Lifetime severe affective symptoms and subsequent cognitive state: over 50 years of follow-up in the 1946 British Birth Cohort Study.

Sarah-Naomi James, PhD
University College London

Sarah.n.james@ucl.ac.uk
@Sarah_naomi_1 @MRCLHA
Cognitive function

**Ability:**
- Remember, Learn, Concentrate, Plan, Think, Reason

**Ageing -> Cognitive decline:**
- Natural, gradual, ongoing and varying change in cognition as people age

**Dementia:**
- Set of symptoms including substantial memory loss and difficulties with thinking, problem-solving. Brain diseases -> e.g. Alzheimer’s Disease

- Understanding who is at greatest risk is an important public health issue
**Background**

- Increased risk for later-life dementia in those with history of **depression** (*OR*=1.90, 1.55-2.33) and **anxiety** (+RR:1.57, 1.02-2.42)
- Variation – frequency, incident timing, age onset

**Relationship is unclear – e.g do affective problems:**
- Directly cause cognitive impairment and decline? (E.g through neurotoxicity)
- Develop in response to emerging cognitive decline?
- Indicate risk of dementia and share an underlying aetiology?

**Detailed life course understanding:**
- Temporal, time periods, accumulation
- Prospective
- Longer follow-up periods

*Ownby et al. 2006 Arch Gen Psychiatry, +Gulpers et al. 2016 Am J Geriatr Psychiatry.*
Background

Life course features

Affective problems:
- Severity
- Frequency? – accumulation?
- Incident timing of problems?

Cognition:
- Dementia
- Cognitive state pre dementia onset?
- Independent of prior cognitive ability?

Aim:
Investigate how affective problems across the life course relate to later-life cognitive state, independent of prior cognitive ability
- Frequency/cumulative effect
- Incident timing
MRC National Survey of Health and Development (British 1946 birth cohort)

History:

1946

http://www.nshd.mrc.ac.uk/
MRC National Survey of Health and Development (British 1946 birth cohort)

- Maternity study of all births in 1 week in March 1946
- Representative sample followed up (~5000)
- ~2800 in active follow-up

http://www.nshd.mrc.ac.uk/
Methods - measures

Affective ratings

- Differing scales
- Validated thresholds

Teacher ratings of emotional problems

Cumulative effect across the life course
1. Meet threshold case-level
2. Sum across testing waves
3. Recode as follows:
   - Never case-level (reference)
   - Only once case-level
   - 2+ case-level

Different periods across the life course
- Never (reference)
- Earlier-life only (pre 60)
- Later-life only (post 60)
- Earlier and later life
Cognitive Function

Verbal and Non-verbal Ability

Age

8

National adult reading test

53

ACE-III

69

Methods - measures
**Aim:**
Investigate how affective problems across the life course relate to later-life cognitive state
- **Cumulative effect**
- **Incident timing**

**Analysis:**
Multivariable linear regression analyses:
- **Predictor categorical** – with never case-level as a reference
- **Outcome continuous** – cognitive measures
Methods - measures

<table>
<thead>
<tr>
<th>Age</th>
<th>Affective ratings</th>
<th>Cognitive Function</th>
<th>Adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-15</td>
<td>Teacher ratings of emotional problems</td>
<td>Verbal and Non-verbal Ability (age 8)</td>
<td>Sex</td>
</tr>
<tr>
<td>36</td>
<td>Present State Examination</td>
<td>National adult reading test</td>
<td>Child occupational position</td>
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<tr>
<td>43</td>
<td>Psychiatric Symptom Frequency Scale</td>
<td></td>
<td>Highest educational qualification</td>
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<tr>
<td>53</td>
<td>28-item General Health Questionnaire</td>
<td>ACE-III (age 69)</td>
<td>Adult occupational position</td>
</tr>
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<td>60-64</td>
<td>28-item General Health Questionnaire</td>
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</table>
Results – cumulative effect

Adjusted for sex, childhood cognition, child and adult occupational status, education, NART.

<table>
<thead>
<tr>
<th>ACE-III scores</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
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<td></td>
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<tr>
<td>Never case-level</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Once case-level</td>
<td>0.04</td>
<td>(-0.68, 0.77)</td>
</tr>
<tr>
<td>≥2 times case-level</td>
<td><strong>-1.08</strong></td>
<td><strong>(-1.90, -0.25)</strong></td>
</tr>
</tbody>
</table>
Results – incident timing

Adjusted for sex, childhood cognition, child and adult occupational status, education, NART.

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<tr>
<td>Never case-level</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-level in earlier-life only</td>
<td>-0.04</td>
<td>(-0.73,0.80)</td>
<td>-0.33</td>
<td>(-1.06,0.40)</td>
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<tr>
<td>Case-level in late-life and earlier-life</td>
<td><strong>-1.36</strong></td>
<td><strong>(-2.31,-0.42)</strong></td>
<td><strong>-1.11</strong></td>
<td><strong>(-2.00,-0.23)</strong></td>
</tr>
<tr>
<td>Case-level in late-life only</td>
<td>-0.21</td>
<td>(-1.26,0.85)</td>
<td>-0.71</td>
<td>(-1.65,0.22)</td>
</tr>
</tbody>
</table>
Summary

Cumulative effect:
• One severe affective problem was not assd with lower later-life cognitive state
• Two+ problems were assd with lower later-life cognitive state and function, controlling for prior cognition

Timing incidence:
• Affective problems in early- and late-life had the strongest assn with lower later-life cognitive state and function

Interpretation:
Suggests recurrent affective problems across the whole life course increases risk of diminished later-life cognitive state, when most SM are still free of dementia
- Window in early late-life when this risk becomes manifest
- Decline is accelerated by age 69 (Davis et al. 2017)
- ACE-III may have captured additional cognitive impairment
Summary and conclusions

Limitations:
- Measures of affective symptoms differed; thresholds validated
- Reverse causation; controlled for prior cognition

Implications:
- Recurrent affective problems should be monitored for later-life diminished cognitive state
- Effective management of recurrent affective problems may reduce the risk of decreased cognitive function.

Future:
- Continued follow-up to determine if recurrent Sx raise dementia risk
- Mechanisms underlying association:
  - Increased Aβ plaques in affective disorders
  - Atrophy
  - Vascular disease
  - Inflammatory pathways
NSHD neuroscience sub-study: Insight46

- Random sample of 500 MRC NSHD individuals
- Attend UCL for detailed neurological and cognitive assessment x 2
- Amyloid PET (18F Florbetapir PET) and multi-modal MRI on a hybrid PET/MRI scanner
Age 69-71/71-73

- Few with clinical Sx
- More with pathology
- Preclinical window
Assessments:
Clinical assessments
Neuropsychology
Sensory testing
Fluid biomarkers
Genetics
Brain donation requested
Neuroimaging

Imaging protocol:
Total acquisition time ~60 minutes
• Attenuation Correction sequences
• Volumetric T1
• Volumetric T2
• Volumetric FLAIR
• Resting state fMRI
• Field Mapping
• Multi-shell Diffusion Weighted Image
• Arterial Spin Labelling
• Susceptibility Weighted Image

Simultaneous acquisition of PET data using Florbetapir
Pathology in vivo

Structure

Vascular

Amyloid load

Perfusion & activation

Networks

Microbleeds
Study protocol: Insight 46 – a neuroscience sub-study of the MRC National Survey of Health and Development

Christopher A. Lane¹, Thomas D. Parker¹, Dave M. Cash¹,², Kirsty Macpherson¹, Elizabeth Donnachie³, Heidi Murray-Smith¹, Anna Barnes⁴, Suzie Barker¹, Daniel G. Beasley², Jose Bras⁵,⁶, David Brown⁴, Ninon Burgos², Michelle Byford⁷, M. Jorge Cardoso², Ana Carvalho⁸, Jessica Collins¹, Enrico De Vita⁸,⁹, John C. Dickson⁴, Norah Epie¹, Miklos Espak², Susie M. D. Henley¹, Chandrashekar Hoskote⁸, Michael Hutel¹,², Jana Klimova¹, Ian B. Malone¹, Pawel Markiewicz², Andrew Melbourne², Marc Modat¹,², Anette Schrag¹⁰, Sachit Shah⁸,⁹, Nikhil Sharma⁷,¹¹, Carole H. Sudre¹,², David L. Thomas³,⁹, Andrew Wong⁷, Hui Zhang¹², John Hardy¹³, Henrik Zetterberg⁵,¹⁴,¹⁵, Sebastien Ourselin², Sebastian J. Crutch¹, Diana Kuh⁷, Marcus Richards⁷, Nick C. Fox¹ and Jonathan M. Schott¹*
Integrating life course and neuroimaging

**NSHD**

- Birth 1946
  - Childhood
  - Adolescence
  - Early adulthood
  - Mid-adulthood
  - Later adulthood

**DATA**

- Cognitive function
- Temperament
- Mental health
- DNA
- Infant feeding
- Diet
- Smoking, physical activity, alcohol and diet
- Social relationships & participation
- Survival; measured body size (height and weight); socioeconomic circumstances
- Health status
- Mother’s experience of care
- Puberty, reproductive history & women’s menopausal transition
- Blood pressure & lung function
- Developmental milestones
- Physical function

**Insight46**
Research questions:
- Do those with affective Sx across specific periods, or across time, have differences in:
  - Amyloid load?
  - Brain volume?
  - Microbleeds?
  - White matter hyper-intensities?

Identify those at risk and provide insight into underlying mechanisms of risk
December 2016:
- 240 participants with analysable amyloid PET & MR data
- MMSE score 29.3 (±0.79, range=26-30)
- Males 50.9%
- Age: 70.1 years (range=69.3-70.8)
- 17.9% were Aβ+

January 2018:
- 502 participants
Thanks!

- Prof Marcus Richards
- Prof Diana Kuh
- Prof Rebecca Hardy
- Dr Daniel Davis
- Dr Celia O’Hare
- Dr Nikhil Sharma
- Dr Amber John
- Dr Darya Gaysina
- Dr Andy Wong and MRC LHA team
- NSHD participants
- Sponsors
Neuropathology of AD

β-amyloid

Atrophy
Affective problems

- Symptoms reach a certain threshold/criteria that impairs function
- 1/5 experience episode **during lifetime**
- Variation – frequency, incident timing, age onset

Zboniznek et al. 2013. Depress Anxiety
Table 1

DSM IV-TR Criteria for Adult MDD and GAD

<table>
<thead>
<tr>
<th>MDD Criteria</th>
<th>GAD Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)</td>
<td>A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance)</td>
</tr>
<tr>
<td>A(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)</td>
<td>B. The person finds it difficult to control the worry</td>
</tr>
<tr>
<td>A(3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day</td>
<td>C(1) Restlessness or feeling keyed up or on edge*</td>
</tr>
<tr>
<td>A(4) Insomnia or hypersomnia nearly every day</td>
<td>C(2) Being easily fatigued</td>
</tr>
<tr>
<td>A(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)</td>
<td>C(3) Difficulty concentrating or mind going blank</td>
</tr>
<tr>
<td>A(6) Fatigue or loss of energy nearly every day</td>
<td>C(4) Irritability</td>
</tr>
<tr>
<td>A(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)</td>
<td>C(5) Muscle tension</td>
</tr>
<tr>
<td>A(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)</td>
<td>C(6) Sleep disturbance (difficulty falling or staying asleep, or restless unsatisfying sleep)</td>
</tr>
<tr>
<td>A(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide</td>
<td></td>
</tr>
</tbody>
</table>

*Bold and italicized symptoms are shared between GAD and MDD

Zboniznek et al. 2013. Depress Anxiety
Insight 46 – aims

To determine:

• The biomarker changes in very early AD
• The influence of other pathologies
• The life course and genetic influences on the onset and progression of cognitive decline

To provide:

• An evidence base for pre-dementia trial design
• A resource for ageing/dementia research
Fluid biomarker collection

- Bloods analysed for:
  - FBC, renal function,
  - B12, TSH
- Samples stored for later biomarker analysis
NSHD neuroscience sub-study: Minimal dataset

- Attendance at a clinic visit at age 60-64
- Parental occupational social class or education
- Memory and processing speed at 60-64 year collection AND at either ages 8, 11 or 15
- Height and weight at ages 4-15
- Highest qualification by age 26
- Mental health: adolescent teacher ratings
- Affective symptoms; BP; lung function; BMI; weight; smoking; exercise at 36, 43, 53 or 60-64
- Blood: either age 53 or 60-64 samples
What has been measured? (ii)
Detailed clinical assessment at age 60-64 years: advancing the study of ageing

Cardiovascular structure and function

Body composition (incl. bone mineral density and fat and muscle mass)

Heart rate and movement (5 days)

2nd measure of biomarkers

For more details see: Kuh et al, IJE 2011;40:e1-e9
Insight46 Preliminary analysis (n=240)

**Affective symptoms:**
- Standardised each measure
- Analysed as continuous variables
- Dichotomised at validated thresholds and sum

**Neuroimaging outcomes**
- Amyloid status – multivariable logistic regression
- Brain volume – multivariable linear regression

**Adjustments**
- Sex, socioeconomic position, smoking, (TIV)
- With and without APOE status
**Amyloid:**
- Binary measure Aβ+ status
- *Cortical grey matter SUVR with cerebellar reference
- Aβ+ SUVR threshold = >1.078
- 17.9% were Aβ+

**Global brain volume:**
- *Calculated from parcellation of volumetric T1 scans

*See team talks/posters #Cash #Schott #Parker*
Insight46 Preliminary Results (n=240): Lifecourse Affective Symptoms and Aβ+ at 70

No adjustments

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affective symptoms at 13-15</td>
<td>0.83</td>
<td>0.64,1.10</td>
<td>0.19</td>
<td>227</td>
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<tr>
<td>Affective symptoms at 36</td>
<td>1.14</td>
<td>0.84,1.55</td>
<td>0.40</td>
<td>227</td>
</tr>
<tr>
<td>Affective symptoms at 43</td>
<td>1.01</td>
<td>0.97,1.06</td>
<td>0.64</td>
<td>224</td>
</tr>
<tr>
<td>Affective symptoms at 53</td>
<td>1.03</td>
<td>0.95,1.11</td>
<td>0.52</td>
<td>236</td>
</tr>
<tr>
<td>Affective symptoms at 60-64</td>
<td>1.03</td>
<td>0.94,1.12</td>
<td>0.52</td>
<td>237</td>
</tr>
<tr>
<td>Affective symptoms at 69</td>
<td>1.07</td>
<td>0.96,1.19</td>
<td>0.22</td>
<td>238</td>
</tr>
</tbody>
</table>

Cumulative effect:

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<tr>
<td>Never case-level</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once case-level</td>
<td>0.82</td>
<td>0.34,1.95</td>
<td>0.65</td>
<td>213</td>
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<tr>
<td>2+ case-level</td>
<td>1.35</td>
<td>0.49,3.73</td>
<td>0.56</td>
<td>213</td>
</tr>
</tbody>
</table>

- Having higher affective Sx in the life course is not associated with amyloid+
Insight46 Preliminary Results (n=240):
Lifecourse Affective Symptoms and brain volume at 70

No adjustments apart from total intracranial volume

<table>
<thead>
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<th>Variable</th>
<th>β</th>
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<th>n</th>
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<tbody>
<tr>
<td>Affective symptoms at 13-15</td>
<td>-0.01</td>
<td>-0.08,0.05</td>
<td>0.67</td>
<td>227</td>
</tr>
<tr>
<td>Affective symptoms at 36</td>
<td>0.02</td>
<td>-0.04,0.08</td>
<td>0.49</td>
<td>227</td>
</tr>
<tr>
<td>Affective symptoms at 43</td>
<td>-0.01</td>
<td>-0.07,0.05</td>
<td>0.76</td>
<td>224</td>
</tr>
<tr>
<td>Affective symptoms at 53</td>
<td><strong>-0.08</strong></td>
<td><strong>-0.02,-0.14</strong></td>
<td><strong>0.01</strong></td>
<td>236</td>
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<tr>
<td>Affective symptoms at 60-64</td>
<td>0.01</td>
<td>-0.05,0.07</td>
<td>0.81</td>
<td>237</td>
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<tr>
<td>Affective symptoms at 69</td>
<td>0.02</td>
<td>-0.04,0.08</td>
<td>0.48</td>
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Cumulative effect:

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<tr>
<td>Once case-level</td>
<td>0.02</td>
<td>-0.17,0.14</td>
<td>0.85</td>
<td>213</td>
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<tr>
<td>2+ case-level</td>
<td>0.05</td>
<td>-0.15,0.26</td>
<td>0.61</td>
<td>213</td>
</tr>
</tbody>
</table>

- Having higher affective Sx with smaller brain volume
- Having more affective episodes in the life course was not associated with smaller brain volume
Insight46 **Preliminary Results:** Discussion

**Preliminary!**

**Affective Sx:**
Some association with smaller brain volume but not with *amyloid load*;
- Not related to amyloid and not AD?
- Related to brain volume? (and cog.function)
- Midlife important for smaller brain volume?

**Future work:**
- Explore in first full wave of Insight46 (n=500)
- Explore amyloid as a continuous, and non linear variable (#Parker)
- Explore relationship between affect, brain volume and cognition
- Investigate other mechanisms – e.g inflammatory, vascular
- Explore as AD-pathology changes in longitudinal follow-up of Insight46
Lifetime antecedents of cognitive state: seven decades of a birth cohort study

Professor Marcus Richards
MRC Unit for Lifelong Health and Ageing at UCL
University College London
Towards a life course framework

Some basic scaffolding
A basic life course path model for cognitive reserve

- Father’s social class
  - Childhood cognition (0.38)
  - Education (0.11)

- Midlife social class (0.25)

- Midlife cognitive reserve
  - National Adult Reading Test

Richards & Sacker, J Clin Exp Neuropsychol 2003
A basic life course path model for cognitive reserve

Richards & Sacker, J Clin Exp Neuropsychol 2003
A basic life course path model for cognitive reserve

Father’s social class

Childhood cognition

Education

Midlife social class

Midlife cognitive reserve

National Adult Reading Test

Richards & Sacker, J Clin Exp Neuropsychol 2003
National Adult Reading Test (NART)

1. CHORD
2. ACHE
3. DEPOT
4. AISLE
5. BOUQUET

15. CATACOMB
16. GAOLED
17. THYME
18. HEIR
19. RADIX
20. ASSIGNATE

31. FACADE
32. ZEALOT
33. DRACHM
34. AEON
35. PLACEBO

45. PRELATE
46. SIDEREAL
47. DEMESNE
48. SYNCOPE
49. LABILE
50. CAMPANILE
Father’s social class → Childhood cognition → Education → Midlife social class → Midlife literacy

Richards, Power & Sacker, J Epidemiol Community Health 2009
Addenbrooke’s Cognitive Examination (ACE-III)

The most comprehensive test of mental state available

Screen-implemented

Five domains tested:
- Attention & orientation (0-18)
- Verbal fluency (0-14)
- Memory (0-26)
- Language (0-26)
- Visuospatial function (0-16)

Maximum total score = 100, with quasi-normal distribution
An updated path model for mental state at age 69
An updated path model for mental state at age 69
NSHD: Trajectory of verbal memory (word learning score) between ages 43 and 69 by APOE status

Rawle et al. Transl Psychiat Jan 2018
An updated path model for mental state at age 69

APOE ε4/ε4

Childhood SEP

Childhood cognition

Education

Midlife SEP

NART age 53

ACE-III age 69
Age 8 reading scores by level of parental interest in education

Douglas JBL, The Home and the School, 1964
Parenting and the intergenerational transmission of cognition

Positive nurturing

Love  Encouragement  Challenge
Parental involvement

“I’m sure you can do better than this.”
Skills for life

“Cognitive and socioemotional function are intertwined across the life course and, we suggest, fuse to form skills for life supporting self-regulation, competence, and quality of life.”

Richards & Hatch, J Gerontology 2011
“... what is needed for optimal cognitive development is a combination of active learning experiences that promote cognitive competence together with a social context in which the style of interaction and relationships promotes self-confidence and an active interest in seeking to learn independently of instruction.”

Rutter, J Child Psychol Psychol Psychiat 1985
An updated path model for mental state at age 69
The long reach of childhood cognition

Childhood cognition correlates strongly with early adult cognition...

Plassman B, Welsh K, Helms M, Brandt J, Page W, Breitner
Journal of Neurology 1995, 45, 1446-50

...midlife cognition (allowing for social class of origin, education, and own social class):


...and later life cognition:

Early cognition and dementia risk

- 93 members of the School Sisters of Notre Dame born before 1917 in the Milwaukee area

- Idea density and grammatical complexity, derived from autobiographies written around age 22 years was a strong predictor of cognitive function and Alzheimer’s disease risk in later life (Snowdon et al. JAMA 1996)

- Childhood IQ was associated with late-onset dementia (Whalley et al. Neurology 2000; McGurn et al. Neurology 2008)
An updated path model for mental state at age 69
Genetics outweighs teaching, Gove adviser tells his boss

Dominic Cummings' 250-page paper attacks fear of elitism and waste of billions of pounds, and calls for slimmed-down ministry

Patrick Wintour, political editor
The Guardian, Friday 11 October 2013 22.06 BST
Three possibilities

Adult cognition

Childhood cognition
Wisconsin 1939 birth cohort  
NSHD 1946 birth cohort  
NCDS 1958 birth cohort

Self-organisation in NSHD: Teacher ratings at 13 and 15 years

A very hard worker; one with high power of concentration; extremely neat and tidy in class work; seldom or never daydreams in class

Xu et al. Psychology and Aging 2013
Thanks to:

Mai Stafford, Nikhil Sharma, Mark Rawle, Sarah-Naomi James, Daniel Davis and Diana Kuh