Cognitive Reserve and Resilience

Yaakov Stern

Cognitive Neuroscience Division, Department of Neurology

Columbia University Vagelos College of Physicians and Surgeons

Disclosures

- My research is supported by the National Institute on Aging
- I consult for Eisai, Lilly, and Arcadia.
- Columbia University licenses the Dependence Scale, and in accordance with university policy, I am entitled to royalties through this license.

Collaboratory on research definitions for reserve and resilience in cognitive aging and dementia

- Goal: To develop consensus definitions for concepts relating to "resilience" for researchers in aging and dementia
- We developed a consensus "Framework" that provides operational definitions acceptable to human and animal researchers for:
  - *resilience* as a general term that captures all concepts
  - *cognitive reserve, brain reserve and brain maintenance*

reserveandresilience.com

The collaboratory is funded by a grant (R24 AG061421) from the National Institute on Aging.

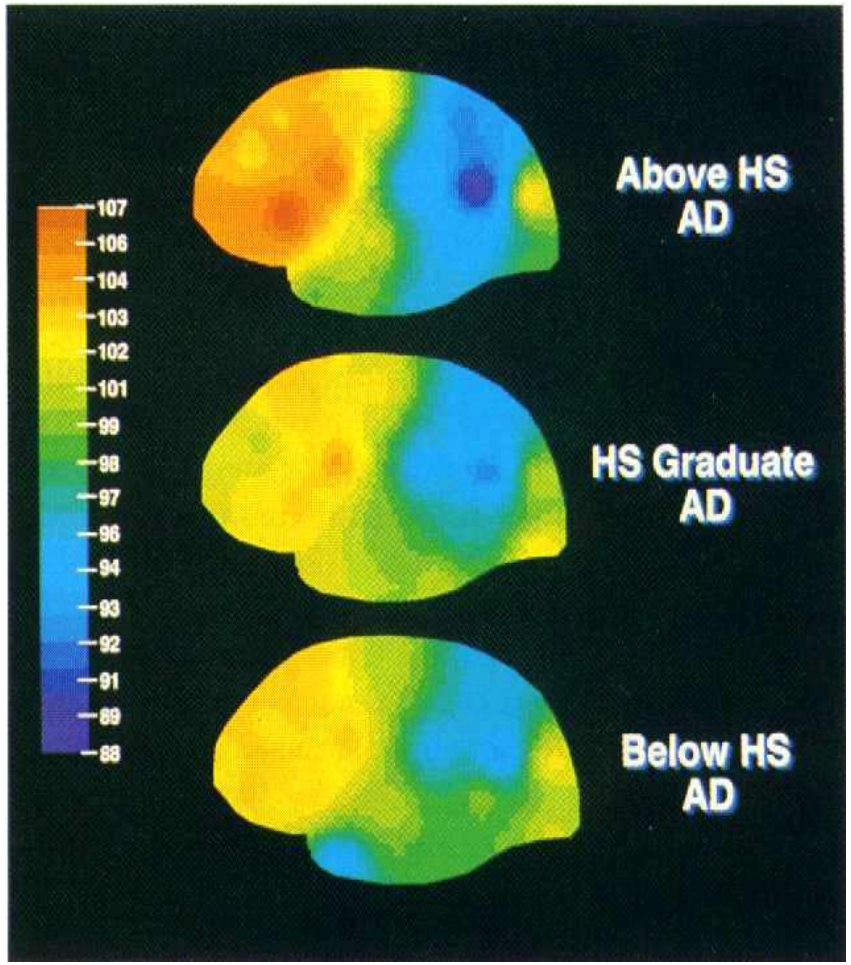
Cognitive Reserve: Definition

Cognitive reserve (CR) is a property of the brain that allows for cognitive performance that is better than expected given the degree of life-course related brain changes and brain injury or disease

- **Property of the brain** refers to multiple potential mechanisms including molecular, cellular and network levels. The working hypothesis is that these mechanisms help cope with or compensate for brain changes and brain injury or disease.
- These mechanisms can be characterized via **biological or cognitive-experimental** approaches.
- Better than expected cognitive performance ideally refers to trajectories measured longitudinally.

CR can be influenced by multiple genetic and environmental factors, operating at various points or continuously across the lifespan.

Education, neurodegeneration and AD severity



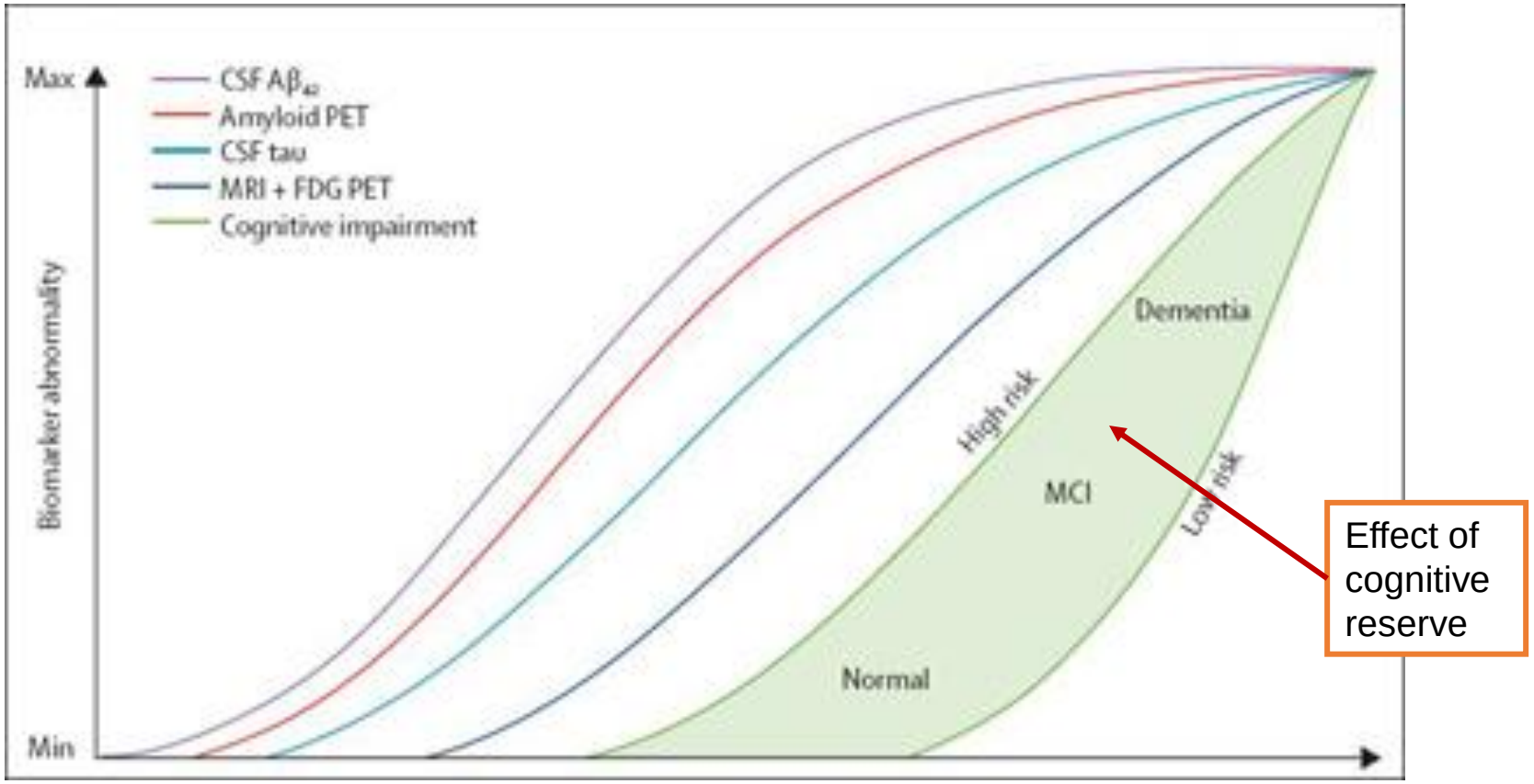
Controlling for clinical disease severity, there is an inverse relationship between education and neurodegeneration (the final expression of AD pathologies)

This observation incorporates the 3 key components of studying cognitive reserve:

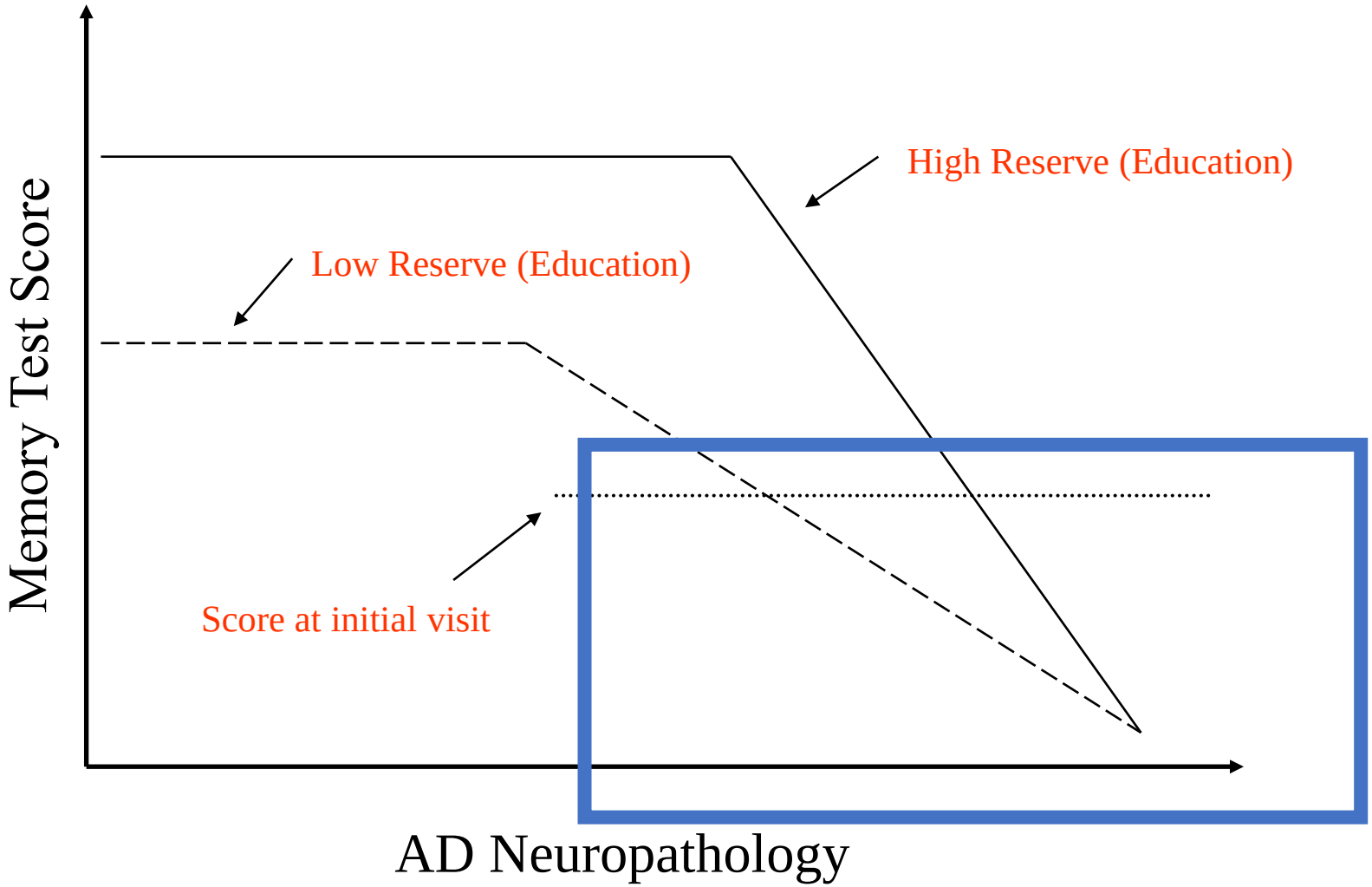
- Pathology or brain change
- Clinical outcome of that pathology
- A moderator of this relationship

Stern et al, Ann Neurol 1992

Neurodegeneration and AD severity

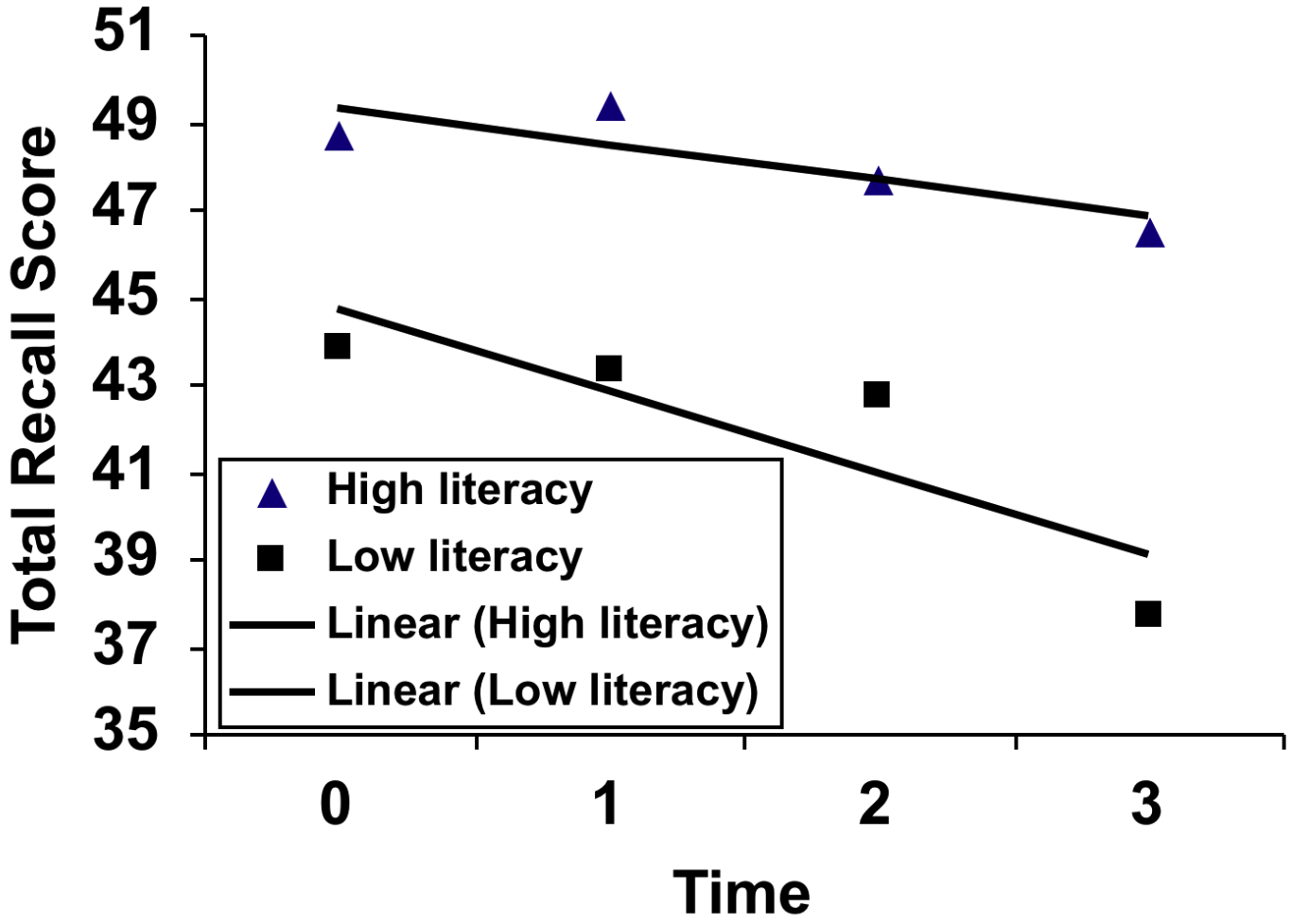


Jack et al. Lancet Neurology 2013



Stern et al Neurology 1999;53:1942-1957

Literacy and memory decline in non-demented elders



Manly et al, JCEN 2003

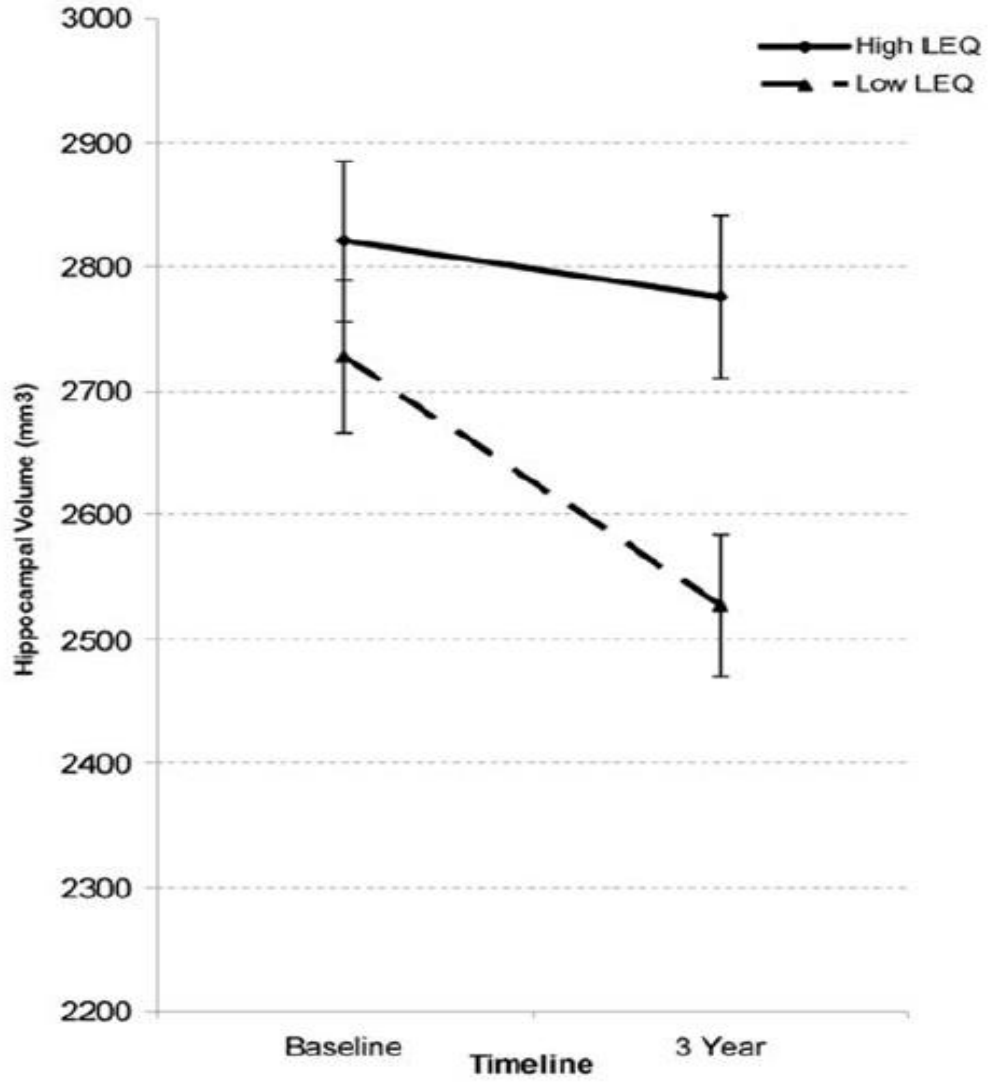
Brain Maintenance: Definition

Brain maintenance (BM) refers to the relative absence over time of changes in neural resources or neuropatholgic changes as a determinant of preserved cognition in older age.

BM can be influenced by multiple genetic and environmental factors, operating at various points or continuously across the lifespan.

Lifespan Mental Activity Predicts Diminished Rate of Hippocampal Atrophy

Michael J. Valenzuela[1,2*], Perminder Sachdev[1,2], Wei Wen[1,2], Xiaohua Chen[1,2], Henry Brodaty[1,3,4]



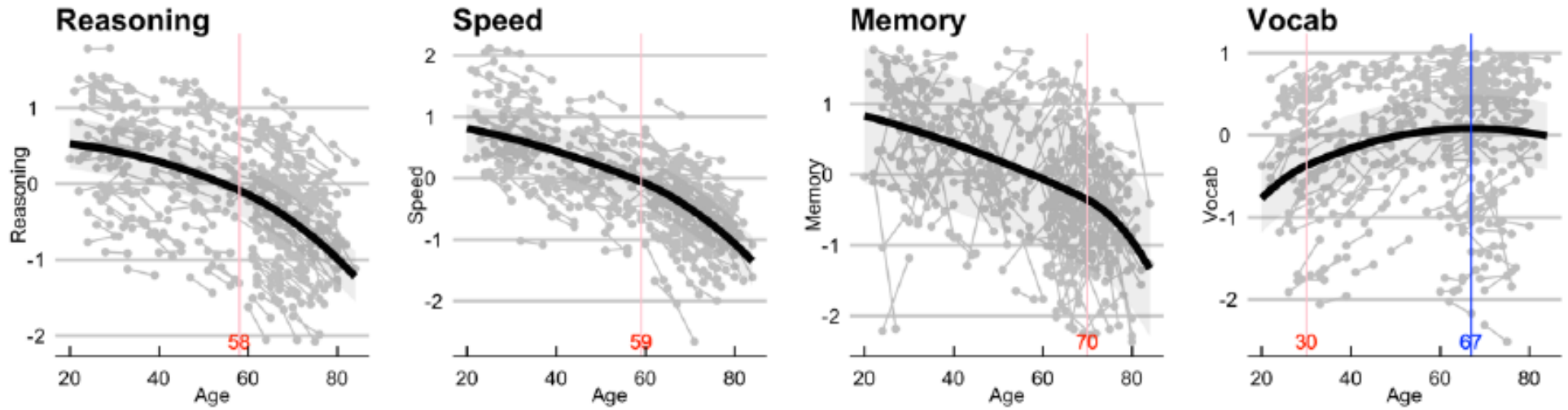
LEQ: Lifetime Experiences Questionnaire

PLoS ONE 2008

Variables potentially associated with imparting resilience

- Genetics
- Family/individual SES
- Education
- IQ
- Occupation
- Leisure activities
- Social networks
- Physical activity/Exercise
- Sleep
- Diet
- Discrimination
- Environmental exposures
- Genetics
- Cognitively stimulating activities
- Personality

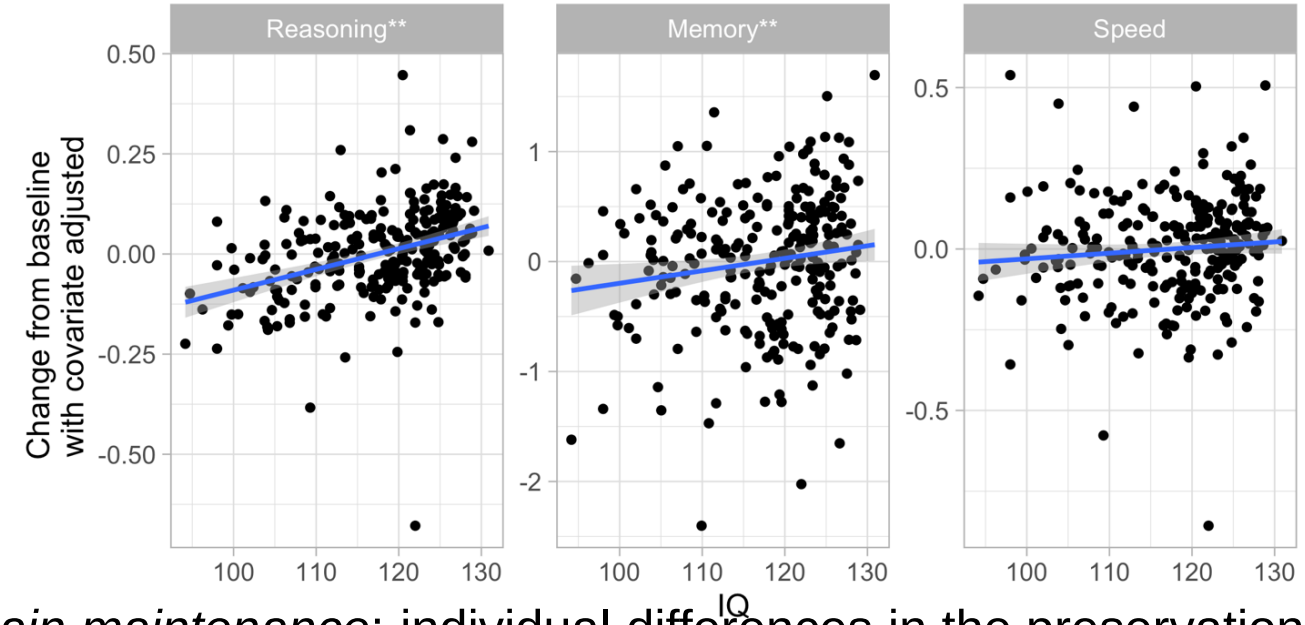
Longitudinal changes in cognitive abilities across life span: Cognitive reserve and brain maintenance.



- Trend in 5-year change for each ability
- Decline in reasoning, speed, and memory were accelerated after their inflection points (red lines)
- Vocabulary showed more gradual improvement after age 30 (red line) and reached its peak at age 67 (blue line).

Gazes et al, medRxiv 2021

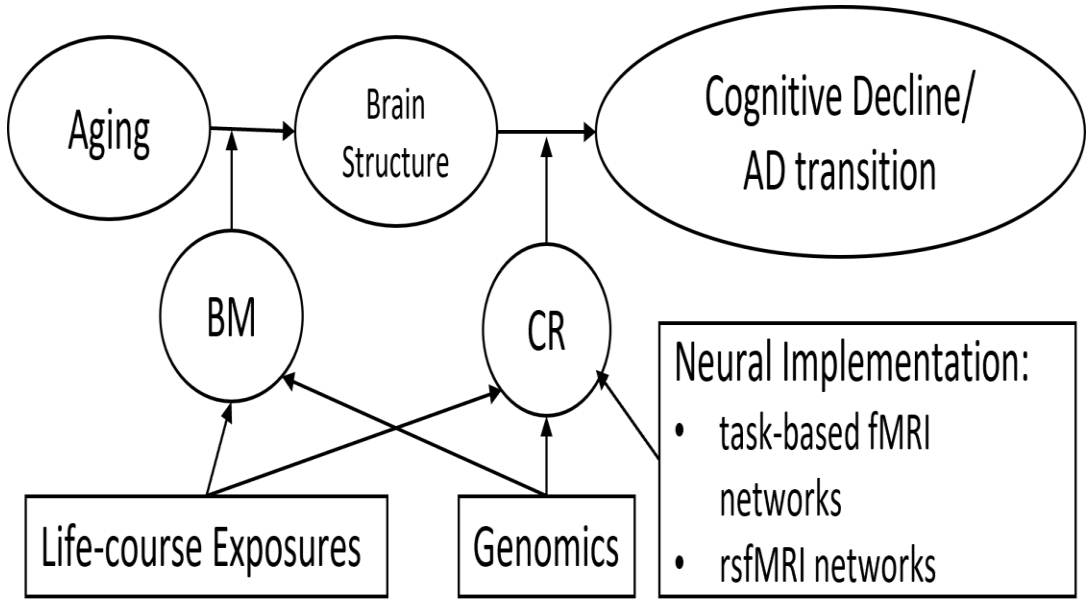
Longitudinal changes in cognitive abilities across life span: Cognitive reserve and brain maintenance.

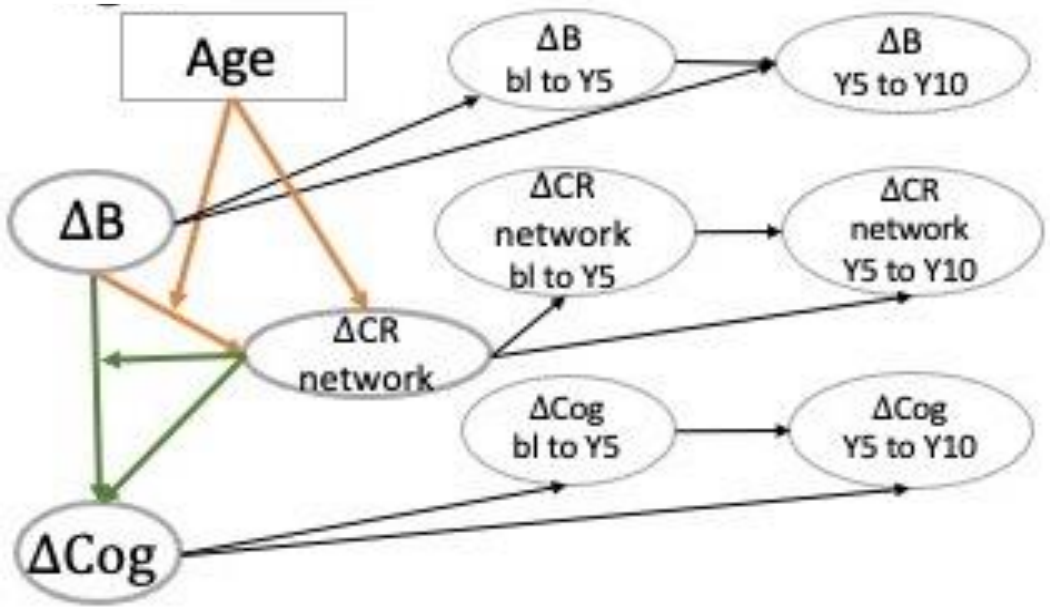


- Consistent with *brain maintenance*: individual differences in the preservation of mean diffusivity for whole brain white matter is associated with relative preservation in all four abilities; differential preservation of cortical thickness is the associated with preservation of reasoning, processing speed, and memory.
- Consistent with *cognitive reserve*: after accounting for structural brain changes, higher IQ is associated with reduced 5-year decline in reasoning (p=.003) and memory (p=.07)
- Similarly, greater leisure activity was associated with improvement in vocabulary; (p = .02) and lower rates of cognitive decline for reasoning (p = .003), speed (p = .004), and memory (p = .05)

Gazes et al, medRxiv 2021
Simon et al. JINS, 2022

Using imaging to study resilience





Knowledge Gaps

- Clarify genetic and lifelong factors that influence resilience
  - When in life do they operate
  - How do they interact
- Human research: what is the “neural implementation” of brain maintenance and cognitive reserve
  - Differential structural changes
  - Network connectivity at rest
  - Efficiency, capacity, flexibility of task-related neural networks
- Non-human studies
  - Insight into more “basic,” “biological” mechanisms underlying BM and CR
  - Mechanisms underlying cognitive reserve can be specified at the molecular, cellular or network levels

Research Opportunities: levels of analysis

- Human/non-human
- Epidemiologic
- Imaging: structural, functional
- Incorporating other modalities: genetics,exposome, etc
- Intervention
- Natural experiments:
  - Response to world events: e.g. the pandemic