Estimating Cognitive Reserve via Decomposition of Memory Variance

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Nothing to disclose

Measuring reserve

- Reserve is a theoretical construct that cannot be directly measured
- Typically, reserve is estimated by measuring something presumed to confer reserve.
- Example. We measure education and infer that the effects of education reflect reserve.
- However, education has broad effects. Associated with lower rates of hypertension, diabetes, obesity, heart disease, stroke, COPD, …
- Other potential indicators of reserve (occupational complexity, cognitive activities) share this problem
- A direct measure of reserve is desirable

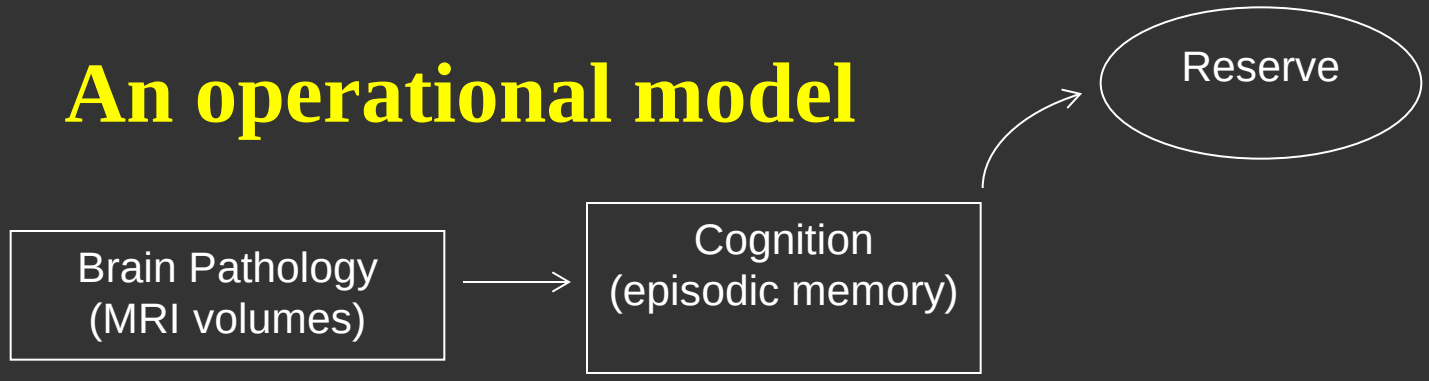
Can reserve be estimated more directly?

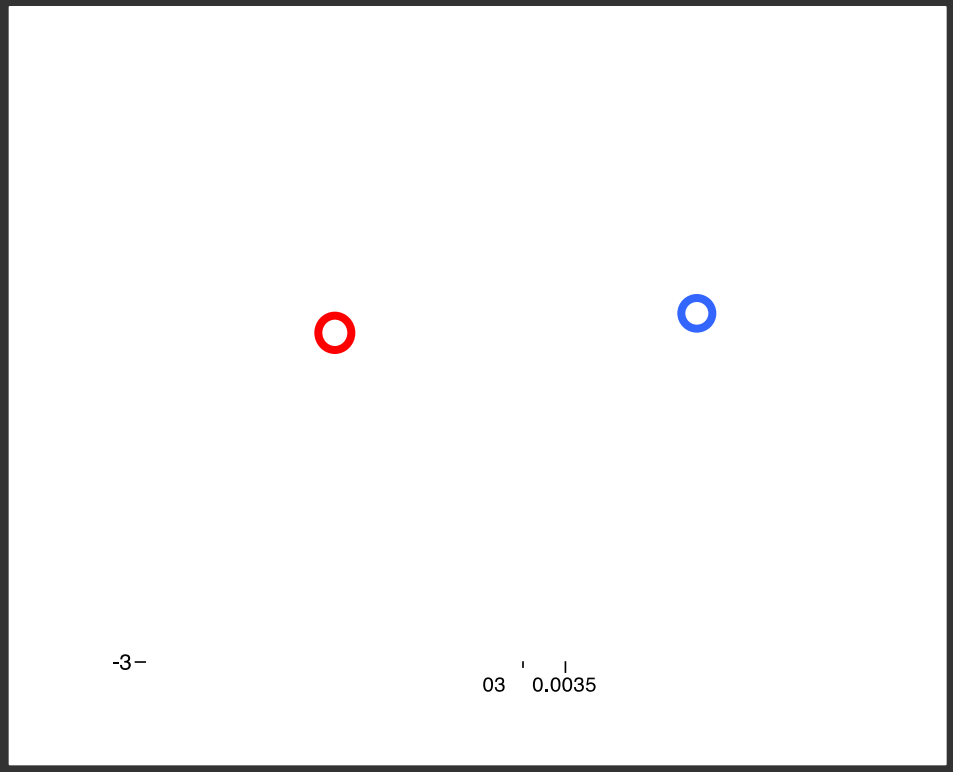
- “reserve has been proposed to account for the disjunction between the degree of … pathology and its clinical manifestations” Stern 2009.

- Restated: reserve accounts for the difference between the expected effects of the degree of pathology present and observed cognitive function.

- $R = C – E(C \mid P)$
  - Reserve = cognition – (expected value of cognition given pathology)

An operational model





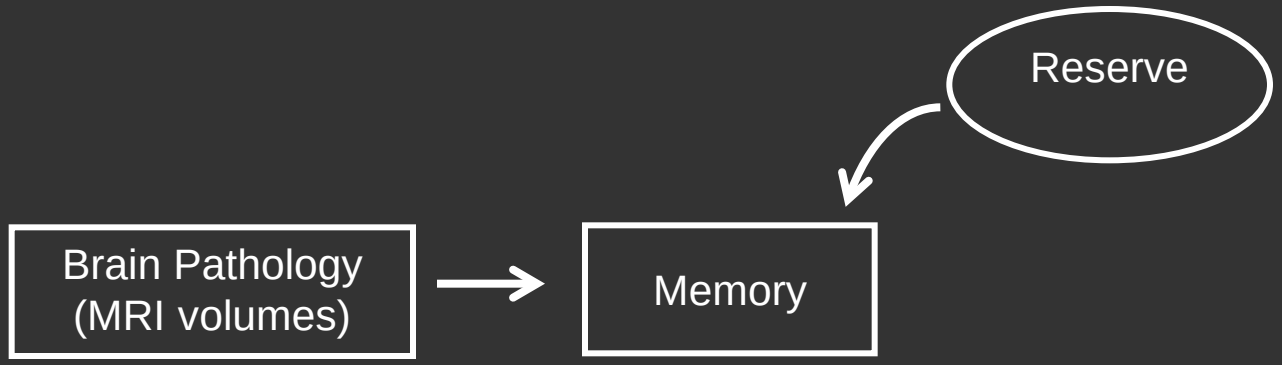
average memory,
high residual memory

average memory,
low residual memory

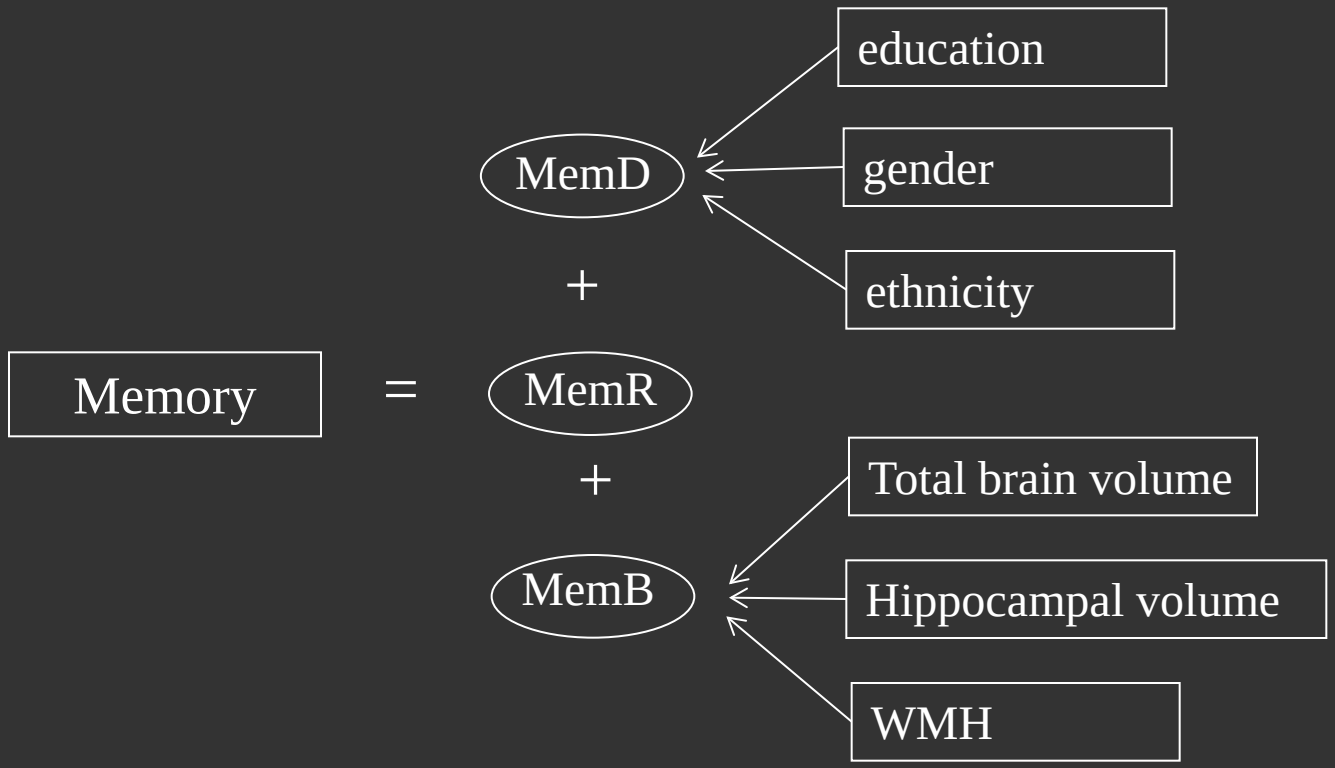
Might this residual serve as a good estimate of reserve?

Not a pure measure: the residual term captures unmeasured systematic variance and measurement error.

> "All models are wrong. Some are useful" George Box



Decomposing memory variance



- The demographic term captures variance related to factors that correlate with test scores but which are not likely part of reserve (e.g. gender)
- It includes effects of education. Thus, any effects of residual are independent of education

Testing residual memory as an estimate of reserve

- Hypotheses based on an adaptive model of cognitive reserve

  1. Higher reserve lowers the risk of conversion to dementia
  2. Higher reserve slows the rate of longitudinal cognitive decline
  3. The association between brain atrophy and longitudinal cognitive decline is stronger in persons with low reserve than in persons with high reserve

- Data from UC Davis Diversity Cohort
  - N = 305, ethnically diverse, wide range of education (M ~ 12 yrs, range 0 -20, 85% cognitively normal or MCI

MemR modifies the risk of conversion to dementia

Memory Component	Relative Risk (confidence interval)
Mem-D	1.09 (0.74 - 1.59)
Mem-B	0.21 (0.13 - 0.36)
Mem-R	0.35 (0.25 - 0.49)

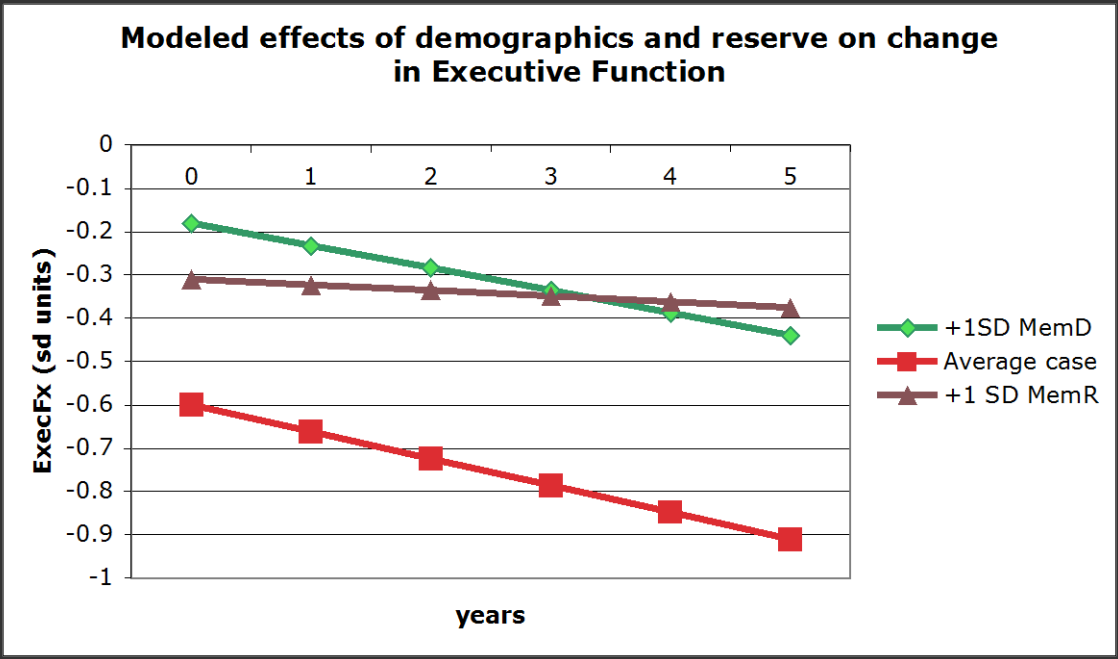
MemR modifies rate of longitudinal cognitive decline

Baseline Executive

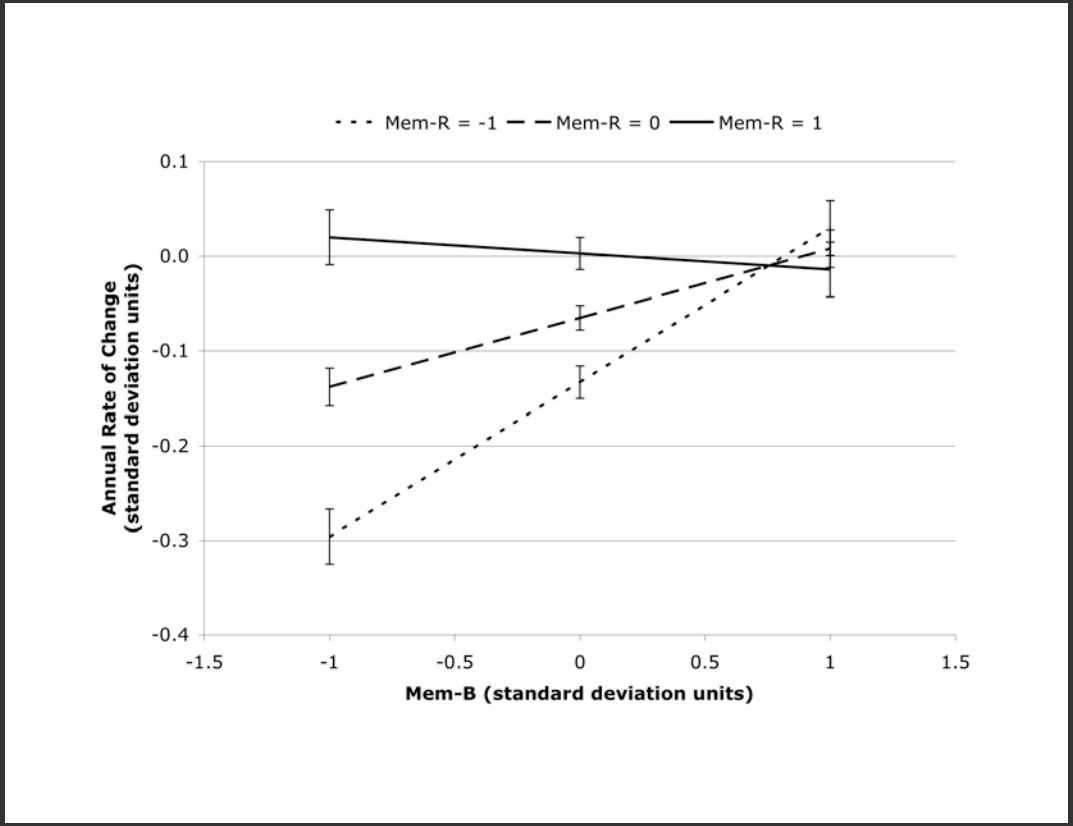
Component	β	p
Mem-D	0.418	0.001
Mem-B	0.352	0.001
Mem-R	0.287	0.001

Change in Executive

β	Coefficient	p
Mem-D	-0.010	ns
Mem-B	0.067	0.001
Mem-R	0.049	0.001



The association between brain atrophy and longitudinal cognitive decline is stronger in persons with low reserve (MemR) than in persons with high reserve (MemR)

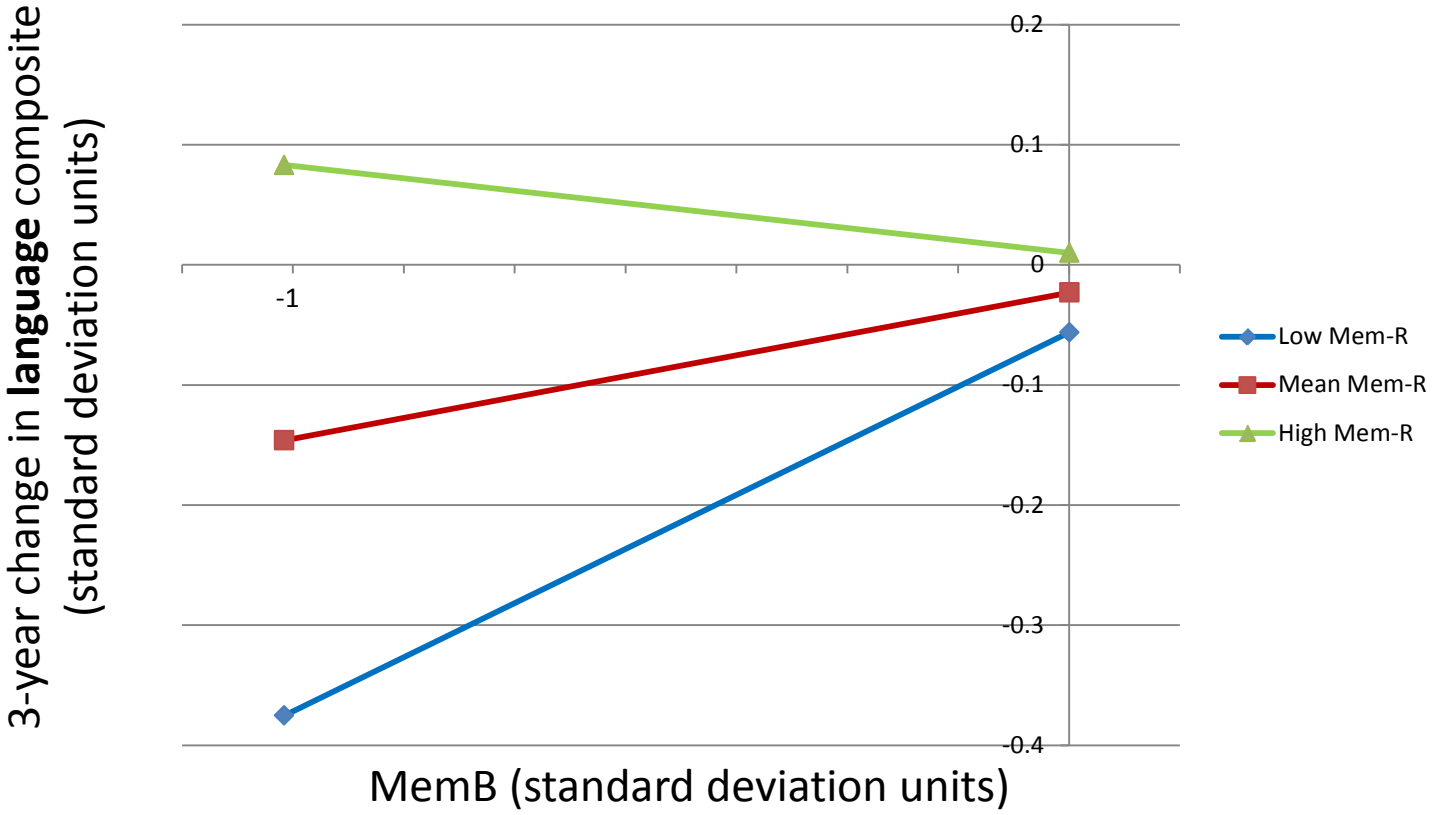


Replication in WHICAP

- Zahodne et al.
- 704 non-demented participants. M age ~80, ethnically diverse, M education 11yrs.
- Memory: composite from SRT
- Cognitive Outcome: Language composite

- Key findings
  - Good model fit
  - Higher MemR associated with
    - lower risk of dementia conversion
    - slower decline in language

WHICAP replication (N=704)



Worse brain status associated with greater 3 year decline in Language;
Effect larger with low MemR, smaller with high MemR

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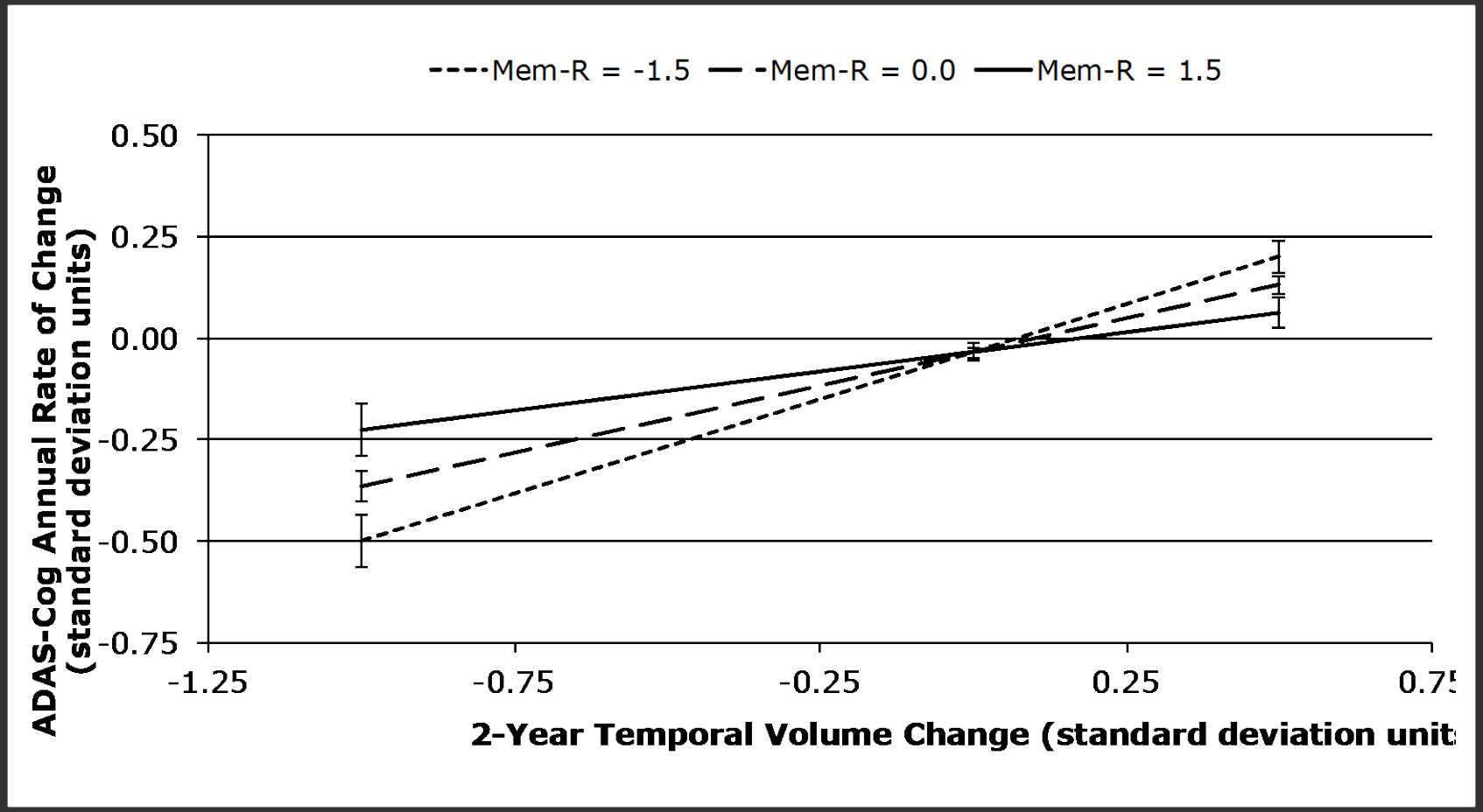
Extension to ADNI

- Longitudinal ADNI 1data
- 3-way decomposition
  - MemD defined by education and gender
  - MemB defined by normalized hippocampus, temporal lobe, ventrical, WMH
- Cognitive outcome = ADAS-Cog
- Modeled change in cognition in relation to change in temporal lobe volume
- Reserve model predicts greater reserve will result in less change in relation to increased pathology.

The rate of cognitive decline associated with progressive temporal lobe atrophy is modified by reserve



What builds reserve?

- Estimating reserve with the residual makes minimal assumptions about what builds reserve. Assuming MemR is an estimate of reserve, correlations with MemR are evidence that a factor contributes to reserve.

- No relationship to reserve:
  - Morphometric markers of early growth
  - Index of economic deprivation

- Associated with reserve independently of education
  - Childhood SES
  - Leisure cognitive activities in middle age and late life
  - Idea Density

Consistent with the reserve hypothesis, a residual memory-based estimate of reserve:

- Modifies the risk of conversion from MCI to dementia
- Modifies rates of decline in language and executive function
- Reduces the effect of baseline brain atrophy on subsequent cognitive decline
- Reduces the effect of longitudinal temporal lobe atrophy on decline in global cognition.

Conclusions

- Operationally estimating reserve as residual cognition is a useful approach
- Provides a direct, quantitative, individually-specific measure
- Can be used either as a predictor, to study reserve effects, or as a dependent measure in investigations of what determines reserve
- Also enables investigation of how reserve changes over time, and of “domain-specific” reserve
- Quantifying “how much” reserve there serves as a heuristic device; it challenges us to find the determinants of reserve and other factors that explain variability in the effects of pathology on cognitive performance

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- Michael Weiner and the ADNI investigators

Caveats

Approach depends on pathology being present and measured

(not useful in cohorts with low prevalence of pathology)

Estimates are model and cohort dependent

- episodic memory the right cognitive measure?
- are multiple domains of reserve useful?

WHICAP replication (N=704)

Washington/Hamilton Heights Columbia Aging Project
Community-based study in Northern Manhattan

	Mean	SD
Age	80	5.5
Education	11	4.8
Sex	67% Female	-
Race and ethnicity	31% Non-Hispanic White 34% African American 35% Hispanic	-
Testing Language	33% Spanish	-

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WHICAP replication (N=704)

Higher MemR associated with:

- Lower likelihood of concomitant MCI diagnosis
- Lower reading ability
- Lower odds of dementia conversion
- Better concomitant language abilities
- Less decline in language abilities over time

	MemD	MemB	MemR
MCI (standardized probit coefficients)	-0.218**	-0.148**	-0.573**
Reading ability (β)	0.588**	0.014	0.156**
Dementia conversion (standardized log odds)	-0.381*	-0.577**	-0.709**
Baseline language composite (β)	0.250**	0.017	0.181*
Change in language composite (β)	0.650**	0.158**	0.370**

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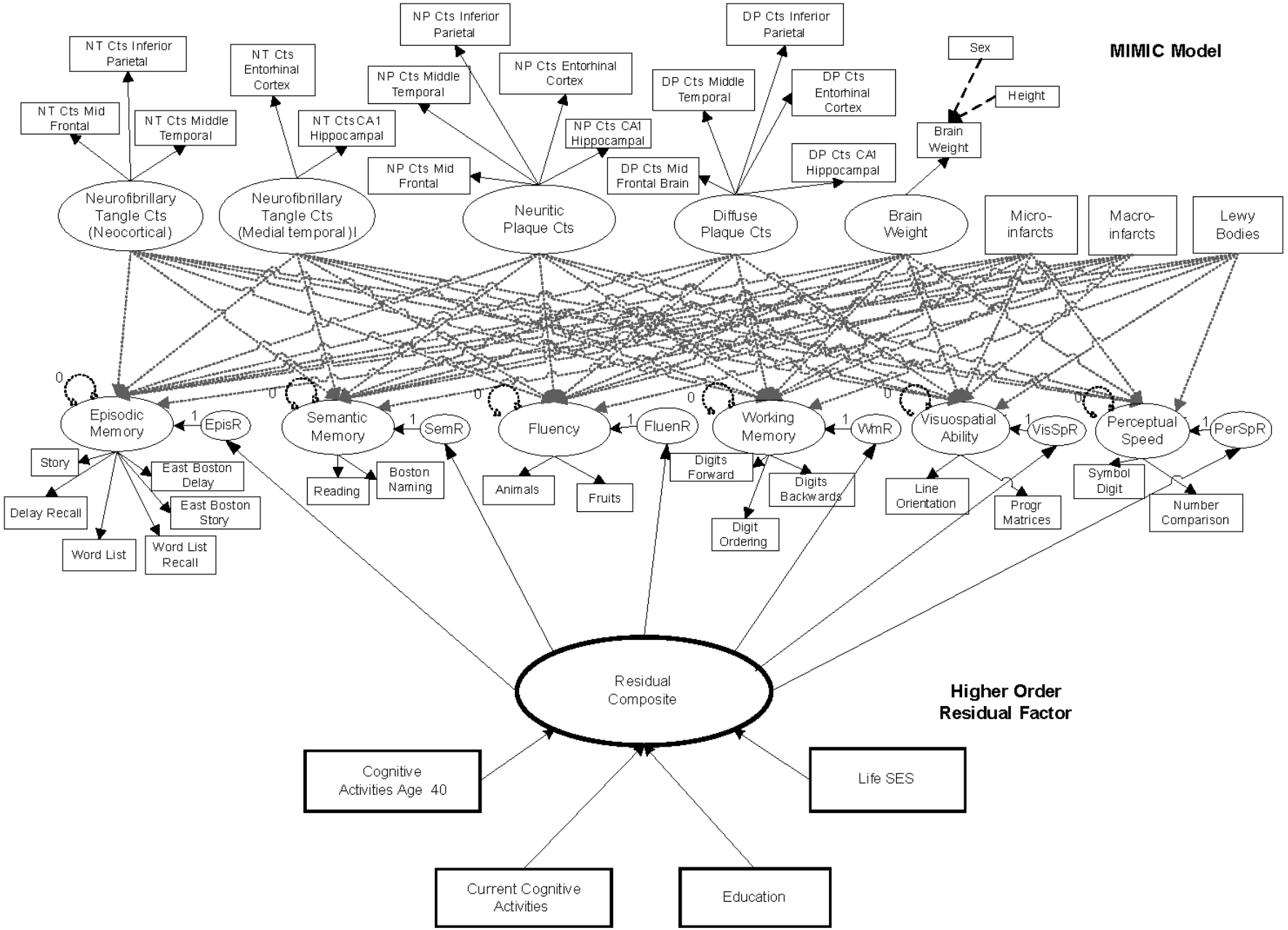
Rush replication

- 652 Neuropathology cases from MAP and ROS
- 17 cognitive tests, 19 neuropathology measures
- Created LVM for neuropathology, LVM for cognitive domains regressed 6 cognitive domains on the Npath measures resulting in 6 estimates of domain specific reserve.
- Created a second order, general reserve factor
- Examined association between general cognitive reserve and potential predictors of reserve
- Education; Leisure time cognitive activities; Childhood SES


MIMIC Model
NT Cts Inferior Parietal
NT Cts Entorhinal Cortex
NP Cts Inferior Parietal
DP Cts Inferior Parietal
Sex
Height
NT Cts Mid Frontal
NT Cts Middle Temporal
NT CtsCA1 Hippocampal
NP Cts Middle Temporal
NP Cts Entorhinal Cortex
NP Cts CA1 Hippocampal
DP Cts Middle Temporal
DP Cts Entorhinal Cortex
Brain Weight
NP Cts Mid Frontal
DP Cts Mid Frontal Brain
DP Cts CA1 Hippocampal
Neurofibrillary Tangle Cts (Neocortical)
Neurofibrillary Tangle Cts (Medial temporal)l
Neuritic Plaque Cts
Diffuse Plaque Cts
Brain Weight
Micro-infarcts
Macro-infarcts
Lewy Bodies
0
Episodic Memory
1
EpisR
Semantic Memory
SemR
Fluency
FluenR
Working Memory
WmR
Visuospatial Ability
VisSpR
Perceptual Speed
PerSpR
Story
East Boston Delay
Delay Recall
East Boston Story
Word List
Word List Recall
Reading
Boston Naming
Animals
Fruits
Digits Forward
Digits Backwards
Digit Ordering
Line Orientation
Progr Matrices
Symbol Digit
Number Comparison
Residual Composite
Higher Order Residual Factor
Cognitive Activities Age 40
Life SES
Current Cognitive Activities
Education

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SPECIAL SERIES

Cognitive Activities During Adulthood Are More Important than Education in Building Reserve

Bruce R. Reed,[1,2] Maritza Dowling,[3] Sarah Tomaszewski Farias,[1] Joshua Sonnen,[4] Milton Strauss,[5] Julie A. Schneider,[6] David A. Bennett,[6] AND Dan Mungas[1]

Idea Density

- Linguistic measure of efficiency in communication: ideas/word
- Nun study reported higher idea density measured in youth associated with reduced risk of dementia decades later

- We measured idea density using spoken language in 137 older adults.
- Idea Density appears to be associated with reserve in ways not wholly mediated by education

r = .28, p < .001

	Normal (n=162)	MCI (n=100)	Demented (n=43)	All (n=305)
Gender				
N (%) Female	111 (69)	57 (57)	25 (58)	193 (63)
Education (years)				
Mean (S.D.)	12.8 (4.4)	13.1 (4.6)	11.3 (4.6)	12.7 (4.5)
Age (years)***				
Mean (S.D.)	73.1 (7.1)	75.1 (6.6)	78.1 (7.4)	74.5 (7.2)
Ethnicity*				
N (%) African Am.	58 (36)	33 (33)	10 (23)	101 (33)
N (%) Hispanic	49 (30)	17 (17)	12 (28)	78 (26)
N (%) Caucasian	55 (34)	50 (50)	21 (49)	126 (41)
Follow-Up Time Mean Years (S.D.)**	3.5 (1.3)	3.2 (1.4)	2.8 (1.4)	3.0 (1.3)
Number of Evaluations				
N(%) 2 Evals	28 (17)	24 (24)	13 (30)	65 (21)
N(%) 3 Evals	41 (25)	29 (29)	12 (28)	82 (27)
N(%) 4 Evals	46 (29)	17 (17)	10 (23)	73 (24)
N(%) ≥5 Evals	47 (29)	30 (30)	8 (19)	85 (28)

UC Davis Alzheimer's

Zahodne

	MemD	MemB	MemR
Reading ability (β)	0.588**	0.014	0.156**
Dementia conversion (standardized log odds)	-0.381*	-0.577**	-0.709**
Baseline language composite (β)	0.250**	0.017	0.181*
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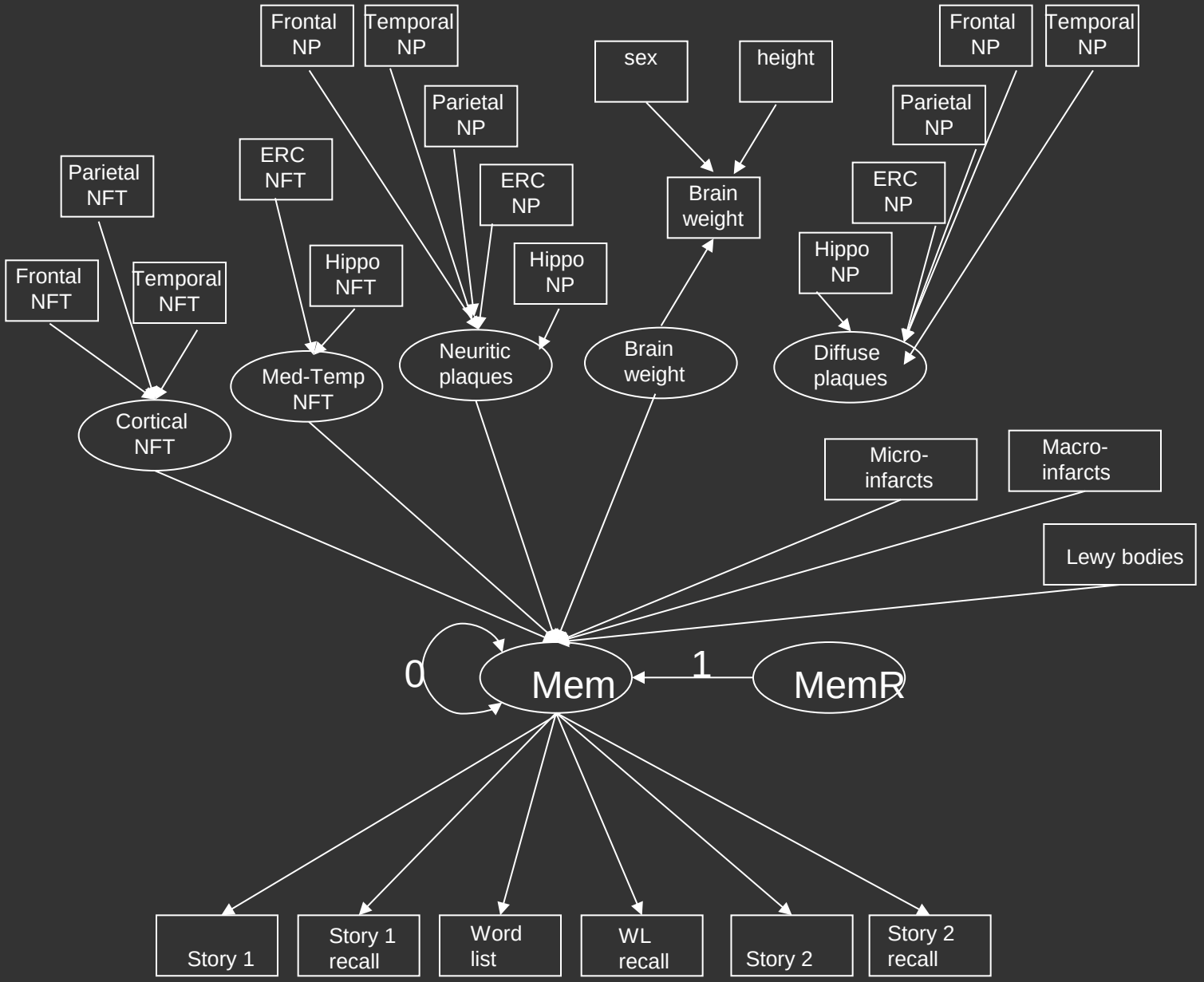
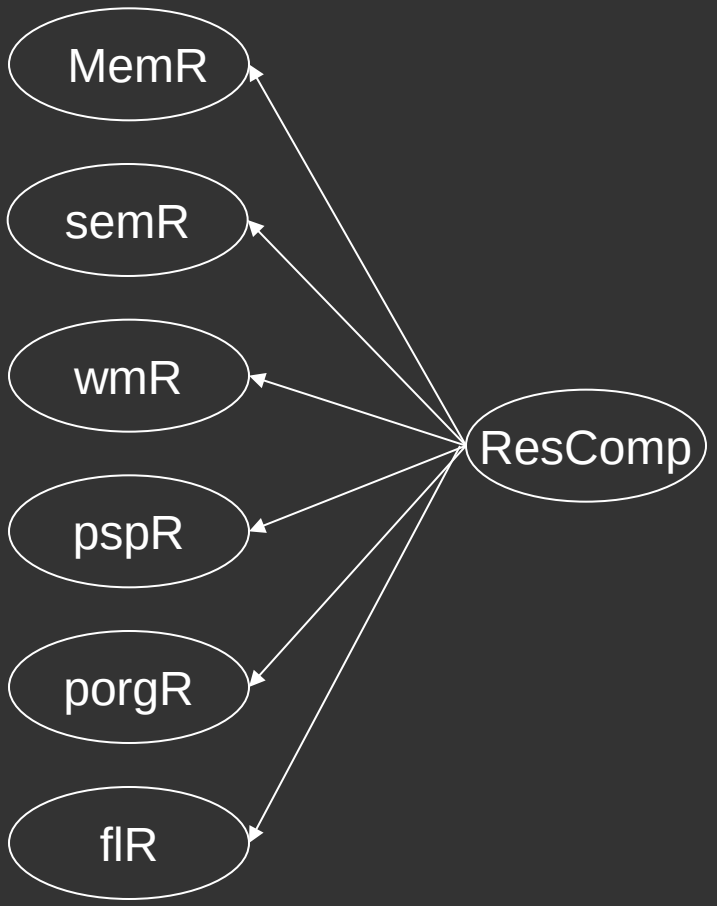
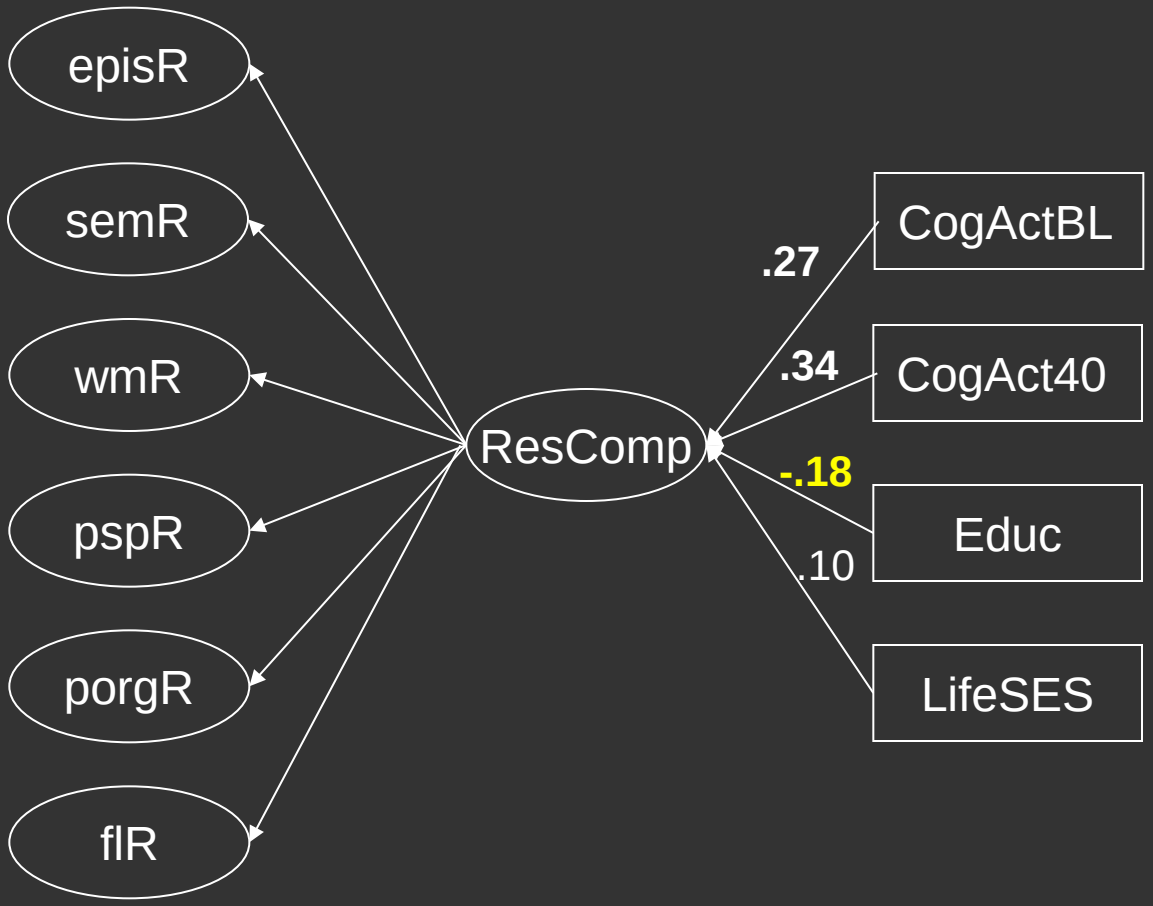

Frontal NP
Temporal NP
Parietal NP
ERC NP
Hippo NP
Parietal NFT
Frontal NFT
Temporal NFT
ERC NFT
Hippo NFT
Cortical NFT
Med-Temp NFT
Neuritic plaques
sex
height
Brain weight
Brain weight
Frontal NP
Temporal NP
Parietal NP
ERC NP
Hippo NP
Diffuse plaques
Micro-infarcts
Macro-infarcts
Lewy bodies
0
Mem
1
MemR
Story 1
Story 1 recall
Word list
WL recall
Story 2
Story 2 recall



- Model estimated 6 residual terms, 1 for each cognitive domain
- Evaluation of covariance structure showed a single, second order factor accounted for variance in the 6 domains very well

* Each residual estimated simultaneously


episR
semR
wmR
pspR
porgR
flR
ResComp
.27
.34
-.18
.10
CogActBL
CogAct40
Educ
LifeSES