THE UNIVERSITY of EDINBURGH
Centre for Cognitive Ageing and Cognitive Epidemiology

Predicting cognitive decline:

Evidence from studies of lifestyle, neuroimaging, and genetics

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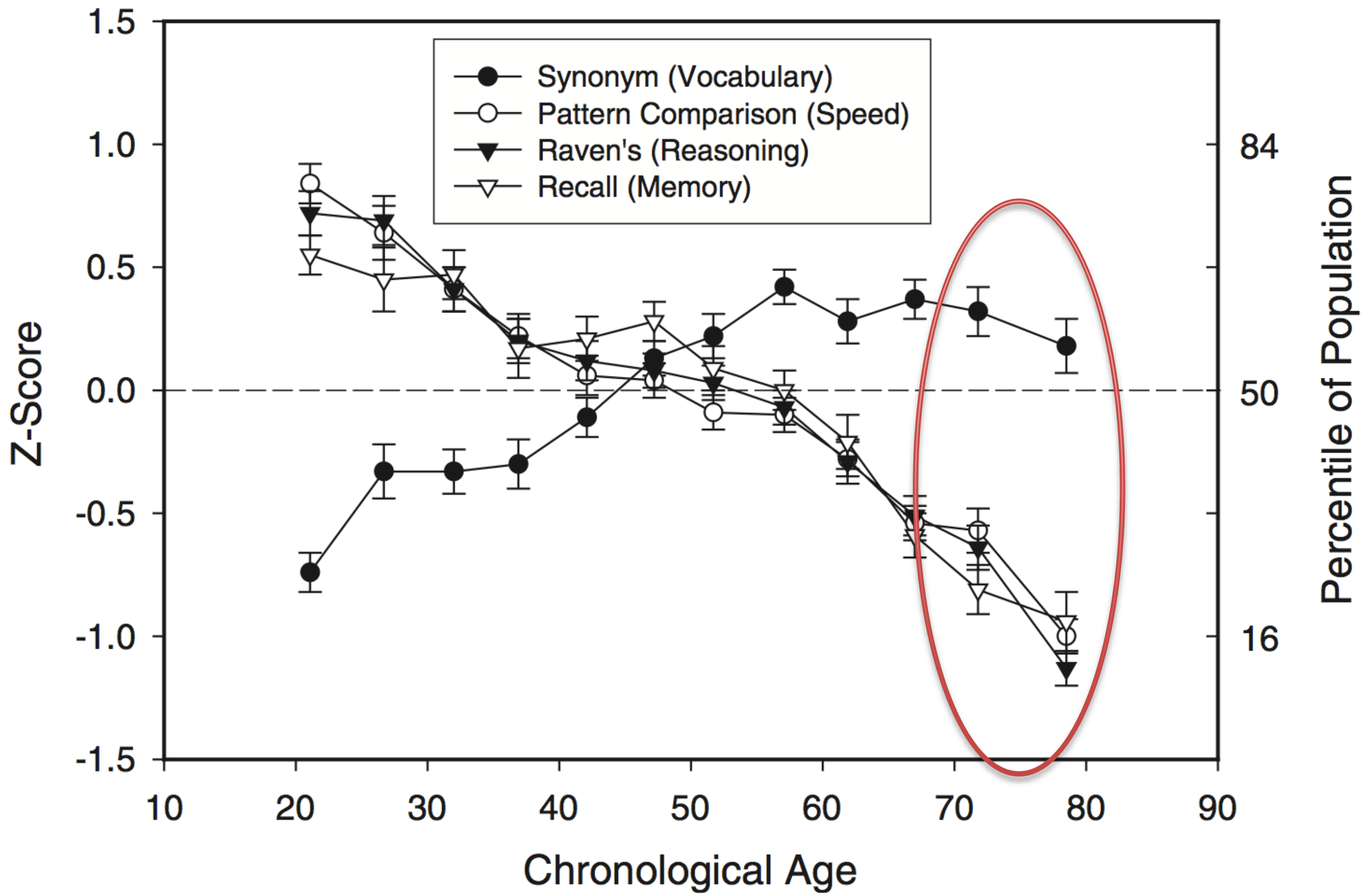
Age-related cognitive decline



Salthouse (2004) *Curr Direct Psych Sci*, p. 141

Neuropsychology
2011, Vol. 25, No. 3, 368–377

0894-4105/11/$12.00 DOI: 10.1037/a0022348

Neurocognitive Functions and Everyday Functions Change Together in Old Age

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University of Texas at Austin

OPEN ACCESS Freely available online
PLOS ONE

Poor Decision Making Is a Consequence of Cognitive Decline among Older Persons without Alzheimer's Disease or Mild Cognitive Impairment

Patricia A. Boyle[1,2]*, Lei Yu[1,3], Robert S. Wilson[1,3], Keith Gamble[1,4], Aron S. Buchman[1,3], David A. Bennett[1,3]

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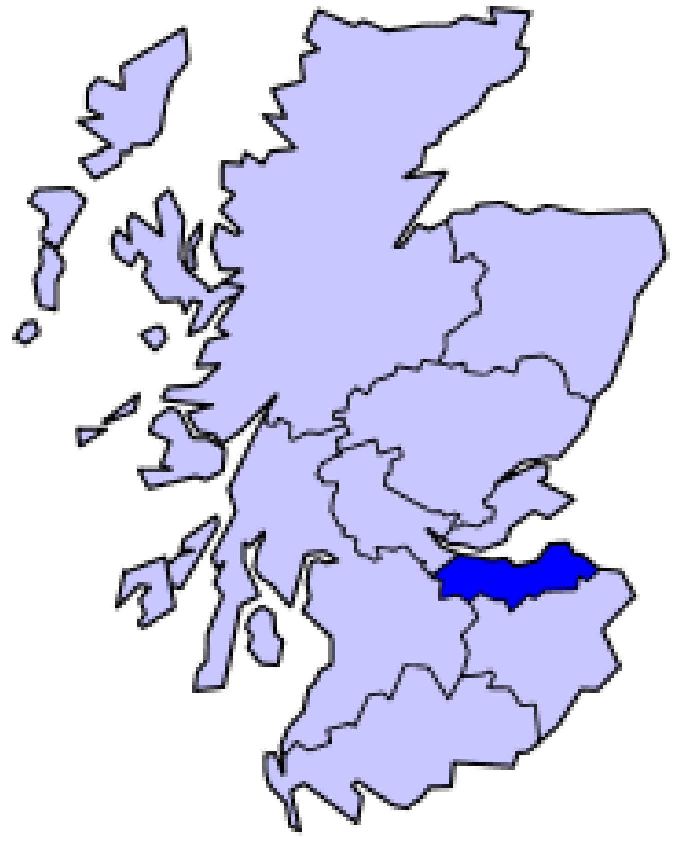
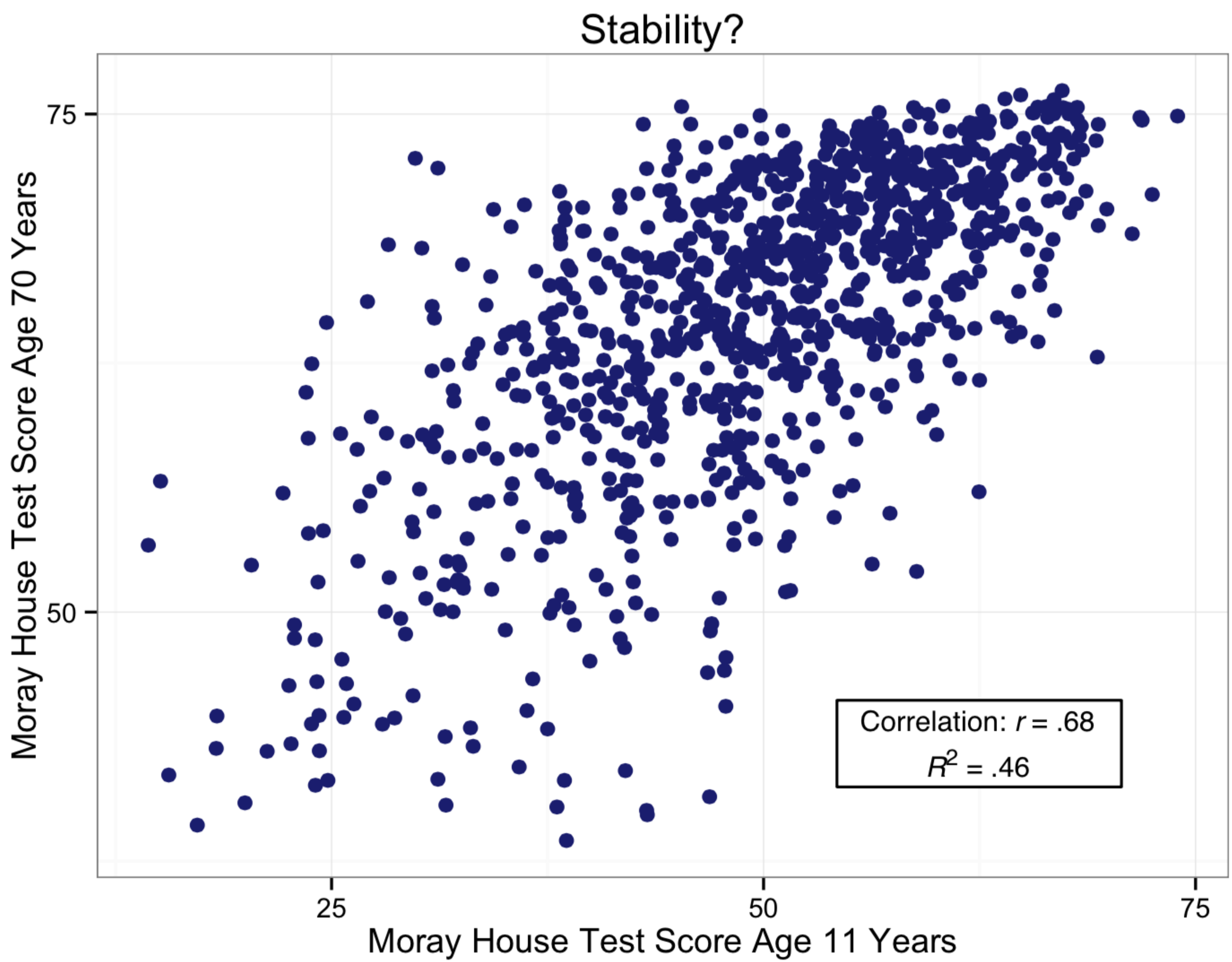
Lothian Birth Cohort 1936

- Born in 1936, tested in Scottish Mental Survey in 1947
- Followed up from 2004 onwards as a study of ageing

- Follow-up testing:
  - n = 1,091 at mean age 70;
  - n = 866 at mean age 73;
  - n = 697 at mean age 76.
- MRI scans:
  - n = 728 at age 73;
  - n = 488 at age 76.




Stability?
Moray House Test Score Age 70 Years
75
50
25
50
75
Moray House Test Score Age 11 Years
Correlation: r = .68
R2 = .46

Studies in this talk

1. **A multivariate model of predictors of cognitive decline**

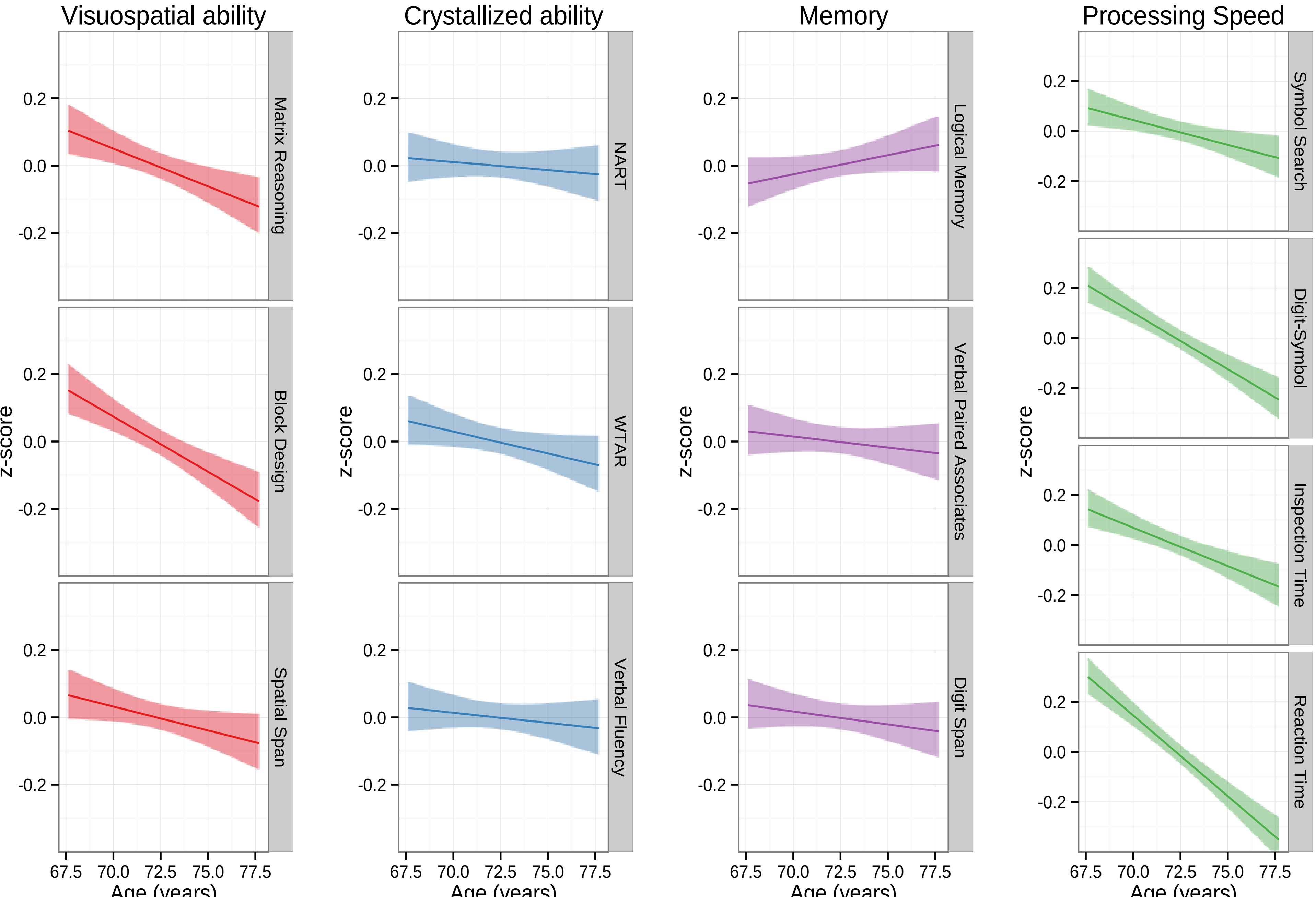
2. **Coupled change in cognitive ability and in the brain**

3. **Schizophrenia genes and cognitive decline**

1. Predictors of cognitive decline

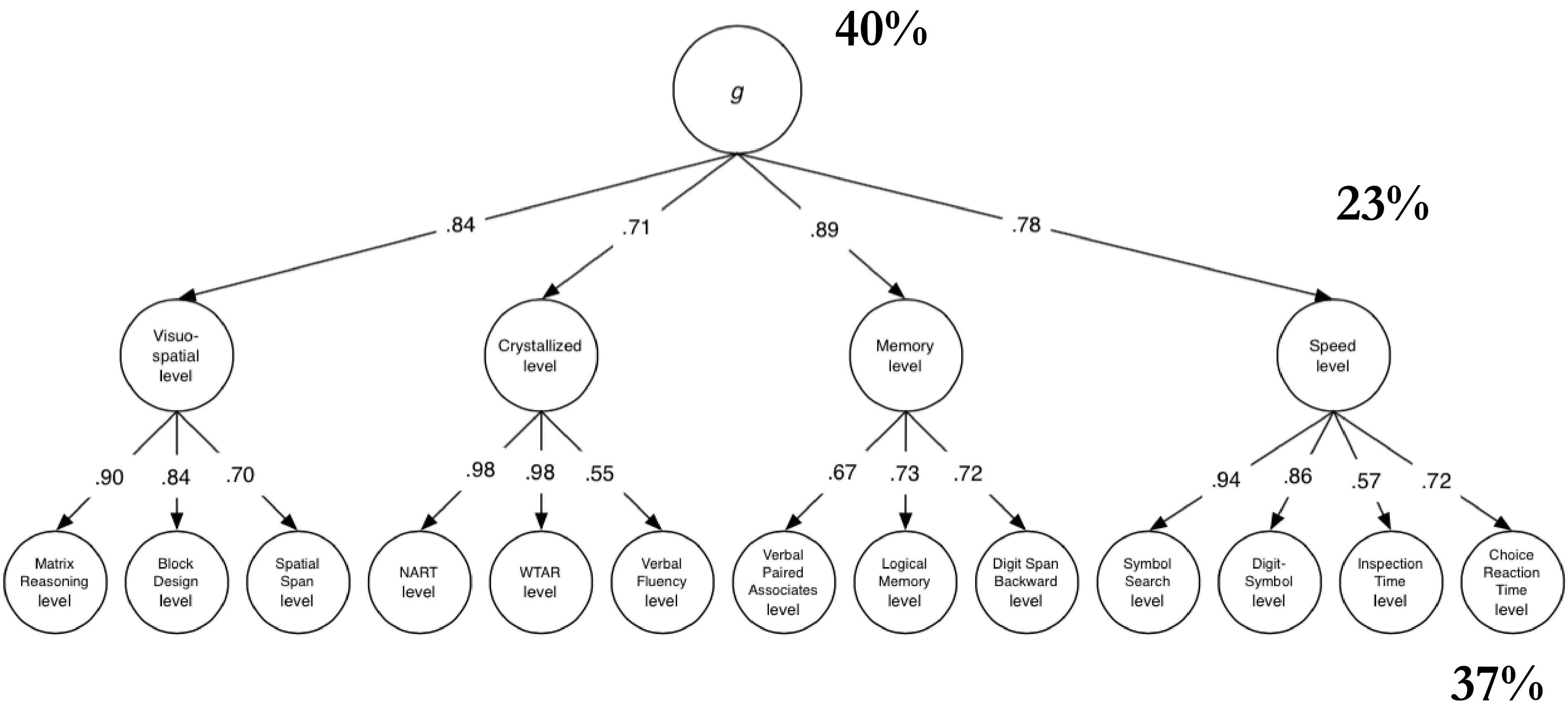
Background

- Model of cognitive change across three waves
  - Ages 70, 73, 76 years
- 13 sensitive, normal-range cognitive measures
- Wide range of potential predictors
  - Lifestyle, sociodemographic, fitness, genetic
  - All entered simultaneously
  - Controlled for effects of each other and of multiple testing
- Latent growth model design (error-free cognitive change estimates) – "factors of curves"



Visuospatial ability
Crystallized ability
Memory
Processing Speed
Matrix Reasoning
Block Design
Spatial Span
NART
WTAR
Verbal Fluency
Logical Memory
Verbal Paired Associates
Digit Span
Symbol Search
Digit-Symbol
Inspection Time
Reaction Time
z-score
0.2
0.0
-0.2
67.5
70.0
72.5
75.0
77.5
Age (years)

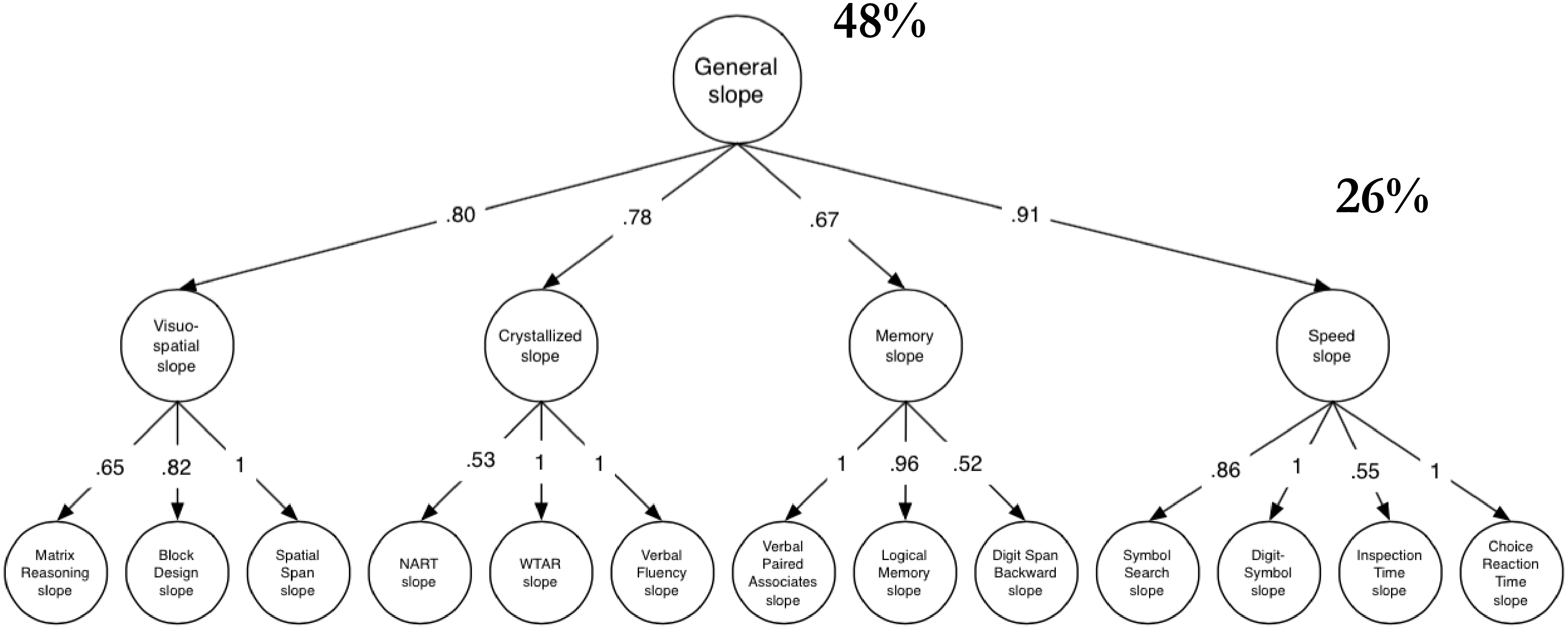
Model of **levels**



Model of **slopes**

48%

26%



26%

Potential predictors

- Sociodemographic
  - Age, sex, education, SES of parents, own SES, neighborhood deprivation
- Physical fitness
  - Forced expiratory volume, 6 metre walk time, grip strength
- Genetic
  - APOE ε4 carrier
- Lifestyle
  - Smoking, BMI
- Medical history
  - Cardiovascular disease, hypertension, diabetes

Covariate	General factor estimate (SE)	Domain estimate (SE)			
	g slope	Visuospatial slope	Crystallized slope	Memory slope	Speed slope
Age (baseline)					
Sex (female) †					
Time lag					
Age 11 IQ					
Education					
Childhood SES					
Own SES					
SIMD					
FEV					
6m Walk time					
Grip strength					
APOE†					
BMI					
Smoking†					
CVD†					
Hypertension†					
Diabetes†					

Conclusions

- Around half the variance in cognitive ageing associated with a single general factor
- Few strong/significant predictors of cognitive decline in a multivariate model
- *APOE* status the most consistent
- Small effects, low power?
- Analogy to polygenic model of complex traits?
- Importance of multivariate models?

2. Coupled change in cognitive ability and the brain

The disconnected mind

DISCONNEXION SYNDROMES IN ANIMALS AND MAN[1]

BY

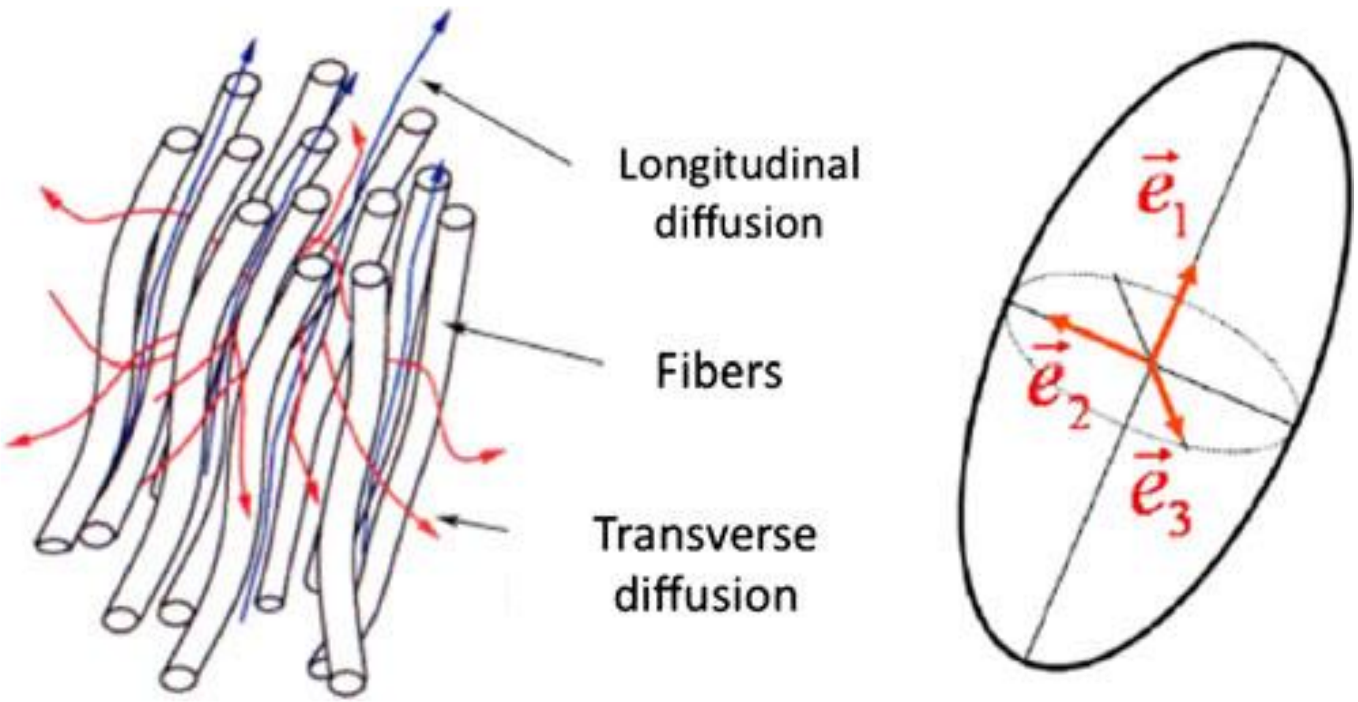
NORMAN GESCHWIND

PART I

(From the Aphasia Research Section, Neurology Service, Boston Veterans Administration Hospital and the Department of Neurology, Boston University Medical School)

- Geschwind (1965), *Brain* (Parts I and II)
- White matter lesions may cause agnosias, aphasias, apraxias
- What about age-related cognitive decline?

Diffusion Tensor MRI



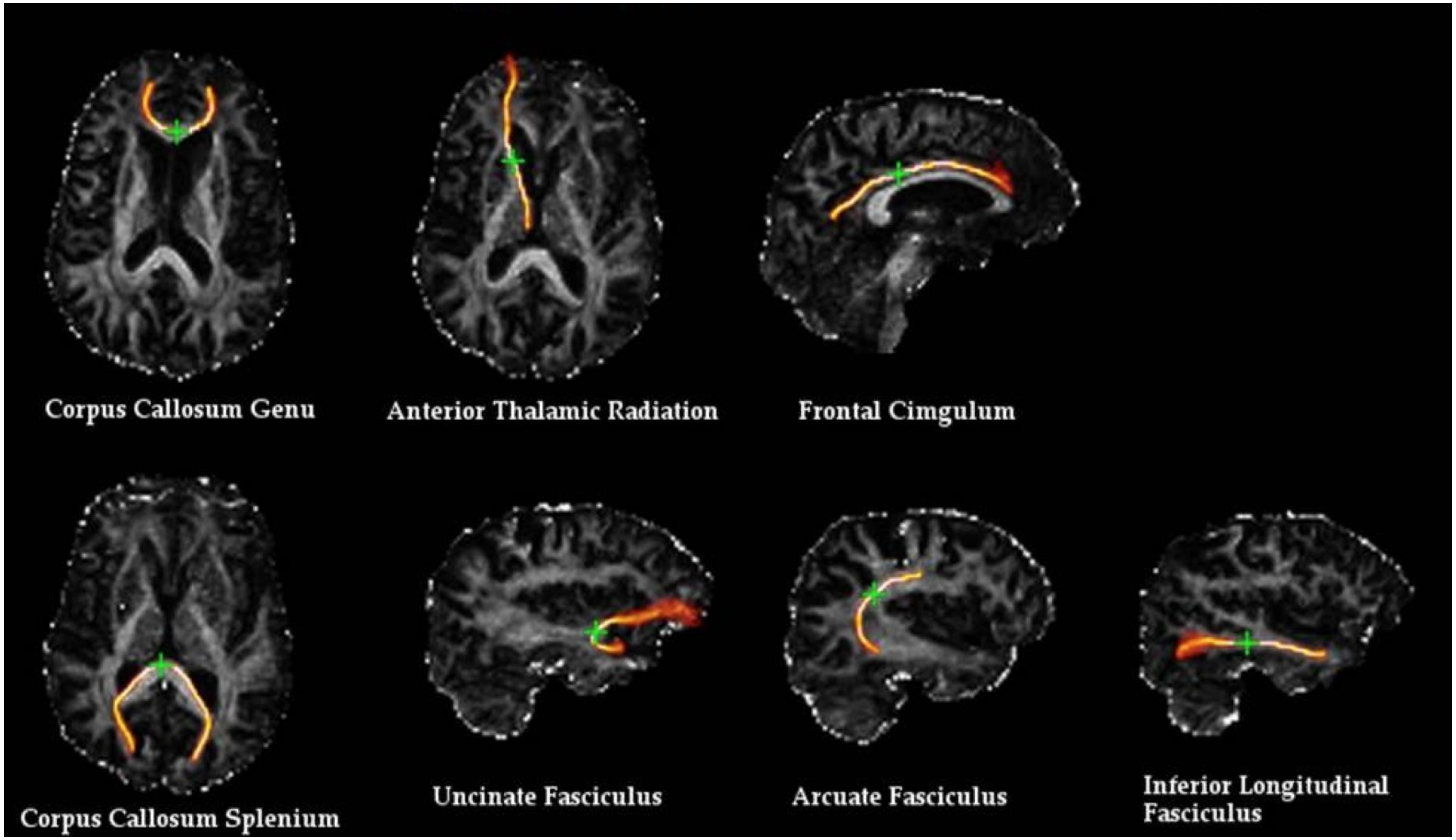
Background

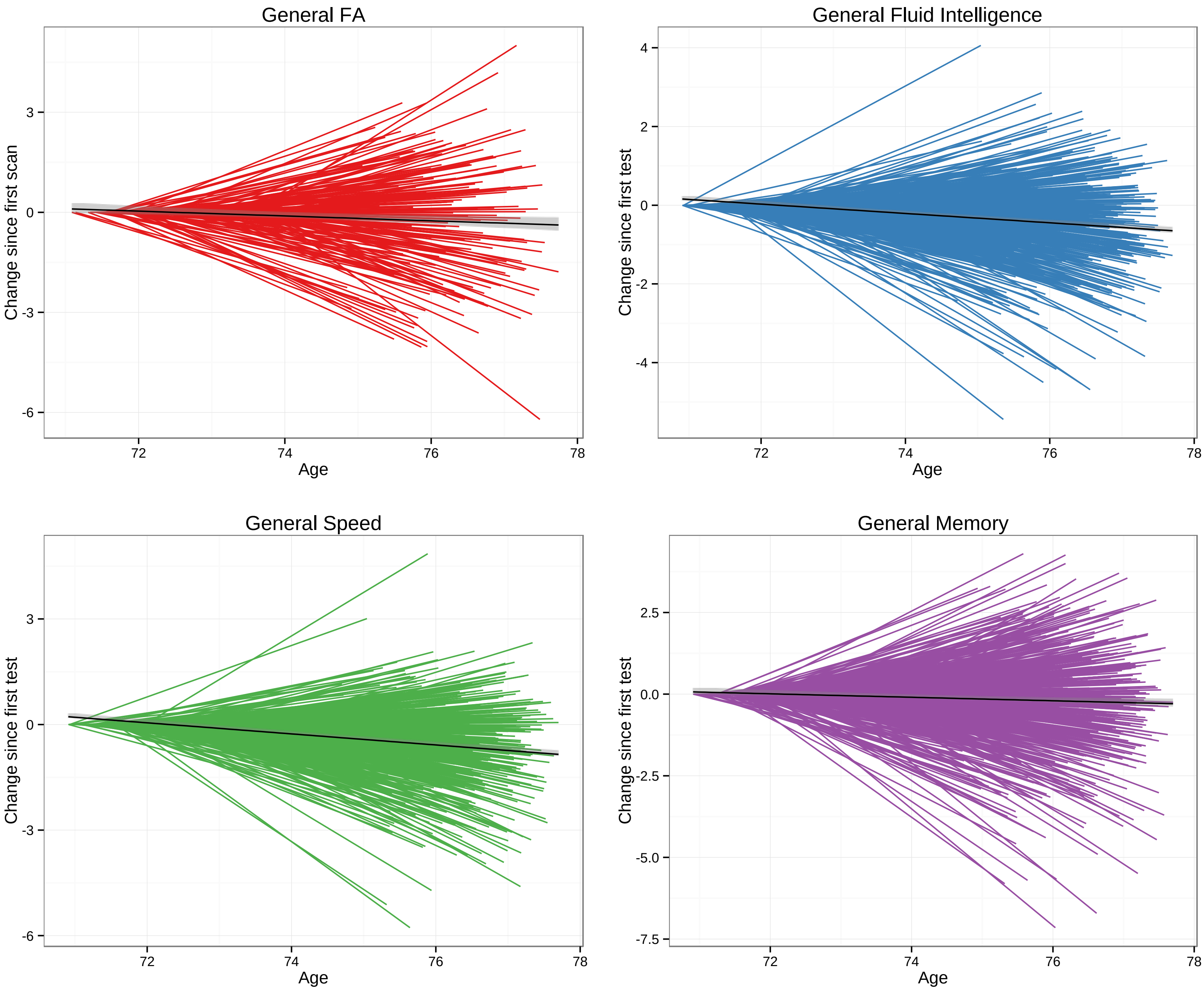
- Only 2 previous longitudinal studies of white matter microstructure change and cognitive ageing
  - n = 73 (Charlton et al., 2010, *J Neurol Neurosurg Psychiatr*)
  - n = 40 (Lövdén et al., 2014, *NeuroImage*)
- Correlated change between working memory, processing speed, and white matter microstructure

- Our sample: n = 731 age 73, n = 488 age 76.

I. White matter tractography

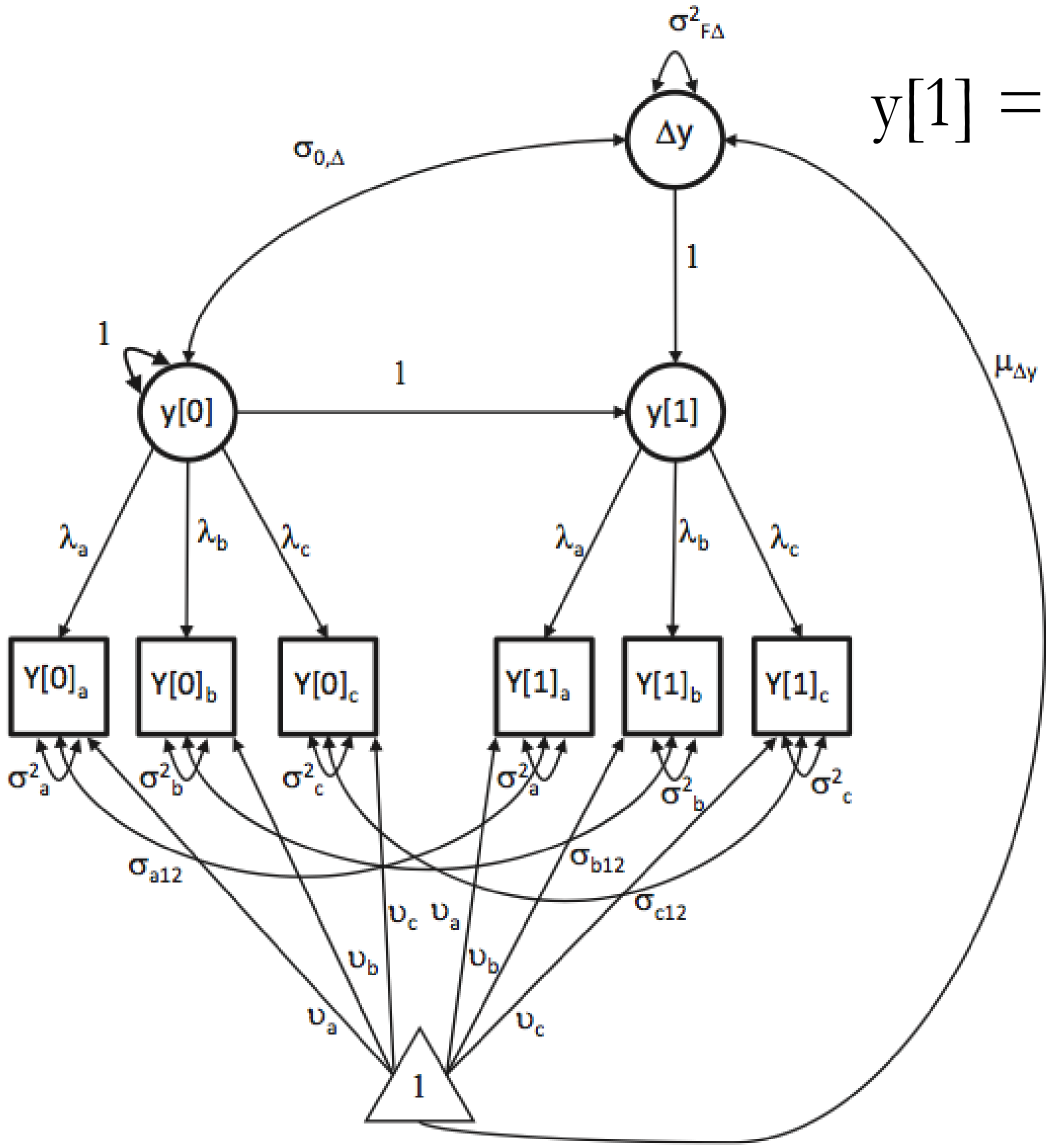
- General FA calculated (age 73 and age 76) from 12 white matter tracts across the brain

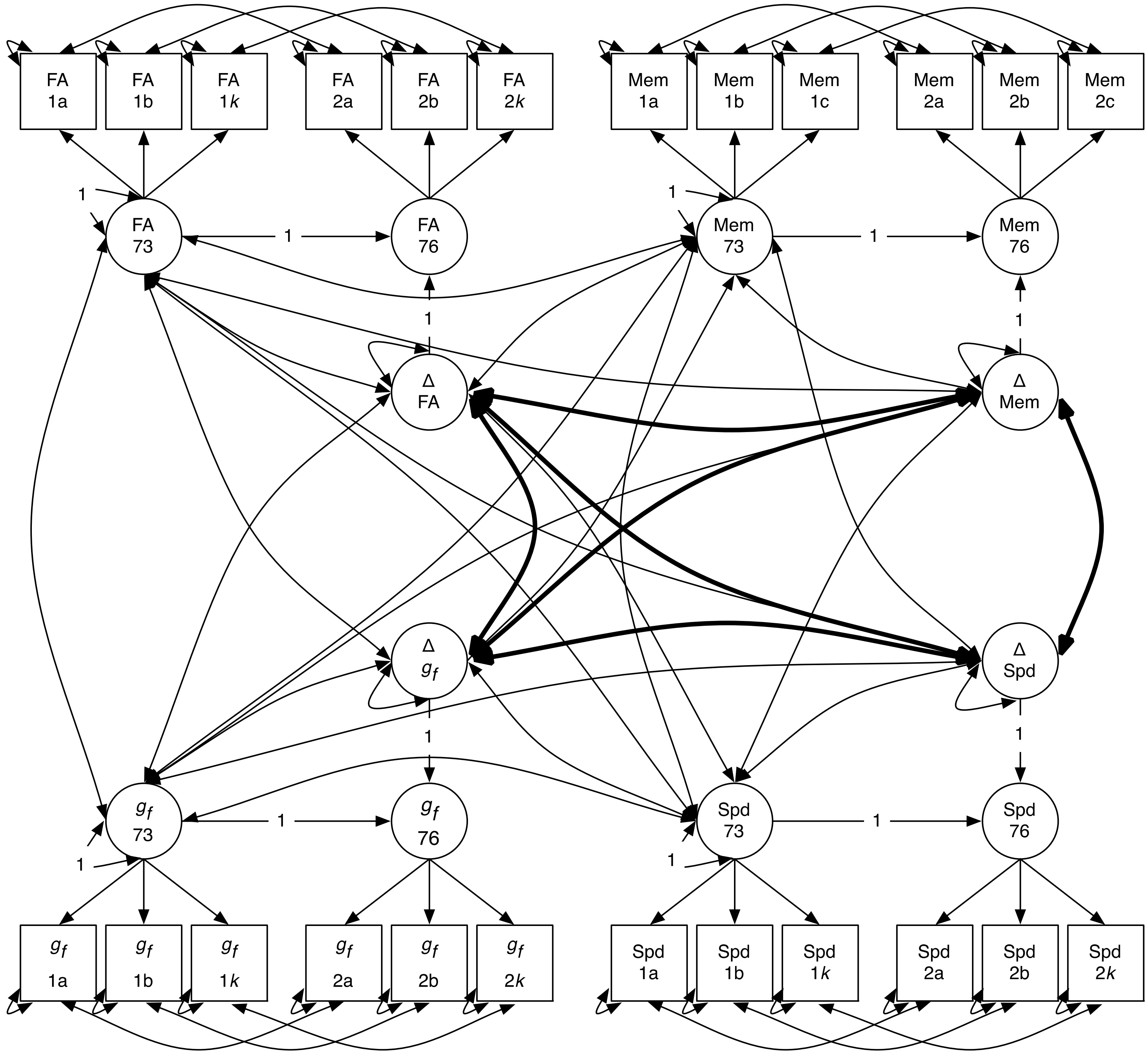



General FA
Change since first scan
3
0
-3
-6
72
74
76
78
Age
General Fluid Intelligence
Change since first test
4
2
0
-2
-4
72
74
76
78
Age
General Speed
Change since first test
3
0
-3
-6
72
74
76
78
Age
General Memory
Change since first test
2.5
0.0
-2.5
-5.0
-7.5
72
74
76
78
Age

Latent Difference Score model

$$y[1] = (1*y[0]) + (1*\Delta y)$$



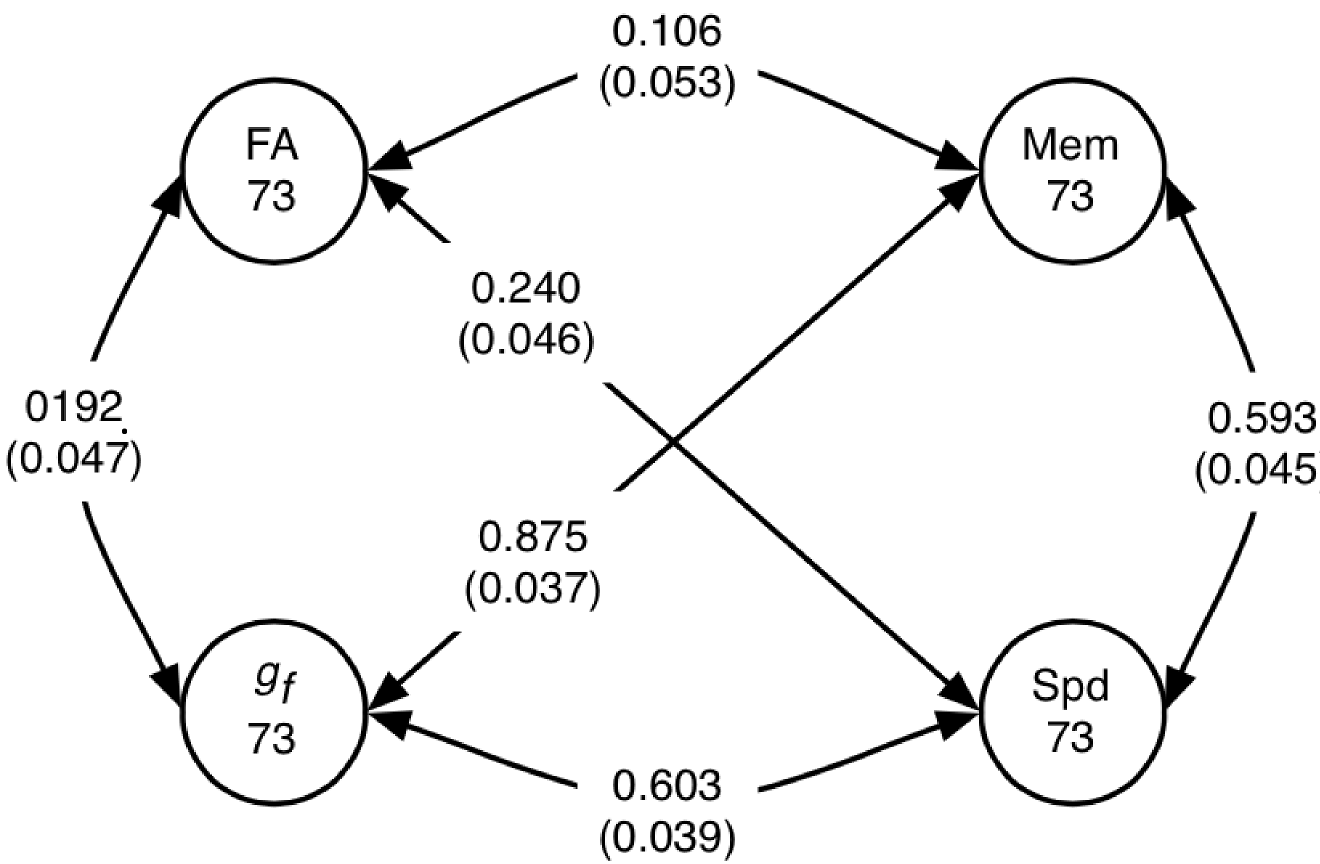


FA 1a
FA 1b
FA 1k
FA 2a
FA 2b
FA 2k
Mem 1a
Mem 1b
Mem 1c
Mem 2a
Mem 2b
Mem 2c
FA 73
FA 76
Mem 73
Mem 76
Δ FA
Δ Mem
Δ g_f
Δ Spd
g_f 73
g_f 76
Spd 73
Spd 76
g_f 1a
g_f 1b
g_f 1k
g_f 2a
g_f 2b
g_f 2k
Spd 1a
Spd 1b
Spd 1k
Spd 2a
Spd 2b
Spd 2k
1

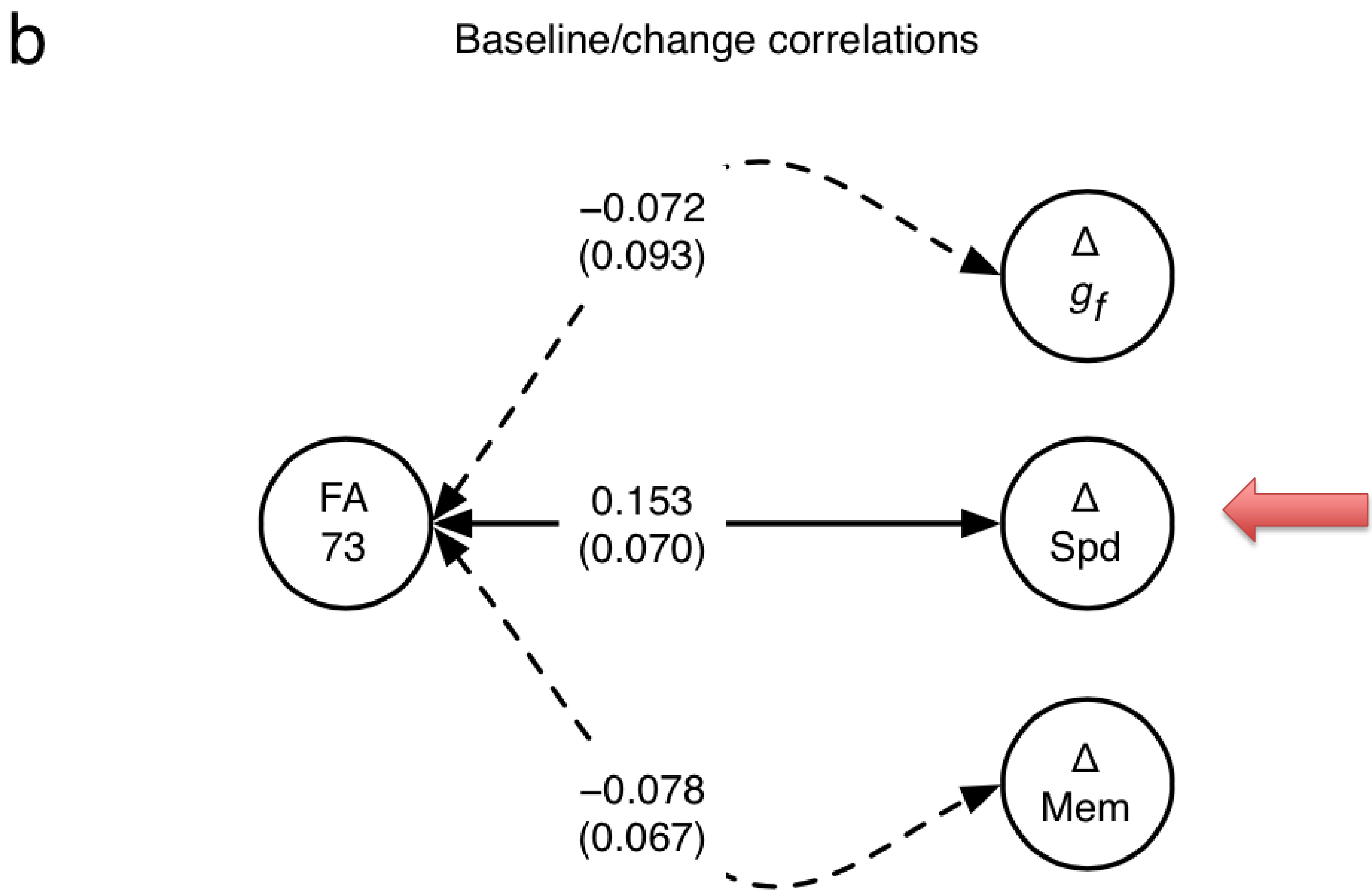
Results: Level-Level

a

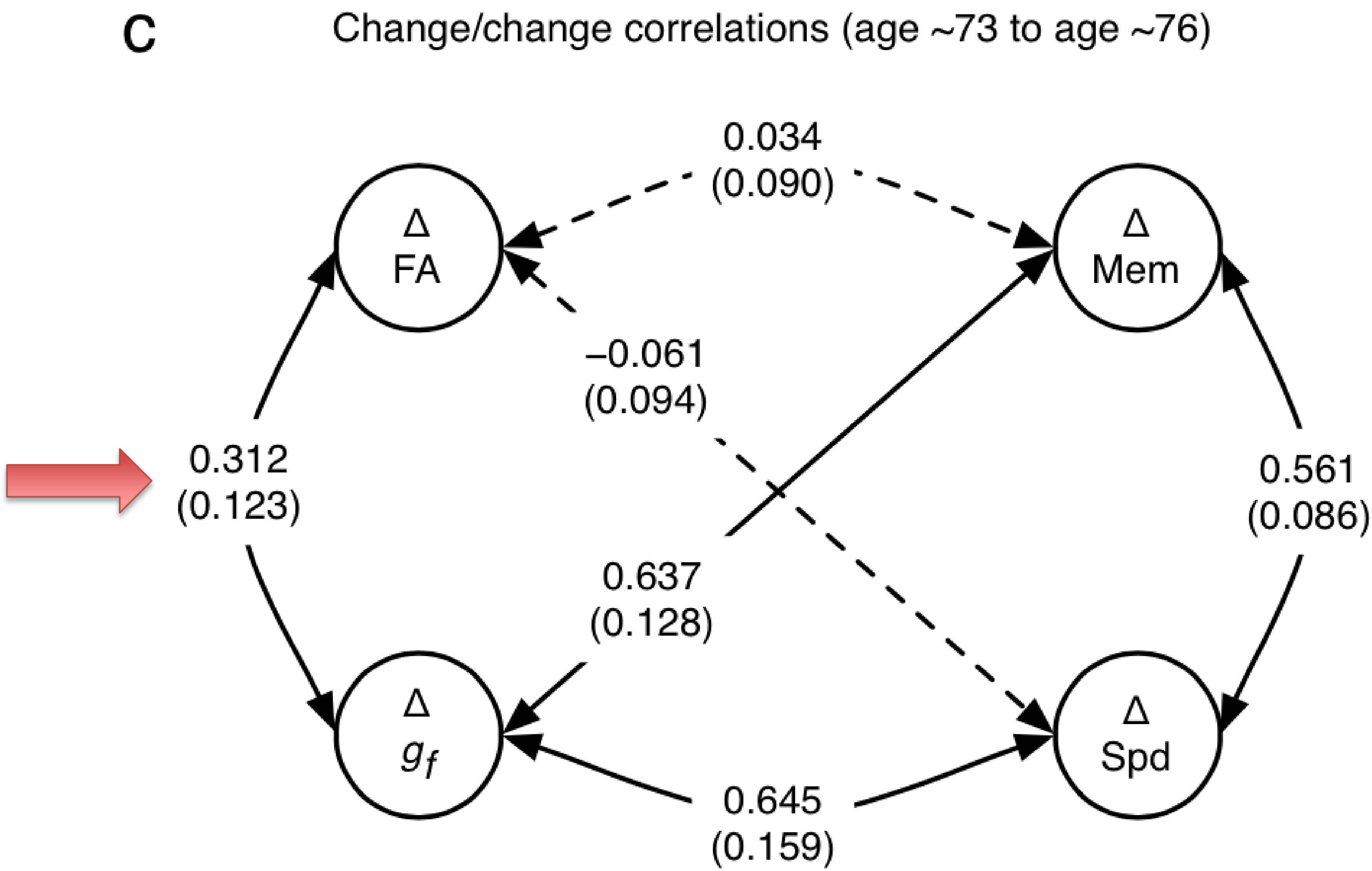
Baseline/baseline correlations (age ~73)



Results: Level-Change



Results: Change-change



White matter microstructure: conclusions

- Decline in white matter integrity is associated with decline in fluid intelligence from age 73 to age 76
- No such correlation for declines in memory (expected) or processing speed (unexpected)
- Longer time window needed for more power to detect change-change correlations?
- Best evidence to date for "the disconnected mind" underlying age-related cognitive decline?

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Behavioral/Cognitive

Coupled Changes in Brain White Matter Microstructure and Fluid Intelligence in Later Life

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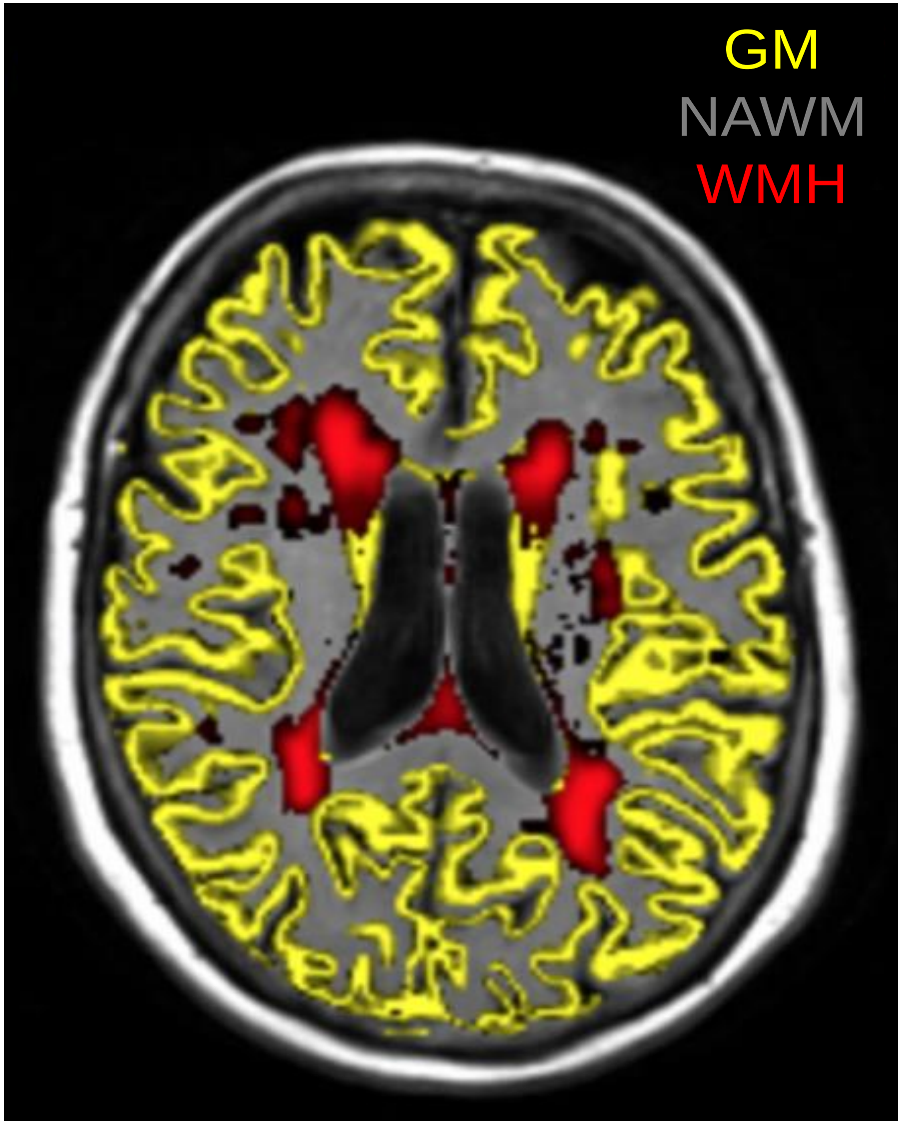
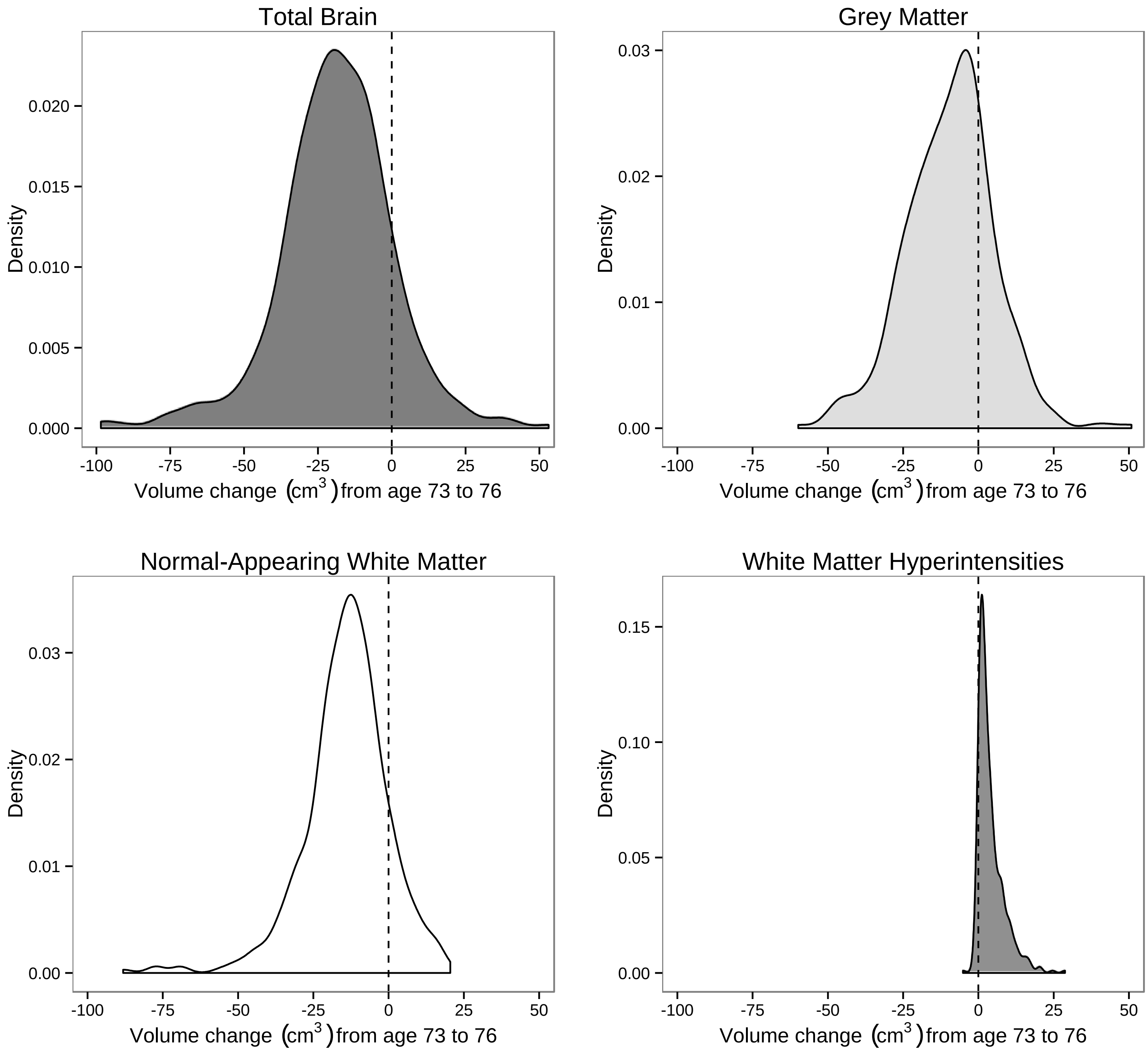
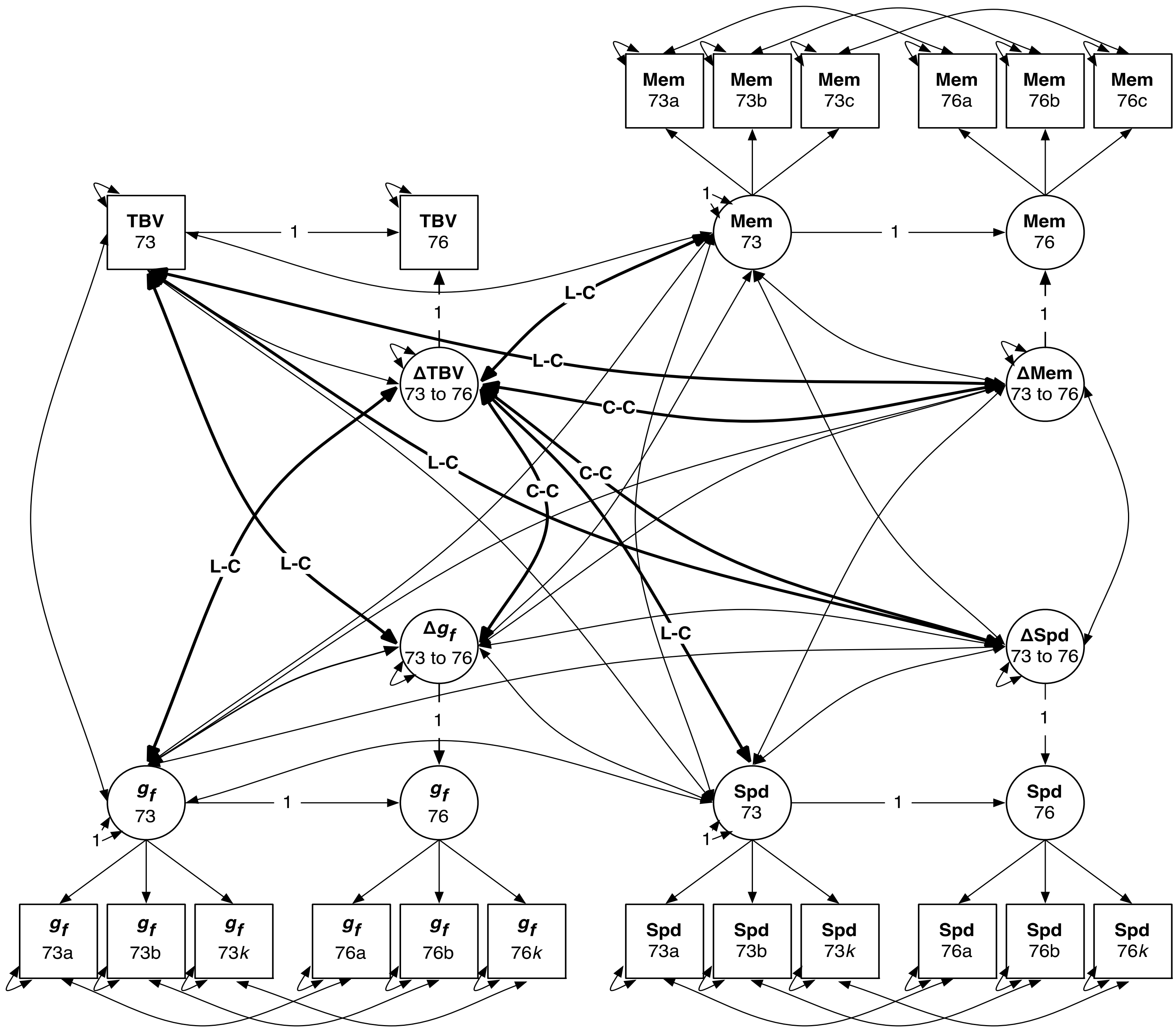
[1]Department of Psychology, [2]Centre for Cognitive Ageing and Cognitive Epidemiology, and [3]Alzheimer Scotland Dementia Research Centre, The University of Edinburgh, Edinburgh EH8 9JZ, UK, [4]Centre for Clinical Brain Sciences, The University of Edinburgh, Edinburgh EH16 4SA, UK, [5]Brain Research Imaging Centre, The University of Edinburgh, Edinburgh EH4 2XU, UK, [6]Scottish Imaging Network, a Platform for Scientific Excellence (SINAPSE), Edinburgh, UK, [7]Department of Psychology, University of Texas, Austin, Texas 78712-0187, and [8]Department of Psychology, Heriot-Watt University, Edinburgh EH14 4AS, UK

II. Volumetric changes

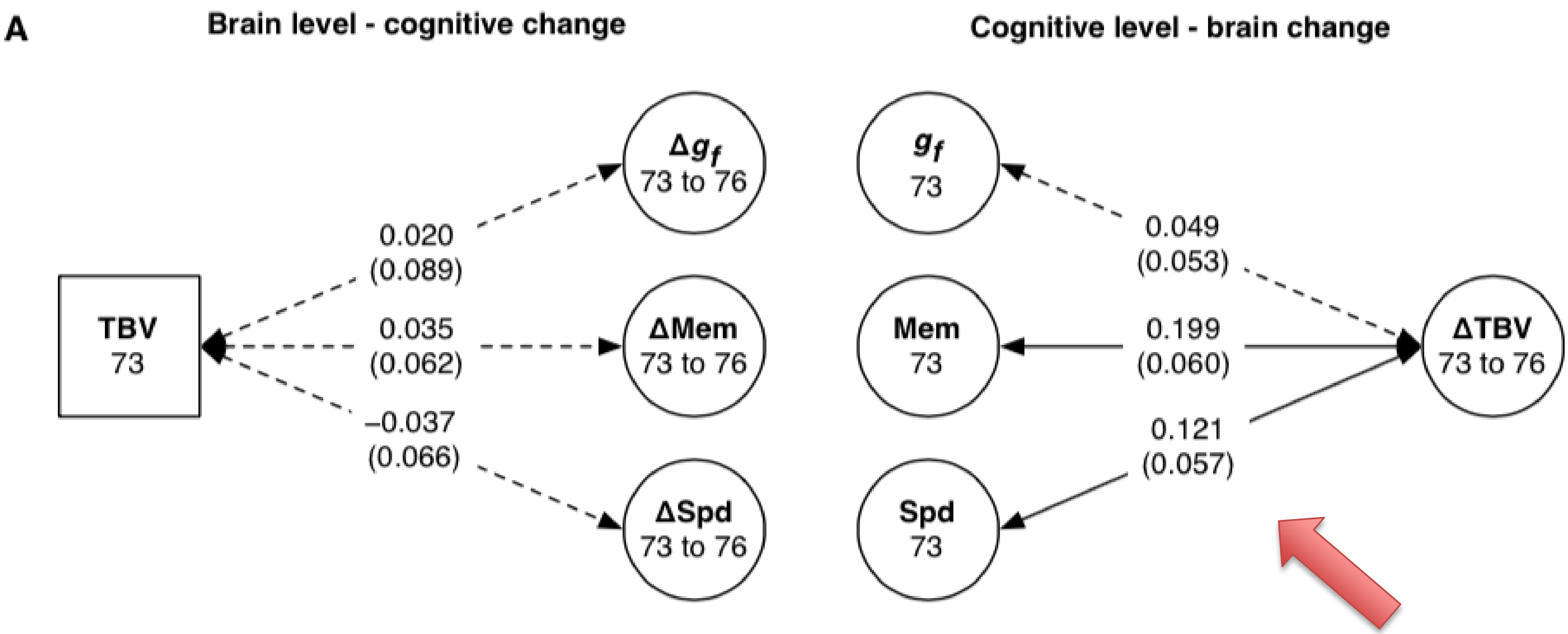




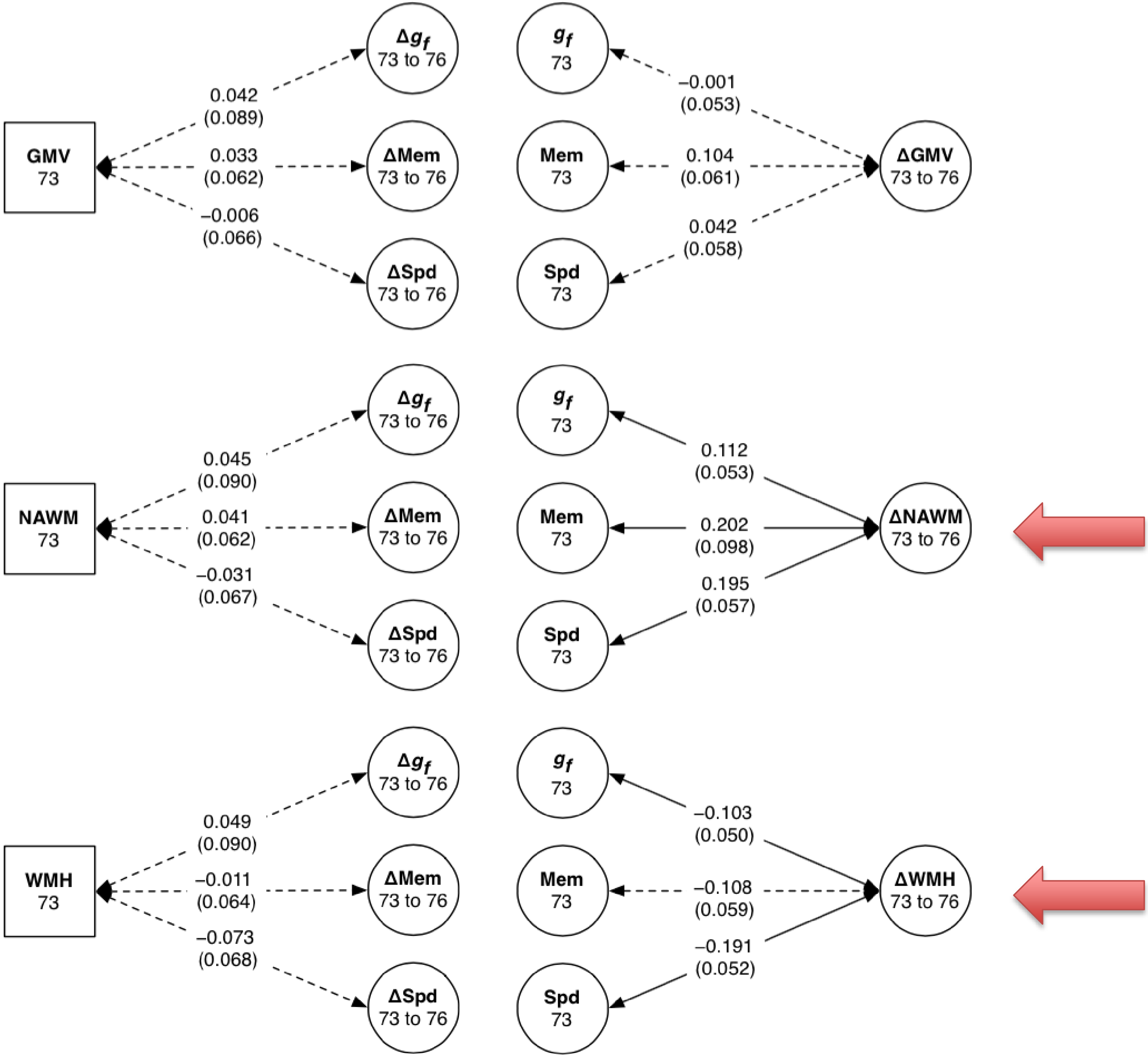
Total Brain
Grey Matter
Normal-Appearing White Matter
White Matter Hyperintensities
Density
0.000
0.005
0.010
0.015
0.020
0.00
0.01
0.02
0.03
0.05
0.10
0.15
-100
-75
-50
-25
0
25
50
Volume change (cm3) from age 73 to 76


Mem 73a
Mem 73b
Mem 73c
Mem 76a
Mem 76b
Mem 76c
TBV 73
1
TBV 76
1
Mem 73
1
Mem 76
L-C
1
1
ΔTBV 73 to 76
L-C
ΔMem 73 to 76
C-C
L-C
C-C
C-C
L-C
L-C
L-C
Δg_f 73 to 76
ΔSpd 73 to 76
1
1
g_f 73
1
g_f 76
Spd 73
1
Spd 76
1
1
g_f 73a
g_f 73b
g_f 73k
g_f 76a
g_f 76b
g_f 76k
Spd 73a
Spd 73b
Spd 73k
Spd 76a
Spd 76b
Spd 76k

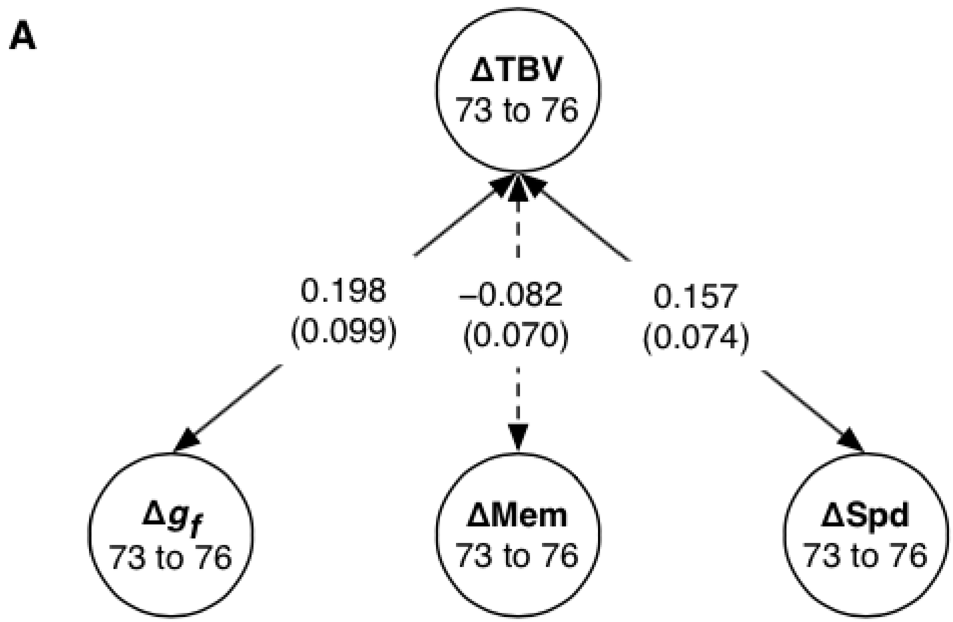
Results: Level-change

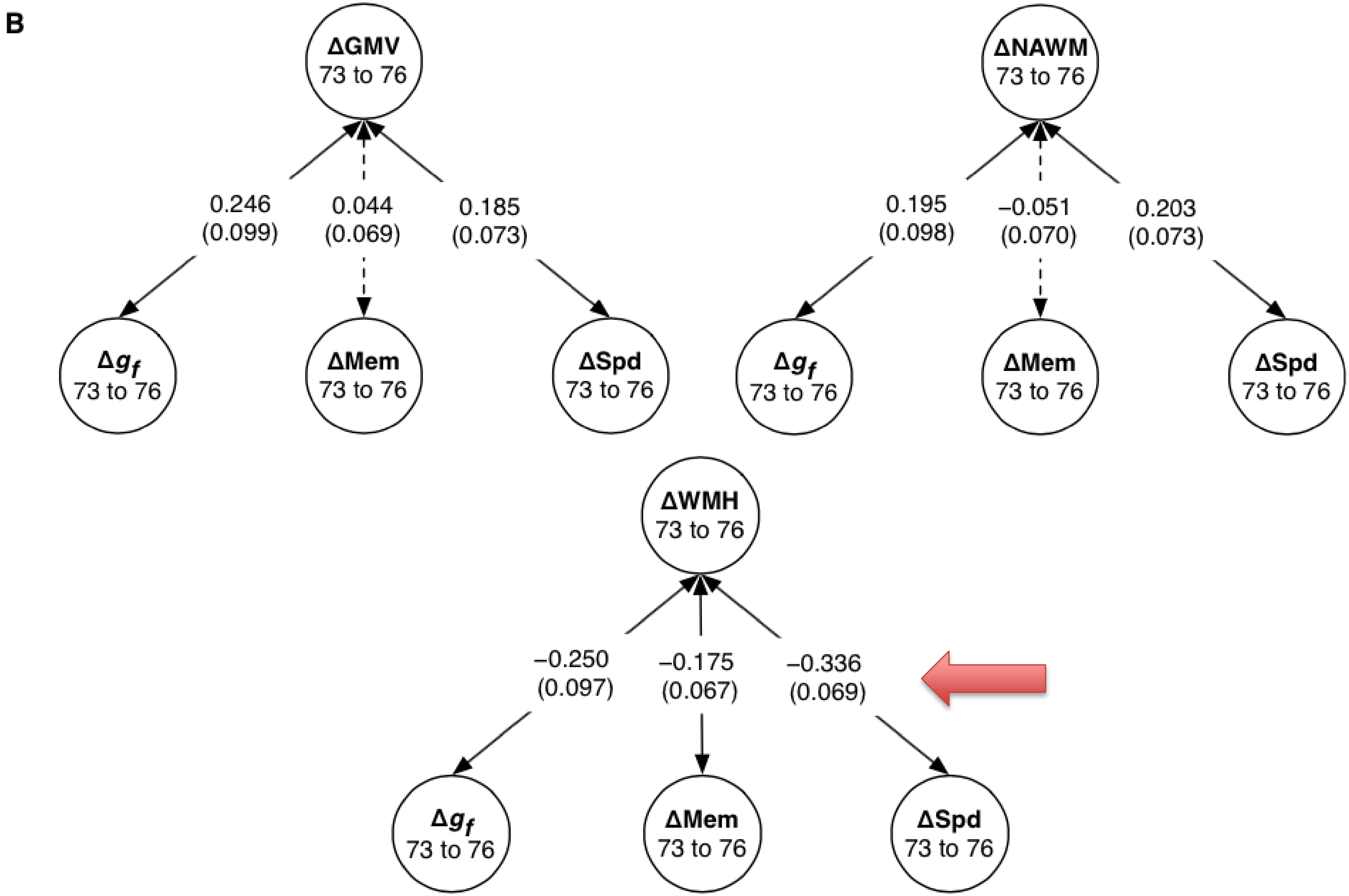


B


GMV
73
Δg_f
73 to 76
ΔMem
73 to 76
ΔSpd
73 to 76
0.042
(0.089)
0.033
(0.062)
–0.006
(0.066)
g_f
73
Mem
73
Spd
73
ΔGMV
73 to 76
–0.001
(0.053)
0.104
(0.061)
0.042
(0.058)
NAWM
73
0.045
(0.090)
0.041
(0.062)
–0.031
(0.067)
ΔNAWM
73 to 76
0.112
(0.053)
0.202
(0.098)
0.195
(0.057)
WMH
73
0.049
(0.090)
–0.011
(0.064)
–0.073
(0.068)
ΔWMH
73 to 76
–0.103
(0.050)
–0.108
(0.059)
–0.191
(0.052)

Results: Change-change



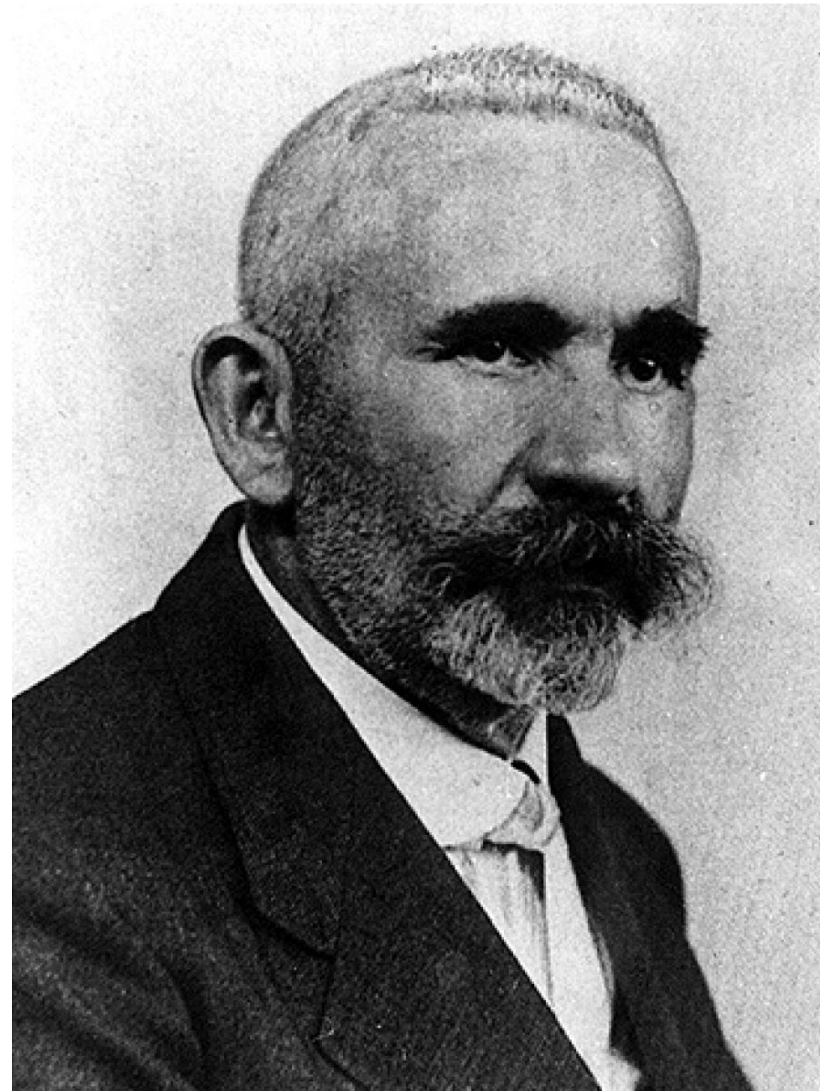

B
ΔGMV
73 to 76
0.246
(0.099)
0.044
(0.069)
0.185
(0.073)
Δg_f
73 to 76
ΔMem
73 to 76
ΔSpd
73 to 76
ΔNAWM
73 to 76
0.195
(0.098)
−0.051
(0.070)
0.203
(0.073)
Δg_f
73 to 76
ΔMem
73 to 76
ΔSpd
73 to 76
ΔWMH
73 to 76
−0.250
(0.097)
−0.175
(0.067)
−0.336
(0.069)
Δg_f
73 to 76
ΔMem
73 to 76
ΔSpd
73 to 76

Brain volumes: Conclusions

- Cognitive level predicts subsequent brain changes…
- …but brain volumes do not predict subsequent cognitive changes.
- Strongest change-change correlations with increases in pathological white matter (hyperintensities)
- More detailed brain imaging, longer time window needed for stronger results?

3. Schizophrenia genes and cognitive decline

Dementia praecox



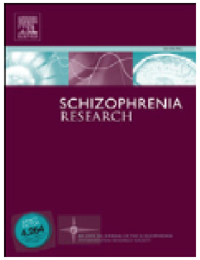
Schizophrenia and intelligence

2011 Meta-analysis, *Schizophrenia Research*:

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres



A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia

Golam M. Khandaker [a,*], Jennifer H. Barnett [a,b], Ian R. White [c], Peter B. Jones [a]

[a] *Department of Psychiatry, University of Cambridge, Cambridge, UK*
[b] *Cambridge Cognition Ltd., Cambridge, UK*
[c] *MRC Biostatistics Unit, Cambridge, UK*

Conclusions: strong link between premorbid IQ and schizophrenia; IQ might be protective against schizophrenia

Schizophrenia and intelligence

2013 Opinion piece, *JAMA Psychiatry*

Special Communication

Schizophrenia Is a Cognitive Illness
Time for a Change in Focus

René S. Kahn, MD, PhD; Richard S. E. Keefe, PhD

Genetic risk for schizophrenia and intelligence

McIntosh et al., 2013, *Biological Psychiatry*:

- Polygenic Risk for Schizophrenia & Cognition in childhood and in later life
  - Lothian Birth Cohorts 1921 and 1936
- Greater genetic risk for schizophrenia associated with lower cognitive ability at age 70 (but not at age 11)
  - Also associated with greater negative change from childhood to later life

Polygenic risk score

- Most recent schizophrenia GWAS
  - Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) *Nature*
- Calculation of score in new sample from weight of each SNP in GWAS
- Scores calculated at five thresholds:

  $p = 1.00$ (least conservative)

  $p < 0.50$

  $p < 0.10$

  $p < 0.05$

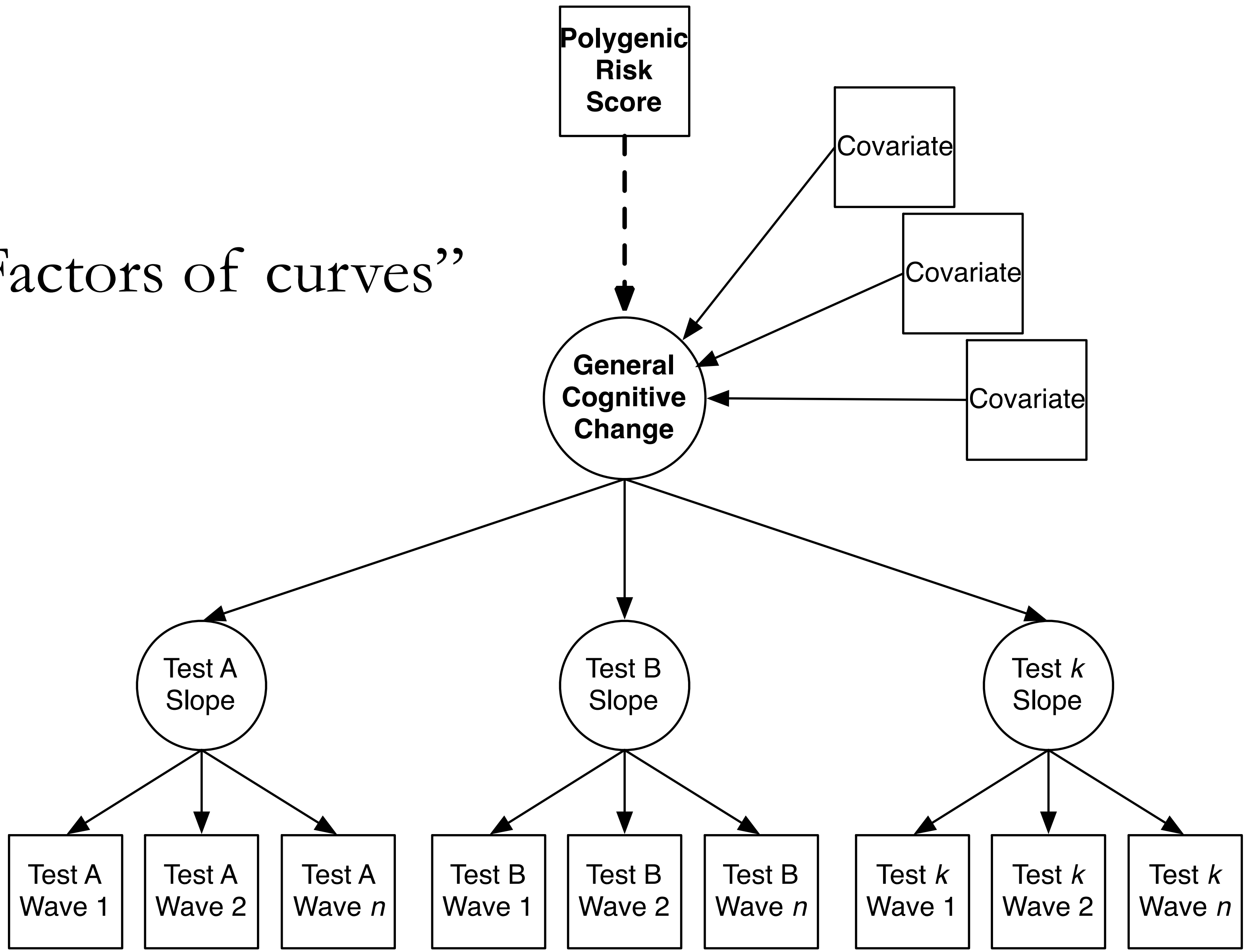
  $p < 0.01$ (most conservative)

Present study

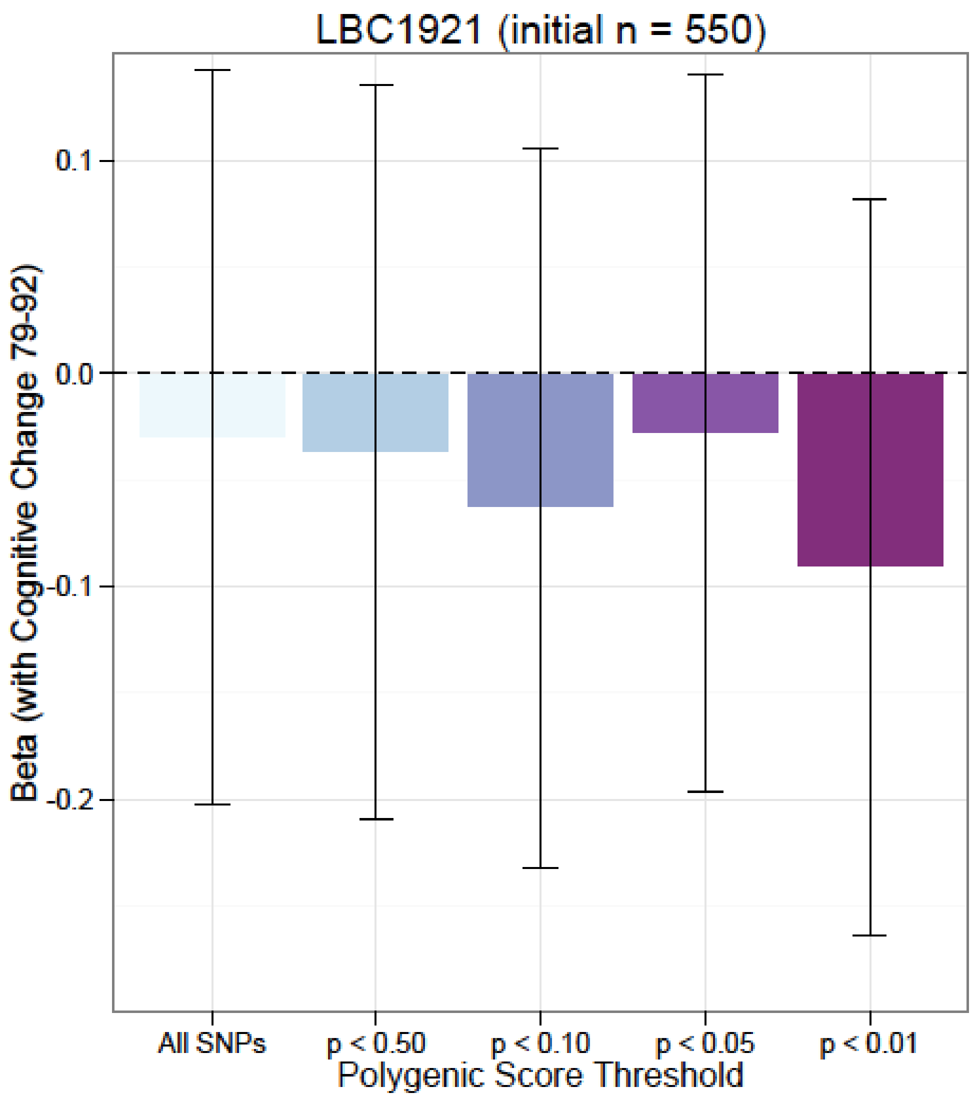
- **Participants:**
- Lothian Birth Cohort 1921 (initial n = 550):
  - Ages 79, 83, 87, 90, 92
  - n = 59 by final wave
  - Logical Memory, Raven's Matrices, Verbal Fluency
- Lothian Birth Cohort 1936 (initial n = 1,091):
  - (see previous studies)
- **Hypothesis:**
  - Higher polygenic risk score for schizophrenia will predict more cognitive decline across testing waves

Latent Growth Curve Model

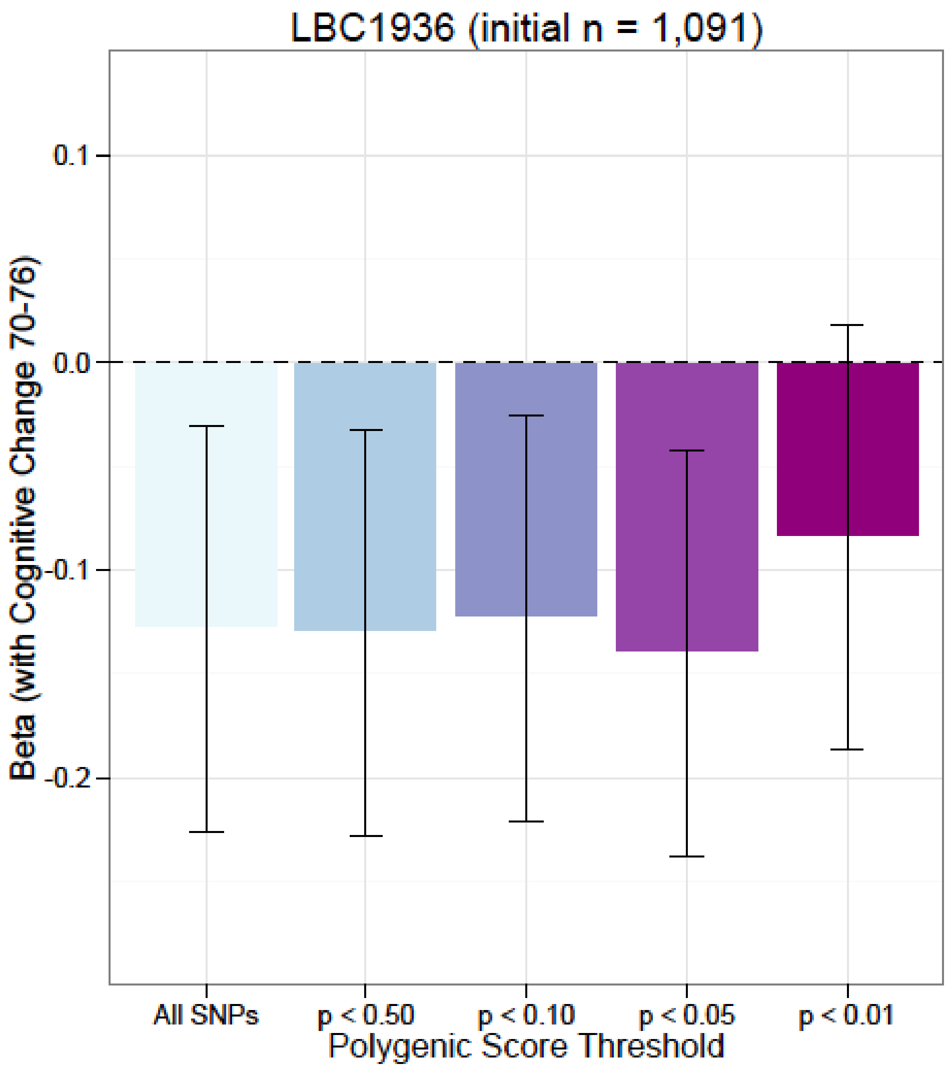
"Factors of curves"



Lothian Birth Cohort 1921



Lothian Birth Cohort 1936

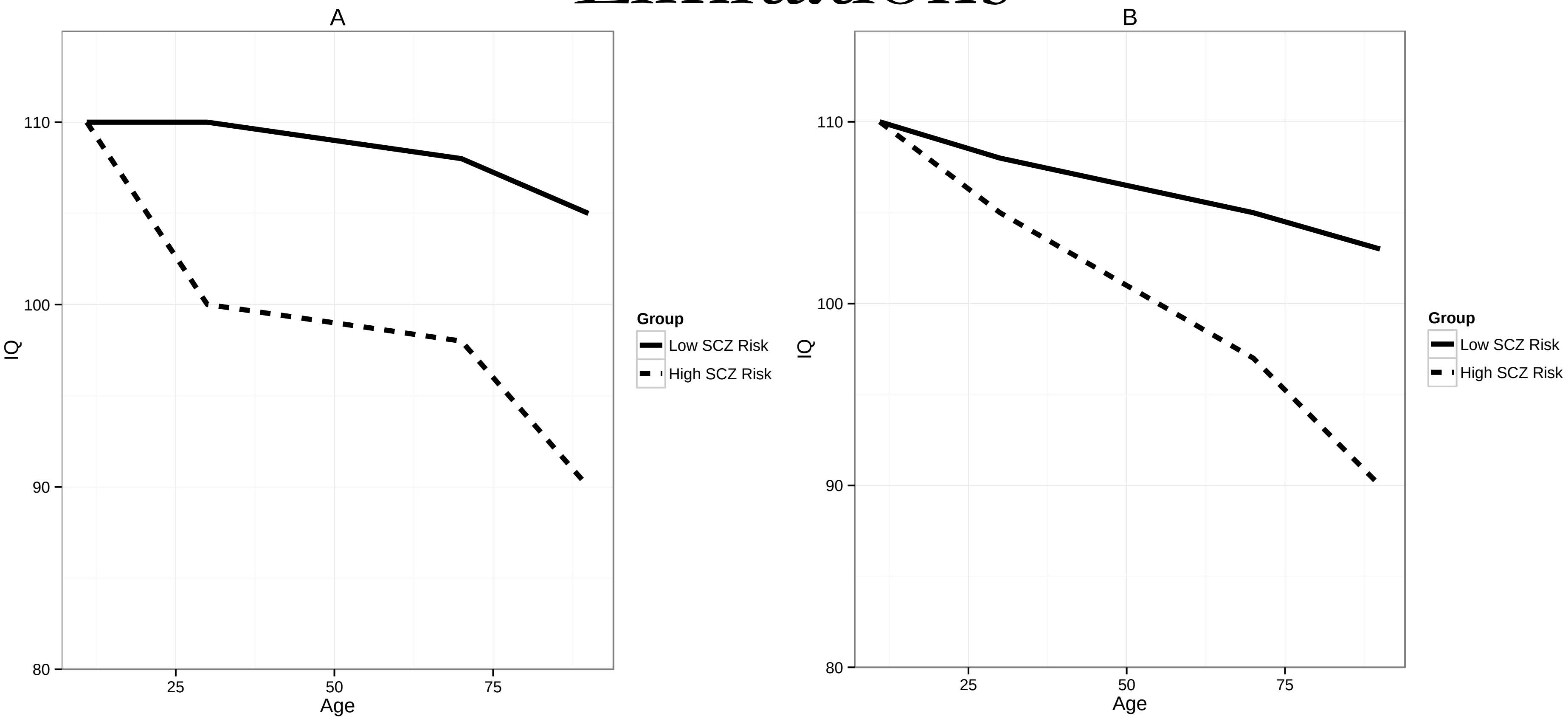


Meta-analysis

Polygenic Threshold	LBC1921 sample			LBC1936 sample			Fixed-effects Meta-analysis (both samples)		
	β	SE	p	β	SE	p	β	SE	p
All SNPs	−0.030	0.088	0.733	−0.128	0.050	0.010	−0.104	0.043	0.016
$p < 0.50$	−0.037	0.088	0.675	−0.130	0.050	0.009	−0.107	0.044	0.014
$p < 0.10$	−0.063	0.086	0.465	−0.123	0.050	0.014	−0.108	0.043	0.013
$p < 0.05$	−0.028	0.086	0.746	−0.140	0.050	0.005	−0.112	0.043	0.009
$p < 0.01$	−0.091	0.088	0.303	−0.084	0.052	0.106	−0.086	0.045	0.056

- Higher polygenic risk scores associated w/ steeper cognitive decline at 4/5 thresholds

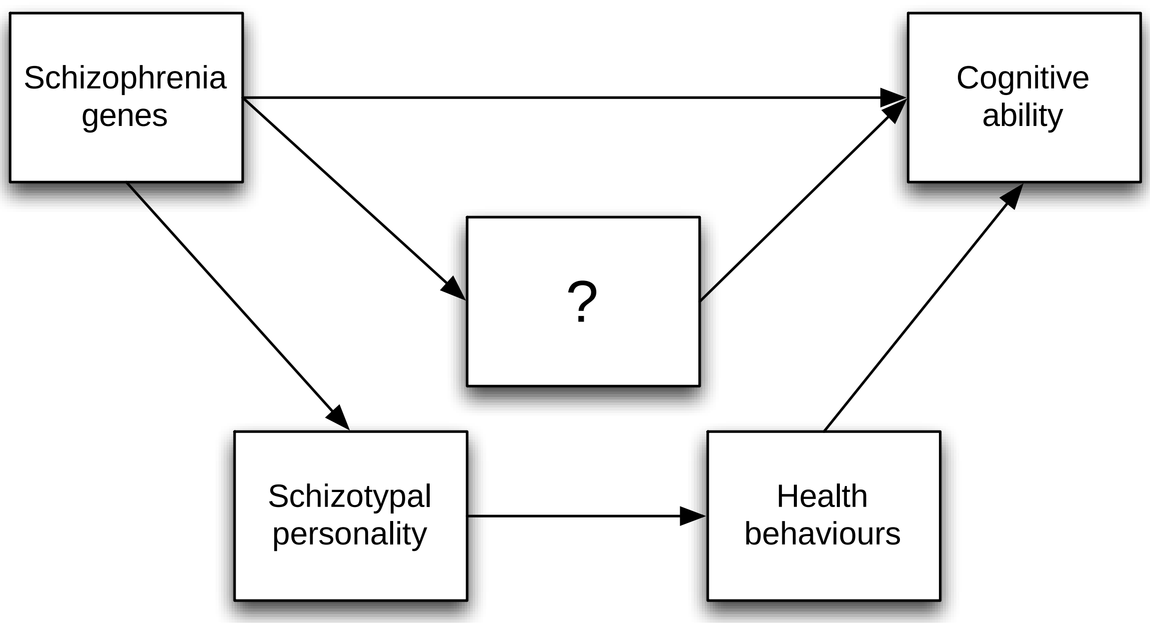
Limitations



- No data between age 11 & age 70 (LBC1936) or 79 (LBC1921)
- Different cognitive measures in LBC1921 & LBC1936 data
- Same samples as previous polygenic schizophrenia study

Implications & Future Directions

- *How* do schizophrenia genes affect IQ?
- At which point in the lifetime does schizophrenia risk most affect changes in IQ?



Conclusions

- Higher polygenic risk scores for schizophrenia are associated with steeper cognitive decline within old age
- Future studies: investigate how polygenic risk scores affect cognition across the whole lifetime, & which ages experience strongest relation between risk score and decline

Overall Conclusions

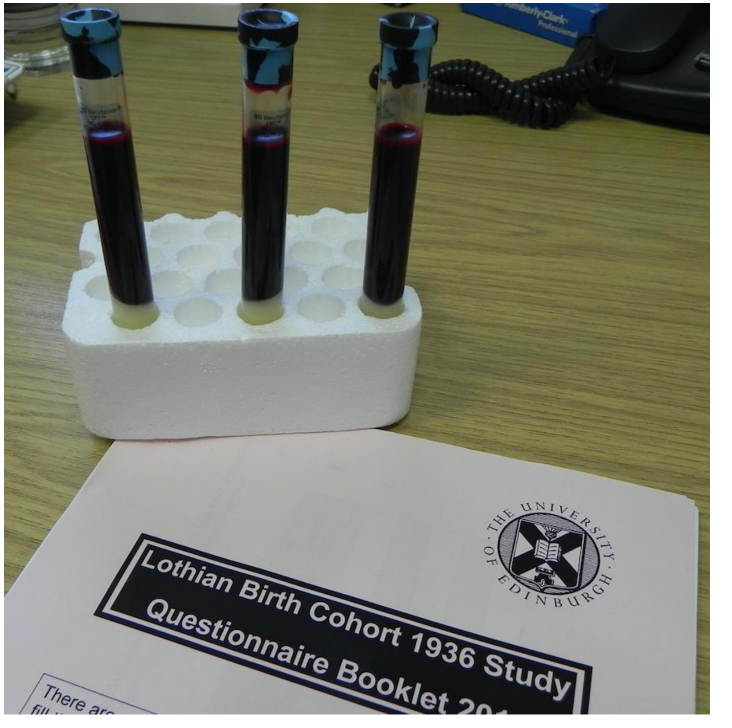
1. Strong predictors of cognitive decline are few and far between

2. Change in broad brain measures correlates modestly with change in cognitive abilities

3. Schizophrenia risk and cognitive decline may be linked

Next up

- 4 waves of testing, 3 waves of neuroimaging (new data at 79 years)
- Grey matter parcellation; connectomic analyses of white matter
- Predictors of brain change?
- Longitudinal epigenetic changes
- Induced pluripotent stem cells



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Thanks

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- Co-authors: Ian Deary, Elliot Tucker-Drob, Mark Bastin, David Alexander Dickie, Simon Cox
- LBC1936 team

MRC Medical Research Council

age UK