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Factors contributing to resistance and resilience in the aging population

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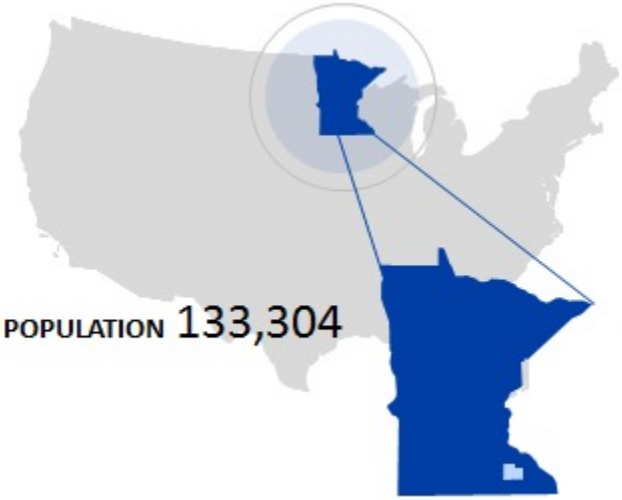
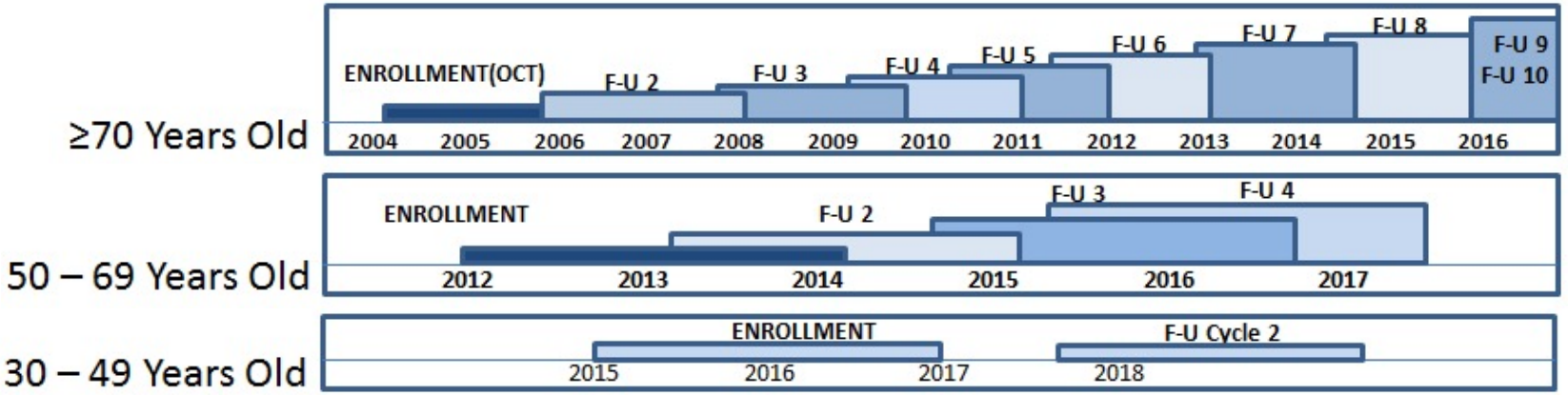
Friday, September 9th, 2022
33rd Annual Southern California AD Research Conference,
UC Irvine, California, USA

Mayo Clinic Study of Aging

Funded by National Institute of Health, GHR Foundation, Alexander Family Foundation



Population-based study of 5000+ (3200 active) persons – age 30-89 years



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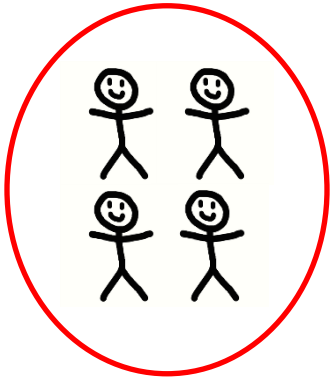
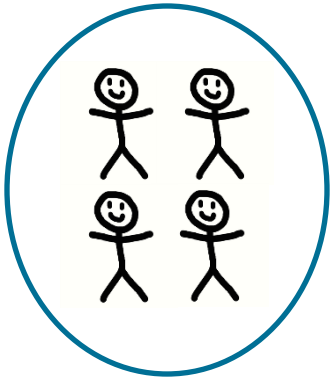
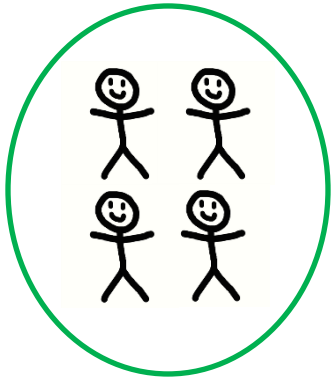
Heterogeneity in the population

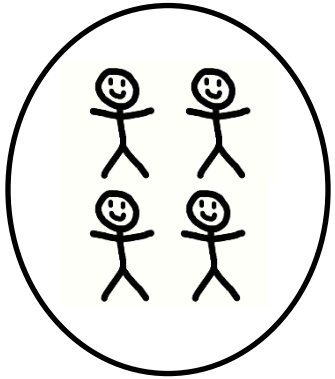
>80 years of age – no AD and CVD

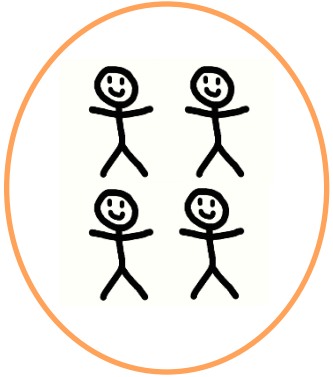


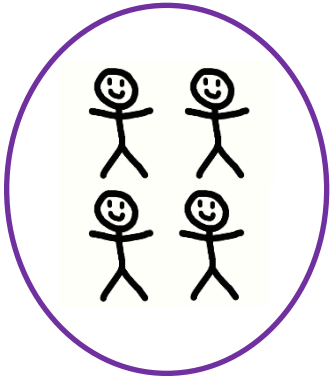




Cognitively intact individuals with amyloid for over 10 years







Individuals at 70 with substantial AD and CVD

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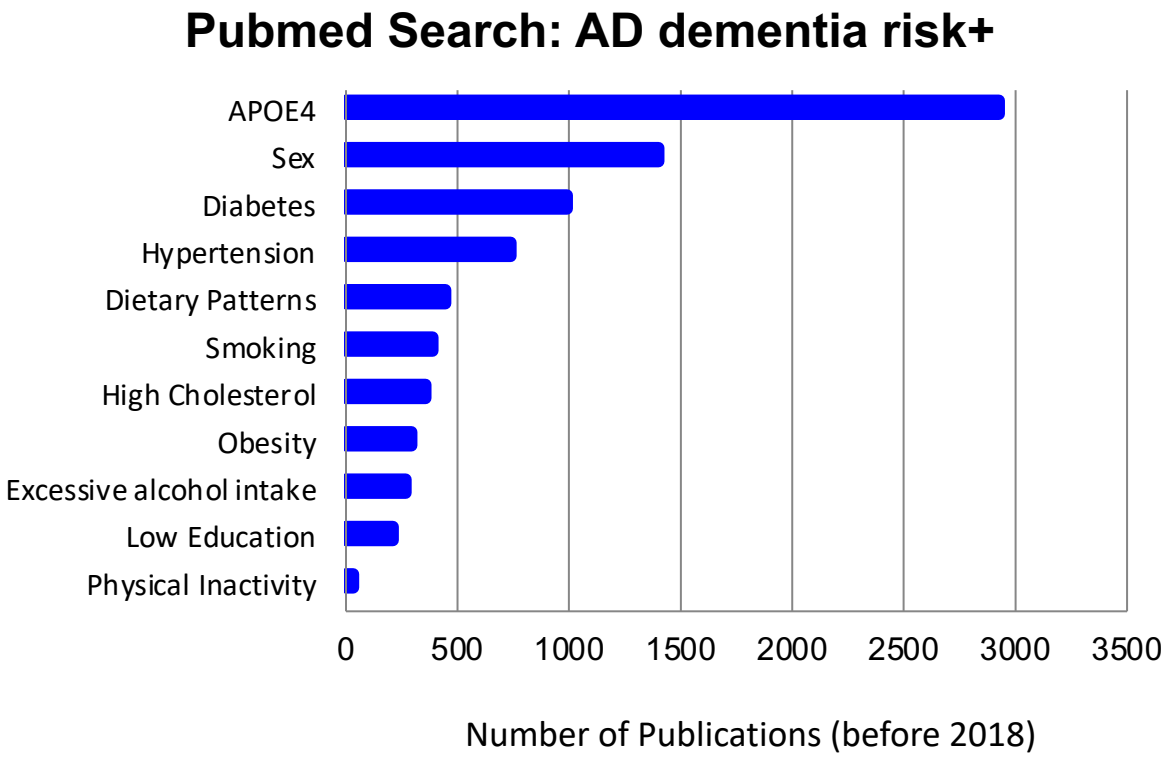
Heterogeneity in Dementia Risk



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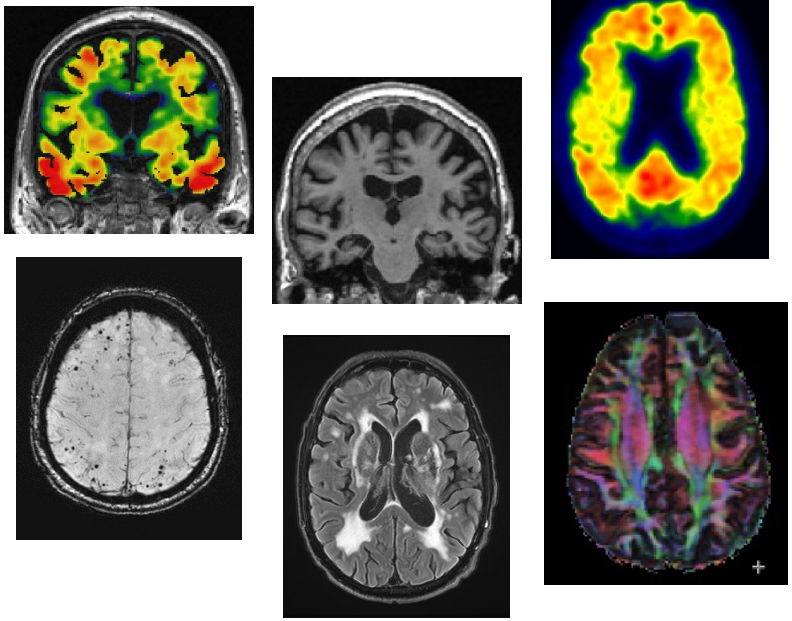
How do these factors cause heterogeneity ?

- APOE4
- Sex
- Diabetes
- Hypertension
- Dietary Patterns
- Smoking
- High Cholesterol
- Obesity
- Excessive alcohol intake
- Low Education
- Physical Inactivity



Wealth of data acquired longitudinally along with cognitive trajectories

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Overview of my talk

Mechanisms and underlying factors that cause this heterogeneity

- Resistance – Avoiding *pathologies
- Resilience – Coping with *pathologies

*For simplicity *pathologies = AD pathologies*

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RESISTANCE – Avoiding Pathologies

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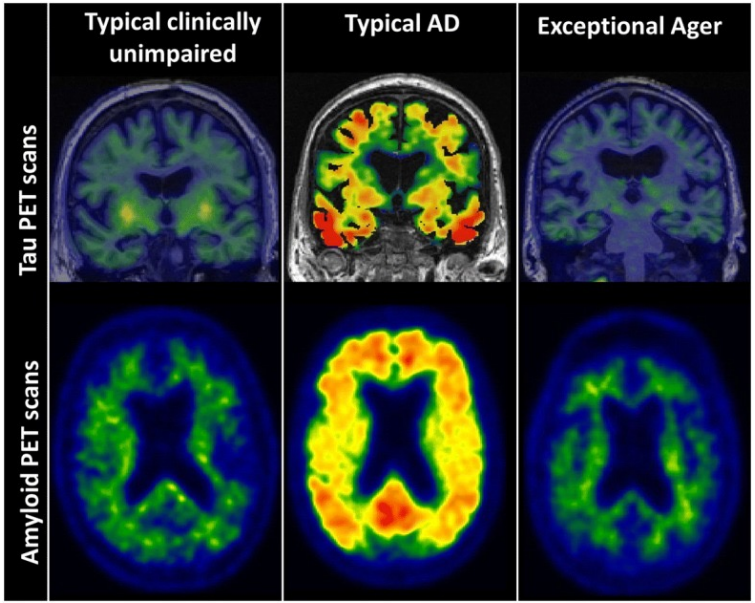
RESISTANCE – Avoiding Pathologies

Aβ

Amyloid PET Imaging
CSF Aβ
*Plasma Aβ

Tau

Tau PET Imaging
CSF p-tau
*Plasma p-tau



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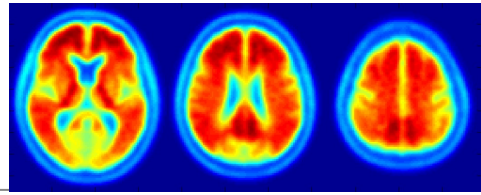
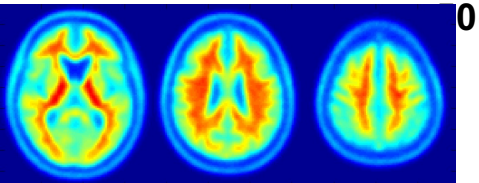
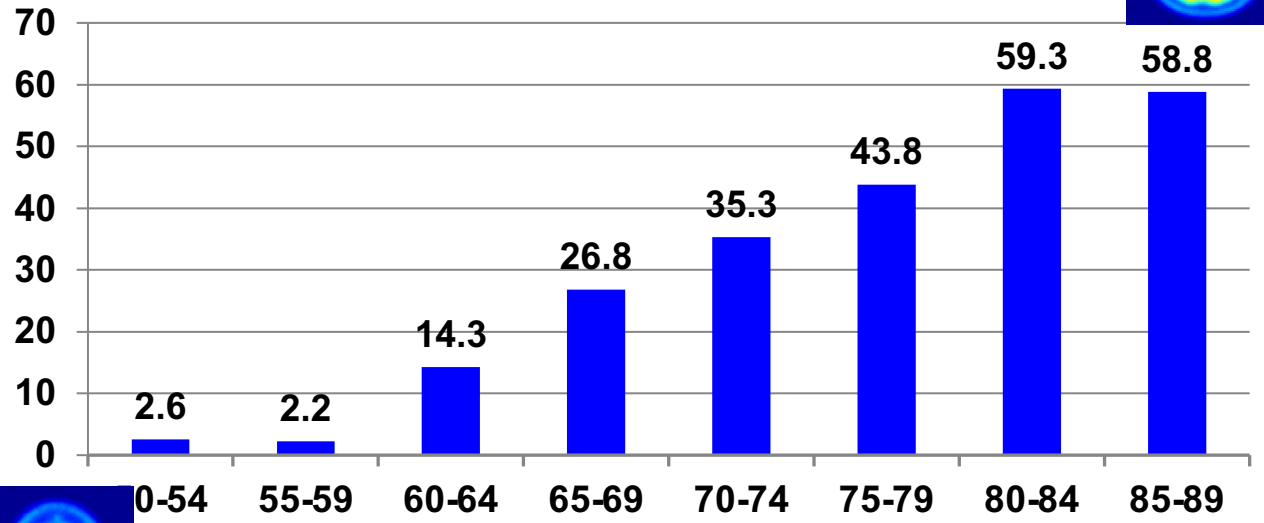
Aβ Amyloid Prevalence in the Community

n= 1,646 without Dementia with Amyloid Imaging





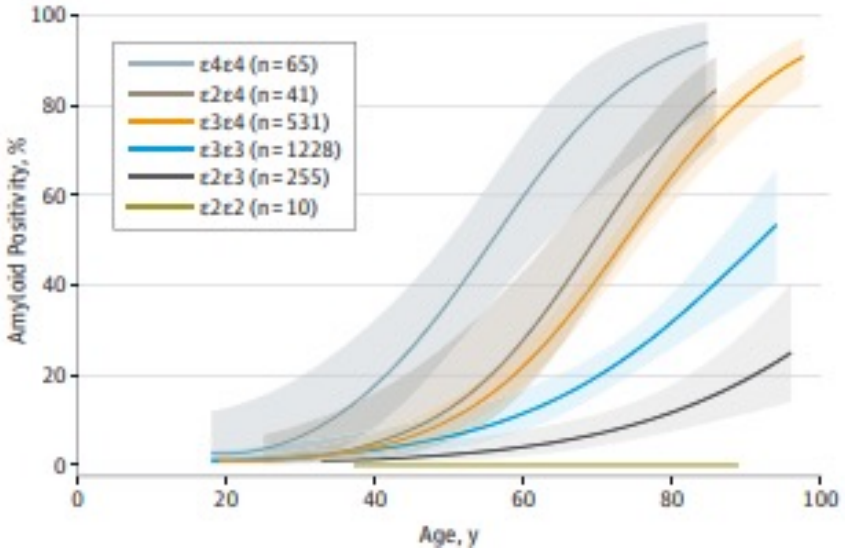


Roberts RO et. al. Neurology 2018

Aβ

Risk Factors for Amyloid: Age & APOE4

Estimates of Amyloid Positivity



Jansen et. al. JAMA 2015

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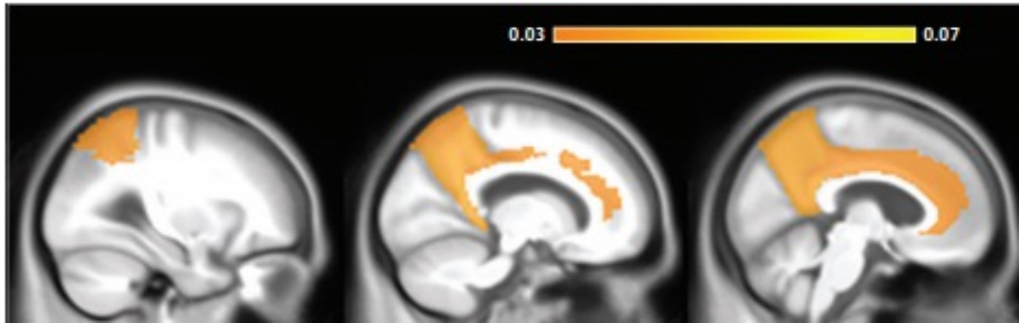
Aβ Sleep Disruption and Amyloid

- Poor sleep quality and the risk for cognitive decline and AD
- Sleep drives metabolite clearance (Xie L Science 2013)

Longitudinal Amyloid Deposition vs. Sleep



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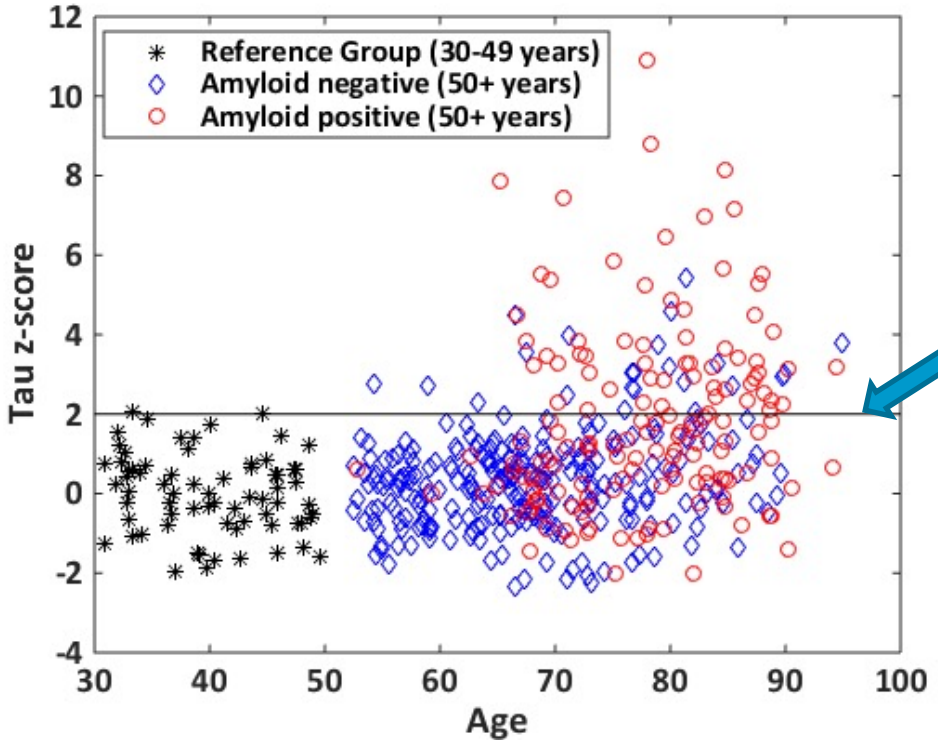
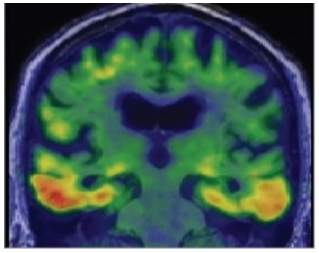
Carvalho DZ JAMA Neurology 2018

Tau

Risk Factors for Tau: Age and Amyloid





ABNORMAL TAU

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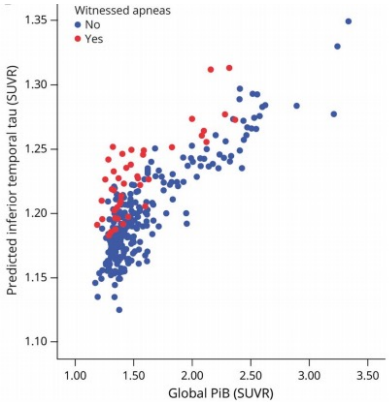
Tau

Resistance to Tau

Better stress coping associated with lower tau in amyloid-positive cognitively unimpaired elderly

Arenaza-Urquijo AM et. al. Neurology 2020



Witnessed apneas are associated with elevated tau-PET levels in cognitively unimpaired elderly

Carvalho DZ et. al. Neurology 2020

Tau phosphorylation regulatory gene *PPP2R2B* (GWAS) associated with higher tau deposition

Ramanan VK et. al. Brain Comm 2021

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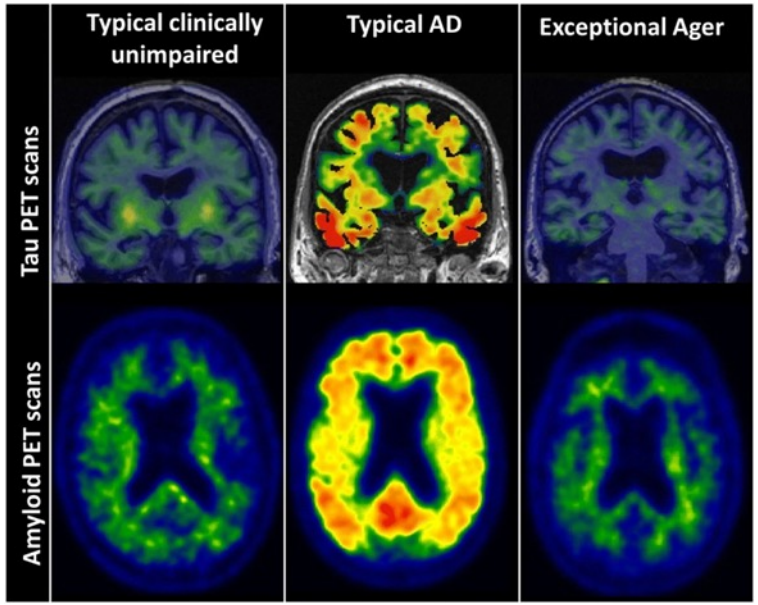
RESISTANCE – Avoiding Pathologies

- Age, genetics, sleep, stress, *physical activity (?)*, *GxE*



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RESILIENCE – Coping with Pathologies

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Resilience Mechanisms – (1)

Brain Reserve

Individual variation in the neurobiological capital that allows some people to better cope with brain aging and pathology

(Stern Y et. al. White Paper 2018)

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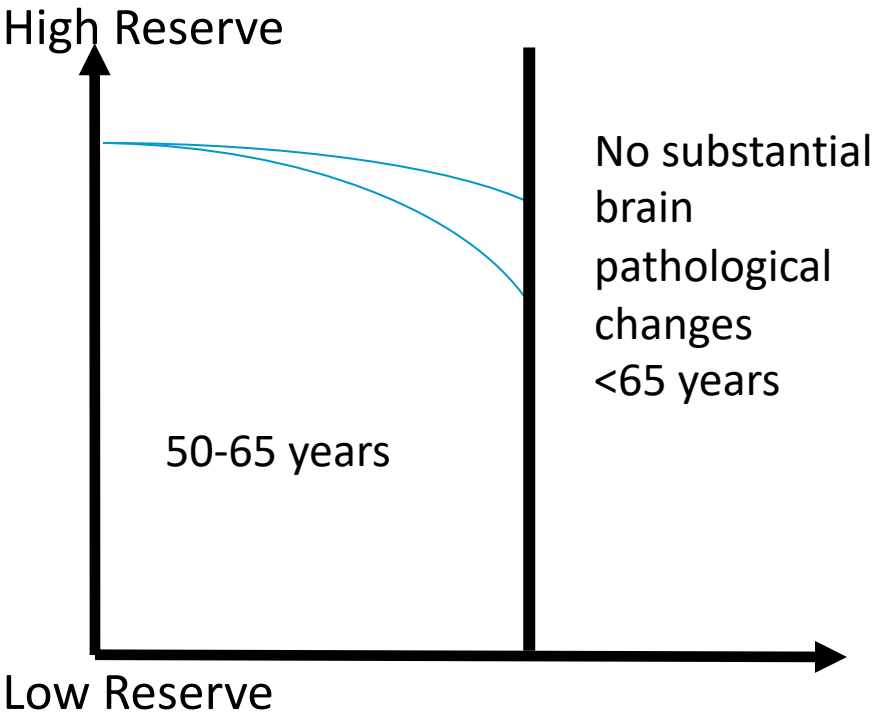
Reserve in Midlife



- Measuring Reserve in midlife
- Which midlife risk factors make the brain vulnerable to age related cognitive disorders ?

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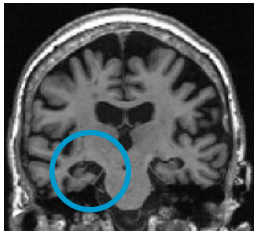
Neth B et al. Frontiers of Aging Neuroscience 2020

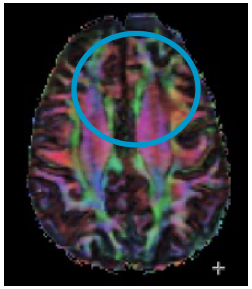
Reserve in Midlife (50-65 years; n=537)

Brain Health

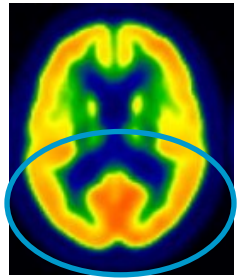
Structure



Microstructural Integrity



Metabolism



General health status was the largest contributor of better brain health in midlife

Midlife Risk Factors:

Intellectual/Physical Activity: education-occupation composite, physical, and cognitive-based activity engagement;

General Health Factors: presence of cardiovascular and metabolic conditions (CMC), body mass index, hemoglobin A1c, smoking status (ever/never), CAGE Alcohol Questionnaire (>2, yes/no), Beck Depression Inventory score

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Midlife and subsequent AD risk

		AMYLOID EFFECTS		BRAIN RESERVE IN TEMPORAL LOBES	
Midlife risk factors					
Physical inactivity	.13	−0.004 (0.01)	.58	−0.01 (0.01)	.04
Obesity	<.001	−0.03 (0.07)	.66	−0.27 (0.06)	<.001
Ever smoked	.01	0.05 (0.06)	.40	−0.15 (0.06)	.01
Diabetes	.01	0.17 (0.13)	.17	−0.28 (0.12)	.02
Hypertension	.11	−0.01 (0.07)	.87	−0.13 (0.06)	.04
Dyslipidemia	.01	−0.18 (0.07)	.01	−0.12 (0.06)	.06

Vemuri P et. al. JAMA Neurology 2017

Exposure to surgery/GA increases likelihood of abnormal cortical thinning: odds ratio (OR)=1.98; P=0.010 in those exposed after age 40 yr, and OR=1.64; P=0.029 in those exposed in the prior 20 yr.

Sprung J et. al. Br J Anaesth 2020

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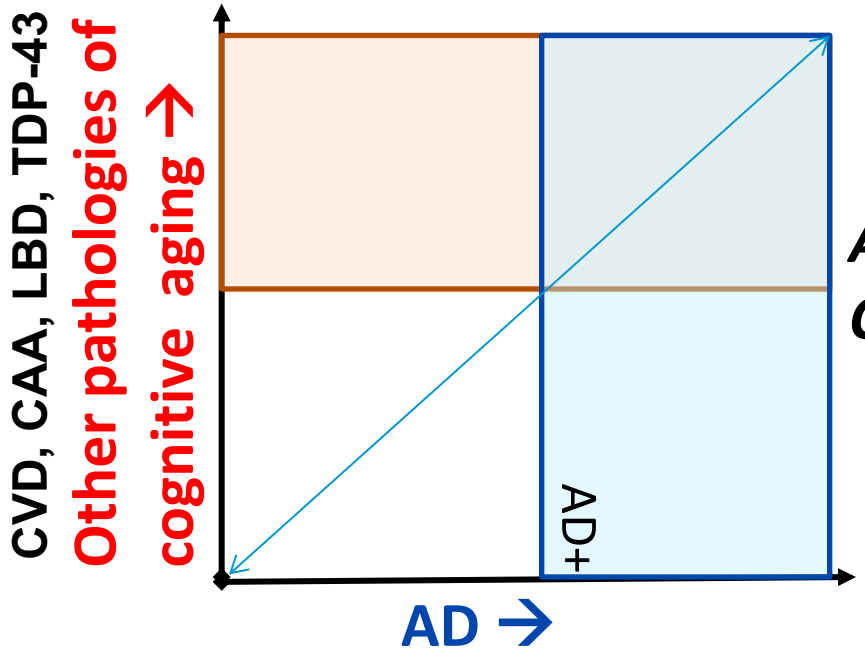
Resilience Mechanisms – (2) – other pathologies/pathways to cognitive impairment



AD + CVD + CAA+ LBD + TDP-43= Cognitive Impairment

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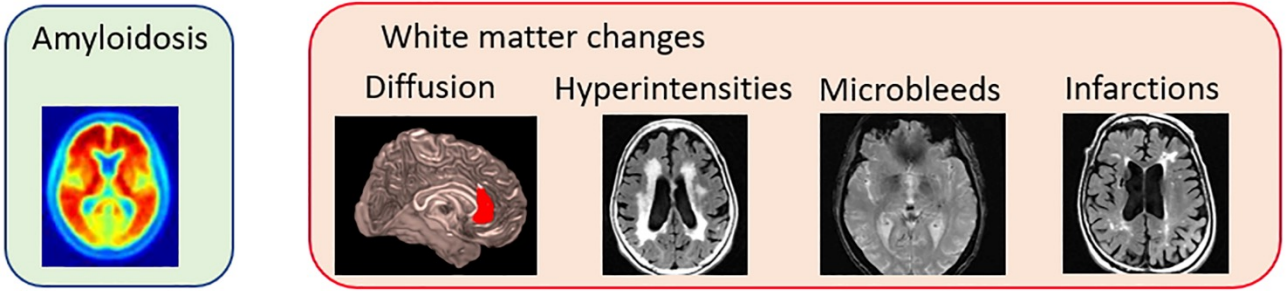
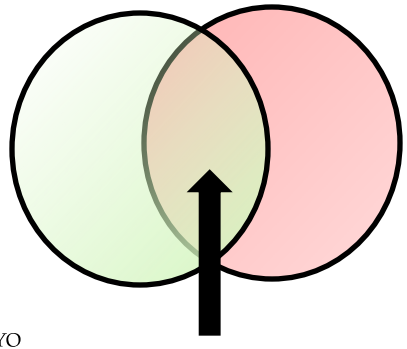
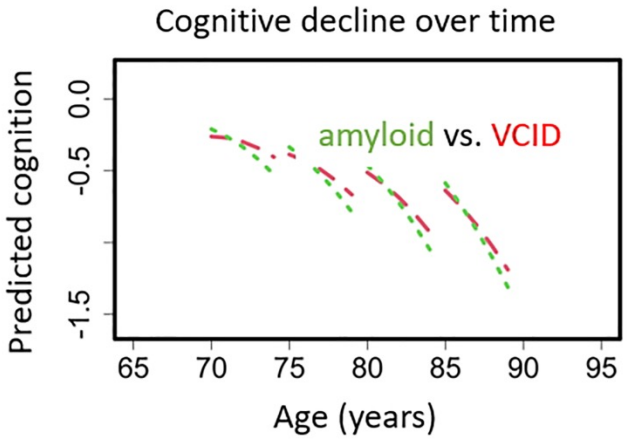
(2) Vascular disease pathway





Low Resilience



VCID and amyloidosis have similar impact on cognitive decline in this population-based sample

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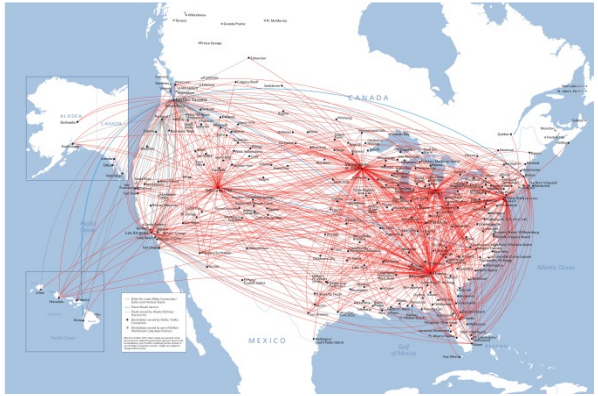
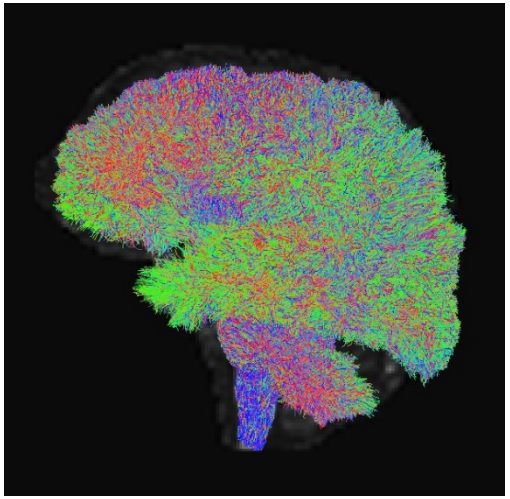
Vemuri P, et. al. Brain Communications 2021

(2) WM connections in the brain

Delta Route Map



White matter connections



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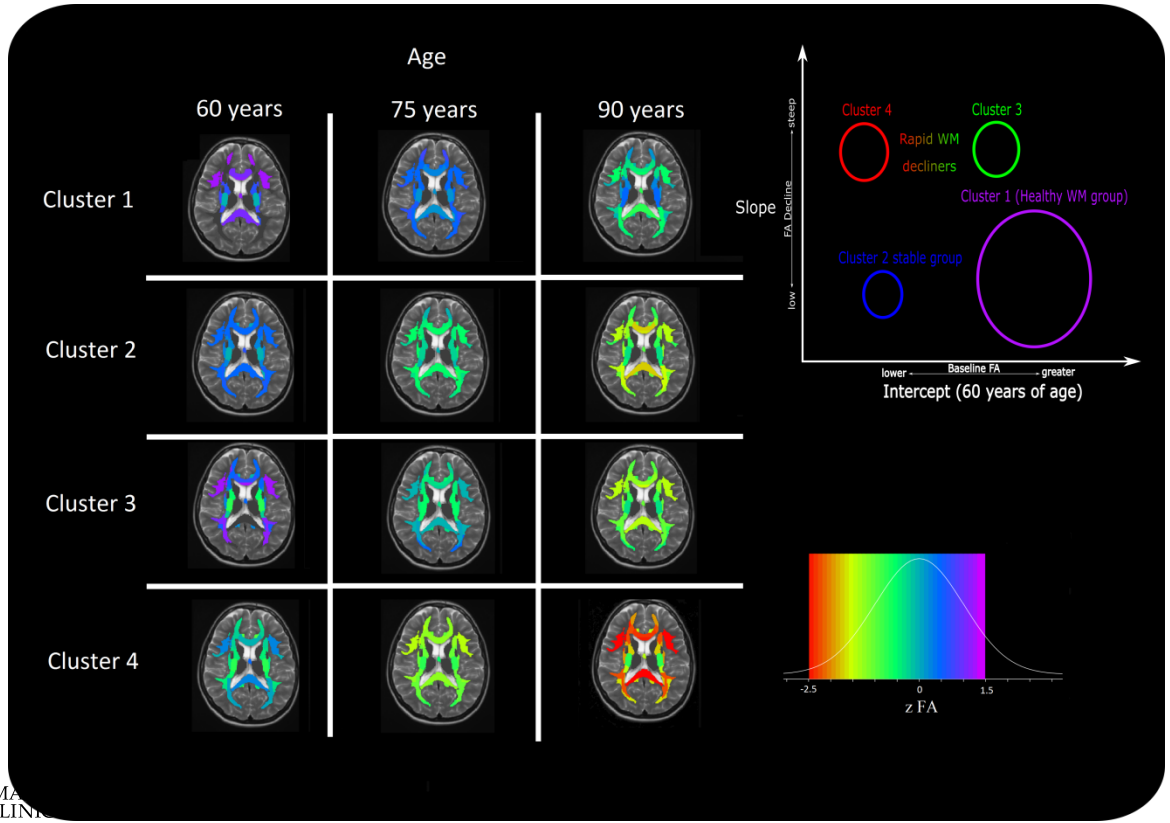
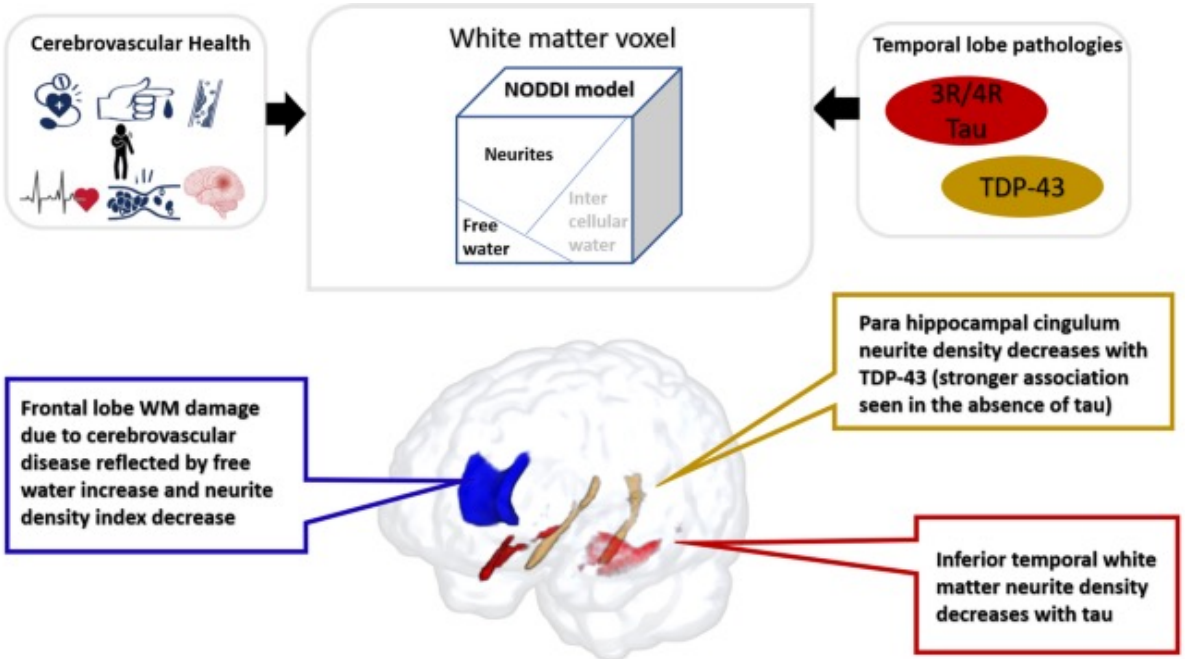
(2) WM pathways as an example



Different clusters (healthy WM, fast WM decliners, and intermediate WM group) based on diffusion changes

Poulakis, Reid et. al Brain Communications 2020

Better imaging models



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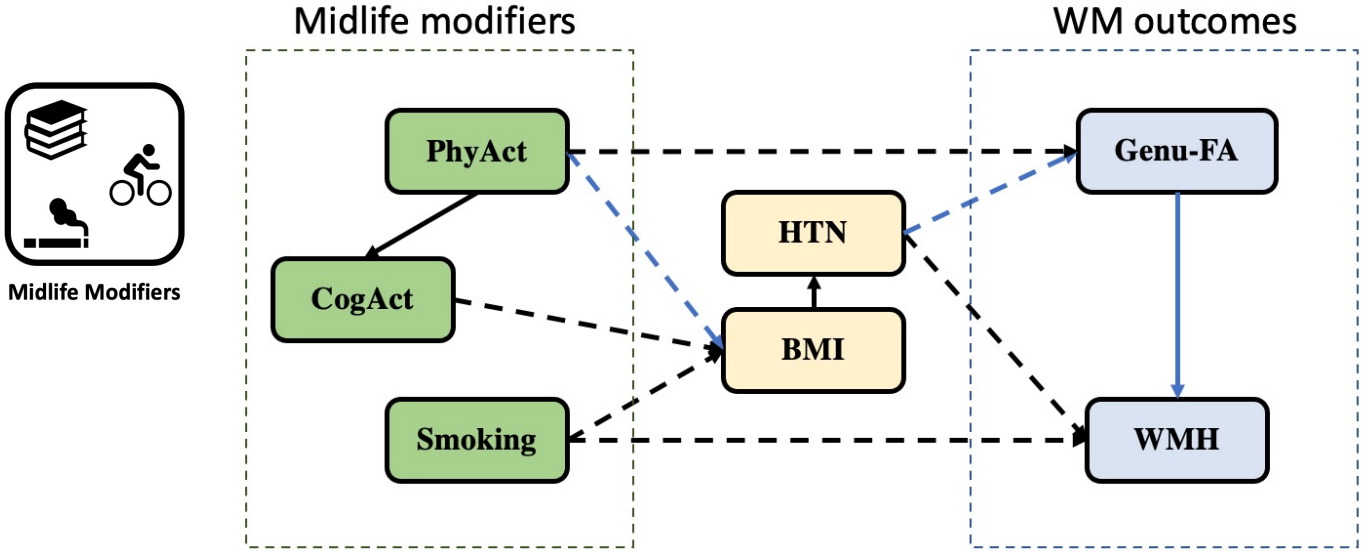
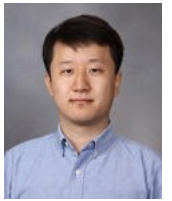
Raghavan et. al. Brain Comm 2022

Raghavan et. al. Acta Neuropathologica Comm 2022

(2) Prevention pathways unrelated to resistance

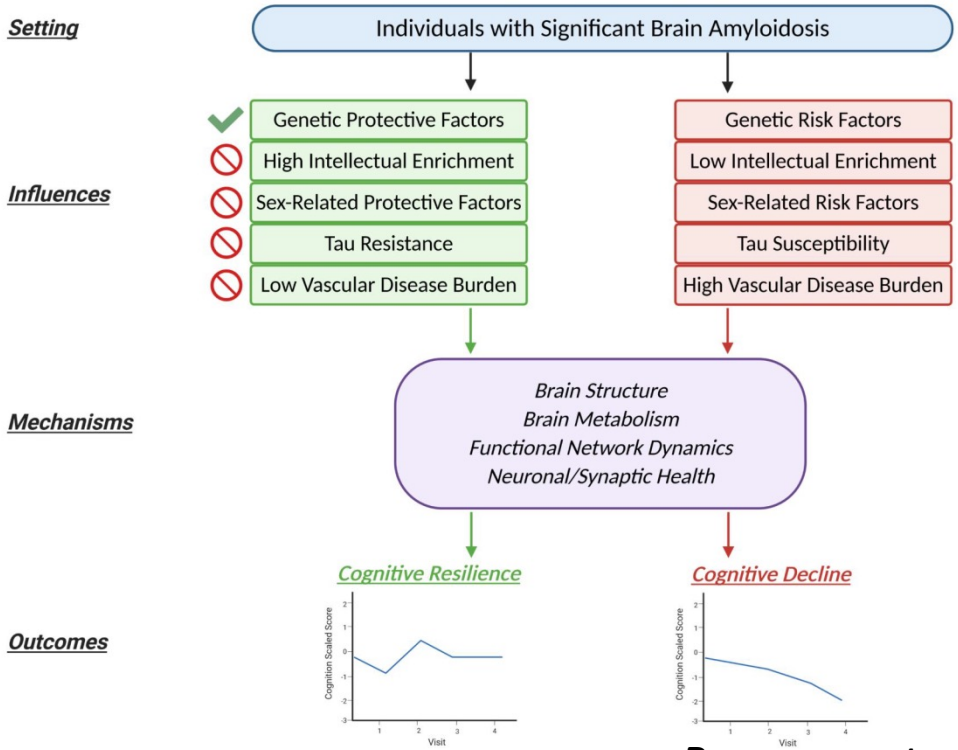
WMH and Intensive blood pressure control intervention ACCORD MIND (de Havenon et. al. Neurology 2019) and SPRINT-MIND Study (JAMA 2019)





Shen et. al. NeuroImage Clinical 2022

(2) Pathways - Genetic Heterogeneity and Cognitive Resilience to AD



CNOT7 (CCR4-NOT Transcription Complex Subunit 7), a gene linked to synaptic plasticity and hippocampal-dependent learning and memory

Ramanan et. al. Acta Neuropath Comm 2021

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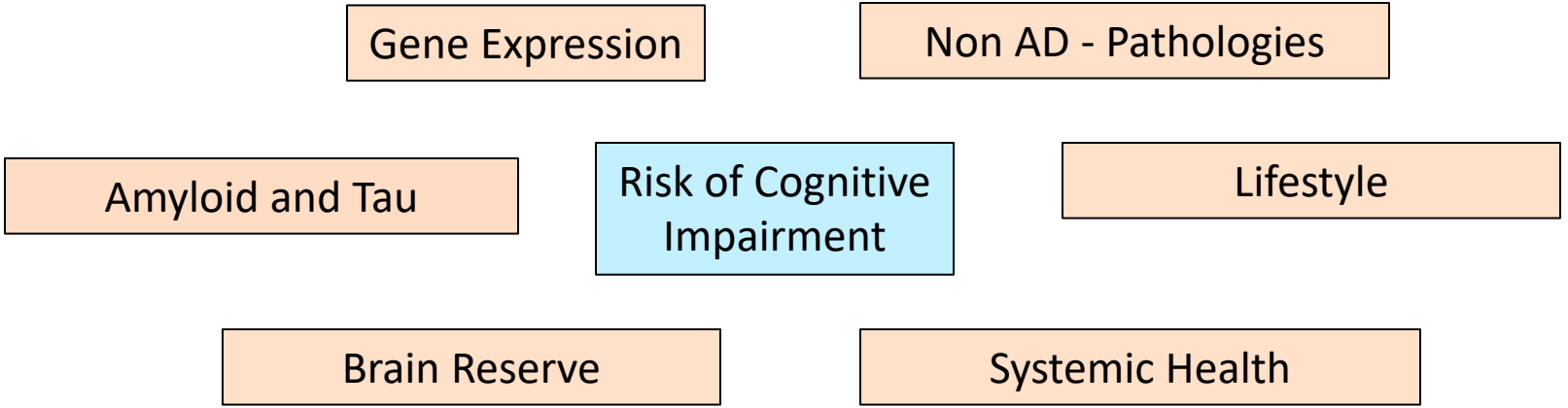
Looking ahead …

Cognitive aging as a multifactorial process

"Generalizable" learning models and methodologies that capture the "*complexity*" and "*heterogeneity*" of the disease



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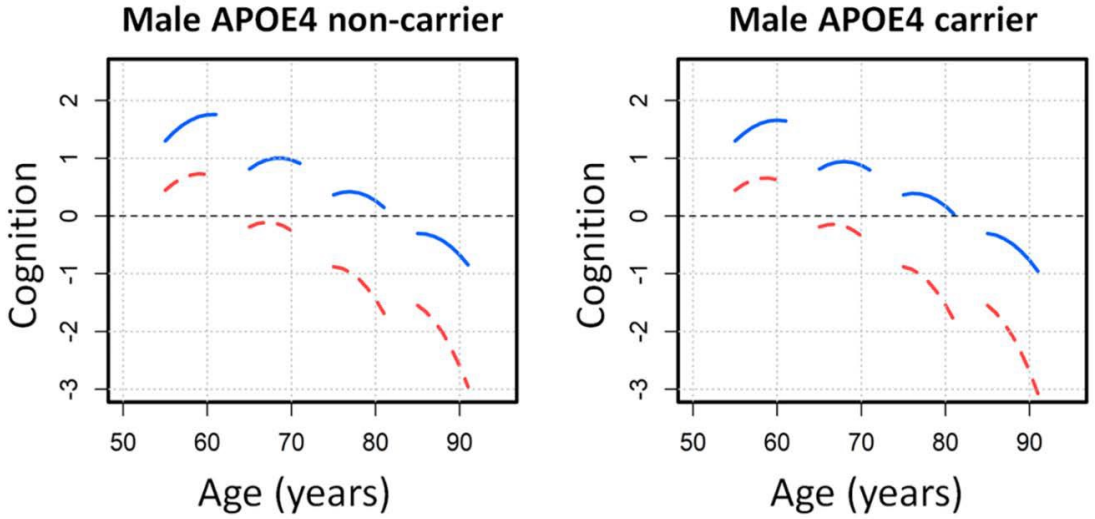
Multiple pathways to cognitive impairment and harnessing AI methods



		Age in years (by decade)			
		50-60	60-70	70-80	80-90
Education/Occupation	Low	11.12	11.08	9.71	9.71
	High	14.63	15.32	15.28	15.32
Amyloid (SUVR)	Low	1.22	1.27	1.30	1.31
	High	1.32	1.42	1.71	2.02
Genu FA	Low	0.60	0.59	0.55	0.52
	High	0.66	0.65	0.63	0.60

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Annals of Neurology 2019

Summary

- Cognitive aging is a multifactorial process
- Two broad mechanisms that can aid in exceptional aging - Resistance & Resilience

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Acknowledgments

Tim Lesnick
Scott Przybelski
Eider Arenaza
Sheela Raghavan
Bryan Neth
Vijay Ramanan
Diego Carvalho
Rob Reid
Robel Gebre
J.Q. Tian
Anna Castillo
Aivi Nguyen
Jon Graff-Radford
Michelle Mielke
Chris Schwarz
Kejal Kantarci
Mary Machulda
Val Lowe
Walter Rocca
Owen Ross
Melissa Murray
David Knopman
Clifford Jack Jr.
Ron Petersen

Study Participants and Families
Aging and Dementia Imaging Lab
Mayo Clinic Study of Aging
Mayo ADRC

GRANT SUPPORT:
NIH: NIA and NINDS, GHR Foundation

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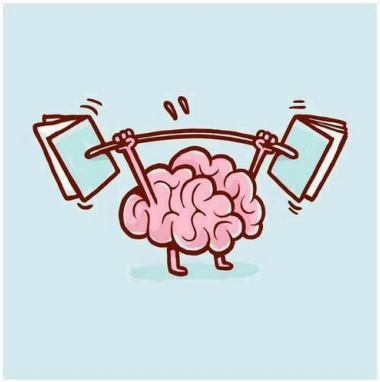

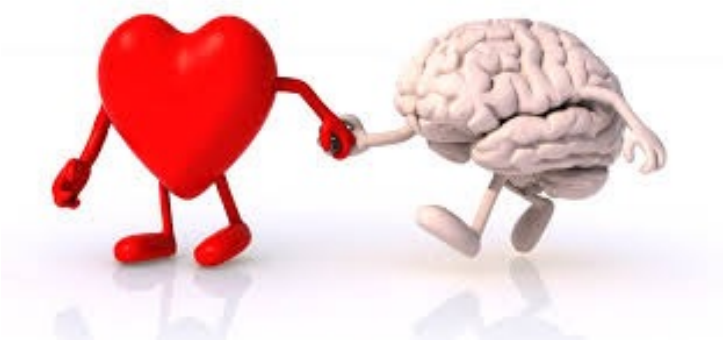

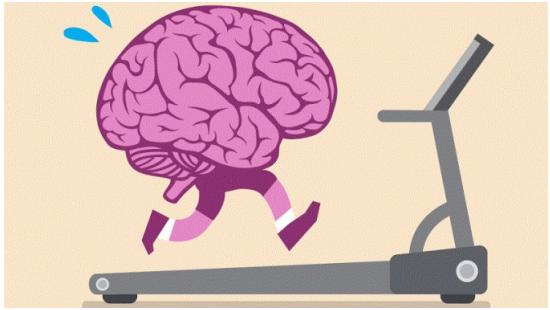

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