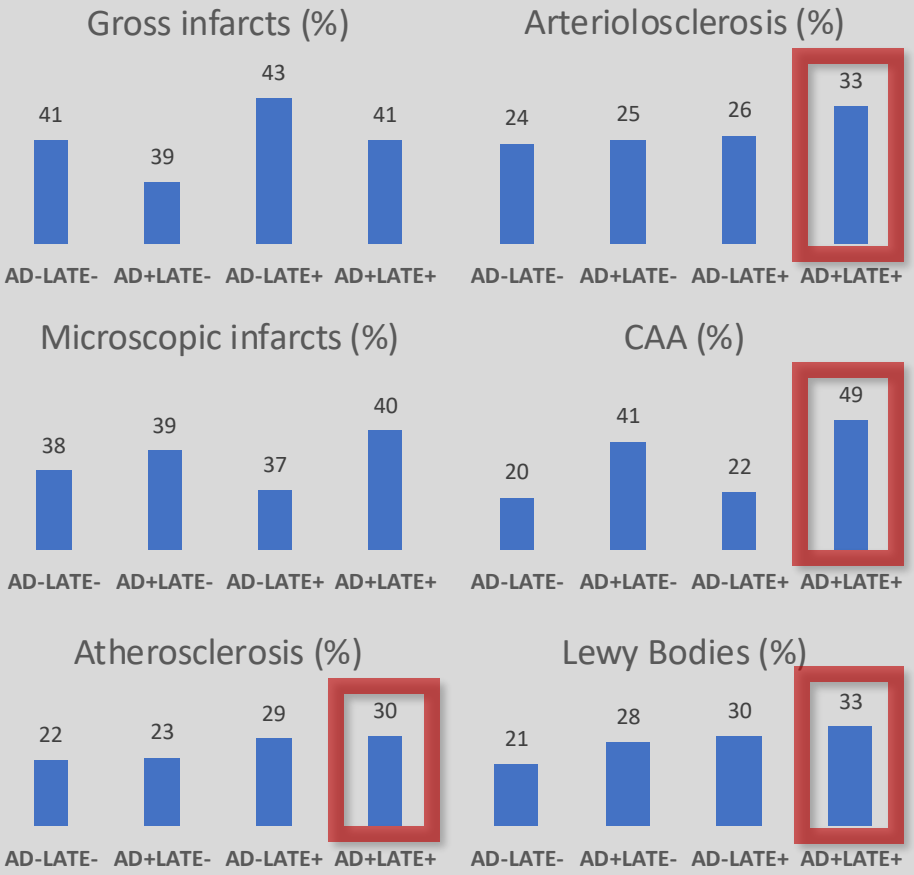
AD-**LATE+**

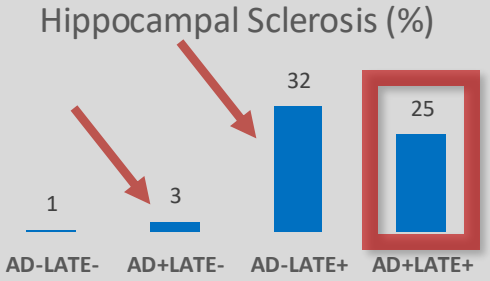


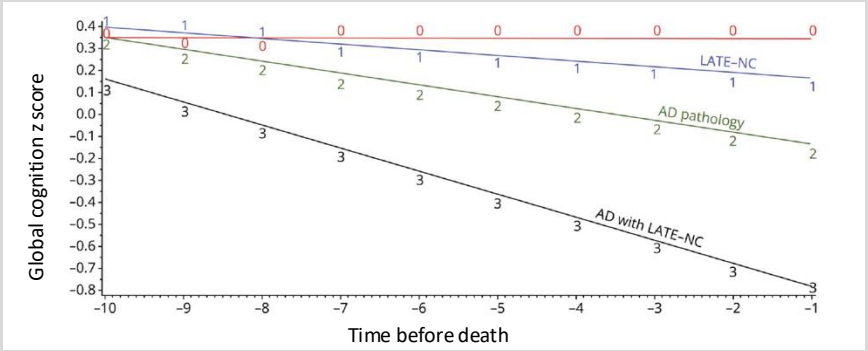
AD+LATE+

Compared to AD-LATE-

Pathology Distribution







Kapasi et. al., Neurology. 2020

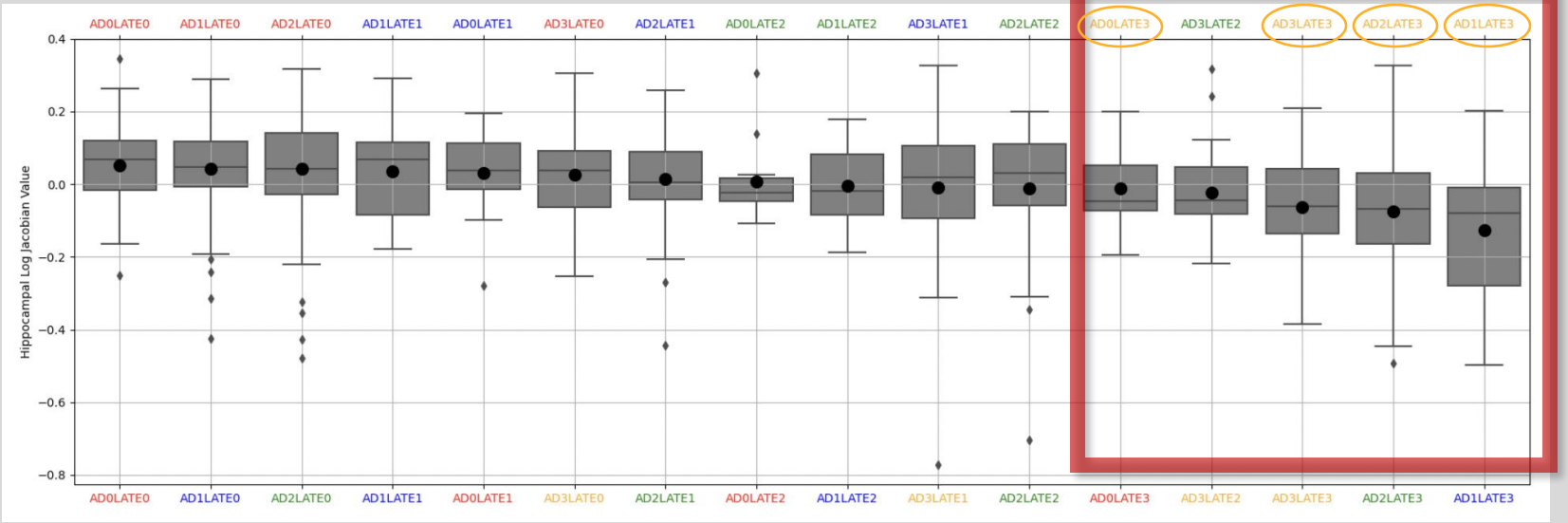
AD and LATE Combinations

ADxLATE3

ADxLATE2

ADxLATE1

ADxLATE0



AD0LATEx

AD1LATEx

AD2LATEx

AD3LATEx

Conclusions

Largest study combining brain morphometry and pathology in community-based older adults

Reveals brain atrophy patterns associated with AD, LATE, AD+LATE and AD vs LATE

AD+LATE- and AD-LATE+ linked to lower volume mainly in medial temporal lobe

Barkhof et. al., Neurology. 2007
Nelson et. al., Brain pathol. 2010

LATE stage 2 or 3 linked to lower tissue volume in anterior hippocampus compared to intermediate or high AD

Dawe et. al., PloS One. 2011
Yu et. al., Neurology. 2020
Teipel et. al., Neurobiol Dis. 2023

AD+LATE+ associated with lower brain tissue volume in more regions

Josephs et. al., Acta Neuropathol. 2014
Kapasi et. al., Neurology. 2020

Acknowledgements

I would like to thank:

My professor Dr. Konstantinos Arfanakis

The faculty and staff at the Rush Alzheimer's Disease Center and my colleagues at MRIIT

The participants of the Rush Memory and Aging Project (MAP), Religious Orders Study (ROS), Minority Aging Research Study (MARS)

Our funding sources

NIA: R01AG064233, R01AG067482, R01AG017917, R01AG015819, RF1AG022018, R01AG056405, R01AG052200, P30AG010161, P30AG072975

NINDS: UH2-UH3NS100599, UF1NS100599