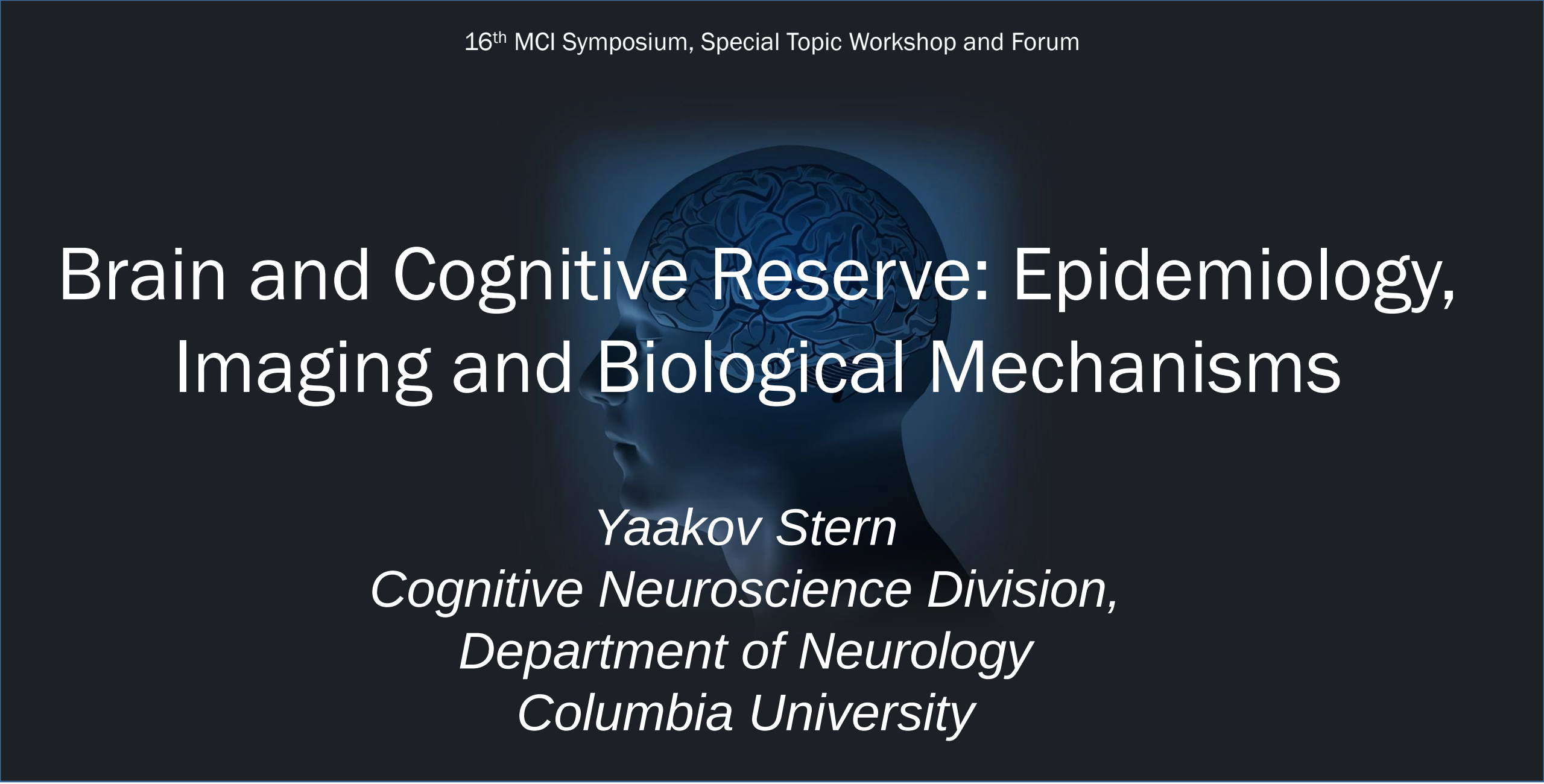

Brain and Cognitive Reserve: Epidemiology, Imaging and Biological Mechanisms

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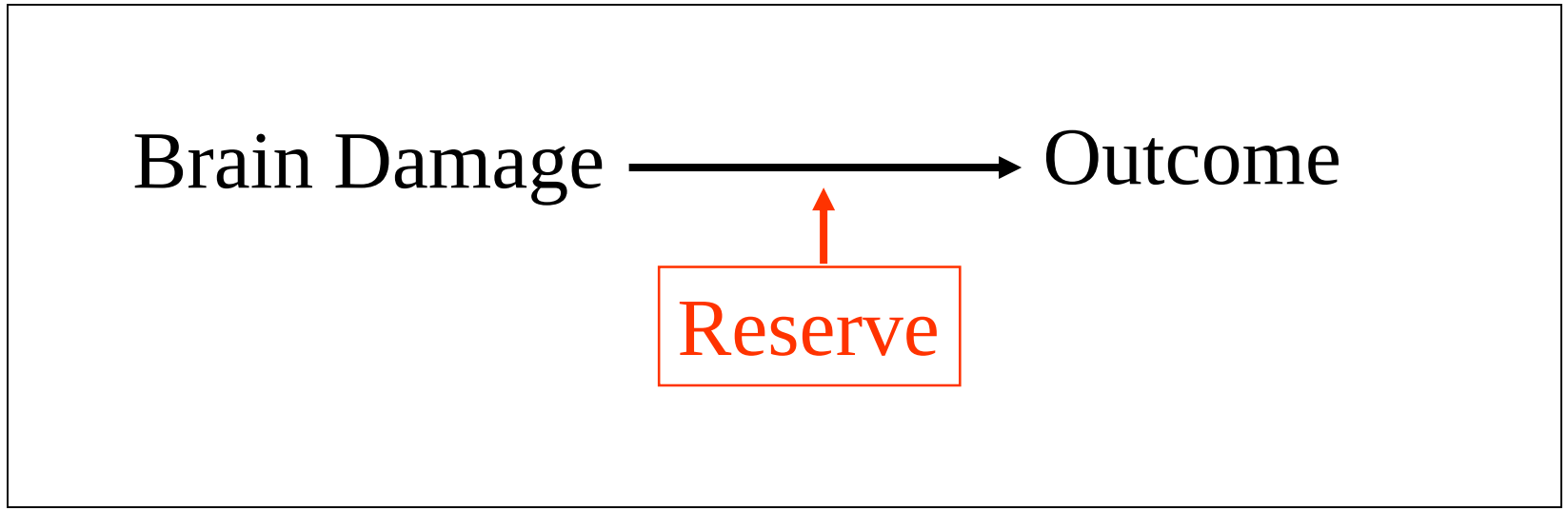
DISCLOSURES

- Supported by the National Institute on Aging
- Consulting: Eli Lilly, Axovant, Takeda, AbbVie
- Other funding: California Walnut Commission

What is reserve?



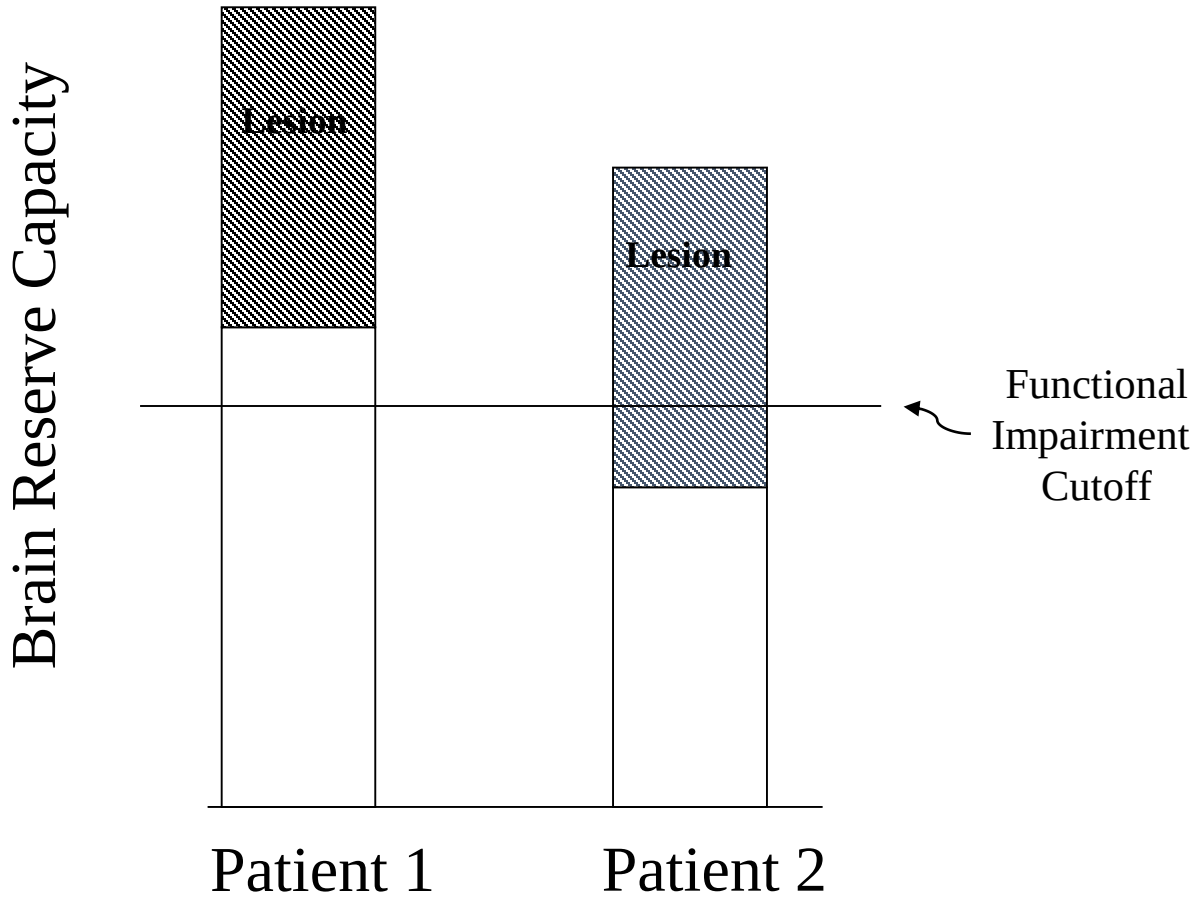
Reserve may explain the disjunction between the degree of brain damage and the clinical manifestation of that damage.

Mechanisms underlying reserve

- Brain reserve:
  - More neurons/synapses to lose
  - Brain maintenance: Direct effect of lifestyle/ activities on the brain

- Cognitive Reserve:
  - Resilience/plasticity of cognitive networks in the face of disruption

Passive, threshold model of reserve



Satz, Neuropsychology 1993

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
- Brain volume/Cortical thickness
- Neuronal survival and resistance to brain insult
- Brain-derived neurotrophic factor (BDNF) -- benefits brain plasticity processes

Feature Review

Memory aging and brain maintenance

Lars Nyberg[1,2,3,7], Martin Lövdén[4,5,6], Katrine Riklund[1,3], Ulman Lindenberger[5] and Lars Bäckman[4]

- Relative lack of brain pathology is the biggest contributor to heterogeneity of cognitive aging
- Various lifestyle factors contribute to resisting the advent of pathology

- Brain maintenance could account for the current level of brain reserve

Trends in Cognitive Sciences May 2012, Vol. 16, No. 5

Relationship between stair climbing and “brain maintenance”

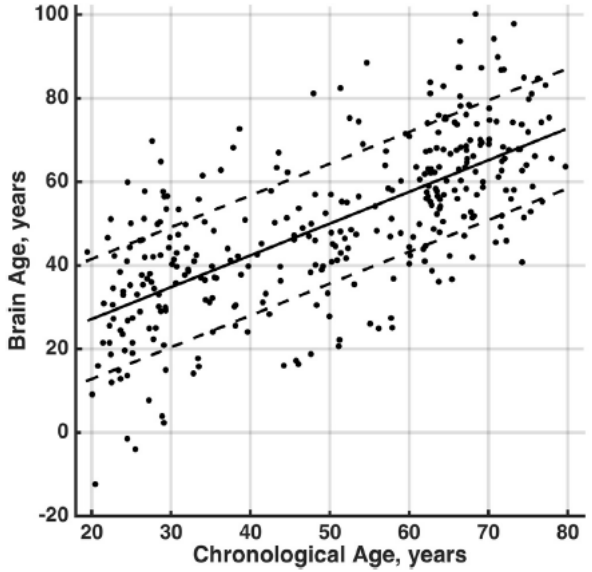


Fig. 1. Scatter plot of chronological age versus brain age in years after adjusting for nuisance variables. The solid line is the regression fit between the 2 variables, and the dashed lines are 1 standard deviation away from the regression fit.

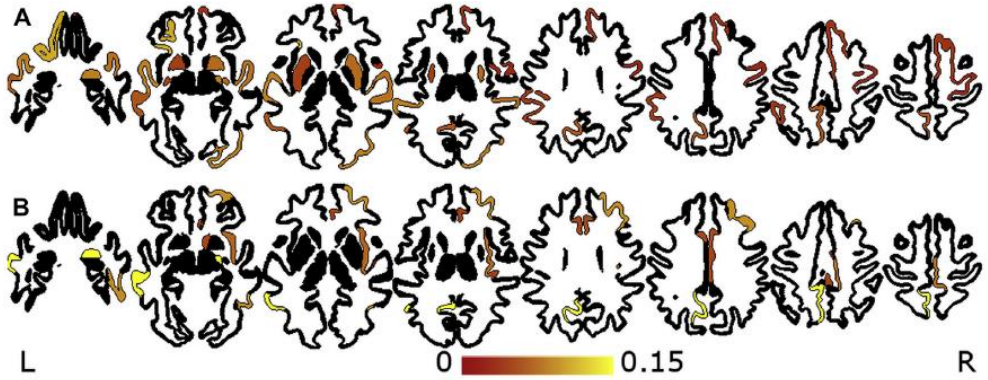


Fig. 2. Overlay of effect sizes for significant regions for education (A) and flights of stairs climbed (B).

Steffener et al, Neurobiology of Aging, 2016

Can lifetime cognitive engagement impact amyloid development?

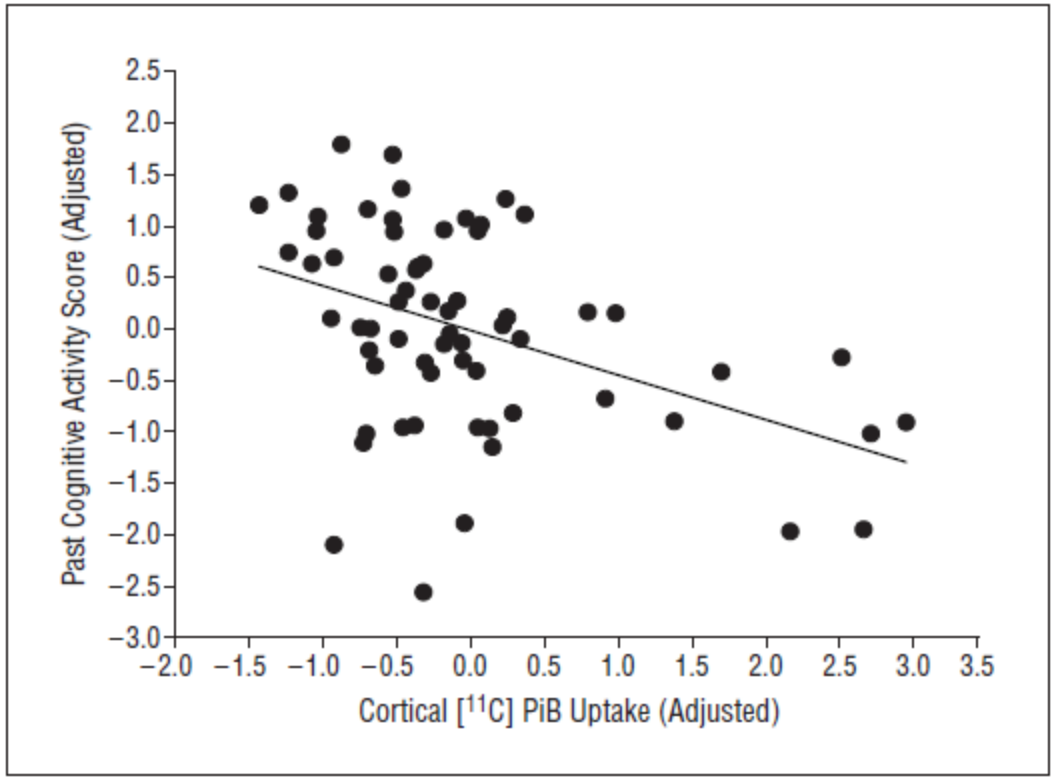
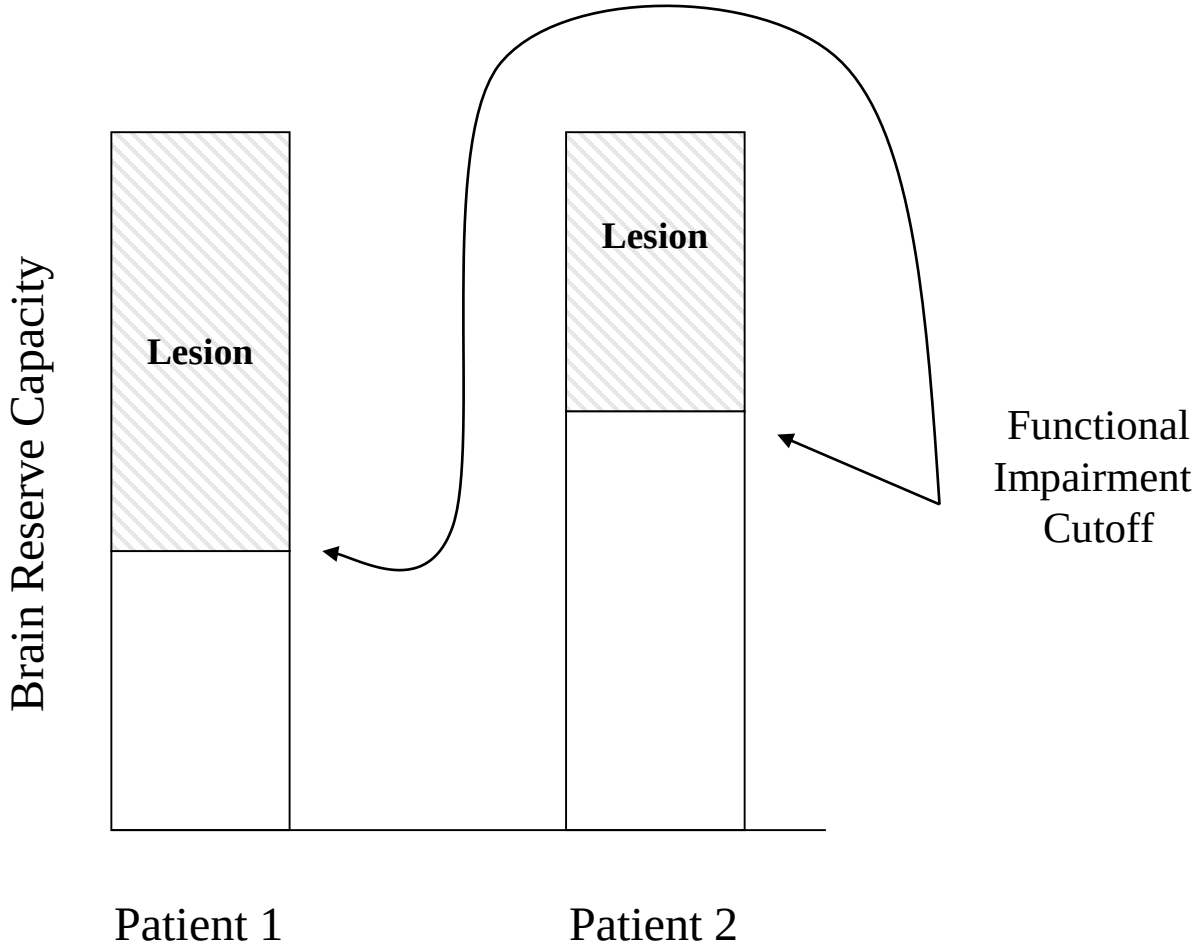


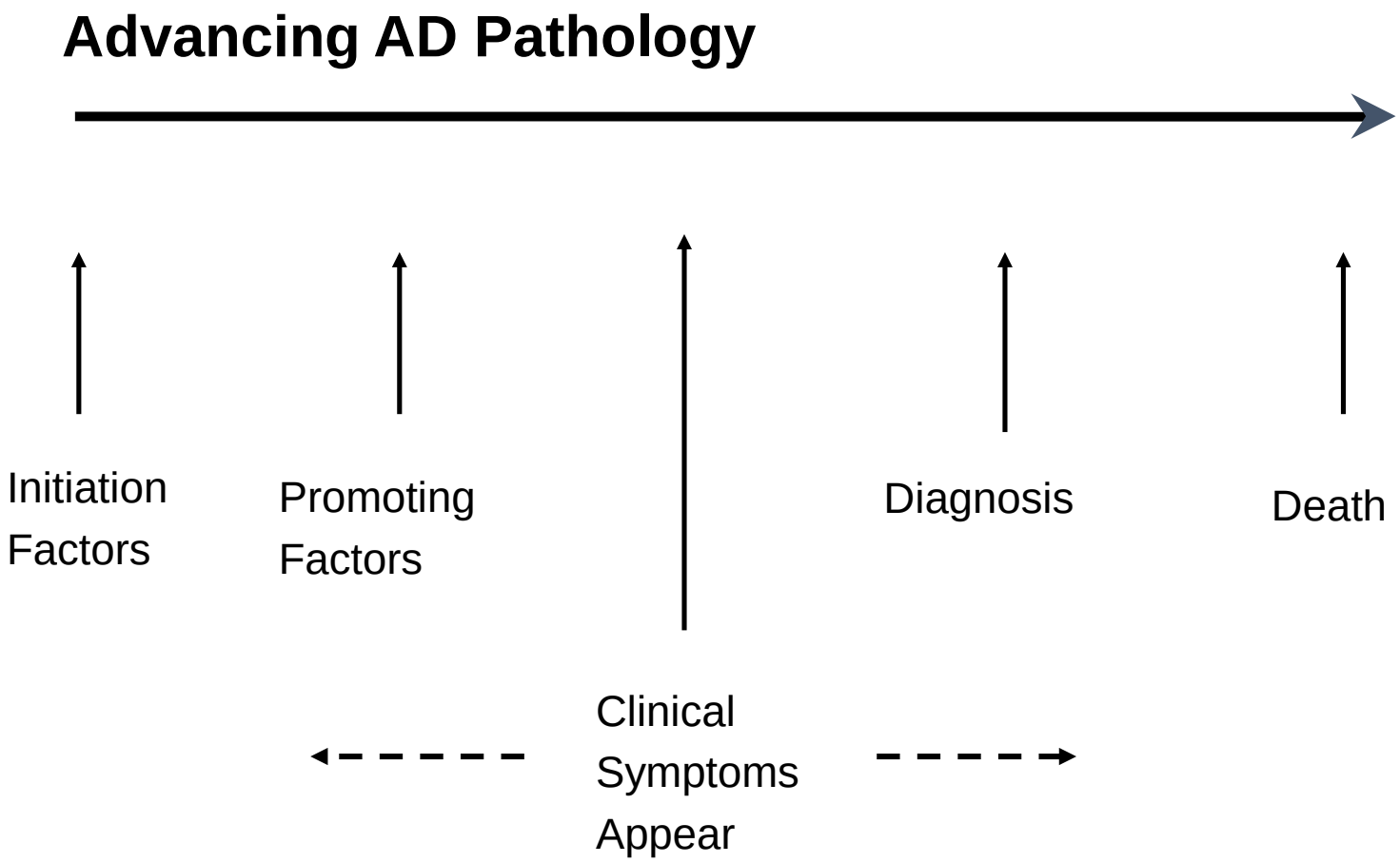
Figure 1. Individuals with greater cognitive engagement show reduced amyloid burden. Carbon 11–labeled Pittsburgh Compound B ([^{11}C]PiB) in cognitively normal older participants (x-axis) is inversely associated with past cognitive activity (y-axis) (linear regression, $\beta = -1.73 \pm 0.47$; $P < .001$). Both variables are residual values after correcting for age, sex, and years of education.

Landau et al, *Arch Neurol. Published online January 23, 2012*

Active model of reserve: 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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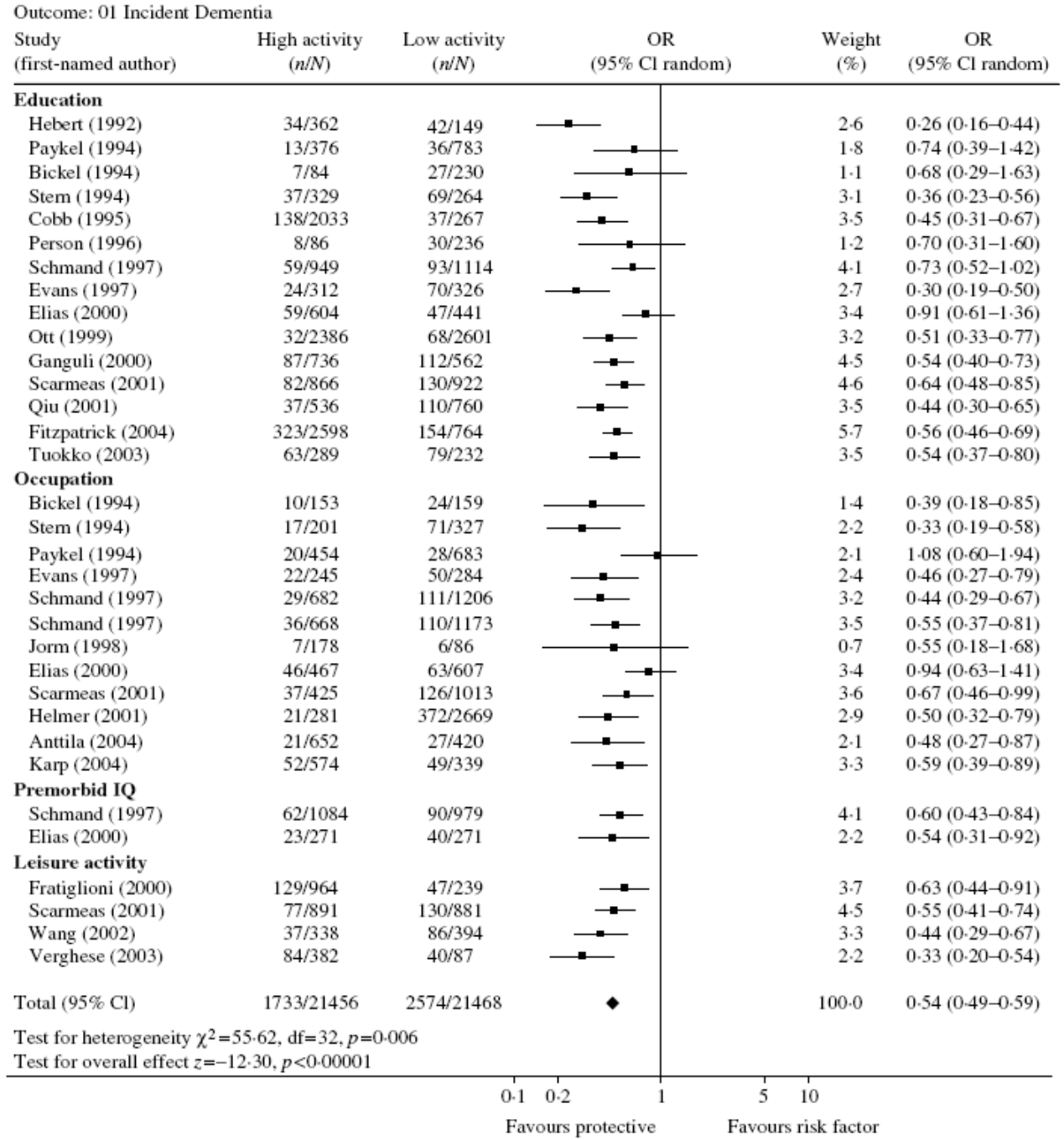
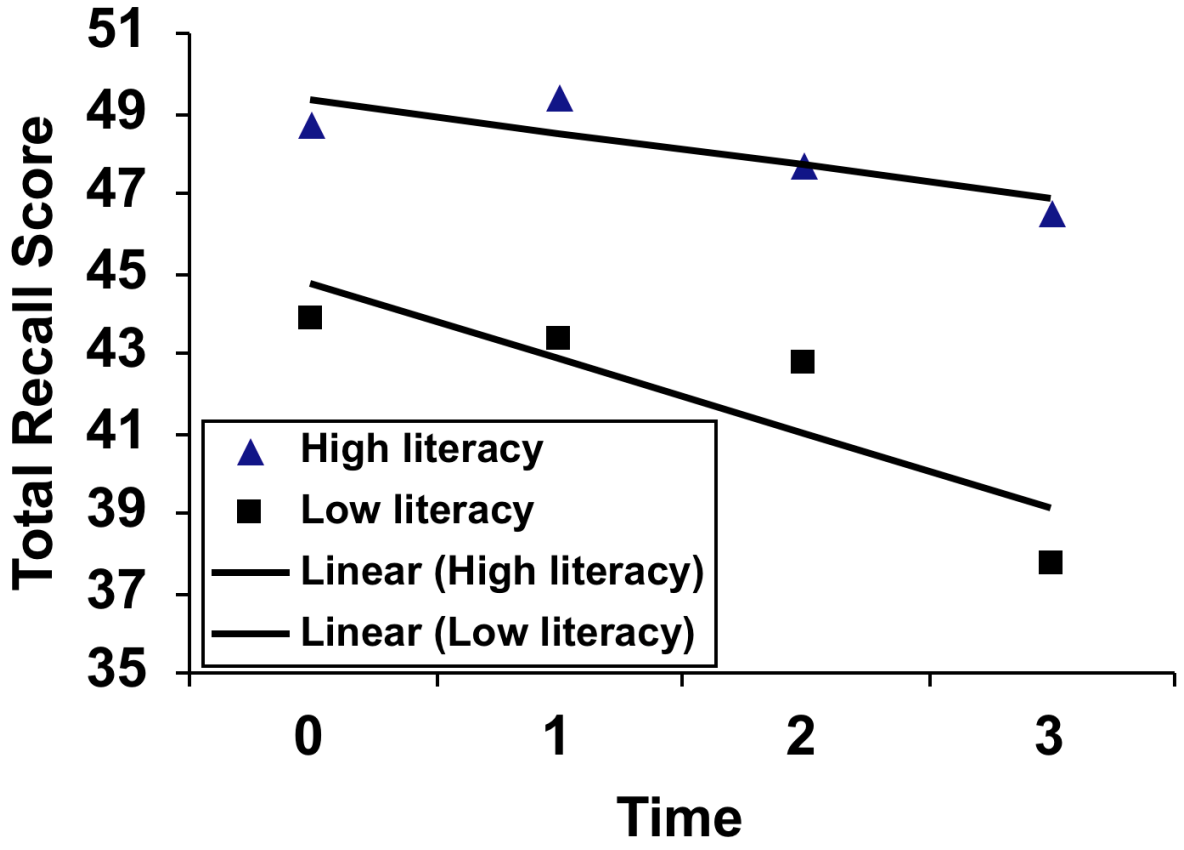


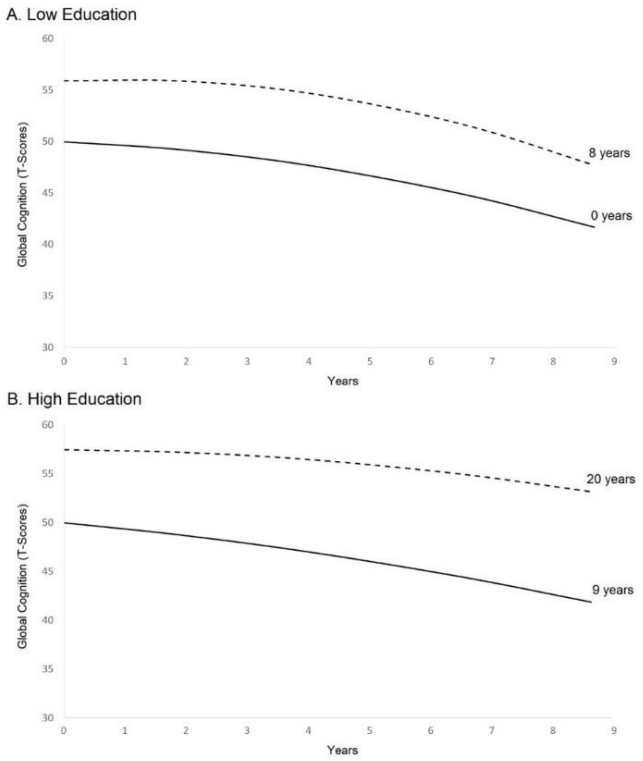
Valenzuela & Sachdev, Psychological Medicine, 2005

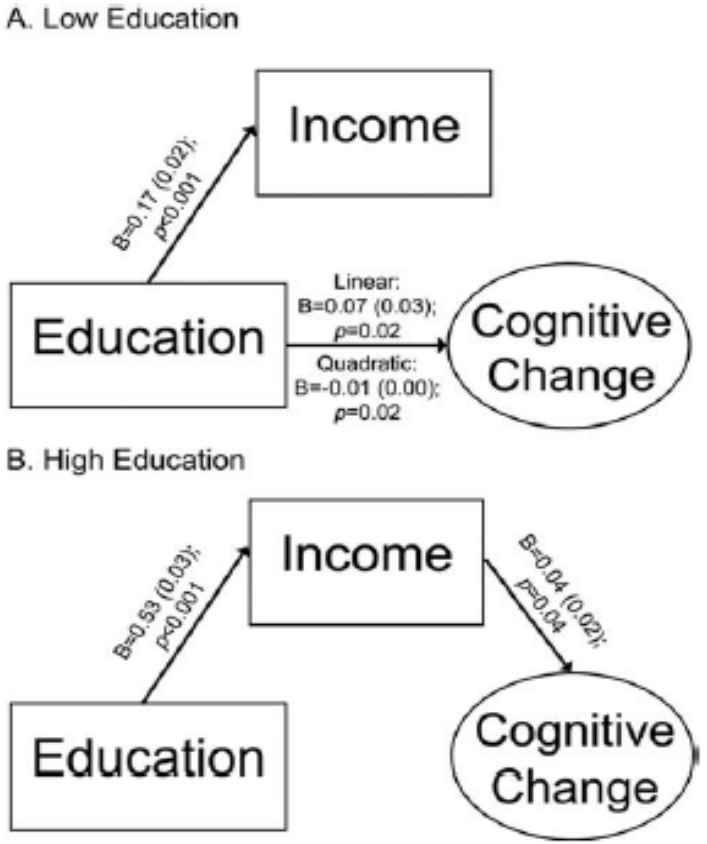
Literacy and memory decline in non-demented elders



Manly et al, JCEN 2003

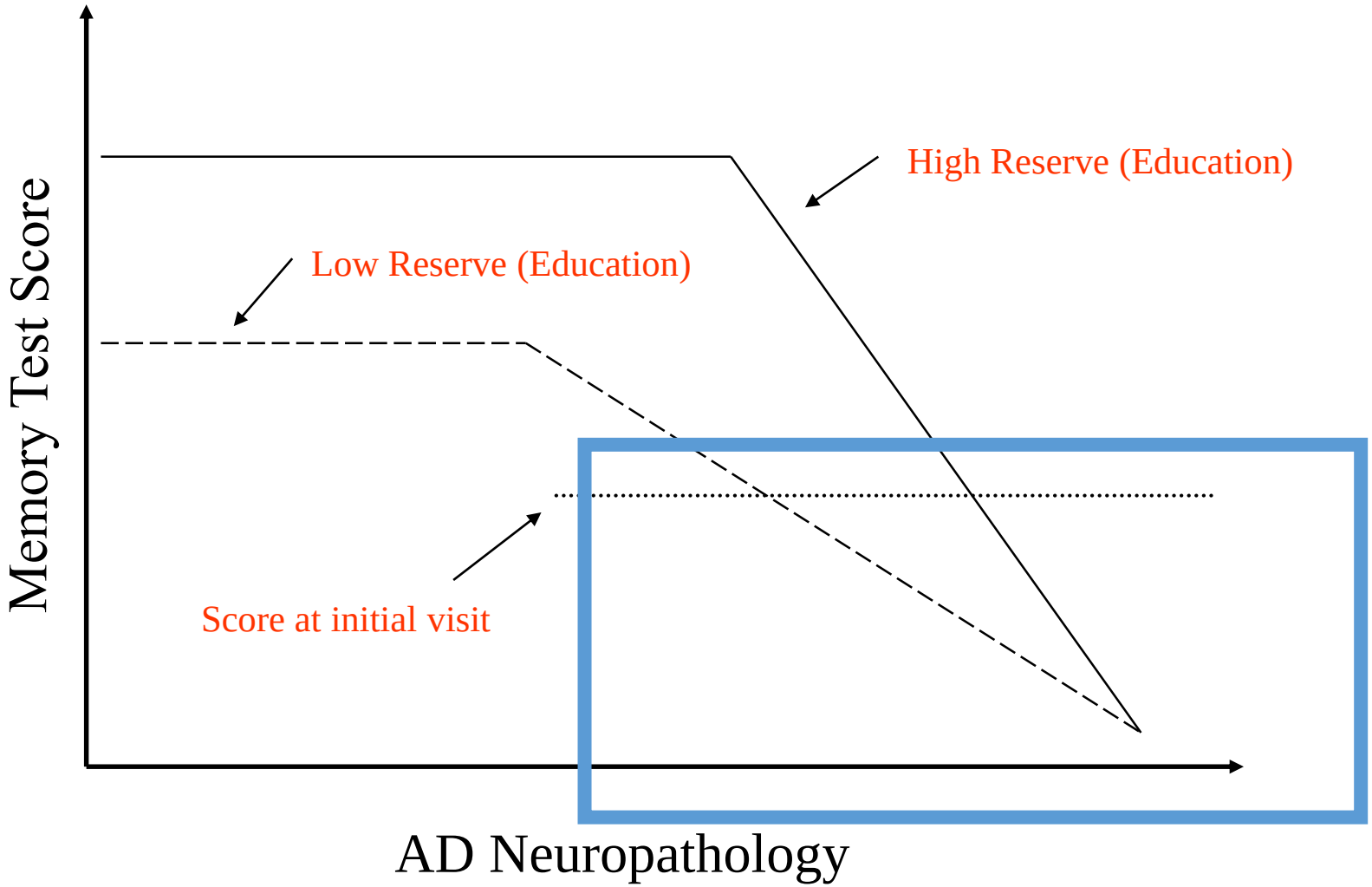
Association of Education With Cognitive Decline in the Washington Heights Study



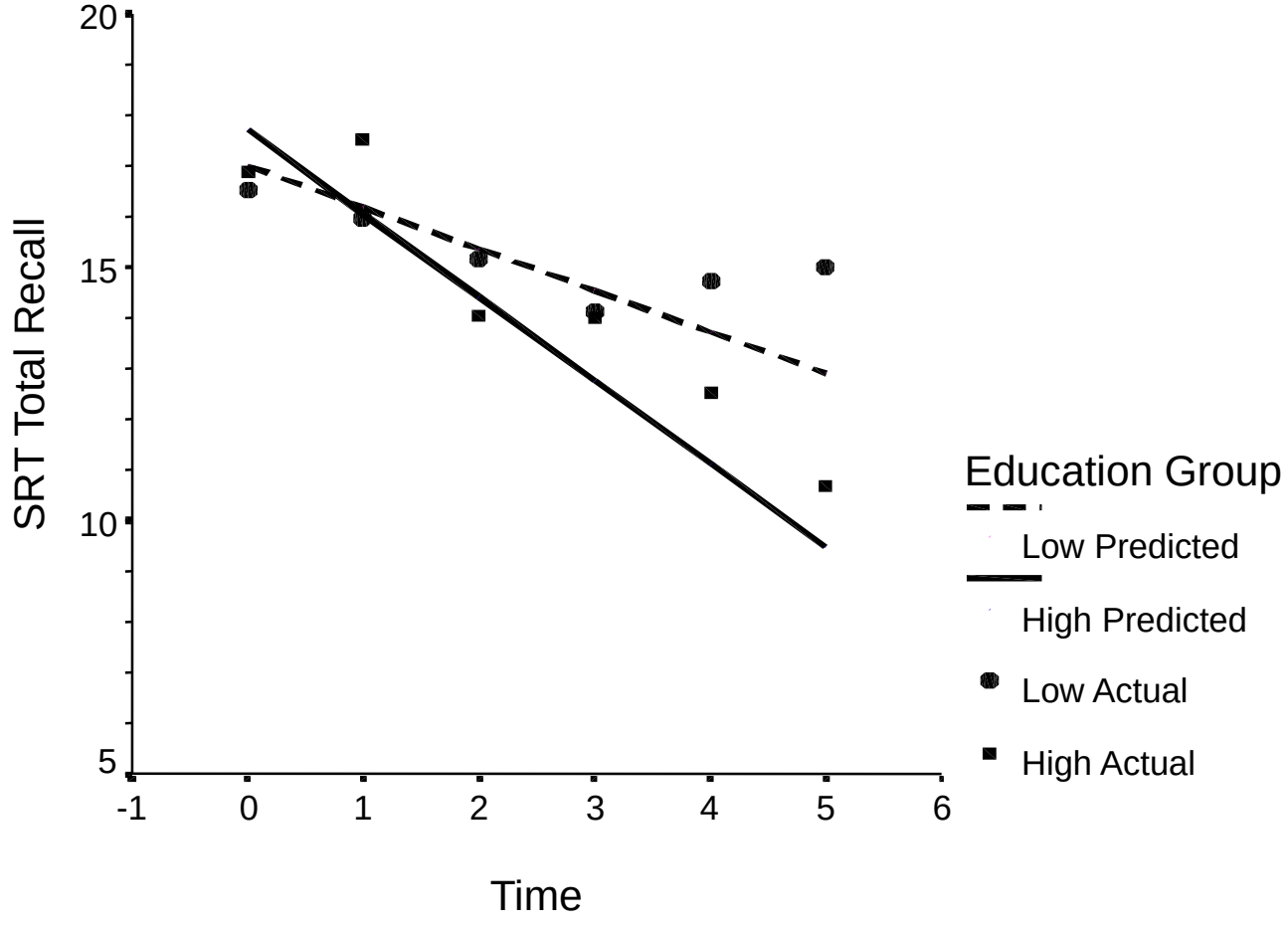


Model-estimated cognitive trajectories for 76-year-old, White, non-Hispanic Males born 1900-1909, recruited in 1992, with low (0-8 years) or high (9-20 years) education

Zahodne et al, Neuropsychology, 2015

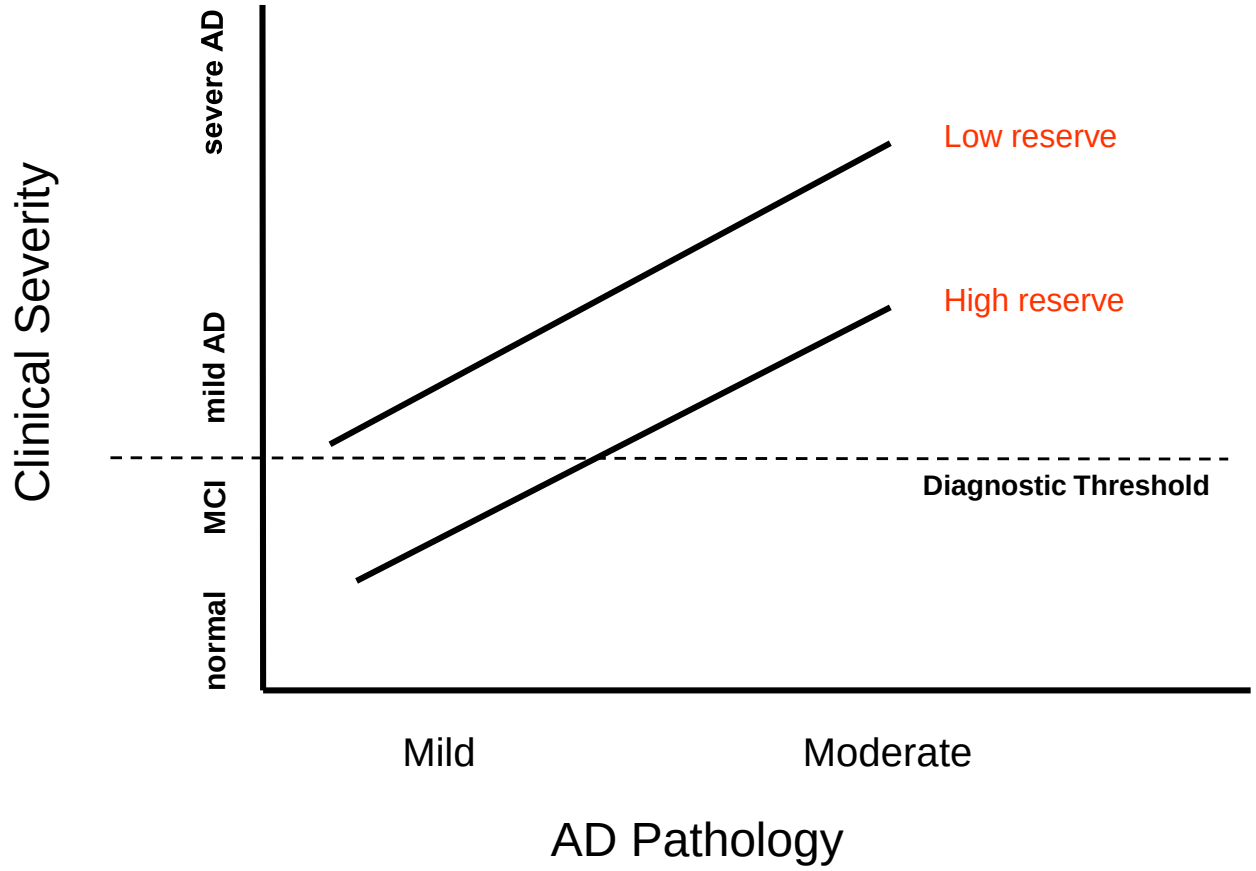

Memory Test Score
High Reserve (Education)
Low Reserve (Education)
Score at initial visit
AD Neuropathology

More rapid memory decline in AD patients with higher educational attainment



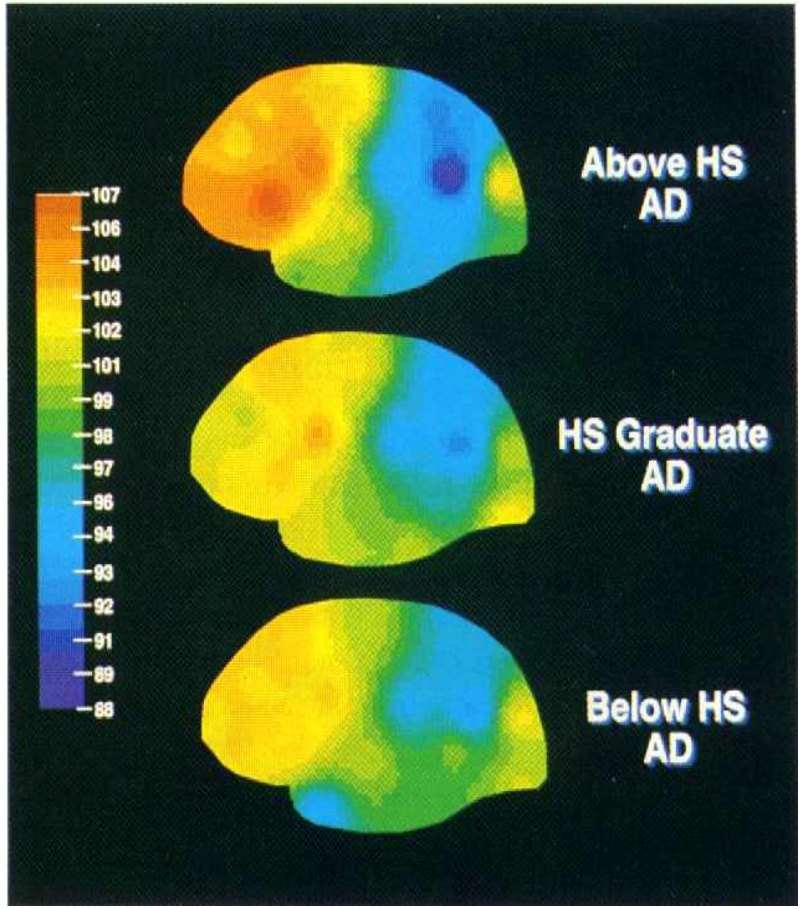
Stern et al Neurology 1999;53:1942-1957

Reserve, AD Pathology, and Clinical Diagnosis



Stern, JINS 2002

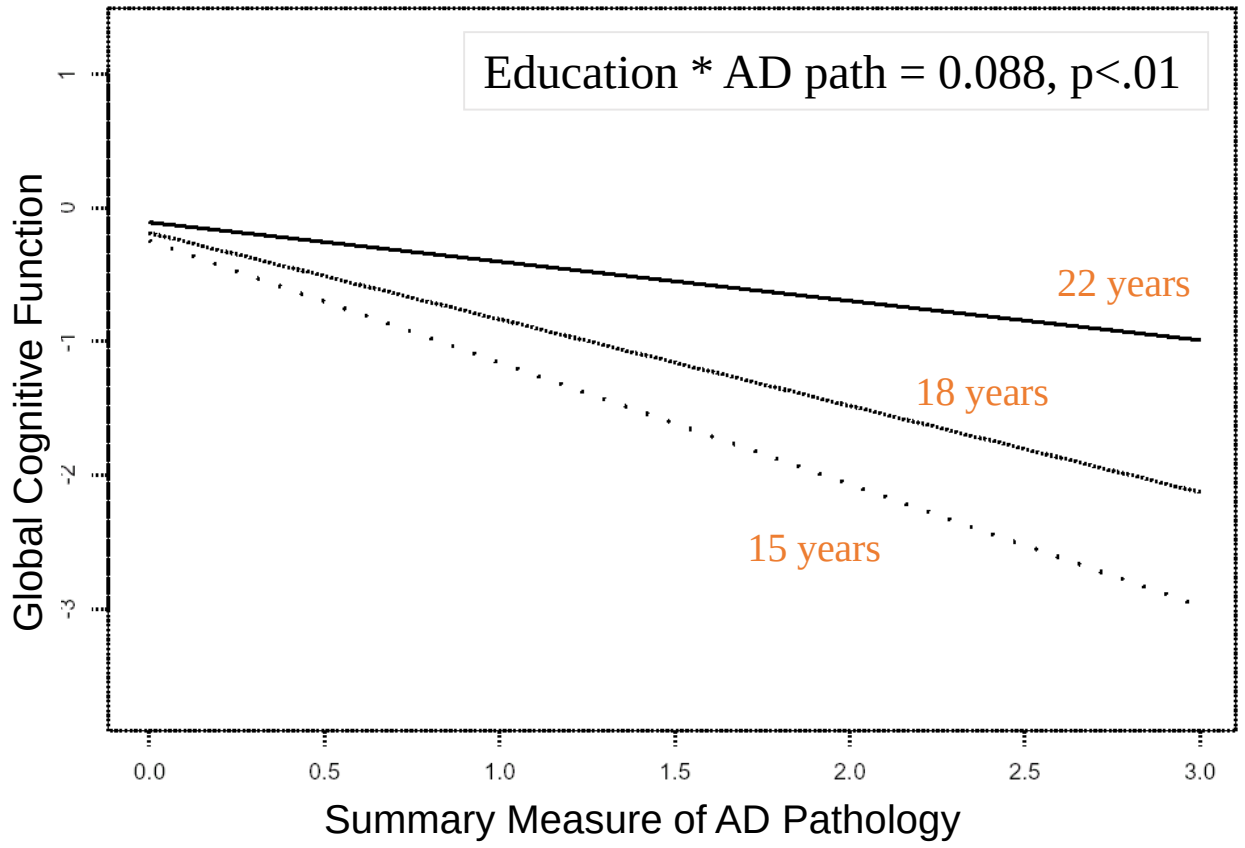
Education and rCBF, a proxy for AD pathology



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

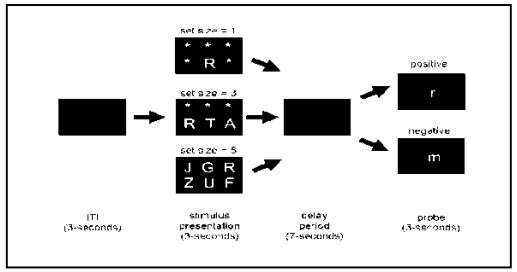
Stern et al, Ann Neurol 1992

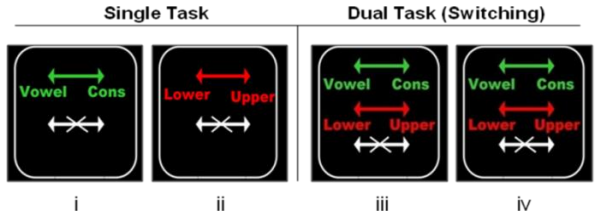
Interaction of AD Pathology and Education

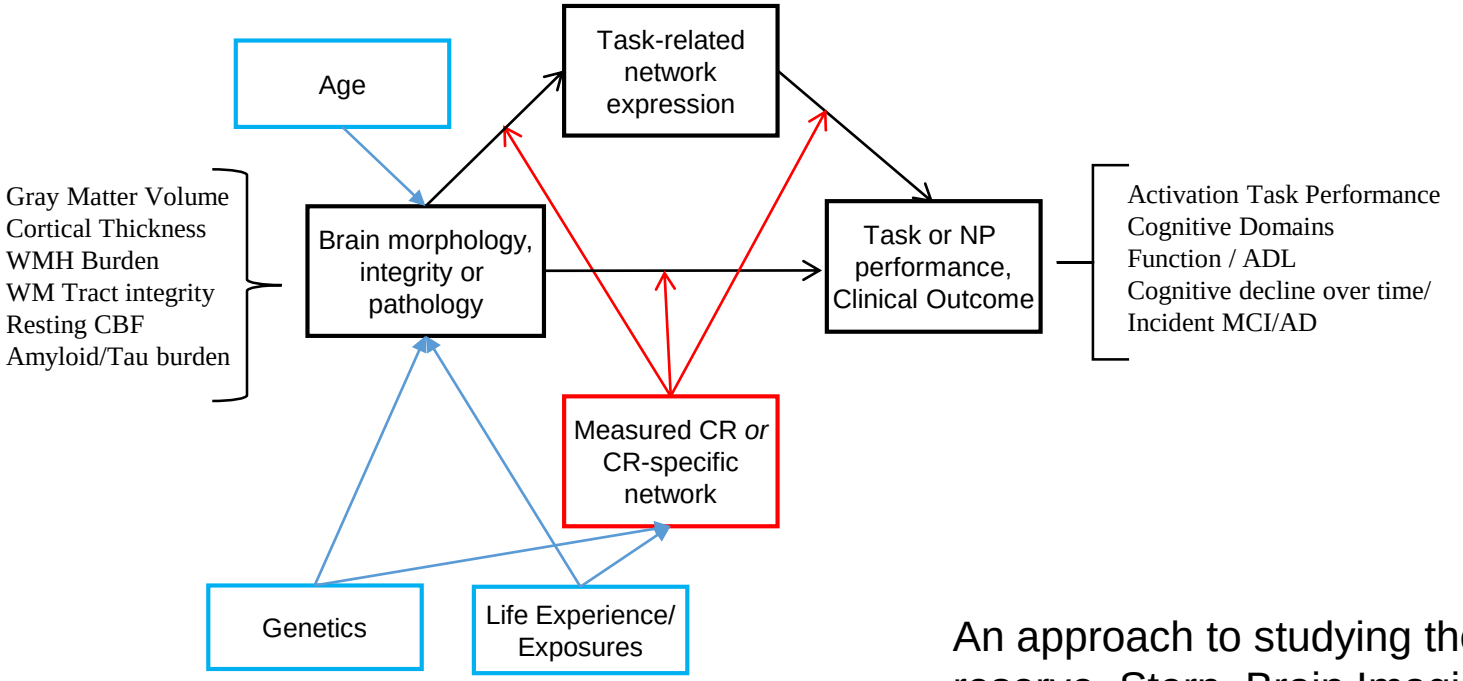


Bennett DA et al, Neurology 2003

Conceptual research models

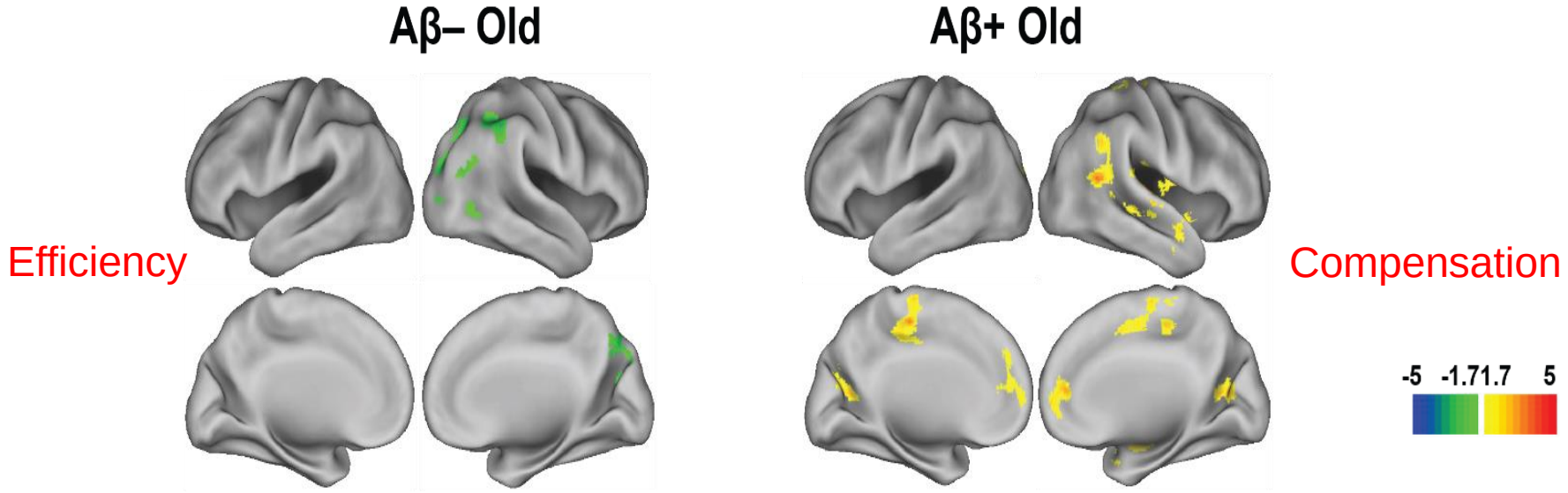






An approach to studying the neural correlates of reserve. Stern, Brain Imaging and Behavior (2017)

Effect of CR on activation in a set switching task differs by amyloid status



- For the dual-single contrast, brain regions demonstrating a relationship between task related activation and CR are presented.
- Among Aβ− older adults, task-related activation was reduced with CR.
- Among Aβ+ older adults, areas were noted where activation was increased in relation to CR. These areas differed from those typically activated in this task.

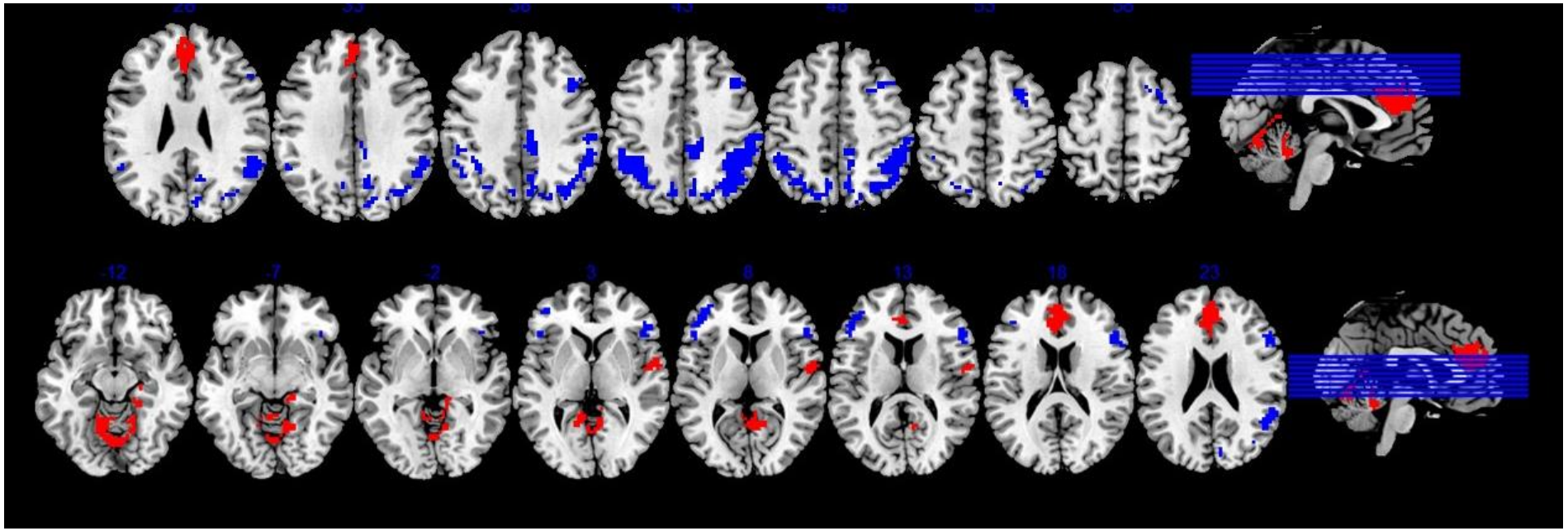
Oh et al, Neurology, in press

Task-invariant cognitive reserve network

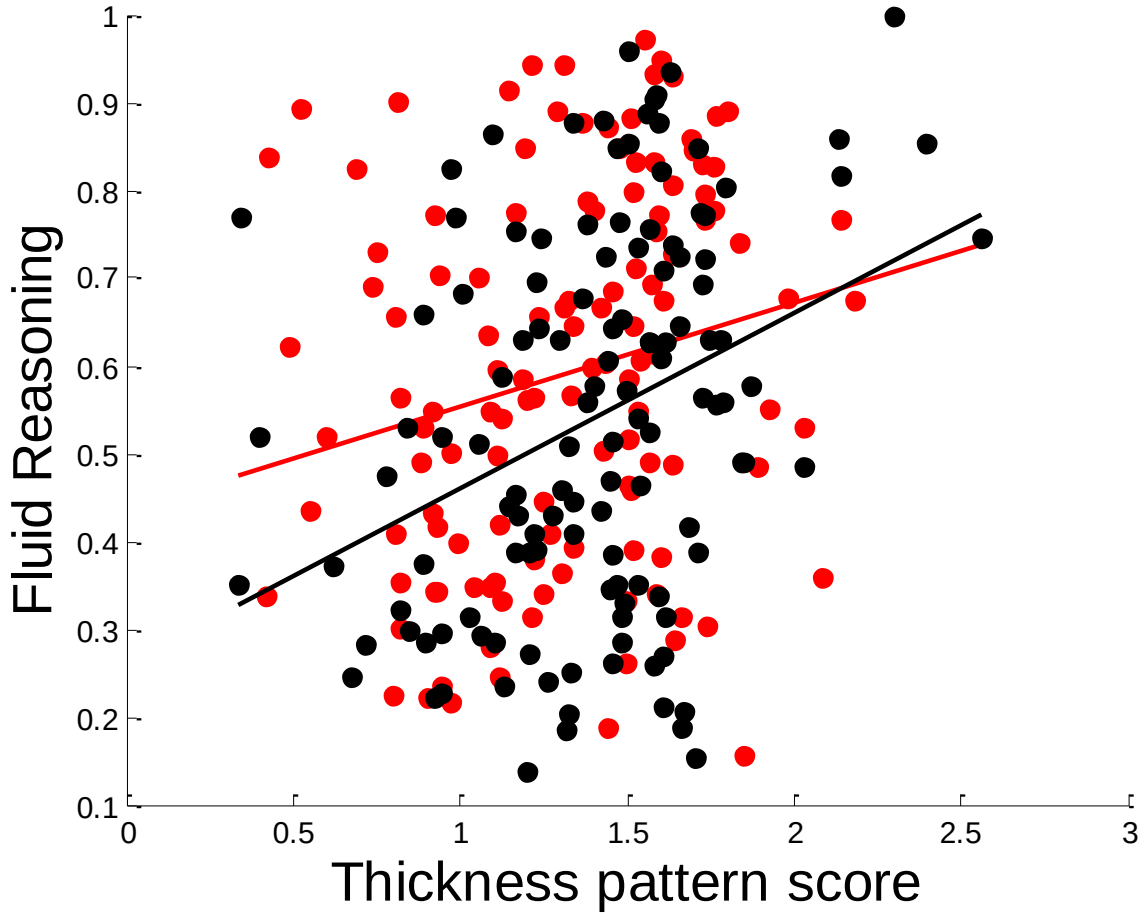
- CR allows people to better maintain function in multiple activities and cognitive domains in the face of brain pathology.
- If a particular brain network subserves CR, it should be active across tasks with varying processing demands.
- Goal: Can we identify a pattern of CR-related brain activity :
  - that is common across 12 different tasks
  - whose expression correlates with a CR proxy
  - whose expression moderates the relationship between cortical thickness and cognition
  - whose expression in other tasks correlates with that proxy

Deriving a task-invariant CR network

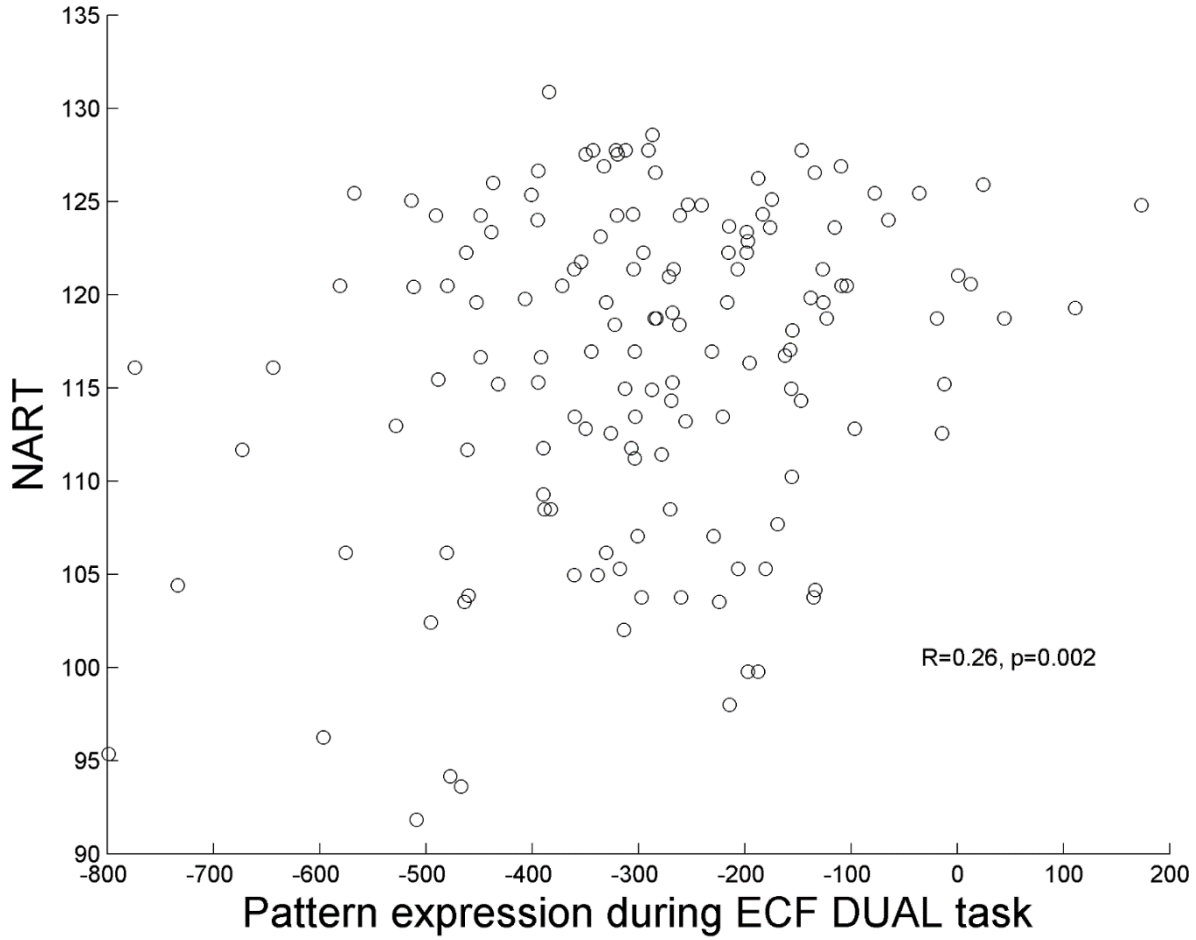
- 255 subjects, age 20-80, with complete neuroimaging for 12 different tasks
- Randomly divide data into derivation and test samples
- In derivation sample, derive best-fit NART patterns
- Project derived pattern into test sample and estimate NART in all 12 tasks
- Repeat steps 500 times, each time storing the derived patterns and the test prediction quality
- Compute weighted Z-map of pattern loadings for the 500 patterns



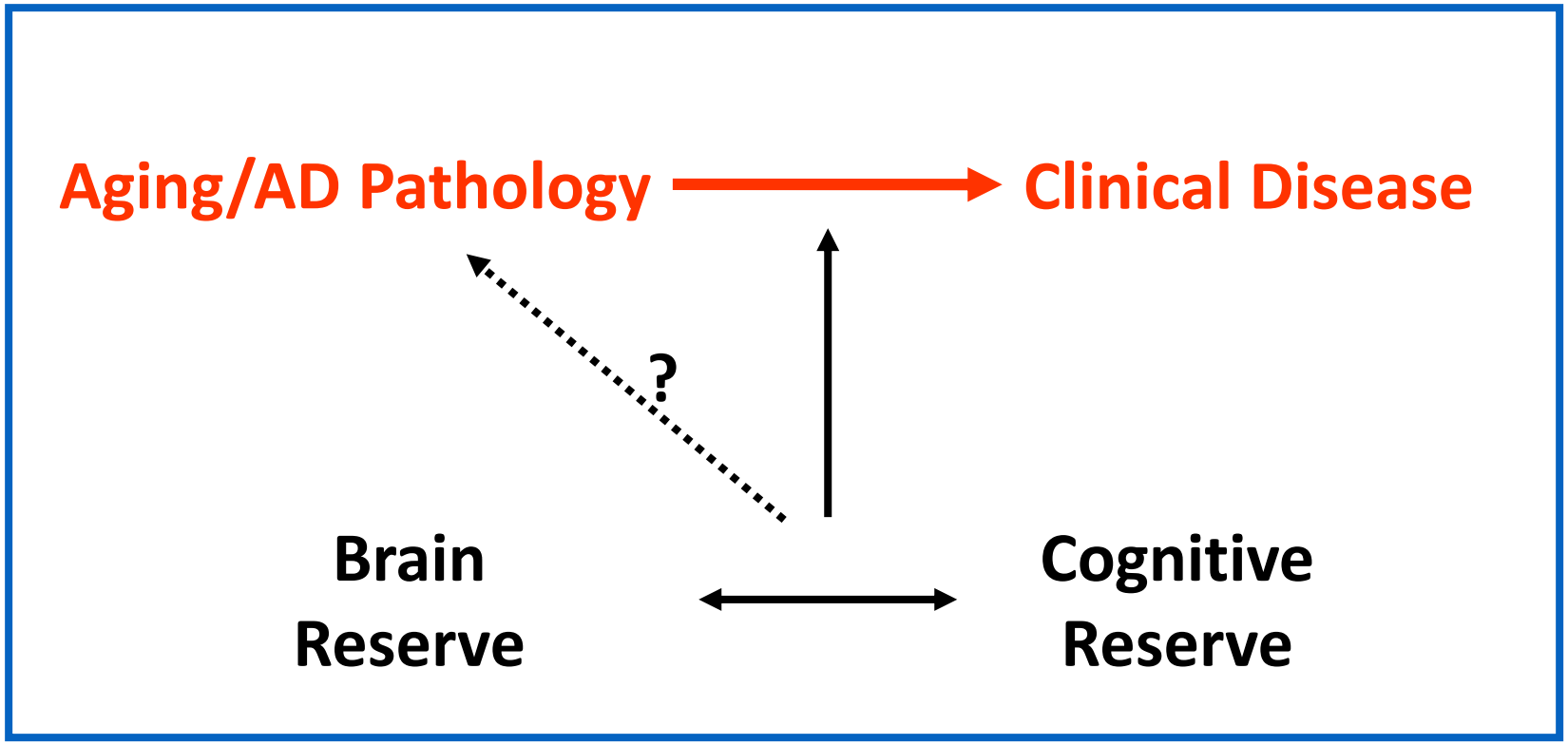
Expression of the task-invariant CR network moderates between cortical thickness and fluid reasoning



Expression of the task-invariant CR network in a different fMRI activation task (in different people) correlates with NART IQ



Reserve-based Interventions



- Important for controlled testing of reserve ideas
- Exciting work pairing intervention with imaging
- Challenging and costly: collaborations will be key

CONCLUSIONS

- Epidemiologic and imaging evidence support the concept of reserve
- Reserve is malleable: it is influenced by aspects of experience in every stage of life
- Two forms of reserve:
  - Brain reserve: passive, supported by brain maintenance
  - Cognitive reserve: active
- Imaging studies can help clarify the neural implementation of reserve
  - Neural reserve: efficiency/capacity
  - Neural compensation
  - Task-invariant networks
- Influencing reserve may delay or reverse the effects of aging or brain pathology