Cognitive Reserve: From Concept to Measurement

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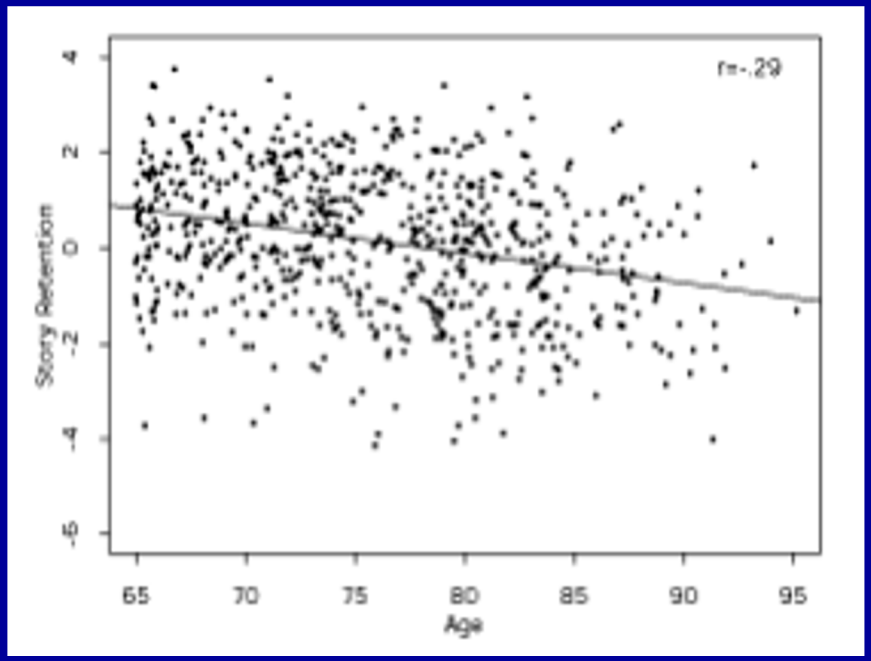
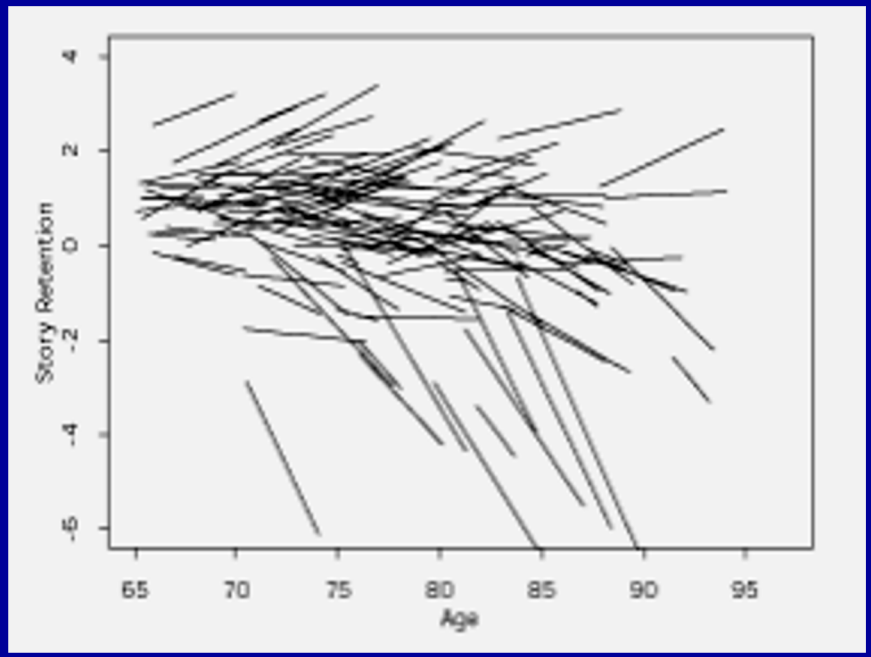
Overview

- What is cognitive reserve – (Why) Is it a useful construct
- Approaches to measuring cognitive reserve
  - Emphasis on reserve as residual approach
- Cognitive reserve – where do we go from here?

Heterogeneity is a defining feature of late life cognition



Wilson et al, Arch Neuro, 1999

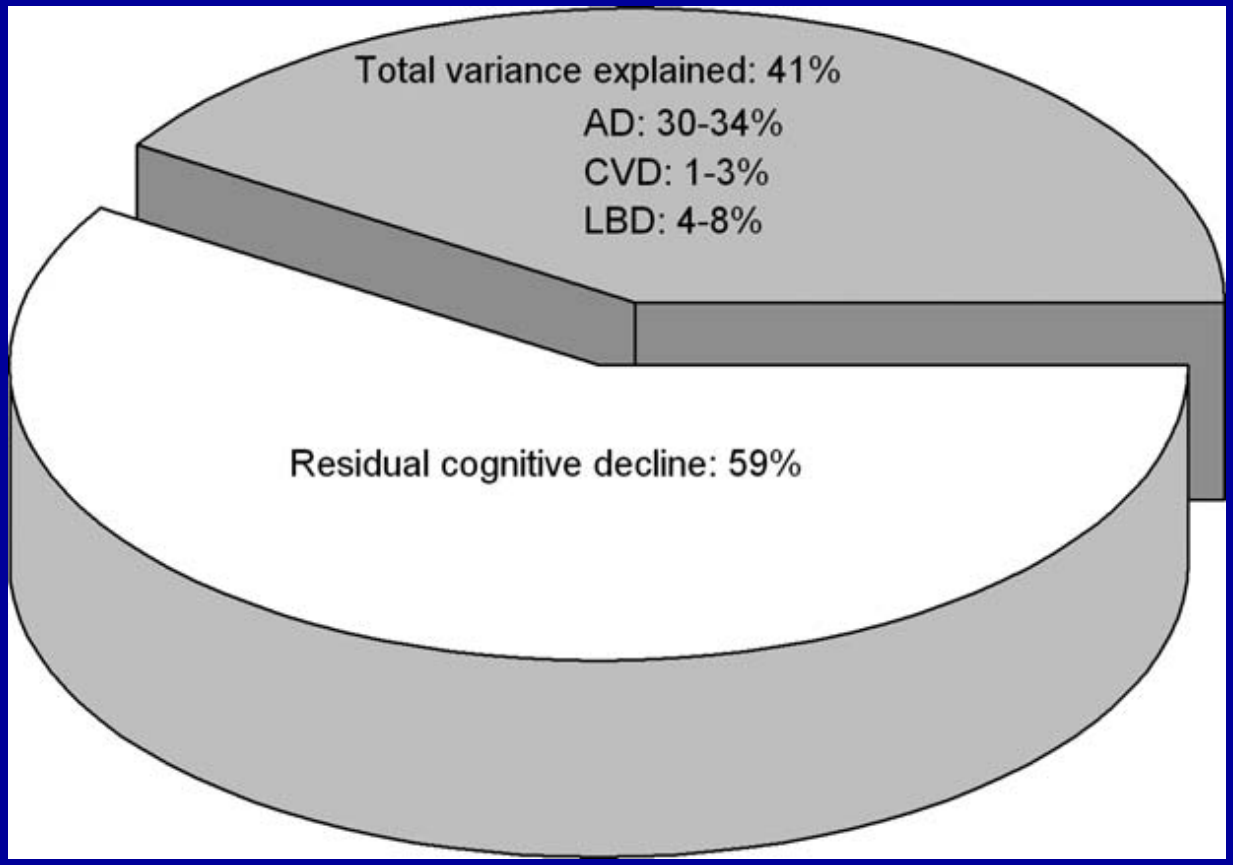


Wilson et al,Psychology and Aging, 2002

Cognitive decline and diseases of aging

- Cognition is multiply determined
  - Brain injury and brain disease account for < 50% of variance in cross-sectional test scores
- Disease effects on cognitive decline are especially salient
- But disease still accounts for < 50% of heterogeneity in cognitive decline

Cognitive decline and major neuropathologies



Boyle et al, Ann Neurol, 2013

Mismatch between clinical outcomes and brain diseases

- Up to 30% of individuals who die without dementia meet neuropathologic criteria for Alzheimer's disease (AD)
  - Including individuals with severe neuropathology and normal cognition
- Why do people with the same brain disease vary in clinical presentation?

The case for reserve

- Reserve is a construct used to explain variability in the impact of brain injury on cognition
  - People with greater reserve are more resilient to brain injury associated with diseases of aging
- Modifiable life experience factors might contribute to cognitive reserve
  - Provide protection against deleterious effects of diseases of aging

The case for reserve

- Studies have shown that life experiences can alter brain structure
  - Animal studies show environmental complexity is associated with brain structure and complexity
  - Human studies have shown link between experience and brain
    - Increased hippocampal volume in taxi drivers after learning London layout
- Suggests biological and potentially modifiable mechanisms for reserve

The case against cognitive reserve

- Cognitive reserve is an abstract, inferred construct to explain complex relations between pathology and clinical outcomes
  - Often post-hoc explanation
- Reserve conceptualization might be unnecessarily complicated – “makes my head hurt”
- Direct measurement of reserve is lacking
- Inadequate construct validation

Approaches to measuring reserve

- Proxy variables
- Moderators of brain-cognition relations
- Residual reserve index

Measurement of cognitive reserve – Reserve proxies

- Most common approach has utilized presumed proxy variables
  - Education, SES, occupational attainment, crystallized intelligence
- Reserve is inferred in many studies to explain observed results
- Many studies simply assume that proxy variable measure reserve - proxy is labelled reserve

Limitations of proxy approach

- Construct validation of proxy as reserve has been inadequate
- If you know that a specific proxy variable (e.g. education) influences cognition in a specific way, why call it reserve?

Measurement of cognitive reserve – Moderators of brain-cognition relations

- Presumed reserve indicators are examined in regression models as moderators of brain effects on cognition
  - Reserve effect is captured by reserve indicator–by-brain interaction effect
- Variables that interact with brain variable provide empirical evidence of modification effect
  - Interaction effect is a strong empirical test of construct validity as reserve indicator

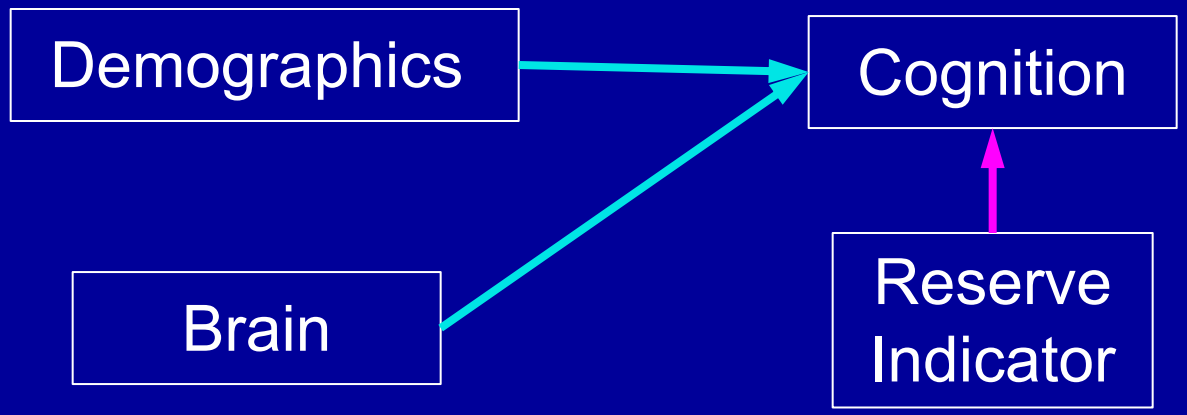
Limitations of moderator approach

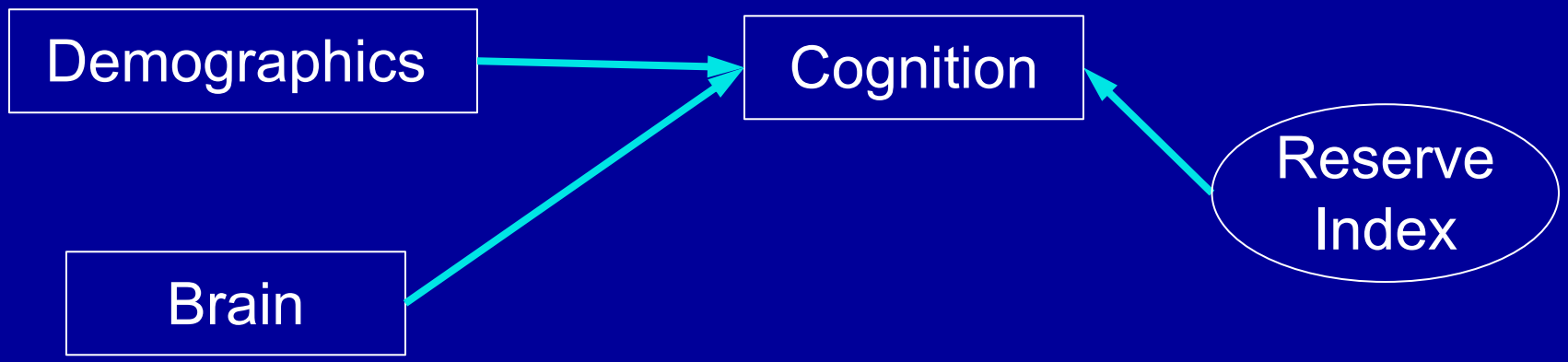
- Can effectively identify specific variables as indicators of reserve
- But does not separate “reserve” from ”non-reserve” components of those variables
- Don’t have measure of reserve that can be used as a target in studies to clarify mechanisms

Measurement of cognitive reserve – Residual reserve index

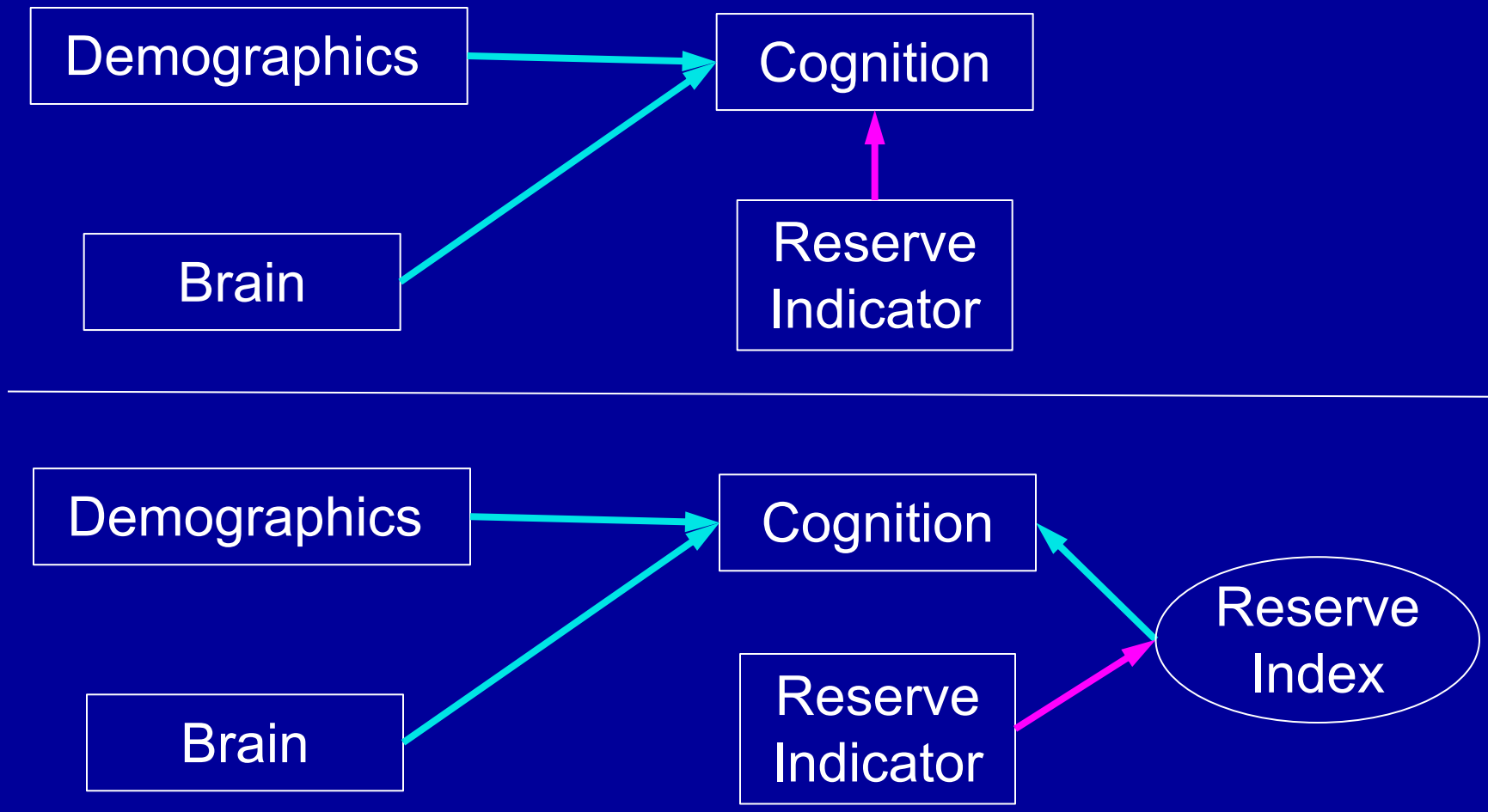
- Reserve is operationalized as the difference between observed cognitive function and cognitive function expected on the basis of brain (and demographic variables)
  - A person whose cognitive performance is better than expected has higher reserve
  - Provides a direct measure of reserve that can be interrogated in construct validity studies
- Provides a measure of reserve for studying variables associated with reserve

Regression and Residual Approaches to Identifying Reserve Indicators





Regression and Residual Approaches to Identifying Reserve Indicators



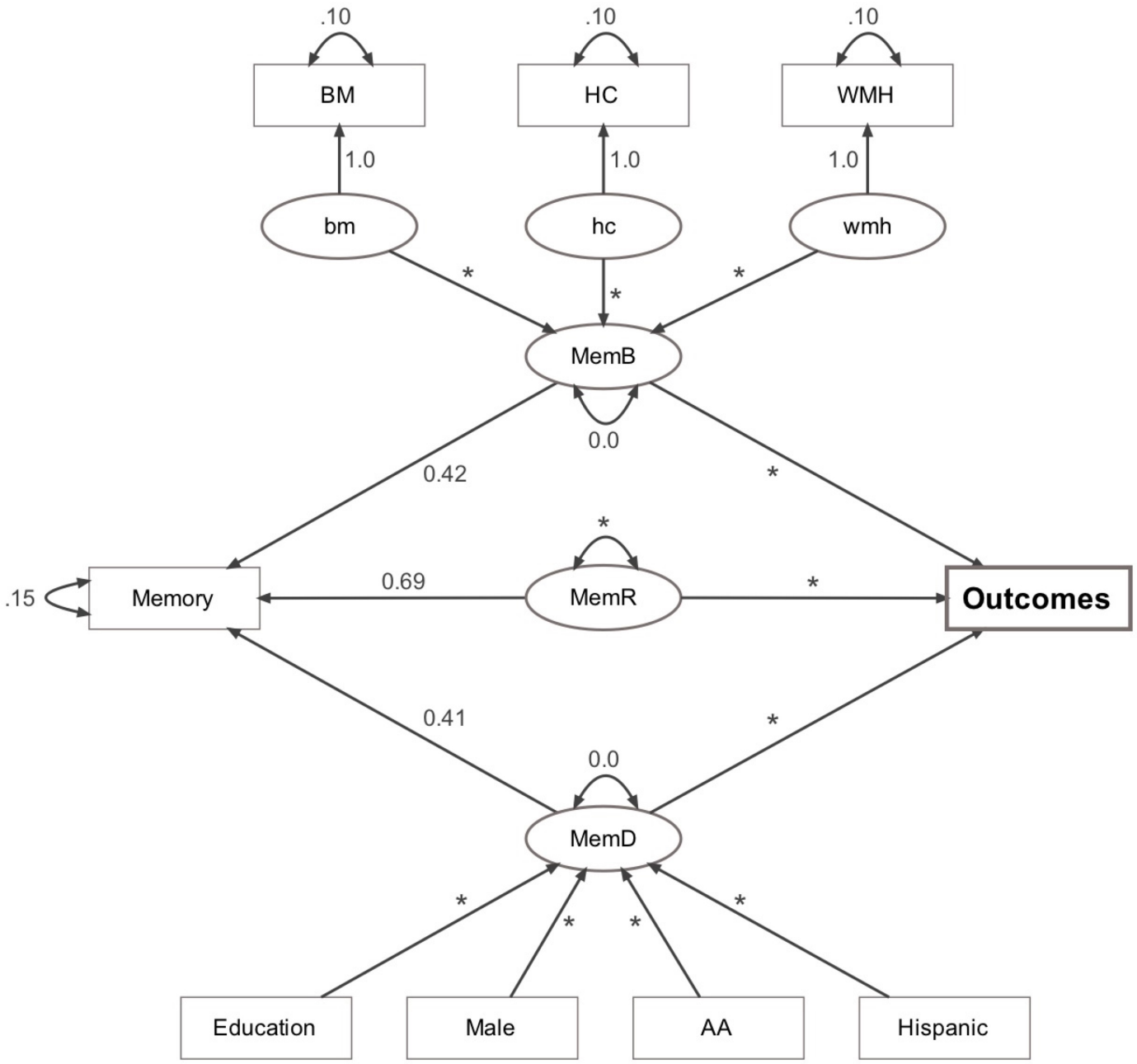
Residual reserve index – development and validation

- Goals
  - Operationalize reserve as residual cognition not explained by brain and demographic variables
  - Evaluate construct validity of this measure in relation to a-priori hypotheses about how a measure of reserve should behave
    - Construct validity is demonstrated if measure fulfills *a-priori* hypotheses

Reed et al., Brain, 2010

Hypotheses for construct validation

- Reserve should be lower in individuals with greater clinical impairment (Dementia < MCI < Normal)
- Reserve should be associated with other indicators of reserve
- Reserve should be associated with rate of future cognitive decline
- Reserve should moderate the brain effect on cognition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Outcomes
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Education
Male
AA
Hispanic

Sample

- 305 participants. 162 normal, 100 MCI, 43 dementia
- 101 African Americans, 78 Hispanics, and 126 Caucasians.
- Education M = 12.7 yrs (range 0-20)
- Age M = 74.5 yrs (range 60-93)
- Mean # evaluations = 3.5; 74% had 3 or more evaluations

Variance explained by memory components

- Mem-D ~ 20% of episodic memory variance
- Mem-B ~ 20% of episodic memory variance
- Mem-R ~ 50% of episodic memory variance

H1: Reserve is associated with global cognitive function: lower reserve -> lower cognitive status.

Component	Odds Ratio	95% CI	p
Mem-D	0.85	0.77 – 0.95	0.003
Mem-B	0.60	0.53 – 0.69	0.001
Mem-R	0.49	0.44 – 0.54	0.001

H1: Reserve is associated with global cognitive function:
reserve correlates with CDR sum of boxes

DV	Memory Component	Standardized Coefficient	p
CDR Sum	Mem-D	-0.09	ns
	Mem-B	-0.43	0.001
	Mem-R	-0.44	0.001

H2: Reserve index is positively associated with another possible index of reserve, reading ability

DV	Memory Component	Standardized Coefficient	p
Reading	Mem-D	0.45	0.001
	Mem-B	0.13	ns
	Mem-R	0.22	0.007

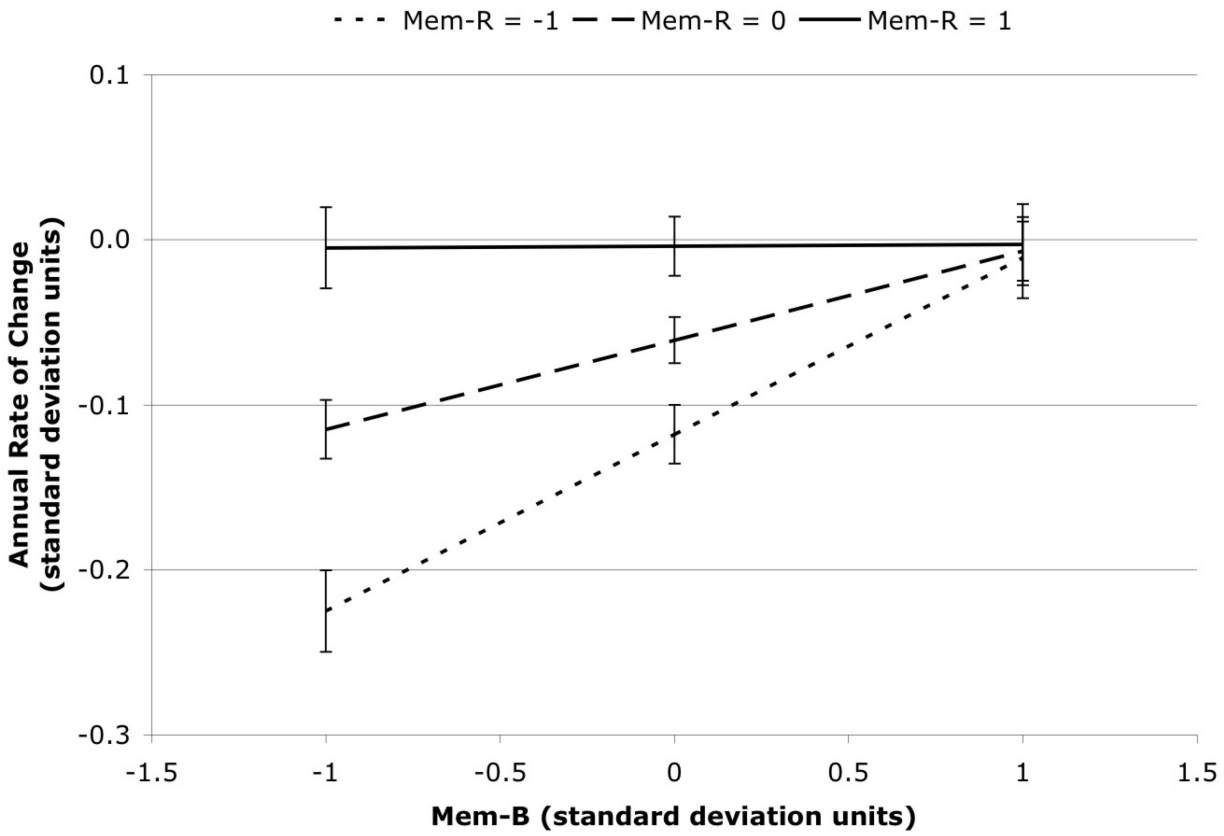
H3: Reserve modifies the risk of conversion to a worse cognitive syndrome
(normal – MCI, MCI – dementia)

Memory Component	Relative Risk Ratio (confidence interval)
Mem-D	1.58 (0.92 – 2.71)
Mem-B	0.19 (0.11 – 0.33)
Mem-R	0.27 (0.18 – 0.40)

H4: Higher Reserve is associated with slower decline in executive function

Memory Component	Random Effect	Parameter	Standard Error	p
Mem-D	baseline	0.364	0.043	0.001
Mem-B	baseline	0.180	0.031	0.001
Mem-R	baseline	0.329	0.034	0.001
Mem-D	change	-0.011	0.010	ns
Mem-B	change	0.050	0.010	0.001
Mem-R	change	0.047	0.011	0.001

H5: Reserve modifies the effect of brain atrophy on rates of decline in executive function



Summary - Construct validity studies

- Residual reserve index:
  - Associated with clinical status
  - Associated with education influenced proxy for reserve (independent of education)
  - Predicts cognitive decline in different domain
  - Modifies the effect of baseline brain on cognitive decline
- Satisfies a-priori criteria for reserve construct

Reserve, education, and midlife intellectual activity

Independent Variable	Estimate	SE	p
Education	-0.254	0.097	0.009
Life SES	0.107	0.079	0.177
Cognitive Activity - Age 40	0.313	0.124	0.011
Cognitive Activity - Current	0.280	0.092	0.002

Results show independent associations of life experience variables with residual reserve index defined as residual cognition not explained by comprehensive measures of neuropathology

Reed et al., J Int Neuropsy Soc, 2011

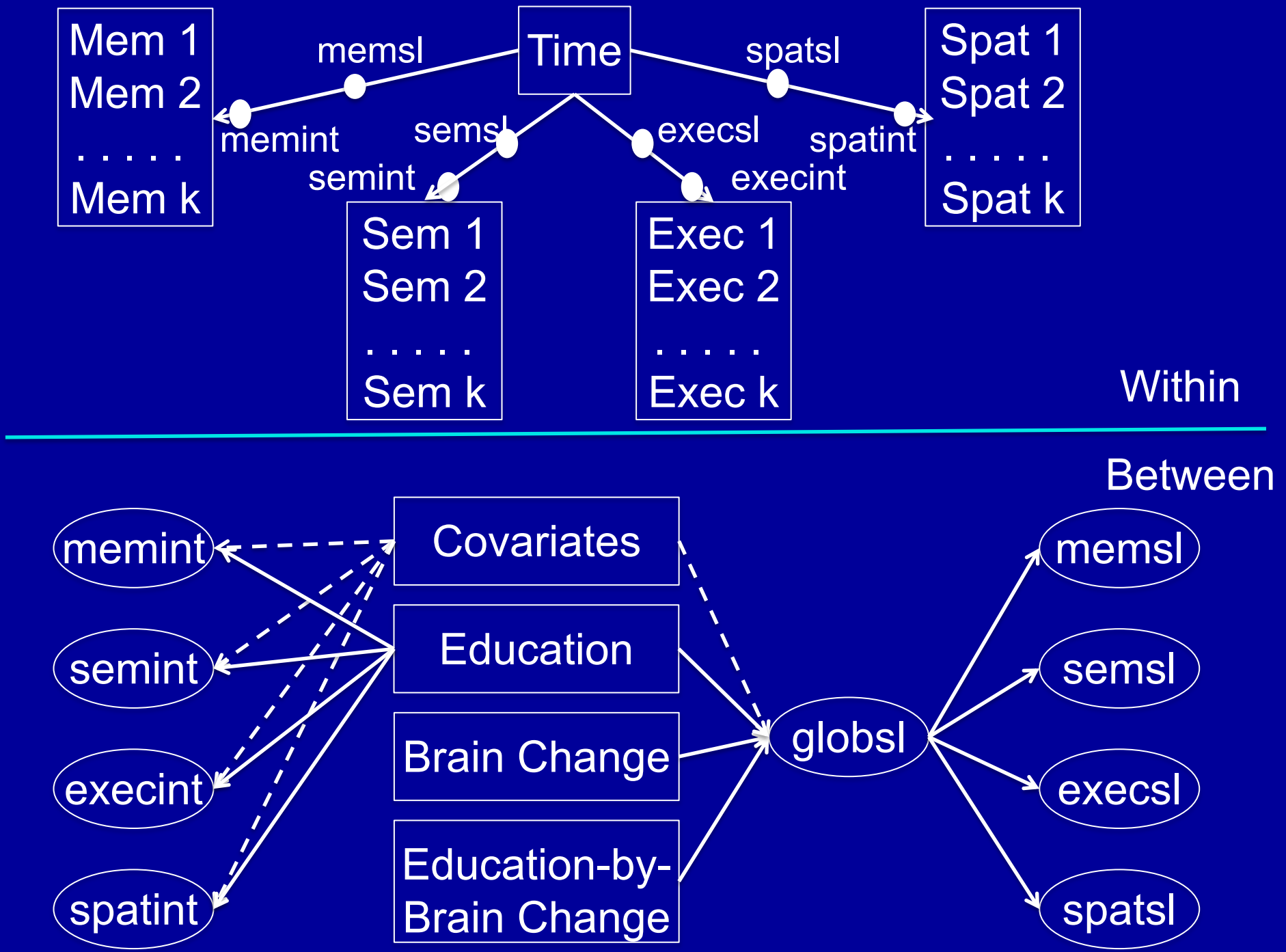
Education, brain change and cognition

- Goals
  - Directly test whether education modifies brain effects on cognition
  - Compare effects of education and residual reserve index

Mungas et al., Neurobiol Aging, 2018

Sample

- 454 participants. 231 normal, 166 MCI, 57 dementia
- 120 African Americans, 108 Hispanics, 126 Caucasians, 16 Other
- Education M = 13.0 yrs (range 0-20)
- Age M = 74.5 yrs (range 52-97)
- Mean # evaluations = 4.2; 86% had 3 or more evaluations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memint
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Covariates
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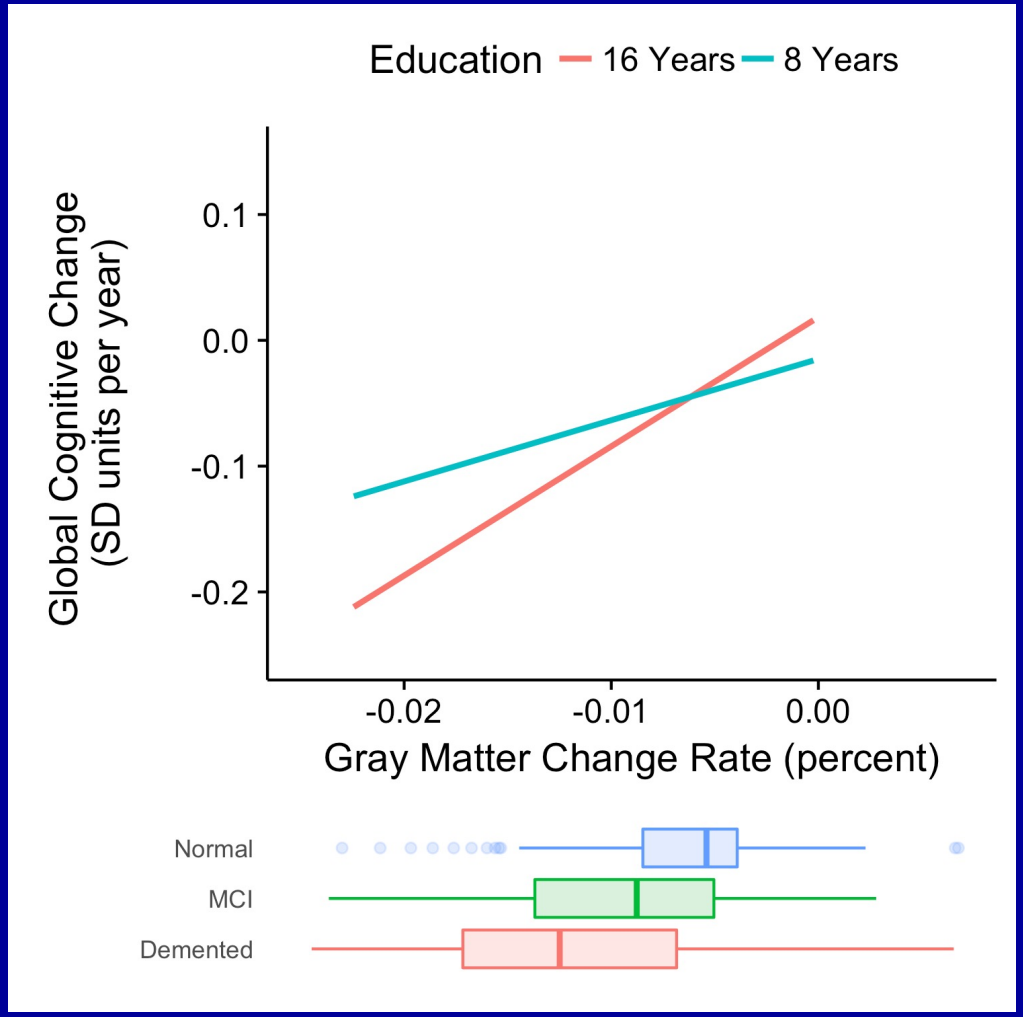
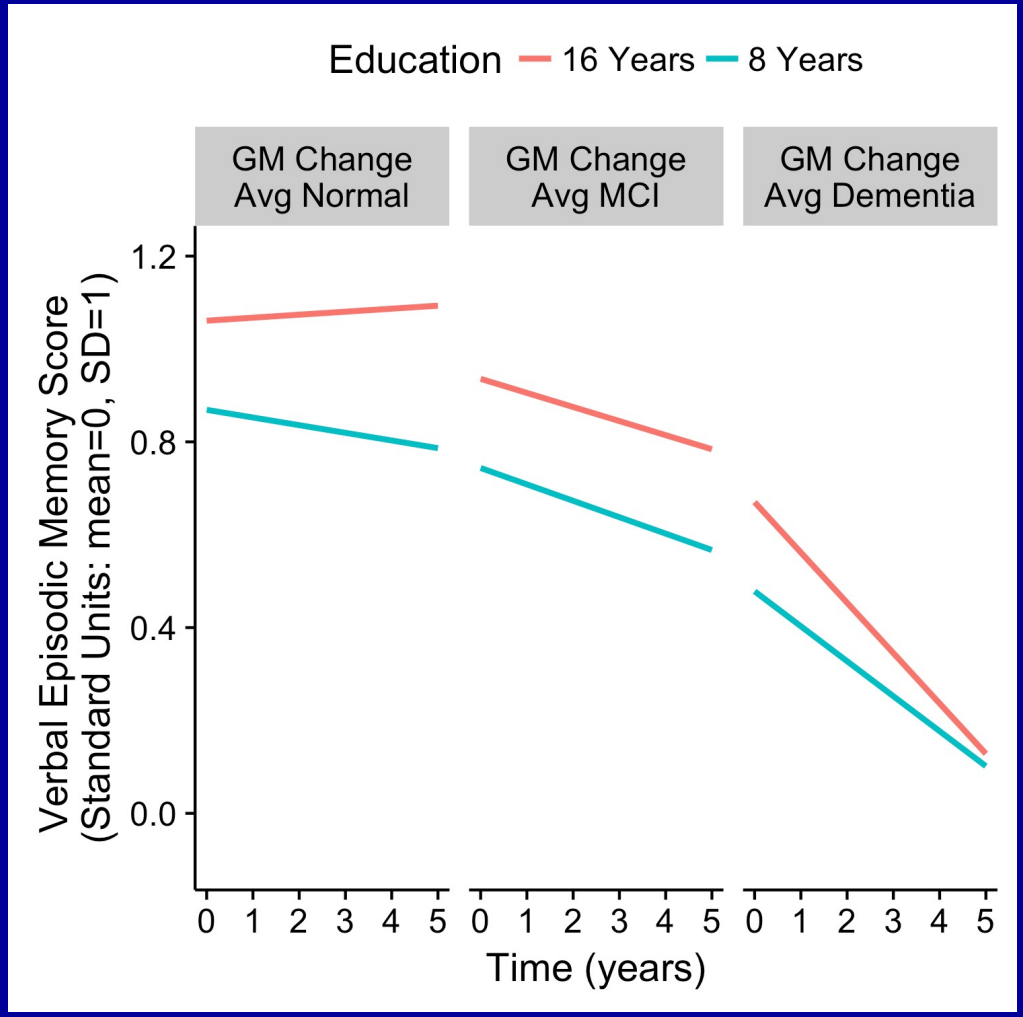
Education-by-gray matter change interaction effect on cognitive change



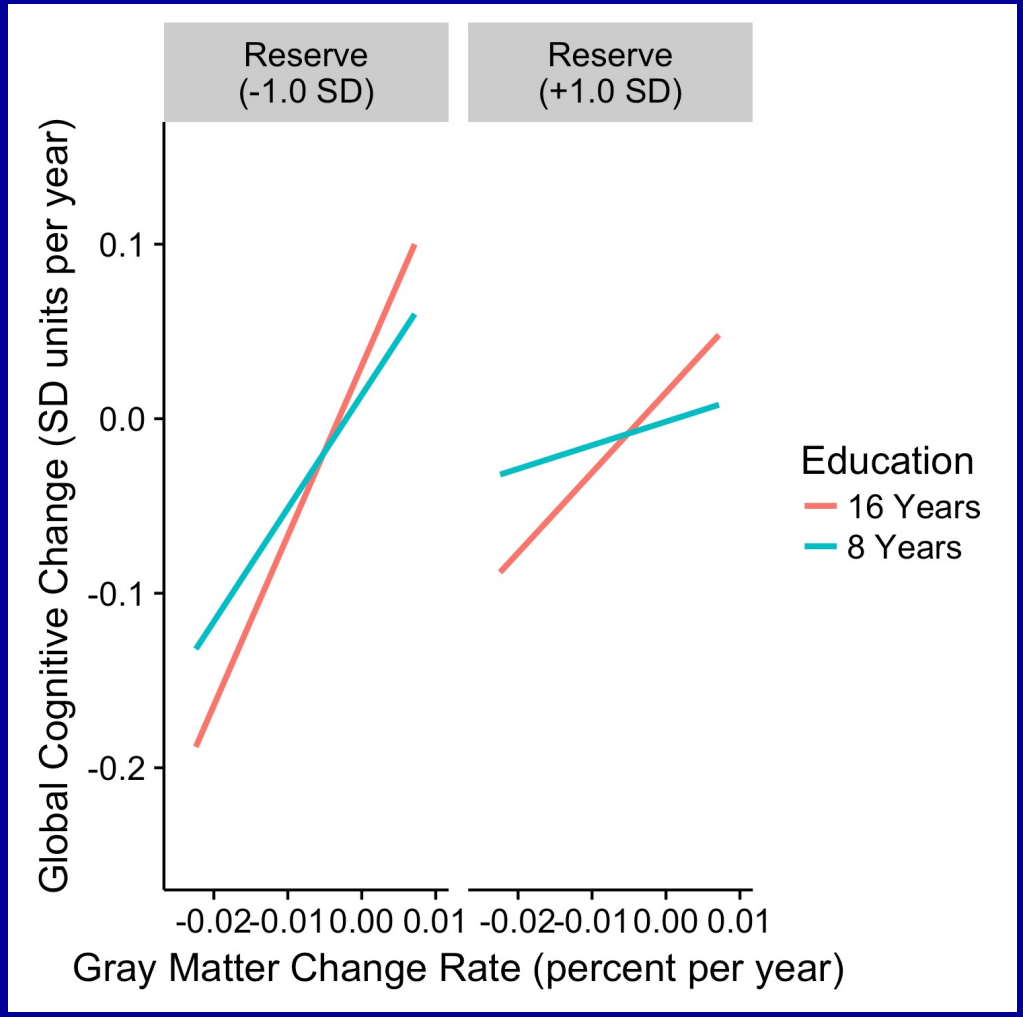
Education-by-gray matter change interaction effect - cognitive trajectories



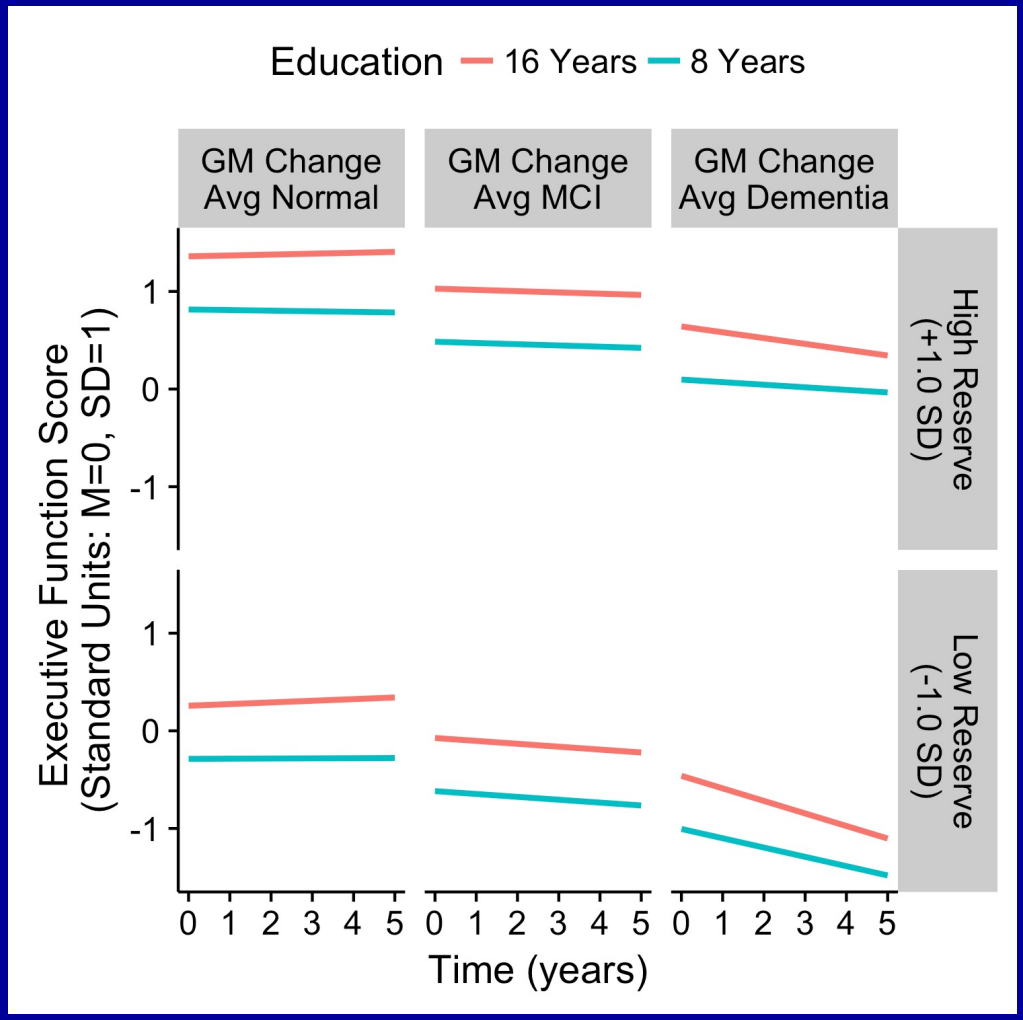
Summary of results

- Education amplified effect of gray matter atrophy on cognitive decline
- Education had a protective effect on cognitive decline in those with low brain degeneration
- Education effect on cognitive change became negative as brain degeneration increased
- Results consistent with research on education and dementia incidence
- Education is not a simple proxy for reserve

Education and reserve index interactions with gray matter change - slopes



Education and reserve index interactions with gray matter change - trajectories



Summary – Education, Brain Change, Reserve Index

- Education is associated with resilience to cognitive decline at low levels of brain degeneration, but this effect reverse as brain injury increases
- Reserve index is associated with greater resilience to cognitive decline across the full spectrum of brain atrophy
- Education may be useful as a proxy for reserve in the relative absence of brain degeneration
- Education level is not an effective measure of reserve as brain degeneration increases

Where do we go from here?

- Dynamic change in reserve
- Does reserve have different mechanisms in minorities
- Brain mechanisms of reserve – structural and functional
- What modifiable life experience variables build reserve

Is reserve a useful construct?

- It helps us explain heterogeneity in brain-cognition associations
  - In an abstract sense
- But reserve ultimately summarizes the effects of unknown variables that influence cognition
  - Refers to what we don't know
- Reserve will have less value as a construct as we better understand determinants of cognition

How can reserve be a useful construct?

- If we can measure it, we can study:
  - Modifiable life history variables that promote reserve
  - Brain mechanisms, genetic, and biological mechanisms
- Our ultimate goal is to replace the hypothetical construct “Reserve” with empirical knowledge of the mechanisms of cognitive decline

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  - AG031563 (Reed/Mungas)
  - AG031252 (Farias)

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Conceptual/Analytic Model of Reserve