Factors contributing to resistance and resilience in the aging population

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Mayo Clinic Study of Aging

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

Pubmed Search: AD dementia risk+

- APOE4: 3000
- Sex: 2500
- Diabetes: 2000
- Hypertension: 1500
- Dietary Patterns: 1000
- Smoking: 500
- High Cholesterol: 500
- Obesity: 500
- Excessive alcohol intake: 500
- Low Education: 500
- Physical Inactivity: 50

Number of Publications (before 2018)
How do these factors cause heterogeneity?

<table>
<thead>
<tr>
<th>APOE4</th>
<th>Sex</th>
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<tr>
<td></td>
<td>Diabetes</td>
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<td>Low Education</td>
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<td>Physical Inactivity</td>
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Wealth of data acquired longitudinally along with cognitive trajectories.
Overview of my talk

Mechanisms and underlying factors that cause this heterogeneity

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

For simplicity *pathologies = AD pathologies
RESISTANCE – Avoiding Pathologies
RESISTANCE – Avoiding Pathologies

- Aβ: Amyloid PET Imaging, CSF Aβ, *Plasma Aβ
- Tau: Tau PET Imaging, CSF p-tau, *Plasma p-tau
Amyloid Prevalence in the Community

n= 1,646 without Dementia with Amyloid Imaging

Roberts RO et. al. Neurology 2018
Risk Factors for Amyloid: Age & APOE4

Estimates of Amyloid Positivity

Jansen et. al. JAMA 2015
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

Carvalho DZ JAMA Neurology 2018
Risk Factors for Tau: Age and Amyloid

- Reference Group (30-49 years)
- Amyloid negative (50+ years)
- Amyloid positive (50+ years)
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
RESISTANCE – Avoiding Pathologies

- Age, genetics, sleep, stress, *physical activity (?), GxE*
RESILIENCE – Coping with Pathologies
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)*
Reserve in Midlife

High Reserve

No substantial brain pathological changes <65 years

50-65 years

Low Reserve

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

Neth B et al. Frontiers of Aging Neuroscience 2020
Reserve in Midlife (50-65 years; n=537)

**Brain Health**
- Microstructural Integrity
- Metabolism

**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

**General health status** was the largest contributor of better brain health in midlife
Midlife and subsequent AD risk

**AMYLOID EFFECTS**

<table>
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<tr>
<th>Midlife risk factors</th>
<th>Physical inactivity</th>
<th>Obesity</th>
<th>Ever smoked</th>
<th>Diabetes</th>
<th>Hypertension</th>
<th>Dyslipidemia</th>
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<tbody>
<tr>
<td></td>
<td>.13</td>
<td>&lt;.001</td>
<td>.01</td>
<td>.01</td>
<td>.11</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>−0.004 (0.01)</td>
<td>−0.03 (0.07)</td>
<td>0.05 (0.06)</td>
<td>0.17 (0.13)</td>
<td>−0.01 (0.07)</td>
<td>−0.18 (0.07)</td>
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<tr>
<td></td>
<td>.58</td>
<td>.66</td>
<td>.40</td>
<td>.17</td>
<td>.87</td>
<td>.01</td>
</tr>
</tbody>
</table>

**BRAIN RESERVE IN TEMPORAL LOBES**

|                      | −0.01 (0.01) | .04 |
|                      | −0.27 (0.06) | <.001 |
|                      | −0.15 (0.06) | .01 |
|                      | −0.28 (0.12) | .02 |
|                      | −0.13 (0.06) | .04 |
|                      | −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
Resilience Mechanisms – (2) – other pathologies/pathways to cognitive impairment

AD + CVD + CAA+ LBD + TDP-43 = Cognitive Impairment
(2) Vascular disease pathway

Amyloidosis

White matter changes
- Diffusion
- Hyperintensities
- Microbleeds
- Infarctions

Cognitive decline over time

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

Low Resilience

Vemuri P, et. al. Brain Communications 2021
(2) WM connections in the brain

Delta Route Map

White matter connections
Different clusters (healthy WM, fast WM decliners, and intermediate WM group) based on diffusion changes
Better imaging models

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)
(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
Cognitive aging as a multifactorial process

“Generalizable” learning models and methodologies that capture the “complexity” and “heterogeneity” of the disease

- Gene Expression
- Amyloid and Tau
- Risk of Cognitive Impairment
- Brain Reserve
- Non AD - Pathologies
- Lifestyle
- Systemic Health

Looking ahead ...
Multiple pathways to cognitive impairment and harnessing AI methods

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<tr>
<th>Education/Occupation</th>
<th>Age in years (by decade)</th>
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<tr>
<td></td>
<td>50-60</td>
</tr>
<tr>
<td>Low</td>
<td>11.12</td>
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<tr>
<td>High</td>
<td>14.63</td>
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<tr>
<td>Amyloid (SUVR)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.22</td>
</tr>
<tr>
<td>High</td>
<td>1.32</td>
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<td>Genu FA</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.60</td>
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<tr>
<td>High</td>
<td>0.66</td>
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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
Acknowledgments

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