Predicting cognitive decline:
Evidence from studies of lifestyle, neuroimaging, and genetics

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Age-related cognitive decline

Neurocognitive Functions and Everyday Functions Change Together in Old Age

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

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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.
Correlation: $r = .68$

$R^2 = .46$
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”
Model of levels

40%

g

.84

.71

.89

.78

Visuospatial level

Crystallized level

Memory level

Speed level

.90 .84 .70

.98 .98 .55

.67 .73 .72

.94 .86 .57 .72

Matrix Reasoning level

Block Design level

Spatial Span level

NART level

WITAR level

Verbal Fluency level

Verbal Paced Associates level

Logical Memory level

Digit Span Backward level

Symbol Search level

Digit-Symbol level

Inspection Time level

Choice Reaction Time level

23%

37%
Model of slopes

General slope

48%

Visuo-spatial slope

.80

.65

.53

.86

Memory slope

.78

1

1

.96

.52

Speed slope

.67

.91

.55

.52

.86

26%

Spatial Span slope

NART slope

WTAR slope

Verbal Fluency slope

Verbal Paced Associates slope

Logical Memory slope

Digit Span Backward slope

Symbol Search slope

Digit Symbol slope

Inhibition Time slope

Choice Reaction Time slope

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
<table>
<thead>
<tr>
<th>Covariate</th>
<th>General factor estimate (SE)</th>
<th>Domain estimate (SE)</th>
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<tbody>
<tr>
<td></td>
<td>g slope</td>
<td>Visuospatial slope</td>
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<tr>
<td></td>
<td>Crystallized slope</td>
<td>Memory slope</td>
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<td></td>
<td>Speed slope</td>
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<td>Age (baseline)</td>
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<tr>
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<tr>
<td>Time lag</td>
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<tr>
<td>Education</td>
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<tr>
<td>Childhood SES</td>
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<td>Own SES</td>
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<tr>
<td>SIMD</td>
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<tr>
<td>FEV</td>
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<td>6m Walk time</td>
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<tr>
<td>Grip strength</td>
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<tr>
<td>APOE †</td>
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<tr>
<td>BMI</td>
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<td>Diabetes †</td>
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</table>
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

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
Latent Difference Score model

\[ y[1] = (1 \times y[0]) + (1 \times \Delta y) \]
Results: Level-Level

Baseline/baseline correlations (age ~73)
Results: Level-Change

Baseline/change correlations

- $\Delta g_f$
- $\Delta \text{Spd}$
- $\Delta \text{Mem}$

FA 73

$0.153 \ (0.070)$

$-0.072 \ (0.093)$

$-0.078 \ (0.067)$
Results: Change-change

Change/change correlations (age ~73 to age ~76)

- $\Delta$ FA
  - $\Delta$ Mem
    - 0.034 (0.090)
    - -0.061 (0.094)
  - $\Delta$ Spd
    - 0.637 (0.128)
    - 0.645 (0.159)
  - $\Delta$ $g_f$
    - 0.312 (0.123)
    - 0.561 (0.086)
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?
Behavioral/Cognitive

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

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Laura E. Engelhardt,7 Simon R. Cox,1,2 Natalie A. Royle,2,4,5,6 Alan J. Gow,2,8 Janie Corley,1 Alison Pattie,1
Adele M. Taylor,1 María del C. Valdés Hernández,2,4,5,6 John M Starr,2,3 Joanna M. Wardlaw,2,4,5,6 and Ian J. Deary1,2

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II. Volumetric changes
Volume change (cm³) from age 73 to 76

Density

Total Brain

Grey Matter

Normal-Appearing White Matter

White Matter Hyperintensities

-100 -75 -50 -25 0 25 50

-100 -75 -50 -25 0 25 50

-100 -75 -50 -25 0 25 50

-100 -75 -50 -25 0 25 50

Volume change (cm³) from age 73 to 76

Density

-100 -75 -50 -25 0 25 50

-100 -75 -50 -25 0 25 50

-100 -75 -50 -25 0 25 50

-100 -75 -50 -25 0 25 50

White Matter Hyperintensities

White Matter Hyperintensities
Results: Level-change

Diagram:

**Brain level - cognitive change**
- TBV 73
- $\Delta g_f$ 73 to 76
  - 0.020 (0.089)
- Mem 73 to 76
  - 0.035 (0.062)
  - $\Delta Mem$ 73 to 76
  - -0.037 (0.066)
- $\Delta Spd$ 73 to 76

**Cognitive level - brain change**
- $g_f$ 73
  - 0.049 (0.053)
- Mem 73
  - 0.199 (0.060)
- Spd 73
  - 0.121 (0.057)
- $\Delta TBV$ 73 to 76
  - 0.049 (0.053)
Results: Change-change
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
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
- 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

![Graph showing beta (with cognitive change 79-92) against polygenic score threshold. The x-axis represents different thresholds (All SNPs, p < 0.50, p < 0.10, p < 0.05, p < 0.01) and the y-axis represents beta values ranging from -0.2 to 0.1.]
Lothian Birth Cohort 1936
## Meta-analysis

<table>
<thead>
<tr>
<th>Polygenic Threshold</th>
<th>LBC1921 sample</th>
<th>LBC1936 sample</th>
<th>Fixed-effects Meta-analysis (both samples)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>SE</td>
<td>$p$</td>
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<tr>
<td>All SNPs</td>
<td>-0.030</td>
<td>0.088</td>
<td>0.733</td>
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<tr>
<td>$p &lt; 0.50$</td>
<td>-0.037</td>
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<td>0.675</td>
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<td>$p &lt; 0.10$</td>
<td>-0.063</td>
<td>0.086</td>
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<td>$p &lt; 0.05$</td>
<td>-0.028</td>
<td>0.086</td>
<td>0.746</td>
</tr>
<tr>
<td>$p &lt; 0.01$</td>
<td>-0.091</td>
<td>0.088</td>
<td>0.303</td>
</tr>
</tbody>
</table>

- 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
Thanks

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