Conceptual Models of Cognitive Reserve

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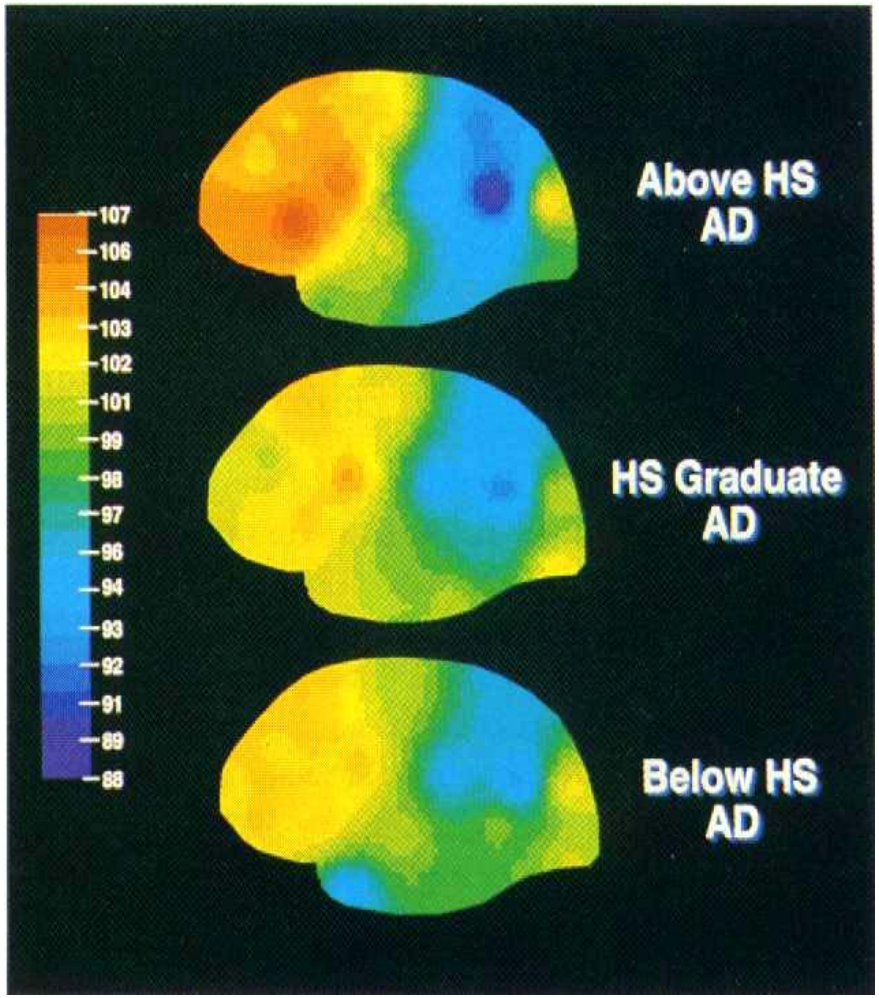
Education and rCBF



Controlling for clinical disease severity, there is an inverse relationship between education and a functional imaging proxy for AD pathology

Stern et al, Ann Neurol 1992

Education and rCBF

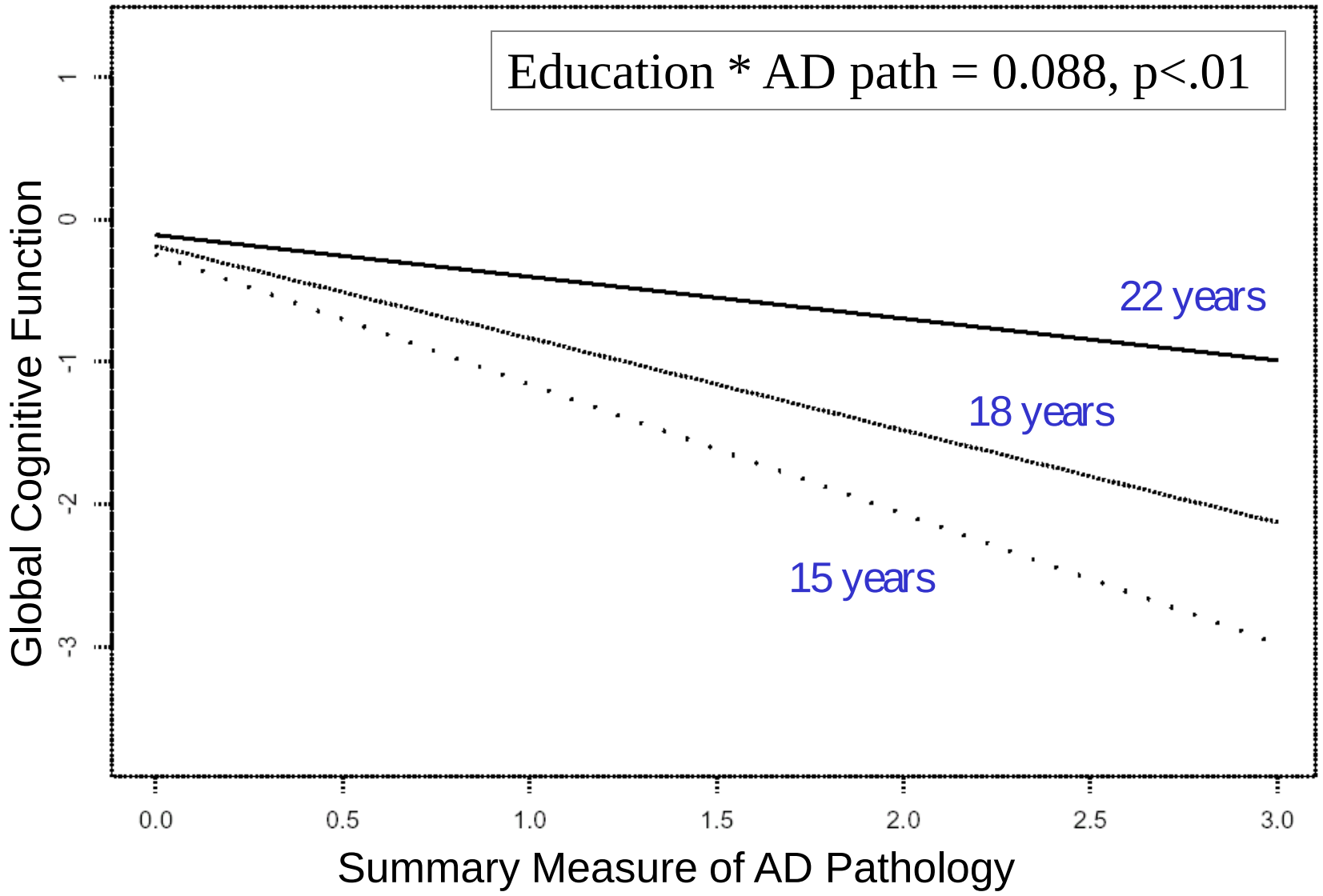
Stepwise multiple regression

Predictors of P3 detector flow:	R squared
mMMS, BDRS, age, age at onset, duration	.190
+ education	.304

Predictors of PI Index flow:	R squared
mMMS, BDRS, age, age at onset, duration	.187
+ education	.251

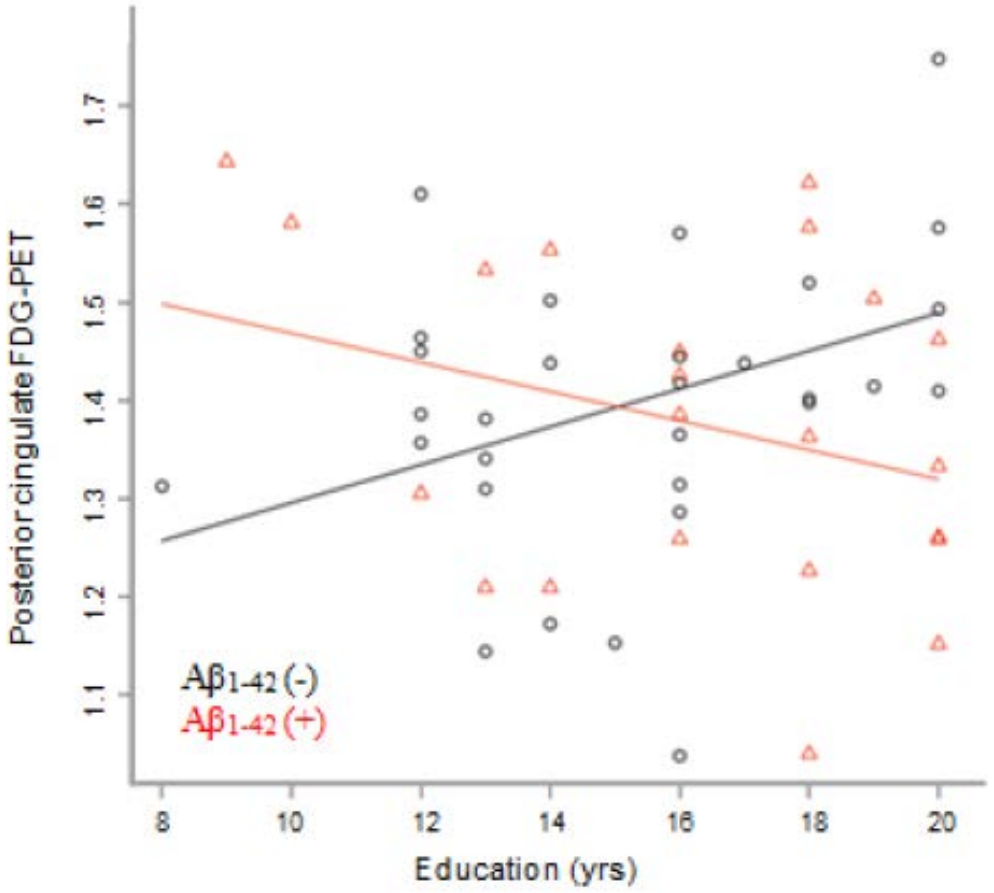
Stern et al, Ann Neurol 1992

Interaction of AD Pathology and Education



Bennett DA et al, Neurology 2003

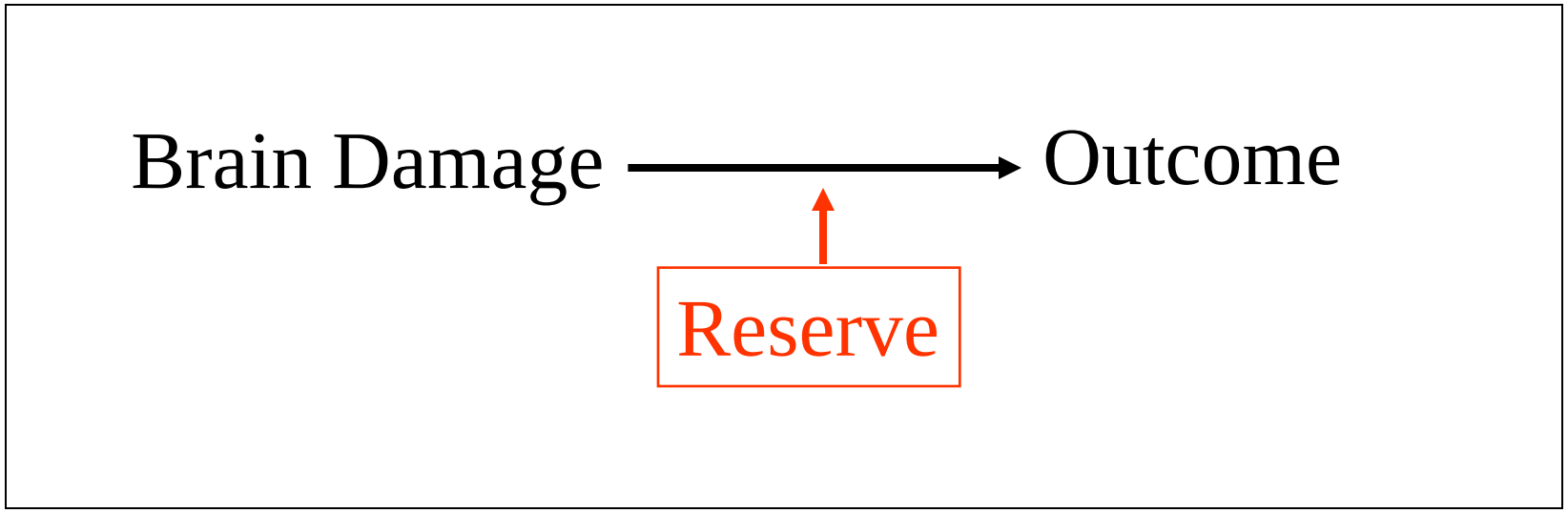
FDG PET in non-demented elders with low and high Aβ1-42 levels



Higher education was associated with *lower* FDG-PET in the Aβ1-42 (+) group, but with *higher* FDG-PET in the Aβ1-42 (-) group.

Ewers et al, Neurology, in press

What is Reserve?

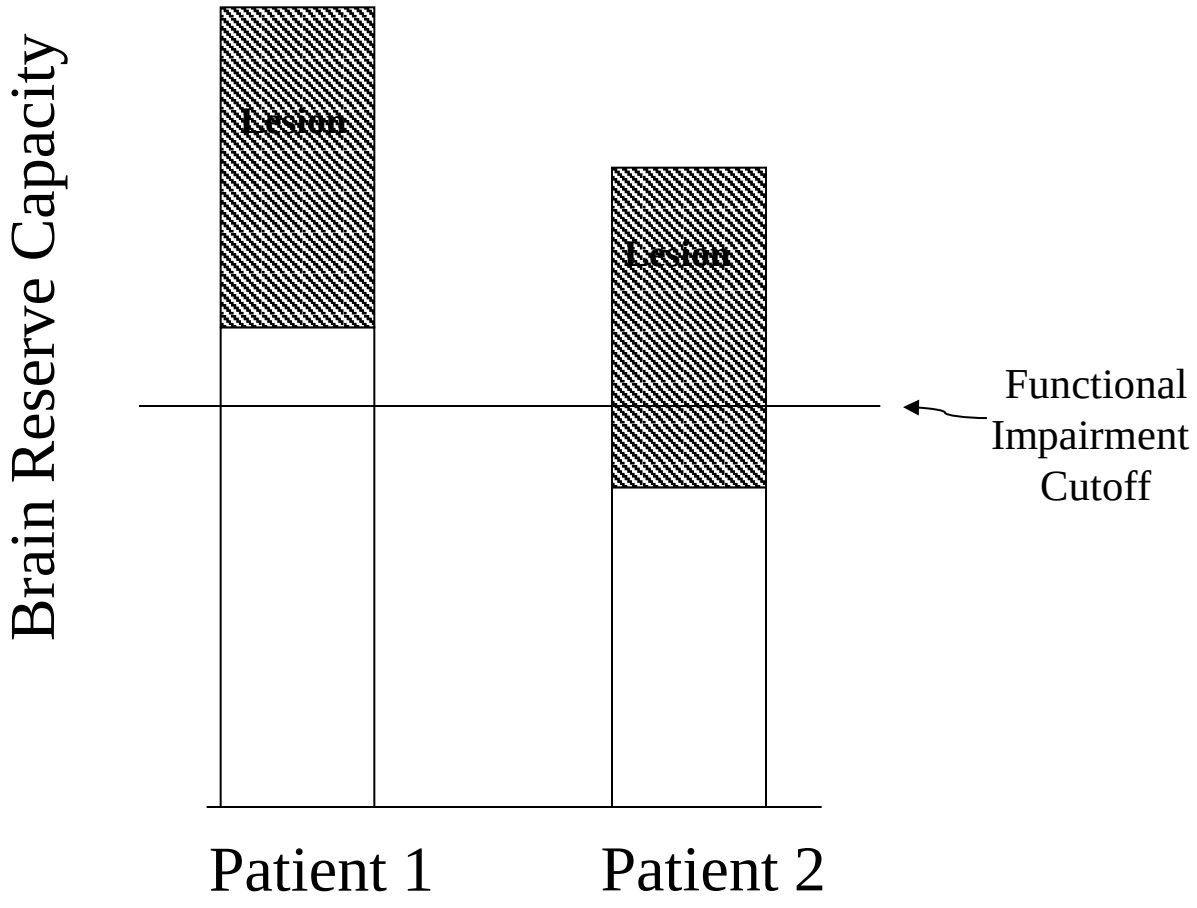


Reserve may explain the disjunction between the degree of brain damage and the clinical manifestation of that damage.

Mechanisms underlying reserve

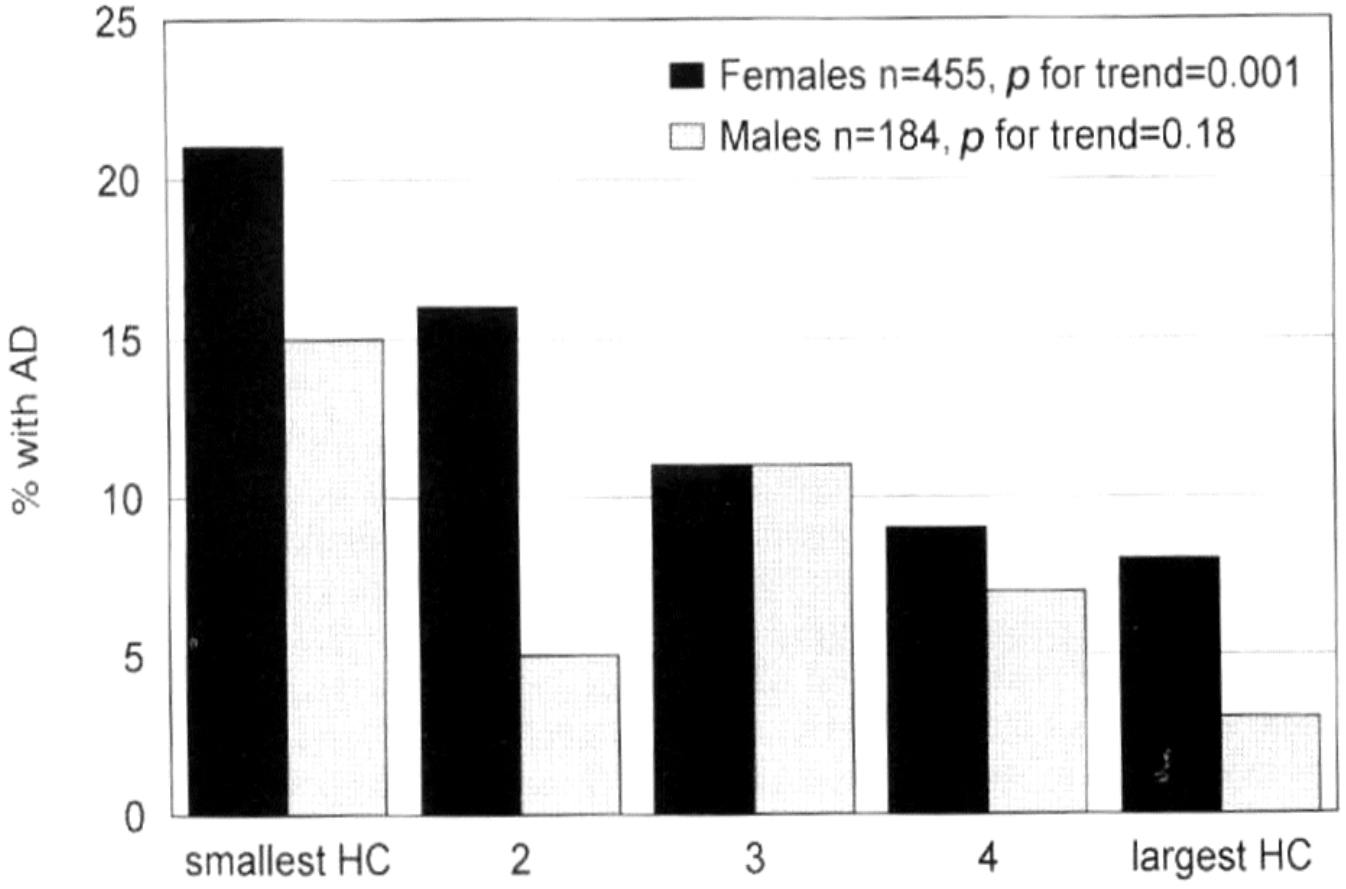
- Brain reserve:
  - More neurons/synapses to lose
  - Anatomic changes on the basis of experience
- Cognitive Reserve:
  - Resilience/plasticity of cognitive networks in the face of disruption

Passive, Threshold Model



Satz, Neuropsychology 1993

Brain Reserve: Association Between Head Circumference and Alzheimer's Disease



Schofield, et al, 1997

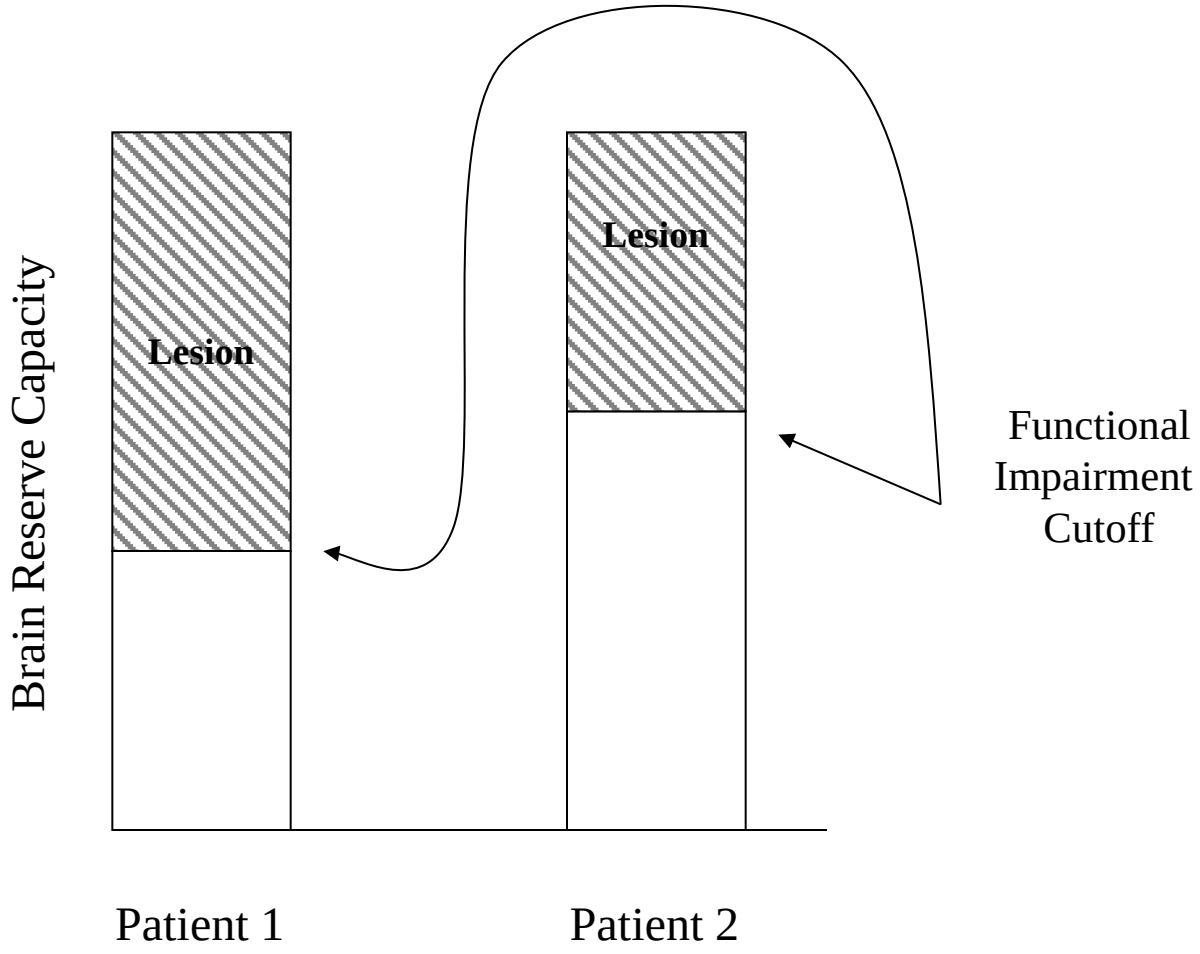
Brain Reserve is Not So Simple

The literature suggests that exercise and environmental stimulation can activate brain plasticity mechanisms and remodel neuronal circuitry in the brain.

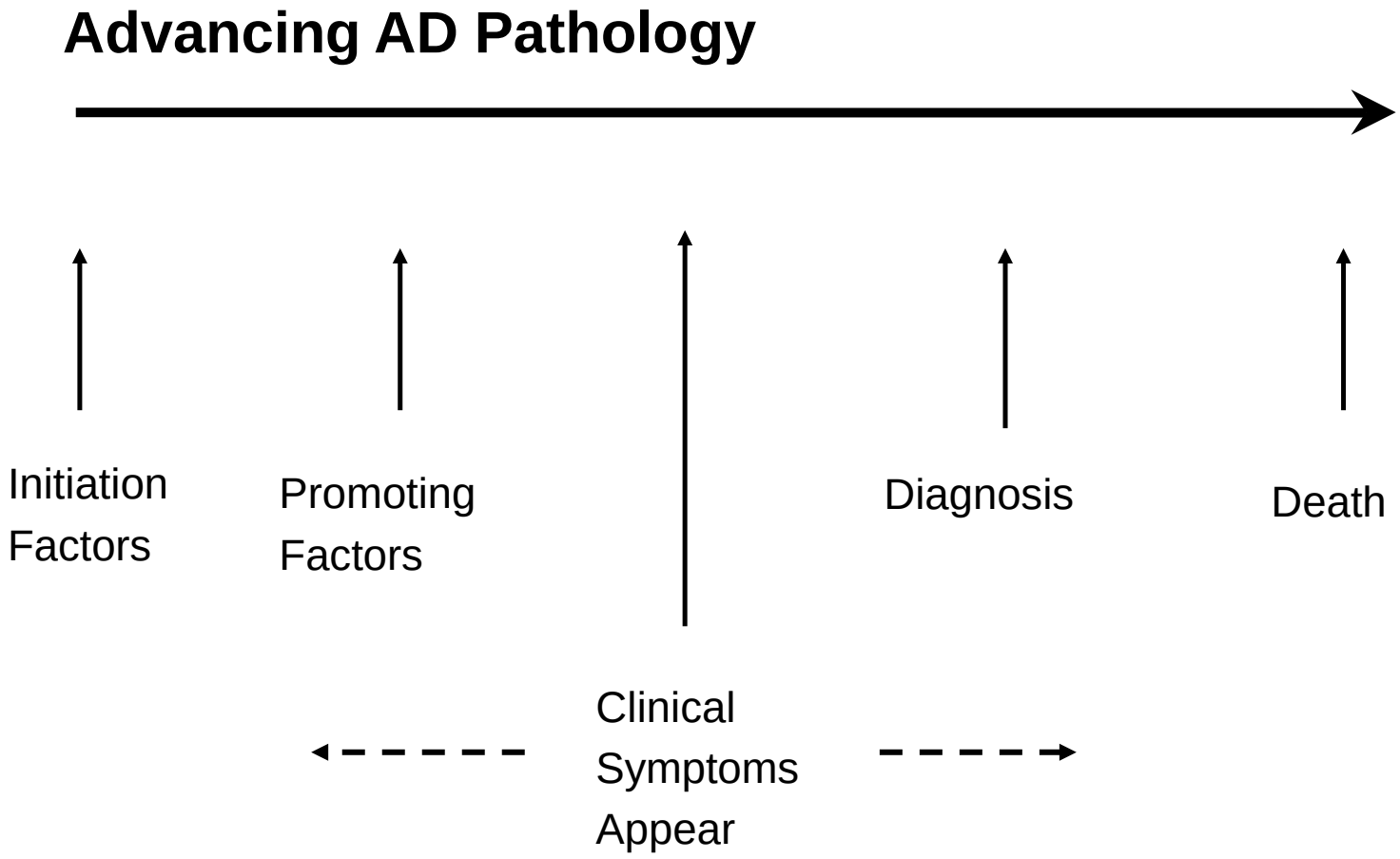
They can increase:

- Vascularization (exercise)
- Neurogenesis in the dentate
- Neuronal survival and resistance to brain insult
- Brain-derived neurotrophic factor (BDNF) -- benefits brain plasticity processes
- Serotonin, dopamine, IGF-1

Active Model (e.g. Cognitive Reserve)



Stern, JCEN 2002


Advancing AD Pathology
Initiation Factors
Promoting Factors
Clinical Symptoms Appear
Diagnosis
Death

Incident Dementia in The Washington Heights Study

Group	N	Incident Cases	Relative Risk	95% CI
Low Education	264	69	2.02	1.3-3.1
High Education	318	37	1	
Low Occupation	327	71	2.25	1.3-3.8
High Occupation	201	17	1	

Stern et al, JAMA 1994

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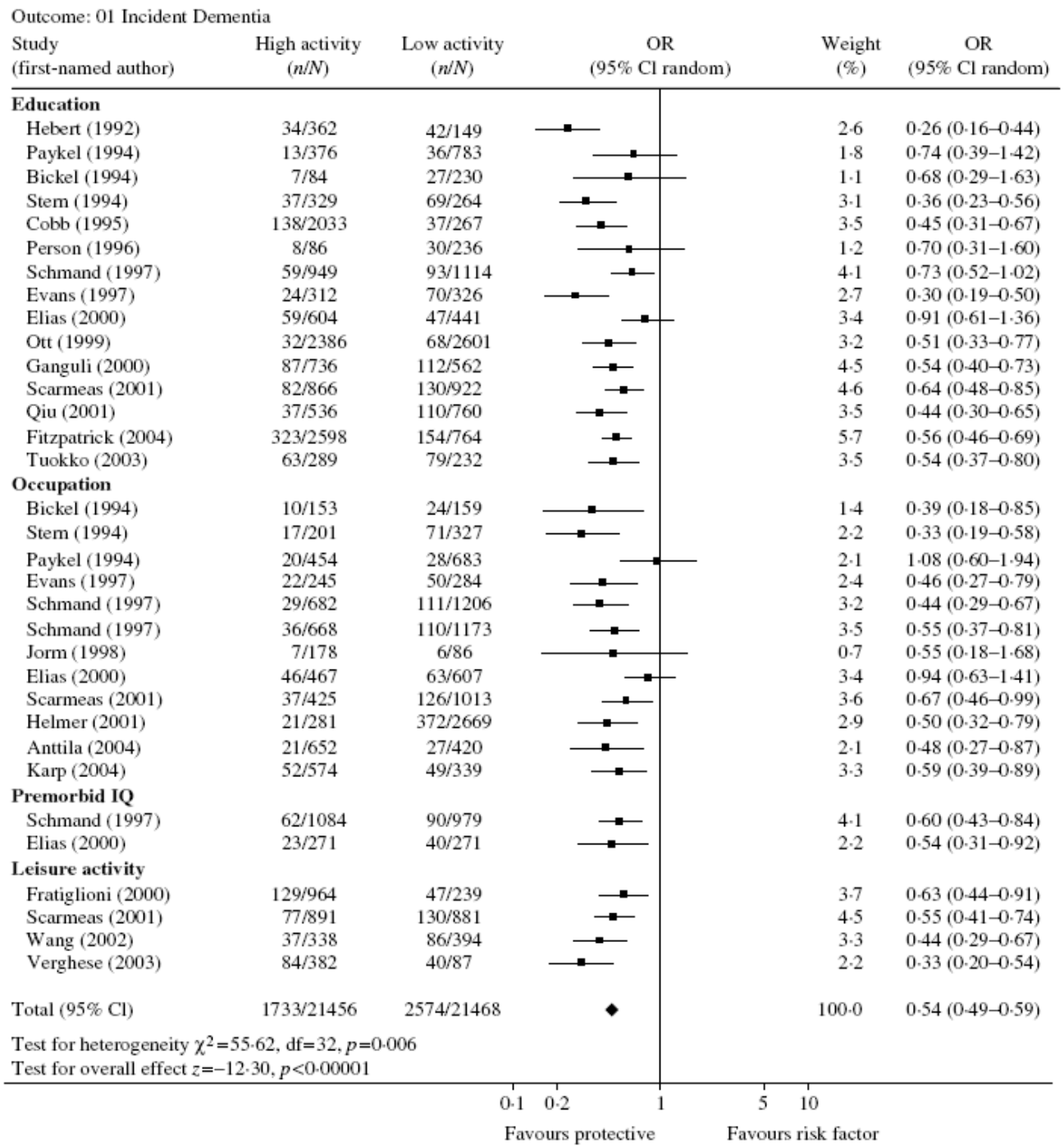
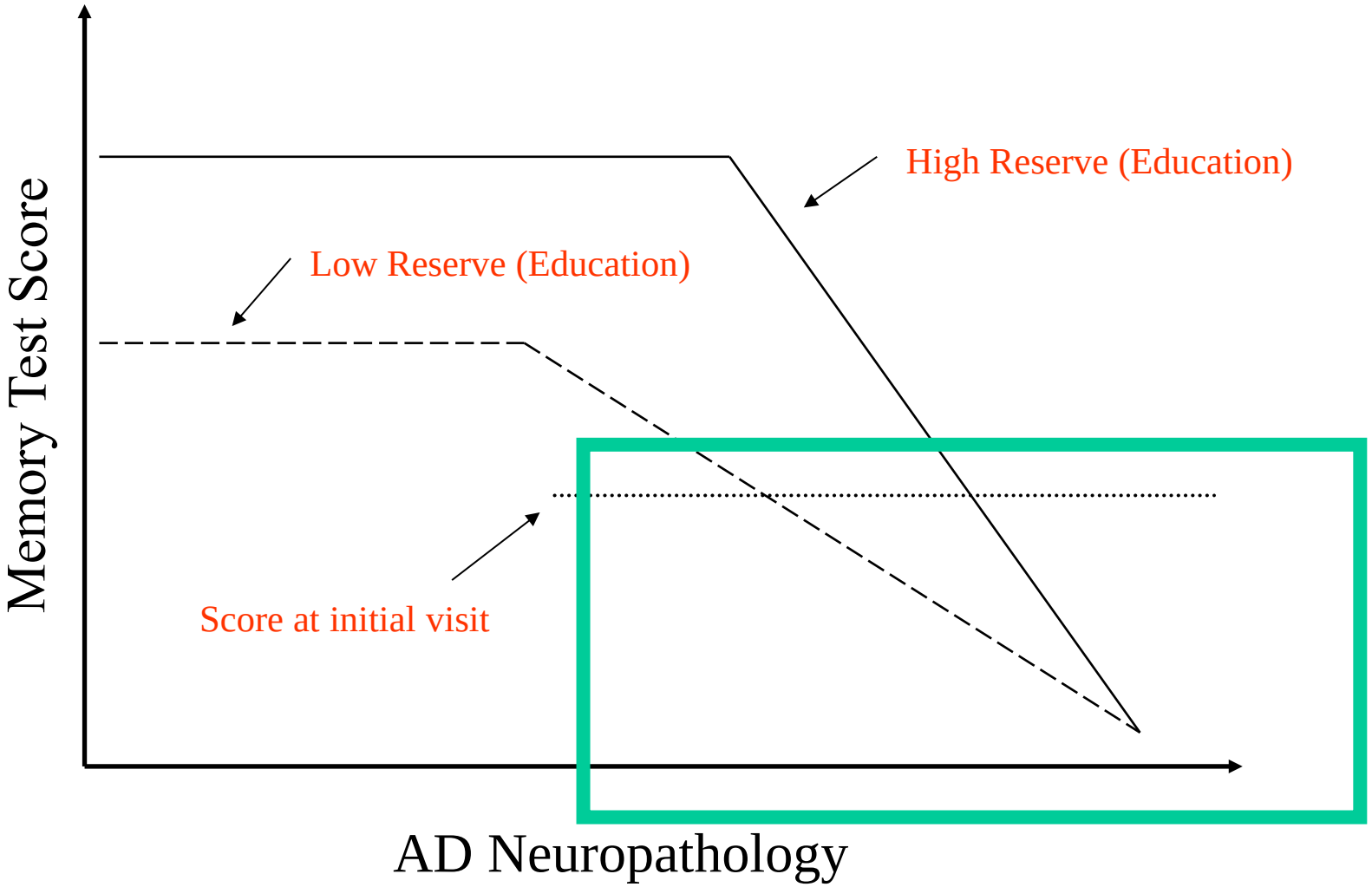
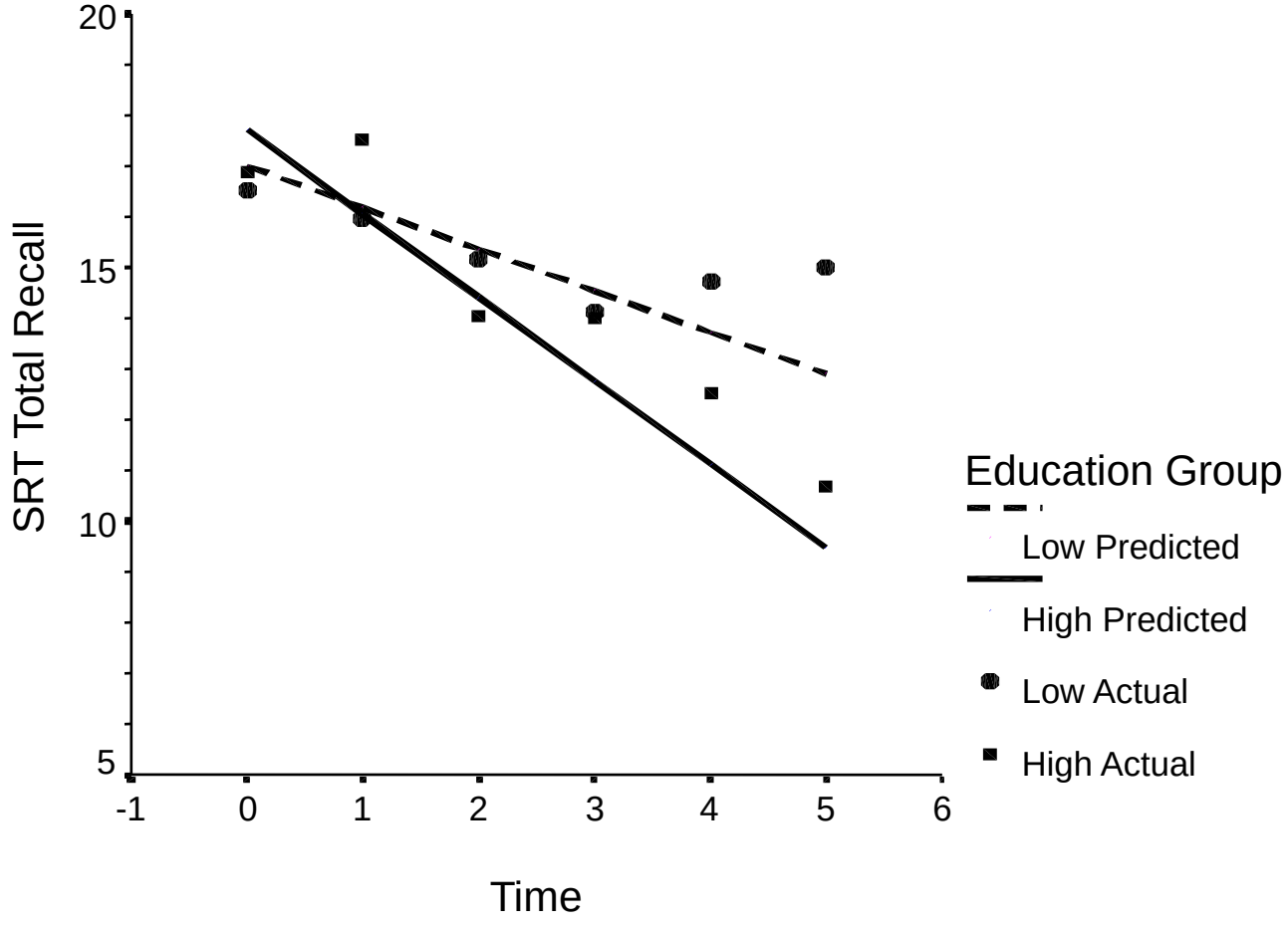


Valenzuela & Sachdev, Psychological Medicine, 2005

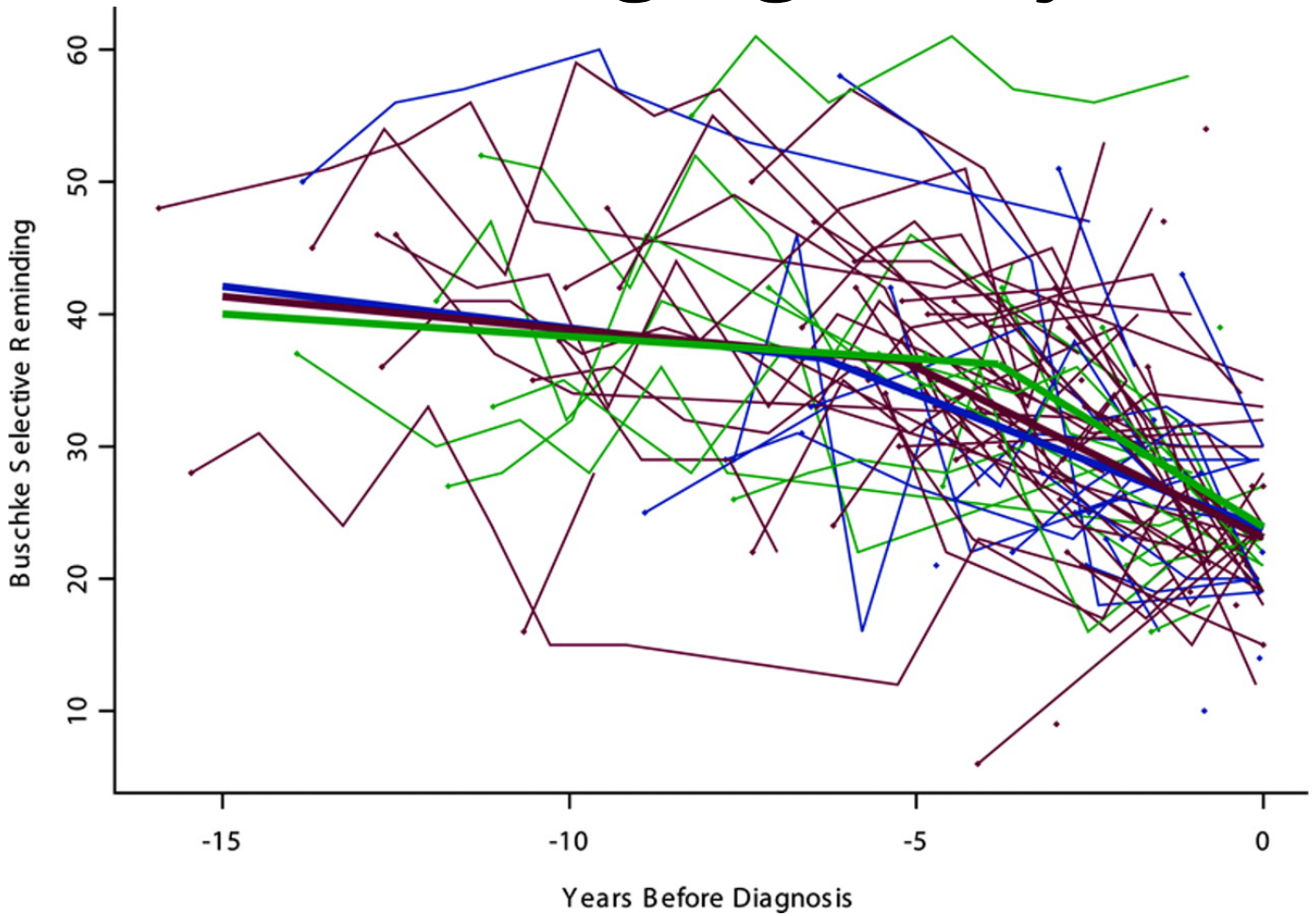

Memory Test Score
High Reserve (Education)
Low Reserve (Education)
Score at initial visit
AD Neuropathology

More rapid memory decline in AD patients with higher educational attainment



Stern et al Neurology 1999;53:1942-1957

Bronx Aging Study



Blue indicates less than 7 years education (32 Ss), red indicates 8 to 11 years (64 Ss), and green indicates 12 or more years education (21 Ss).

Hall, C. B. et al. Neurology 2007

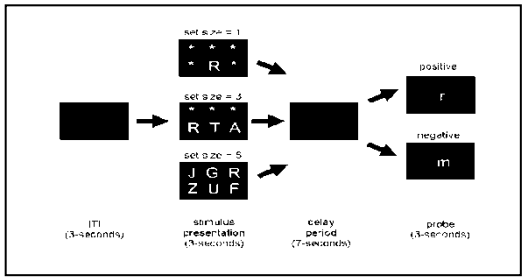
Cognitive Reserve, Aging and AD

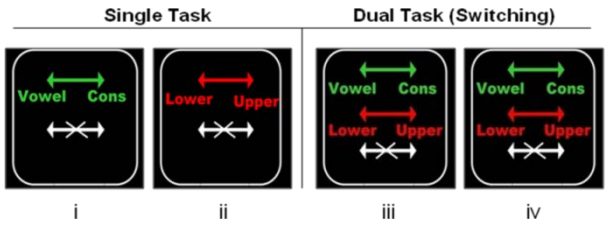
- Two individuals who appear the same clinically, whether demented of non-demented, can have widely divergent levels of underlying age-related neural changes or AD pathology.
- Thus, the clinical diagnosis of normal aging, MCI or AD may be accompanied by very minimal pathology or more than enough to meet pathological criteria for AD.
- Measuring CR therefore becomes an important component of diagnosing and characterizing aging and dementia.

Using Functional Imaging to Study CR

- Goal: To understand how cognitive reserve may be neurally implemented.
  - Emphasis on networks mediating CR, not task performance
- Working hypothesis: CR operates through individual differences in how tasks are processed in the brain.
- Basic approach: Challenge participants with a demanding task and investigate differences in task-related activation between individuals with high and low CR.
- Assumption: Because CR modulates most aspects of cognitive performance in the presence of pathology, this approach should work with most demanding tasks.

Current Study of the Neural Implementation of Cognitive Reserve





Task-related network expression

Volume
Cortical Thickness
WMH Burden
WM Tract integrity
Resting CBF
Resting connectivity
Amyloid burden

Age-or AD-related pathology

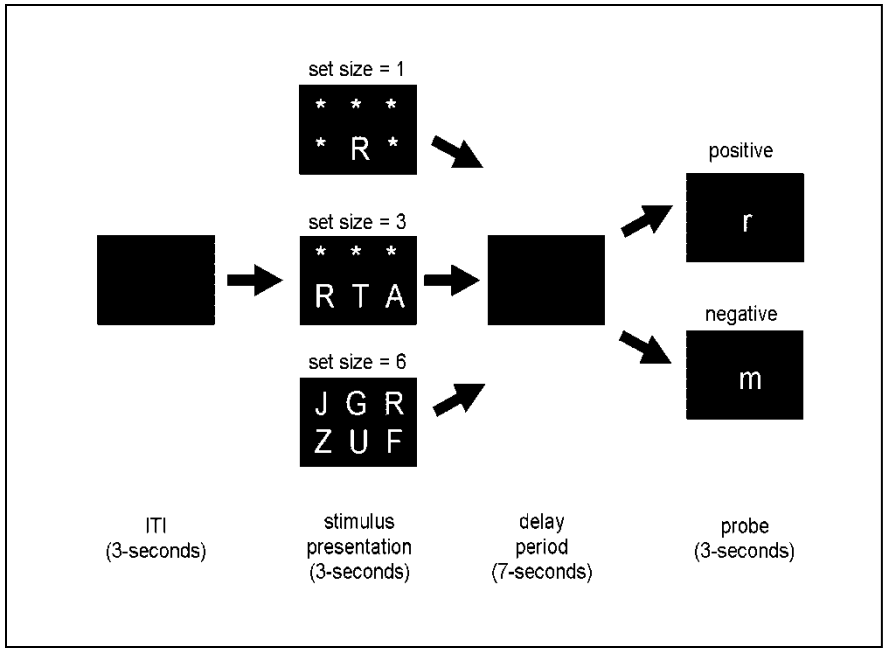
Task or NP performance, Clinical Outcome

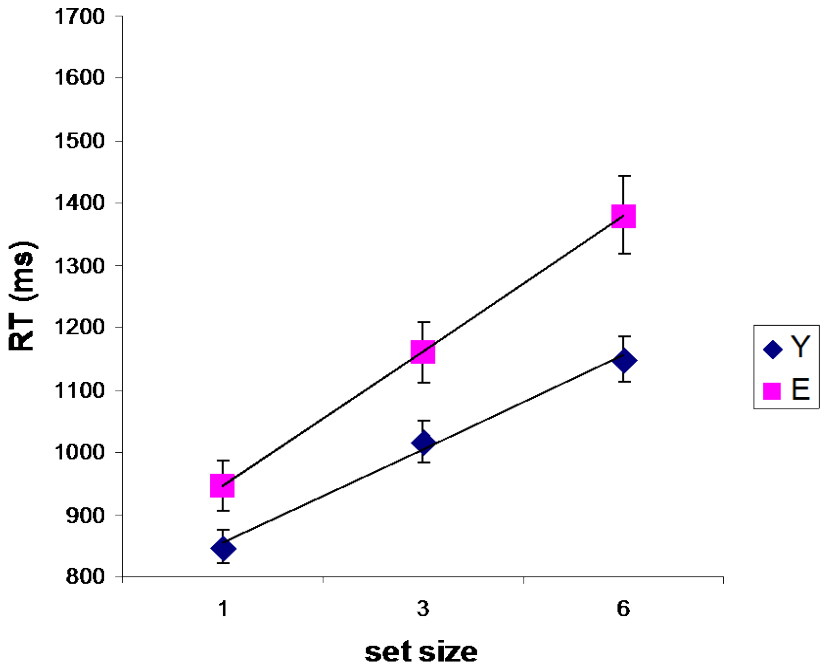
Activation Task Performance
Cognitive Domains
Function / ADL
Cognitive decline over time/
Incident MCI/AD

Measured CR *or* CR-specific network

Measured IQ
Education/Literacy
Leisure Activity
CR Network

Modified Sternberg Task



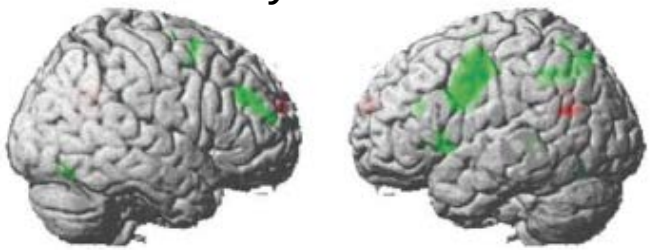


”Load-related” activation: the change in activation as set size increases

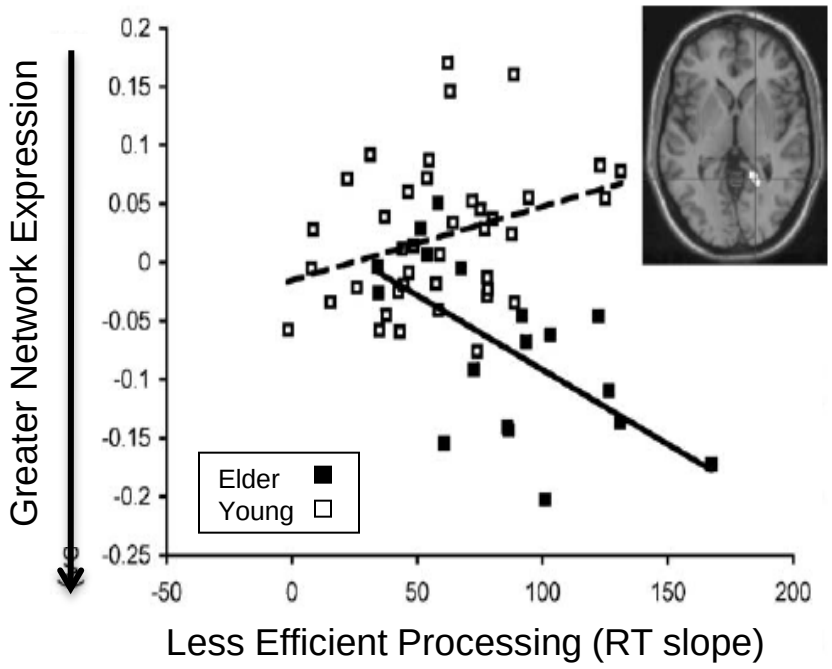
We focus on load-related activation because CR might be more related to the coping with increases in task demand than to task-specific features.

Load-dependent Activation During Retention

Primary Network



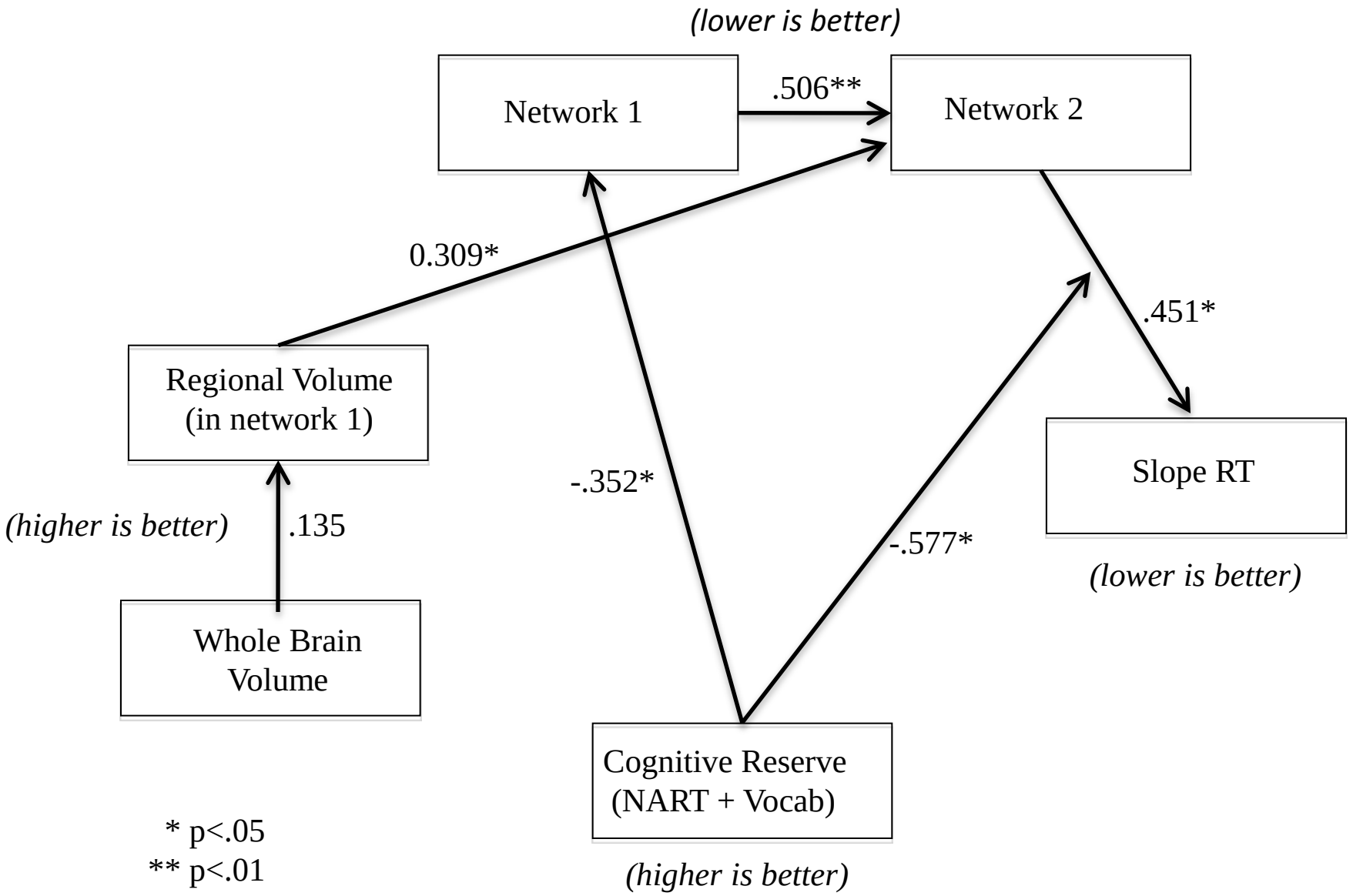
Secondary Network



- Two patterns were expressed during retention
- The first pattern was expressed by young and old.
- The second pattern was expressed primarily by the elders
- Greater expression of pattern 2 was associated with poorer performance by the elders
- When there was brain atrophy in left SMA in pattern 1, pattern 2 expression increased, suggesting pattern 2 maintains function when pattern 1 is damaged

Zarahn et al., Neurobiol Aging 2007
Steffener at al., Brain Imaging and Behavior 2009

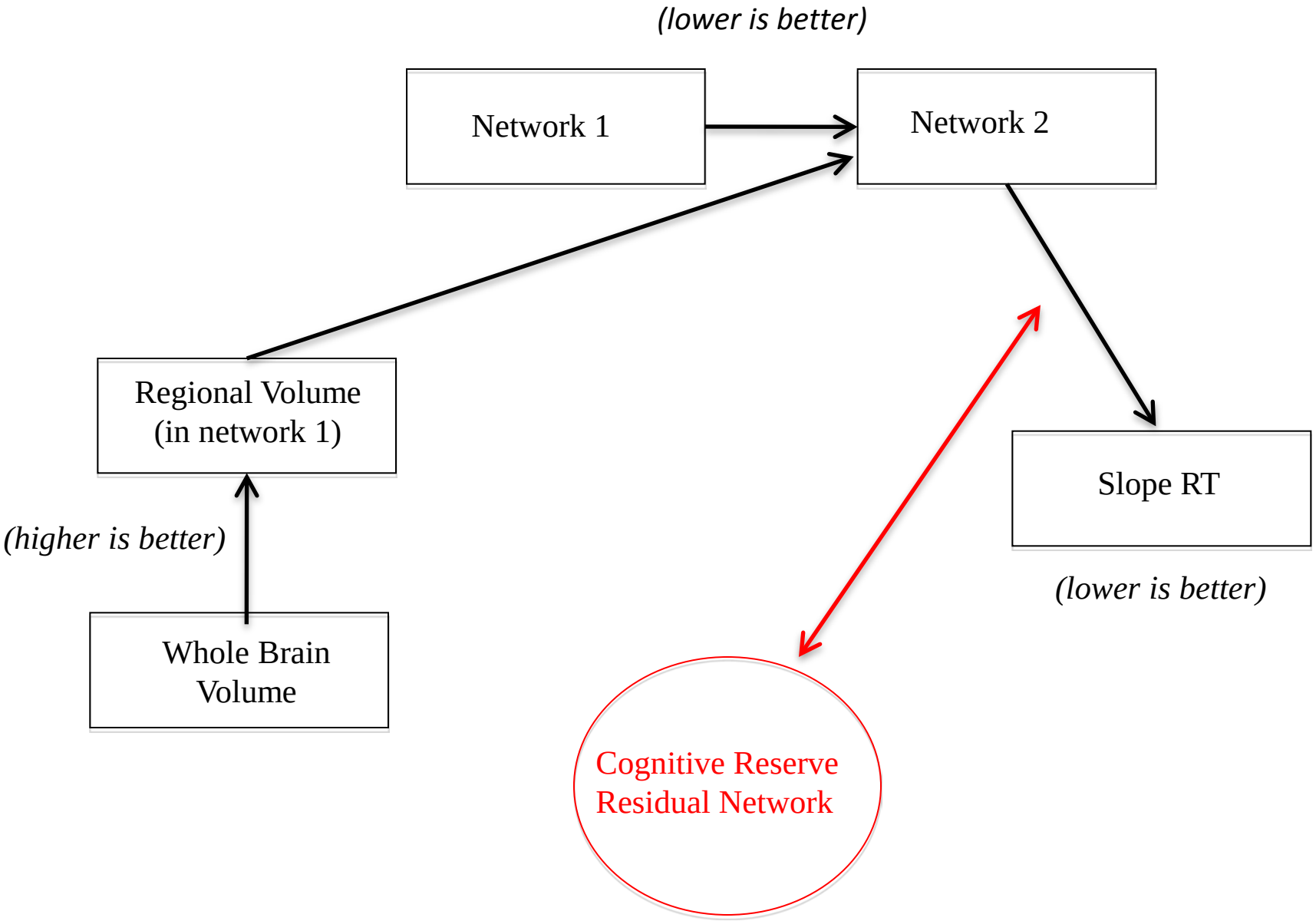
Path Analysis Using Scheme for Studying CR



* p<.05
** p<.01

Steffener at al., Brain Imaging & Behavior, 2010

There must be a CR Network that is independent of observed task-related activation



Conclusions

- Epidemiologic and imaging evidence support the concept of cognitive reserve
- Reserve is malleable: it is influenced by aspects of experience in every stage of life
- Imaging studies can help us understand the neural implementation of cognitive reserve
- The concept of cognitive reserve is applicable to a wide range of conditions that impact on brain function at all ages
- Influencing cognitive reserve may delay or reverse the effects of aging or brain pathology