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<td>10:30</td>
<td>Welcome</td>
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<td>Risk prediction and heritability of reserve and resilience</td>
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<td>10:40</td>
<td>Differential Effects of Early-, Mid- and Late-life experiences on reserve and resilience</td>
<td>Arenaza</td>
<td>Predicting progression in pre-dementia stages of Alzheimer’s disease with a neuroimaging measure of cognitive reserve</td>
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<td>Staff</td>
<td>Genetic Risk Profile for Prediction of Cognitive Decline in Pre-Symptomatic Alzheimer’s Disease</td>
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<td>Kremen</td>
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<td>Discriminating and Predicting Cognitive Exceptionality and Resilience</td>
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<td>Resilience: A Roadmap for Trajectory and Interaction Analyses with Risk and Protective Factors</td>
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<td>Investigating protective factors for amyloid and AD pattern</td>
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<td>neurodegeneration to discover paths to “Exceptional Aging” without AD</td>
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<td>Risk and Protective Factors</td>
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<td>Functional brain mechanisms of reserve and resilience</td>
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<td>The effect of spirituality/religiosity on regional brain atrophy in subjects at risk of Alzheimer’s disease</td>
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<td>Cross-network coupling of the fronto-parietal control network</td>
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<td>The association between personality and tau PET deposition in cognitively normal older adults</td>
<td>Schultz</td>
<td>during memory performance supports protective effects of education in aging</td>
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<td>Impact of Cognitive Reserve and Preclinical AD on Longitudinal Driving Performance</td>
<td>Roe</td>
<td>Working memory and brain maintenance: A longitudinal study</td>
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<td>Neurofunctional activation associated with early and lifelong</td>
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<td>cognitively stimulating activities moderates working memory differences in normal aging</td>
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<td>Beta-Amyloid Accumulation Hurts and Crystallized Knowledge Helps Brain Modulatory Capacity</td>
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</table>
Differential effects of early and late-life experiences on amyloid deposition versus neurodegeneration

Early life intelligence, social class and education and its association with memory and the trajectory of decline in late life

Childhood SES, Cognitive Reserve, Adult SES and Cognitive Activities: Impact on Later Life Cognitive Outcomes
Early Life Intelligence, Social Class And Education And Its Association With Memory And The Trajectory Of Decline In Late Life: Aberdeen Birth Cohort

Roger Staff
NHS-Grampian
Aberdeen birth cohorts 1936

Born in 1936

1947: Scottish Mental Survey 1947 N=75,211 (2620 in Aberdeen)
All Children born in 1936

1999: 934 Traced alive and living in Grampian
664 Matched via the community health index

1999: 647 were eligible for recruitment. No dementia, no recent bereavement....

W1
1999: 498 recruited

W2
2001: 370 retained

W3
2005: 303 retained

W4
2008: 215 retained

W5
2010: 153 retained

Whalley et al Maturitas 2011 69:365-372
<table>
<thead>
<tr>
<th></th>
<th>Mean Standard deviation</th>
<th>Correlation with AVLT score at entry</th>
<th>Male (Standard deviation)</th>
<th>Female (Standard deviation)</th>
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<tbody>
<tr>
<td>N=388 Male 192 (49.5%)</td>
<td></td>
<td></td>
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<tr>
<td>Age when first tested as an adult</td>
<td>64.8 (1.40)</td>
<td>0.04</td>
<td>64.7 (1.2)</td>
<td>64.9 (1.5)</td>
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<tr>
<td>Father Occupational Status</td>
<td>6.22 (2.33)</td>
<td>0.11*</td>
<td>6.33 (2.36)</td>
<td>3.87 (2.31)</td>
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<tr>
<td>Overcrowding</td>
<td>1.75 (0.75)</td>
<td>-0.17*</td>
<td>1.78 (0.78)</td>
<td>1.72 (.072)</td>
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<tr>
<td>Sanitation share</td>
<td>7.88 (4.87)</td>
<td>-0.16*</td>
<td>8.37 (5.69)</td>
<td>7.40 (3.54)</td>
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<tr>
<td>SESc</td>
<td>-</td>
<td>0.21*</td>
<td>-0 (1.13)</td>
<td>0.09 (0.84)</td>
</tr>
<tr>
<td>Education Year</td>
<td>11.11 (1.99)</td>
<td>0.28*</td>
<td>11.0 (2.1)</td>
<td>11.2 (1.9)</td>
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<tr>
<td>Participants Occupation Status</td>
<td>4.47 (2.19)</td>
<td>0.25*</td>
<td>4.79 (2.35)</td>
<td>4.66 (2.03)</td>
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<tr>
<td>SIMD Neighbourhood status</td>
<td>6.66 (3.03)</td>
<td>0.22*</td>
<td>6.73 (3.05)</td>
<td>6.60 (3.01)</td>
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<tr>
<td>SESa</td>
<td>-</td>
<td>0.28*</td>
<td>0.01 (1.04)</td>
<td>0.01 (0.96)</td>
</tr>
<tr>
<td>SESm Life-course change</td>
<td>-</td>
<td>0.28*</td>
<td>0.09 (1.21)</td>
<td>-0.08 (1.04)</td>
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<tr>
<td>MHT</td>
<td>42.61 (12.52)</td>
<td>0.38*</td>
<td>41.8 (12.7)</td>
<td>43.4 (12.3)</td>
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<tr>
<td>AVLT Score at entry</td>
<td>44.97 (7.80)</td>
<td>-</td>
<td>41.8 (9.7)*</td>
<td>48.1 (8.9)</td>
</tr>
</tbody>
</table>
1168 data points were acquired
Cognitive longitudinal studies in the old
Effects of Practice

Initial practice model: All the gains are assumed to be realised at the second occasion of testing

\[ \text{AVLT}_{\text{St},ij} = \beta_{0ij}\text{Con} + \beta_{1ij}\text{Age}_{60,ij} + \beta_{2ij}\text{Practice}_{ij} \]

Practice Gains ($\beta_2$)
DS: ns
AVLT: 4.5
RPM: 2.3

Staff et al Intelligence 2014 47: 194-201
Staff et al Social Science & Medicine 2016 151:130-8
Staff et al 2017 In Press
Cognitive longitudinal studies in the old
Education and decline

<table>
<thead>
<tr>
<th></th>
<th>Model A</th>
<th>Model B</th>
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</thead>
<tbody>
<tr>
<td><strong>AVLT</strong></td>
<td>Effect (standard error)</td>
<td>Effect (standard error)</td>
</tr>
<tr>
<td>Intercept (60 years)</td>
<td>70.7 (6.3)</td>
<td>89.7 (5.0)</td>
</tr>
<tr>
<td>Age</td>
<td>-1.73 (0.54)</td>
<td>-1.74 (0.54)</td>
</tr>
<tr>
<td>Practice</td>
<td>4.42 (0.66)</td>
<td>4.51 (0.66)</td>
</tr>
<tr>
<td>Gender</td>
<td>8.57 (1.12)</td>
<td>8.94 (1.15)</td>
</tr>
<tr>
<td>Childhood Ability</td>
<td>0.24 (0.05)</td>
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<tr>
<td>Education</td>
<td>0.20 (0.44) ns</td>
<td>0.60 (0.44) ns</td>
</tr>
<tr>
<td>SESc</td>
<td>2.47 (1.16)</td>
<td>4.00 (1.14)</td>
</tr>
<tr>
<td>SESm</td>
<td>1.88 (0.96)</td>
<td>3.00 (0.95)</td>
</tr>
<tr>
<td>Age x Education</td>
<td>0.11 (0.05)</td>
<td>0.11 (0.05)</td>
</tr>
<tr>
<td>Age x SESc</td>
<td>-0.10 (0.13) ns</td>
<td>-0.10 (0.13) ns</td>
</tr>
<tr>
<td>Age x SESm</td>
<td>-0.12 (0.11) ns</td>
<td>-0.12 (0.11) ns</td>
</tr>
<tr>
<td>Intercept Variance (60 years)</td>
<td>87.1 (16.3)</td>
<td>95.2 (16.9)</td>
</tr>
<tr>
<td>Age Variance</td>
<td>0.61 (0.16)</td>
<td>0.61 (0.16)</td>
</tr>
</tbody>
</table>

- SES advantage in Childhood (SESc) and Adult (SESm) has a positive influence on late life memory
- SESc and SESm have no influence on the trajectory with age
- The interaction between Education and the trajectory with age implies the less education the steeper the downward trajectory

Staff et al 2017 In Press
Cognitive longitudinal studies in the old Practice and Proxies of reserve

Those with higher reserve proxies appear the exhibit greater practice gains

\[ \text{AVLT}_{tij} = \beta_0 + \beta_1 \text{Age}_{60} + \beta_2 \text{Practice}_{ij} \]

Staff et al 2017 In Press
Acknowledgements:
Alison Murray
Chris McNeil
Dorota Chapko
Lawrence Whalley
Trevor Ahearn
Michael Hogan
Differential effects of early and late-life experiences on amyloid deposition versus neurodegeneration

Early life intelligence, social class and education and its association with memory and the trajectory of decline in late life

Childhood SES, Cognitive Reserve, Adult SES and Cognitive Activities: Impact on Later Life Cognitive Outcomes
Childhood SES, Cognitive Reserve, Adult SES and Cognitive Activities: Impact on Later Life Cognitive Outcomes

William S. Kremen, Ph.D.

University of California, San Diego

Reserve, Resilience, and Protective Factors
PIA, AAIC, July 2017
The heritability of general cognitive ability increases linearly from childhood to young adulthood

CMA Haworth1, MJ Wright1, M Luciano1, NG Martin2, EJC de Geus3, CEM van Beijsterveldt4, M Bartels2, D Posthuma3,4, DI Boomsma2, OSP Dave1, Y Kovas1, RP Corley5, JC DeFries6, JK Hewitt1, Rik Olsen7, S-A Reiner8, SJ Wissmath1, WG Iacono9, M McGue1, LA Thompson1, SA Hart1, SA Petrill1, D Lubinski7,8 and R Plomin1

1King’s College London, Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, London, UK; 2Queensland Institute of Medical Research, Brisbane, Qld, Australia; 3Faculty of Psychology and Education, Department of Biological Psychology, VU University, Amsterdam, The Netherlands; 4Section of Medical Genomics, VU Medical Centre, Amsterdam, The Netherlands; 5Section of Functional Genomics, Faculty of Earth and Life Science, VU University, Amsterdam, The Netherlands; 6Institute for Behavioral Genetics, University of Colorado at Boulder, Boulder, CO, USA; 7Department of Psychology, University of Minnesota, Minneapolis, MN, USA; 8Department of Psychology, Case Western Reserve University, Cleveland, OH, USA; 9Human Development and Family Science, Ohio State University, Columbus, OH, USA and 10Department of Psychology and Human Development, Vanderbilt University, Nashville, TN, USA

A = Additive genetic influences

C = Common Environmental Influences

E = Unique Environmental Influences
Gene-Environment (G-E) Correlation

• When people with a genetic propensity for some trait also live in an environment that supports expression of that trait.

From Plomin et al., *Psychological Bulletin*, 1977
Gene-Environment (G-E) Correlation

• When people with a genetic propensity for some trait also live in an environment that supports expression of that trait.

• **Passive G-E Correlation:** When the environments are not sought out or selected.

• **Active G-E Correlation:** When the environments are sought out or selected.

• **Evocative (Reactive) G-E Correlation:** When genetic propensities evoke responses from the environment.

From Plomin et al., *Psychological Bulletin*, 1977
Age 62 Cognitive Outcomes

\[N = 1009\]

<table>
<thead>
<tr>
<th></th>
<th>Childhood SES</th>
<th>Childhood Urbanicity</th>
<th>Age 20 Educ.</th>
<th>Age 20 GCA</th>
<th>Age 56 SES</th>
<th>Age 56 Cognitive Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract Reasoning</td>
<td>p = 0.019</td>
<td>p = 0.002</td>
<td>p &lt; 0.030</td>
<td>p = 0.001</td>
<td>p = 0.018</td>
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</tr>
<tr>
<td>Working Memory</td>
<td>p = 0.020</td>
<td>p = 0.011</td>
<td>p &lt; 0.004</td>
<td>p = 0.001</td>
<td>p = 0.514</td>
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<tr>
<td>Episodic Memory</td>
<td>p = 0.657</td>
<td>p = 0.956</td>
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<td>p = 0.001</td>
<td>p = 0.021</td>
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<tr>
<td>Verbal Fluency</td>
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<td>p &lt; 0.001</td>
<td>p = 0.001</td>
<td>p &lt; 0.001</td>
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</tr>
<tr>
<td>Processing Speed</td>
<td>p = 0.316</td>
<td>p = 0.197</td>
<td>p &lt; 0.047</td>
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<tr>
<td>Visual-Spatial</td>
<td>p = 0.038</td>
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<td>p &lt; 0.032</td>
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<td>p = 0.001</td>
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<tr>
<td>Inhibition</td>
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Type III Effects
Age 62 Cognitive Outcomes
[N = 1009]

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<td>Abstract Reasoning</td>
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<td>p=.018</td>
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<tr>
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<td>p=.321</td>
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<td>p=.514</td>
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<tr>
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<td>p=.956</td>
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<td>Processing Speed</td>
<td>p=.316</td>
<td>p=.197</td>
<td>p&lt;.047</td>
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<td>p&lt;.001</td>
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<td>p&lt;.001</td>
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<tr>
<td>Inhibition</td>
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<td>p=.001</td>
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<th>Age 20 GCA</th>
<th>Age 56 SES</th>
<th>Age 56 Cognitive Activities</th>
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<tbody>
<tr>
<td>Abstract Reasoning</td>
<td>p=.061</td>
<td>p=.001</td>
<td>p&lt;.000000</td>
<td>p=.001</td>
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Type III Effects
Age 62 Cognitive Outcomes:

All have 12 years education at age 20

[N = 711]
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<tr>
<th>Predictors</th>
<th>Effect Size (Cohen’s d)</th>
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<td>Adult Education</td>
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<tr>
<td>Age 20 GCA</td>
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</table>

Age 62 Cognitively Normal (N=774) vs. Amnestic MCI (N=126)
GCA in Individuals with Exactly 12 Years of Education
**Concluding Thoughts**

- **Educational Attainment:**
  - More about active GE correlation than exposure to intellectual stimulation.

- Much of education differences in older adult outcomes are really a function of longstanding IQ/GCA differences.
  - Education/intellectual stimulation in later life can enhance reserve
  - But effects are very small relative to early influences on education, brain, and cognition.

- People are *not* randomly assigned to their amount of educational exposure or engagement in educational activities.
  - An issue for study design.
The people who did all the work.

Dr. Carol Franz  Asad Beck
# Age 62 Cognitive Outcomes

[N = 1009]

<table>
<thead>
<tr>
<th></th>
<th>Childhood SES</th>
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<td>p &lt; .001</td>
<td>p = .018</td>
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<tr>
<td><strong>Working Memory</strong></td>
<td>p = .180</td>
<td>p = .531</td>
<td>p = .004</td>
<td>p &lt; .001</td>
<td>p = .514</td>
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<tr>
<td><strong>Episodic Memory</strong></td>
<td>p = .657</td>
<td>p = .956</td>
<td>p &lt; .001</td>
<td>p &lt; .001</td>
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<td>p = .083</td>
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<tr>
<td><strong>Processing Speed</strong></td>
<td>p = .316</td>
<td>p = .197</td>
<td>p = .047</td>
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<td>p = .038</td>
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<td><strong>Inhibition</strong></td>
<td>p = .284</td>
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<td>p &lt; .001</td>
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</tr>
<tr>
<td><strong>Verbal Fluency</strong></td>
<td>p = .941</td>
<td>p = .991</td>
<td>p &lt; .004</td>
<td>p &lt; .001</td>
<td>p &lt; .001</td>
<td></td>
</tr>
<tr>
<td><strong>Processing Speed</strong></td>
<td>p = .416</td>
<td>p = .007</td>
<td>p &lt; .0001</td>
<td>p &lt; .001</td>
<td>p = .005</td>
<td></td>
</tr>
<tr>
<td><strong>Visual-Spatial</strong></td>
<td>p = .144</td>
<td>p = .155</td>
<td>p &lt; .00001</td>
<td>p = .012</td>
<td>p = .018</td>
<td></td>
</tr>
<tr>
<td><strong>Inhibition</strong></td>
<td>p = .180</td>
<td>p = .332</td>
<td>p &lt; .004</td>
<td>p &lt; .009</td>
<td>p = .197</td>
<td></td>
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</tbody>
</table>

*Type III Effects*
<table>
<thead>
<tr>
<th>Cognitive Activities</th>
<th>Childhood SES</th>
<th>Childhood Urbanicity</th>
<th>Age 20 Educ.</th>
<th>Age 20 GCA</th>
<th>Age 56 SES</th>
<th>Age 56 Cognitive Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract Reasoning</td>
<td>p=.019</td>
<td>p=.002</td>
<td>p&lt;.030</td>
<td>p=.001</td>
<td>p=.018</td>
<td></td>
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<tr>
<td>Working Memory</td>
<td>p=.180</td>
<td>p=.331</td>
<td>p&lt;.004</td>
<td>p=.001</td>
<td>p=.514</td>
<td></td>
</tr>
<tr>
<td>Episodic Memory</td>
<td>p=.657</td>
<td>p=.956</td>
<td>p&lt;.001</td>
<td>p=.001</td>
<td>p=.021</td>
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<tr>
<td>Verbal Fluency</td>
<td>p=.830</td>
<td>p=.006</td>
<td>p&lt;.001</td>
<td>p=.001</td>
<td>p&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Processing Speed</td>
<td>p=.316</td>
<td>p=.197</td>
<td>p&lt;.047</td>
<td>p=.001</td>
<td>p=.001</td>
<td></td>
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<tr>
<td>Visual-Spatial</td>
<td>p=.038</td>
<td>p=.437</td>
<td>p&lt;.032</td>
<td>p=.001</td>
<td>p&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Inhibition</td>
<td>p=.284</td>
<td>p=.228</td>
<td>p&lt;.558</td>
<td>p=.001</td>
<td>p=.244</td>
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<tr>
<td>Cognitive Activities</td>
<td>Childhood SES</td>
<td>Childhood Urbanicity</td>
<td>Age 20 Educ.</td>
<td>Age 20 GCA</td>
<td>Age 56 SES</td>
<td>Age 56 Cognitive Activities</td>
</tr>
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<td>------------------------------</td>
<td>---------------</td>
<td>----------------------</td>
<td>--------------</td>
<td>------------</td>
<td>------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Abstract Reasoning</td>
<td>p=.061</td>
<td>p=.001</td>
<td>p&lt;.0000000</td>
<td>p=.001</td>
<td>p=.087</td>
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</tr>
<tr>
<td>Episodic Memory</td>
<td>p=.981</td>
<td>p=.991</td>
<td>p&lt;.0000000</td>
<td>p=.001</td>
<td>p=.070</td>
<td></td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>p=.941</td>
<td>p=.007</td>
<td>p&lt;.001</td>
<td>p=.001</td>
<td>p&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Processing Speed</td>
<td>p=.416</td>
<td>p=.155</td>
<td>p&lt;.00001</td>
<td>p=.001</td>
<td>p=.005</td>
<td></td>
</tr>
</tbody>
</table>
Average heritability of environmental measures = .27
Risk and Protective Factors

The effect of spirituality/religiosity on regional brain atrophy in subjects at risk of Alzheimer’s disease  Sheardova

The association between personality and tau PET deposition in cognitively normal older adults  Schultz

Impact of Cognitive Reserve and Preclinical AD on Longitudinal Driving Performance  Roe
The effect of spirituality/religiosity on regional brain atrophy in subjects at risk of Alzheimer disease. 3-year follow-up data from Czech Brain Aging study.

Katerina Sheardova\textsuperscript{1,2}, Zuzana Nedelska\textsuperscript{1,3}, Rastislav Sumec\textsuperscript{1,2,4}, Rafal Marciniak\textsuperscript{1}, Silvie Belaskova\textsuperscript{1}, Miroslav Uller\textsuperscript{1}, Jakub Hort \textsuperscript{1,3}

\textsuperscript{1}ICRC, St. Anne’s University Hospital, Brno, CR
\textsuperscript{2}Dept. of Neurology, St. Anne’s University Hospital Brno, CR
\textsuperscript{3}Memory Clinic, Dept. of Neurology, 2\textsuperscript{nd} Faculty of Medicine, Charles University and Motol University Hospital, Prague, CR
\textsuperscript{4}Faculty of Medicine, Masaryk University, Brno, CR
Czech Brain Aging Study
Longitudinal multi-centric memory clinic-based study

Memory Clinic, Charles University
Motol Teaching Hospital, Prague

Memory Center ICRC
St. Anne’s Teaching Hospital, Brno

Inclusion criteria:
Age 55 and more
MMSE 24-30, CDR 0 – 0.5
Informant available
Consecutive recruitment

Synchronized assessment:
Neuropsychology, MRI, PET
Bio fluid and CSF analysis,
questionnaires
Shared database system
Annual follow up

- **Neuropsychological** battery
  - UDS + hippocampal specific tests
  - Experimental psychology + spatial navigation
- **MRI**
  - MPRAGE, DTI, fMRI, micro bleeds
- **Clinical and socio-economic data**
- **Questionnaires**
  - Life-style, subjective cognitive complaints
- **Amyloid imaging**
  - PET, CSF
- **Biological sample bank**
  - CSF, serum, DNA

Biomarkers

Consensual
Assessment of Spiritual Well-being and religiosity

- **SWB = Shalom** (Spiritual Health And Life-Orientation Measure)
- 20 items
- Reflecting connectedness in 4 SWB domains:
  - Personal, Communal, Environmental and Transcendental

- **Religiosity = DUREL** (Duke University Religion Index)
- 5 items
- Reflecting religious practices

Neuroprotective effect of spirituality/religiosity is frequently reported.

Meditation mainly explored:
- ↑ blood flow in frontal and prefrontal regions, cingulum and thalami,
- ↑ cortical thickness in right insula, right frontal cortex and larger right hippocampal volume in meditators versus controls.

**Objectives:**
Is the level of SWB/religiosity associated with lower rates of regional brain atrophy in subjects at risk of Alzheimer disease (AD)?

Methods

- 3 year follow up data - Brno cohort
- Subjects from CBAS
- 1.5T brain MRI at baseline and 2 years later
- FreeSurfer 5.3 volumetric and cortical thickness analysis

- **MRI variables:**
  - regions connected to disease model, and to behavioral symptoms of AD were analyzed

- **Statistics:**
  - MANOVA - MRI volumes as repeated measures within subject dependent
  - Post hoc analyses with independent tests on variables showing significant main effects.
Results

- Basic characteristics of the cohort:

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>SCD</th>
<th>MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>134</td>
<td>90</td>
<td>44</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>45/89</td>
<td>27/63</td>
<td>18/26</td>
</tr>
<tr>
<td>Age</td>
<td>68.23(7.52)</td>
<td>67.24(7.66)</td>
<td>69.23(7.15)</td>
</tr>
<tr>
<td>Education level(P/S/T)</td>
<td>61/134/101</td>
<td>18/52/37</td>
<td>20/23/16</td>
</tr>
<tr>
<td>Depression by GDS score</td>
<td>3.78(2.86)</td>
<td>3.78(2.78)</td>
<td>3.85(3.11)</td>
</tr>
<tr>
<td>APOE 4/- No.</td>
<td>33/101</td>
<td>21/69</td>
<td>12/32</td>
</tr>
</tbody>
</table>
SWB/Durel score and regional atrophy rates

<table>
<thead>
<tr>
<th>Adj. for age, sex, APOE, dg</th>
<th>SWB</th>
<th>Durel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hipocampus right</td>
<td>0.0777</td>
<td>0.5040</td>
</tr>
<tr>
<td>Hipocampus left</td>
<td>0.7066</td>
<td>0.5022</td>
</tr>
<tr>
<td>Medial-orbito-frontal thick. left</td>
<td>0.3374</td>
<td>0.5177</td>
</tr>
<tr>
<td>Medial-orbito-frontal thick. right</td>
<td><strong>0.0491</strong></td>
<td>0.3361</td>
</tr>
<tr>
<td>PPC left</td>
<td>0.0964</td>
<td>0.9224</td>
</tr>
<tr>
<td>PPC right</td>
<td>0.4281</td>
<td>0.9501</td>
</tr>
<tr>
<td>Lingual gyrus left</td>
<td>0.5184</td>
<td>0.3635</td>
</tr>
<tr>
<td>Lingual gyrus right</td>
<td><strong>0.0473</strong></td>
<td><strong>0.0537</strong></td>
</tr>
<tr>
<td>Temporal pole left</td>
<td>0.5035</td>
<td><strong>0.0166</strong></td>
</tr>
<tr>
<td>Temporal pole right</td>
<td>0.9249</td>
<td>0.8247</td>
</tr>
<tr>
<td>Parahip. gyrus left</td>
<td>0.1729</td>
<td>0.1804</td>
</tr>
<tr>
<td>Parahip. gyrus right</td>
<td>0.9868</td>
<td>0.7552</td>
</tr>
</tbody>
</table>

Significant p<0.05
Trend p<0.10
Conclusion

- Level of SWB was associated with lower atrophy rates in brain regions related to memory, visuospatial attention and behavioral deficits in AD.
- The effect of religiosity is less pronounced.
- SWB has more protective effect in MCI then SCD subjects

Limitations:
  - More observations needed
Thank you for your attention!

Contact:
sheardova@fnusa.cz

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International Clinical Research Center
Pekařská 53
656 91 Brno, Czech Republic
Phone: +420 603198029

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The effect of spirituality/religiosity on regional brain atrophy in subjects at risk of Alzheimer’s disease

Sheardova

The association between personality and tau PET deposition in cognitively normal older adults

Schultz

Impact of Cognitive Reserve and Preclinical AD on Longitudinal Driving Performance

Roe
PERSONALITY TRAITS AND TAU DEPOSITION IN COGNITIVELY NORMAL OLDER ADULTS

Stephanie Schultz, BS
Lab of Tammie Benzinger, MD, PhD

The Knight Alzheimer’s Disease Research Center
Washington University in St. Louis
Department of Radiology
Acknowledgements

• Nothing to disclose

• Benzinger & Ances Imaging Core Laboratory Members
• Knight Alzheimer Disease Research Center
• Avid Radiopharmaceuticals
• NIH funding: P50AG005681, P01AG026276, P01AG003991, UF1AG032438, UL1TR000448, P30NS098577, and The German Center for Neurodegenerative Diseases (DZNE).
Background and Objective

- Personality traits, such as neuroticism and conscientiousness, are associated with the onset of AD
- May represent potential risk and resilience factors
- Neuroticism has been associated with AD-related neuropathology including β-amyloid and neurofibrillary tangles at autopsy

**Objective:** Examine the cross-sectional relationship between personality traits and regional PET tau deposition in CN older adults.
Methods

- 94 adults from Knight ADRC
- Selected based on:
  - Cognitive normalcy (CDR=0)
  - Tau (18 F-AV-1451)- and Amyloid (18 F-AV-45)-PET
Methods

NEO 5-factor inventory assessment
  • Assessed traits of neuroticism, extroversion, openness, agreeableness, and conscientiousness.

Example questions:
  • Neuroticism: “I am seldom sad or depressed.”
  • Extroversion: “I like to have a lot of people around me”
  • Openness: “I believe letting students hear controversial speakers can only confuse and mislead them”
  • Agreeableness: “I would rather cooperate with others than compete with them.”
Statistical Analyses

Model 1: Linear regression to compare personality traits with tau accumulation in each region examined.
  • Adjusted for age and sex.

Model 2: Linear regression to compare each personality trait with tau accumulation in each region examined.
  • Adjusted for age, sex, and β-amyloid deposition.
## Background Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Age, Years (Mean (SD), Range)</td>
<td>67.4 (8.7), 46-91</td>
</tr>
<tr>
<td>Female, %</td>
<td>52.1</td>
</tr>
<tr>
<td>APOE4 positive, %</td>
<td>29.8</td>
</tr>
<tr>
<td>Education, Years (Mean (SD), Range)</td>
<td>16.1 (2.1), 12-20</td>
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<tr>
<td>Mini Mental State Exam (§)</td>
<td>29.4 (1.0), 25-30</td>
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<tr>
<td>Neuroticism (†)</td>
<td>13.3 (7.8), 0-38</td>
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<tr>
<td>Extroversion (†)</td>
<td>29.5 (6.1), 4-44</td>
</tr>
<tr>
<td>Agreeableness (†)</td>
<td>35.2 (6.1), 7-46</td>
</tr>
<tr>
<td>Conscientiousness (†)</td>
<td>35.4 (6.2), 12-48</td>
</tr>
<tr>
<td>Openness (†)</td>
<td>29.2 (6.1), 11-44</td>
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</table>
Neuroticism is associated with tau

Covariate adjusted residuals from linear regression models examining the relationship between tau-PET SUVR in the inferior temporal cortex and neuroticism, extroversion, openness, agreeableness, and conscientiousness.
Results are not driven by amyloid

<table>
<thead>
<tr>
<th>Region</th>
<th>Model</th>
<th>B (SE)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Amygdala</td>
<td>Model 1</td>
<td>.008 (.002)</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>.006 (.002)</td>
<td>.015</td>
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<tr>
<td>Entorhinal</td>
<td>Model 1</td>
<td>.008 (.003)</td>
<td>.031</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>.005 (.003)</td>
<td>.007</td>
</tr>
<tr>
<td>Inferior Temporal</td>
<td>Model 1</td>
<td>.009 (.002)</td>
<td>&lt;.001</td>
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<td></td>
<td>Model 2</td>
<td>.008 (.002)</td>
<td>.004</td>
</tr>
<tr>
<td>Lateral Occipital</td>
<td>Model 1</td>
<td>.005 (.003)</td>
<td>.127</td>
</tr>
<tr>
<td></td>
<td>Model 2</td>
<td>.004 (.003)</td>
<td>.203</td>
</tr>
</tbody>
</table>
Summary

• Results indicate that increased neuroticism is associated with higher tau pathophysiology CN participants.
  • Results were similar across all ROIs examined

• These effects were not driven by β-amyloid, suggesting a unique relationship between neuroticism and tau levels.

• High neuroticism scores are associated with increased levels of stress, which in turn may serve as a potential risk factor for tau accumulation.

• Alternatively, personality has been shown to change with the onset of AD, thus increased tau levels may affect neuroticism scores
Risk and Protective Factors

The effect of spirituality/religiosity on regional brain atrophy in subjects at risk of Alzheimer’s disease  
Sheardova

The association between personality and tau PET deposition in cognitively normal older adults  
Schultz

Impact of Cognitive Reserve and Preclinical AD on Longitudinal Driving Performance  
Roe
Impact of Cognitive Reserve and Preclinical AD on Longitudinal Driving Performance

Catherine M. Roe, PhD
July 17, 2017
Preclinical AD may have subtle systemic changes (e.g., cognitive, visual, spatial, motor function, etc.) that combined could affect driving.
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cognitive, visual, spatial, motor function, etc.) that combined could effect driving
Preclinical AD may have subtle systemic changes (e.g., cognitive, visual, spatial, motor function, etc.) that combined could affect driving.
Background

Preclinical AD measured using CSF & imaging biomarkers

Symptomatic AD

Driving

Cognitive Reserve
Five year longitudinal study: Is preclinical AD & cognitive reserve associated with impaired driving?

- Knight ADRC participants
  - Normal cognition (CDR 0)
  - 65+ years old
  - Drive at least once/week
- Follow 2y-4y

<table>
<thead>
<tr>
<th>Assessed for:</th>
<th>Baseline</th>
<th>Yearly FU</th>
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</thead>
<tbody>
<tr>
<td>Amyloid imaging</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lumbar puncture (CSF)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>ADRC Clinical &amp; psychometric tests</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>On-road driving test</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Office testing: Driving, cognitive reserve, mood, navigation, etc. questionnaires</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Stepwise Cox Proportional Hazards models: candidate variables

- **Biomarkers**
  - $A\beta_{42}$
  - tau
  - $ptau_{181}$
  - tau/$A\beta_{42}$
  - $ptau_{181}/A\beta_{42}$
  - Amyloid imaging
- **Time to Marginal/Fail road test**

- **Cognitive reserve**
  - Years of education
  - WRAT IV Reading Subscale scores$^1$
  - Questionnaire: intellectual, social, & physical activities$^2$

- 6 Stepwise Cox Proportional hazards

---

$^1$Wilkinson & Robertson, 2006
$^2$Scarmeas et al., 2003
Results

- N=121
- Age 72.4y (4.6)
- Education 16.3y (2.5)
- Followed 2.2y (0.8)
- Criteria enter/stay in models= .10

- Only two candidate variables entered and stayed in each model:
  - Biomarker $p<.052$ (except for $A\beta42$ $p=.096$)
  - Education $p<.048$
AD biomarker results

HR=4.37, 95%CI=1.88-10.17, p<.001
Education results

- CR: ↑ education = later dementia sx onset
- Eg. tau model:
  - HR=1.28, 95%CI=1.06-1.53, p=.009
- Here, ↑ education = earlier onset of driving problems!!!
  ↑ education, ↓ driving performance
How to explain this?

- ↑ educ lived closer university, more familiar road test route
  - Correlation education and distance from participants home?
- Mirshahi et al., 2014: ↑ educ, ↓ vision, which in turn may impact driving
  - Correlation educ, near acuity, far acuity, contrast sensitivity
How to explain this?

- ↑ educ lived closer to university, more familiar road test route
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  - Correlation education and distance from participants' home?
- Mirshahi et al., 2014: ↑ educ, ↓ vision, which in turn may impact driving
  - Correlation educ, near acuity, far acuity, contrast sensitivity
Conclusion

- Conclusion: Effect of CR (education) on driving may differ from its effect on cognition
Predicting progression in pre-dementia stages of Alzheimer’s disease with a neuroimaging measure of cognitive reserve

Loenhoud

Genetic Risk Profile for Prediction of Cognitive Decline in Pre-Symptomatic Alzheimer’s Disease

Laws

Heritability of Asymptomatic Alzheimer’s Disease

Hohman

Discriminating and Predicting Cognitive Exceptionality and Resilience: A Roadmap for Trajectory and Interaction Analyses with Risk and Protective Factors

Dixon

Investigating protective factors for amyloid and AD pattern neurodegeneration to discover paths to "Exceptional Aging" without AD

Vemuri
Predicting progression in pre-dementia stages of Alzheimer’s Disease:

A neuroimaging measure of cognitive reserve

Anita van Loenhoud, PhD Student
VU University Alzheimer Center
Amsterdam, The Netherlands

Reserve, Resilience
and Protective Factors
AAIC London – 07/15/2017
Proxies: how useful are they?
Proxies: how useful are they?
Proxies: how useful are they?
Proxies: how useful are they?

Other factors:
- Intelligence
- Occupation
- Physical activity
- ??
A “proxy-free” measure of CR
A “proxy-free” measure of CR

A “proxy-free” measure of CR

A “proxy-free” measure of CR

A “proxy-free” measure of CR

A “proxy-free” measure of CR

Aβ+ subjects with SCD/MCI/dementia

A “proxy-free” measure of CR

La Joie et al (2012), J. of Neuroscience

A “proxy-free” measure of CR

W-score (CR) = (GM_{obs} – GM_{pred}) / SD_{res}

# Relationship with progression

**Subsample of original cohort:** pre-dementia subjects with follow-up measurements available:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>total</th>
<th>without dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>119</td>
<td>35</td>
</tr>
<tr>
<td>follow up-time (months)</td>
<td>26.5 (13.6)</td>
<td>21.3 (13.2) *</td>
</tr>
<tr>
<td>conversion (n, %)</td>
<td>56 (47.1)</td>
<td>13 (37.1)</td>
</tr>
</tbody>
</table>
# Relationship with progression

**Subsample of original cohort:** pre-dementia subjects with follow-up measurements available:

<table>
<thead>
<tr>
<th>diagnosis</th>
<th>total</th>
<th>without dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SCD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCI</td>
</tr>
<tr>
<td>N</td>
<td>119</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>follow up-time (months)</td>
<td>26.5 (13.6)</td>
<td>21.3 (13.2) *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28.7 (13.3) *</td>
</tr>
<tr>
<td>conversion (n, %)</td>
<td>56 (47.1)</td>
<td>13 (37.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34 (51.2)</td>
</tr>
</tbody>
</table>
**Relationship with progression**

**Subsample of original cohort:** pre-dementia subjects with follow-up measurements available:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total (N)</th>
<th>Without dementia (SCD, MCI)</th>
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<tbody>
<tr>
<td><strong>N</strong></td>
<td>119</td>
<td>35 (35)</td>
</tr>
<tr>
<td><strong>Follow-up time (months)</strong></td>
<td>26.5 (13.6)</td>
<td>21.3 (13.2) *</td>
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<tr>
<td><strong>Conversion (n, %)</strong></td>
<td>56 (47.1)</td>
<td>13 (37.1)</td>
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### Relationship with progression

**W-scores** predicted conversion to more advanced AD stages, while **education** did not:

<table>
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<tr>
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<tr>
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<td>hazard ratio</td>
<td>p-value</td>
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<tr>
<td>W-scores whole-brain</td>
<td>.549*</td>
<td>.028</td>
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<tr>
<td>AD specific</td>
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<td>.008</td>
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<tr>
<td>education intermediate</td>
<td>1.485</td>
<td>.174</td>
</tr>
<tr>
<td>high</td>
<td>.823</td>
<td>.482</td>
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* refers to statistically significant results.
### Relationship with progression

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</tbody>
</table>
Application to the CR model

Stern (2012), The Lancet Neurology
Application to the CR model

Higher CR = later onset

faster cognitive decline

Cognitive test score

Neurodegeneration

Stern (2012), The Lancet Neurology
Thank you!

Email: a.vanloenhoud@vumc.nl

**Oral:** Monday, July 17, 2017: 4:15 PM - 5:45 PM, Capital Hall

**Poster:** Saturday, July 15, 2017: 12:15 PM - 1:30 PM, S9
Predicting progression in pre-dementia stages of Alzheimer’s disease with a neuroimaging measure of cognitive reserve

Genetic Risk Profile for Prediction of Cognitive Decline in Pre-Symptomatic Alzheimer’s Disease

Heritability of Asymptomatic Alzheimer’s Disease

Discriminating and Predicting Cognitive Exceptionality and Resilience: A Roadmap for Trajectory and Interaction Analyses with Risk and Protective Factors

Investigating protective factors for amyloid and AD pattern neurodegeneration to discover paths to "Exceptional Aging" without AD
Genetic Risk Profile for Prediction of Cognitive Decline in Presymptomatic AD Clinical Trials

Tenielle Porter, Victor L. Villemagne, Greg Savage, Lidija Milicic, Charley A. Budgeon, Colin L. Masters, Paul Maruff, Christopher C. Rowe, Ralph N. Martins, Giuseppe Verdile, Samantha C. Burnham, Simon M. Laws*, on behalf of the AIBL Research Group

*s.laws@ecu.edu.au
@Simon_M_Laws

No disclosures
The Setting

- No therapeutic interventions emanating from clinical trials
- Move towards running clinical trials earlier in the disease course - at the pre-symptomatic stage (e.g. A4)
- Target population are biomarker positive (Aβ positive)
- Need population to decline on the primary endpoint (cognitive measure)
- Between person variability in rates of decline
- Can genetic markers be used to predict those most likely to decline?
Genetics and Rates of Decline

BDNF Val66Met, Aβ amyloid, and cognitive decline in preclinical Alzheimer’s disease

Yen Ying Lim1,2, Victor L. Villeneuve3,4, Simon M. Levin5,6,7, David Ames3,4, Robert H. Pietrzak1, Kathryn A. Ellis1,2,3,4, Karra D. Harrington3, Pieterr Bourgat5, Olivier Salvador6, David Darby7, Peter J. Snyder1, Ashley J. Bush1, Ralph N. Martins8, Colin L. Masters4, Christopher C. Rowe9, Pradeep J. Nathan9,10, Paul Maruff10,11, for the Australian Imaging, Biomarkers and Lifestyle (AIBL) Research Group

Neurolology of Aging 34 (2013) 2457–2464

- **ε4+/BDNF<sub>Val66Met</sub> Met+ group**
  - declines 0.27 SD/year
  - Captures 16.8%

- Can further “cognitive genes” be used to predict those most likely to decline?
Objective

• **Primary Aim:** Identify a cognitive genetic risk profile (Cog-GRP): for pre-symptomatic (CN), biomarker positive individuals
  
  – Aβ positive – PET, tracer specific thresholds
    • $\geq 1.5$, $\geq 1.10$ and $\geq 0.62$ for PiB, florbetapir and flutemetamol, respectively
  
  – **APOE, BDNF, KIBRA, KL, COMT, CSMD1, SPON1**
  
  – Cognitive Composites:
    • Pre-symptomatic AD cognitive composite, PACC\(^{(Donohue et al 2014)}\)
    • Clinical Rating, Global cognitive composite, Verbal and Visual Episodic Memory, Executive Function, and Language composites\(^{(Burnham et al 2014)}\)
Defining the Cog-GRP

Decision tree Analysis “rpart” package in R
- Episodic memory
Defining the Cog-GRP

Decision tree Analysis “rpart” package in R
• Episodic memory

APOE
- ε4+ve
- ε4–ve

KIBRA
- KLOTHO
- CSMD1
- BDNF
- SPON1

APOE ε4+ Risk
APOE ε4- Risk
APOE ε4+ Resilient
APOE ε4- Resilient

Rate of Change (Verbal Episodic Memory Composite, SD)

Time (Years)

5-years
-1.5SD
Defining the Cog-GRP

Decision tree Analysis “rpart” package in R
- Episodic memory

APOE
- ε4+ve
- ε4–ve

KIBRA
- KLOTHO
- BDNF

SPON1
- KLOTHO

CSMD1

-0.13
-0.08
0.011
-0.04
0.013
-0.01
0.011
0.065

n=8
n=21
n=8
n=11
n=18
n=43
n=11
n=7

APOE ε4+ Risk
APOE ε4- Risk
APOE ε4+ Resilient
APOE ε4- Resilient

Rate of Change (Verbal Episodic Memory Composite, SD)

Time (Years)

-1.5SD

5-years

~12-years
Summary

- *APOE, KL, KIBRA, BDNF* variants partition pre-symptomatic, biomarker positive individuals in AIBL into at-risk and resilient groups for cognitive decline.

- ε4+ at Risk Profile associated with significantly accelerated decline in Verbal EM and additionally global cognition, language, clinical progression (composites) and AIBL-PACC.

- Profile may have utility in participant selection for pre-clinical AD trials
  - Interpretation of trial data

- Supports the investigation of additional genes for defining further polygenic risk scores for cognitive decline in pre-symptomatic, biomarker positive individuals
  - Particularly the inclusion of genes beyond those identified in AD-risk GWAS.
A special thank you to all our study participants and their families

AIBL study team
http://www.aibl.csiro.au

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Bozinovski (nee Pejoska)
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Kanagasingam
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Bill Wilson
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Fernanda Yevenes
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Heritability of Asymptomatic Alzheimer’s Disease

Timothy J Hohman, PhD
Assistant Professor of Neurology
Vanderbilt Memory & Alzheimer’s Center

Reserve and Resilience PIA
Alzheimer’s Association International Conference
London, UK
February 16, 2017
Asymptomatic Alzheimer’s Disease

- Heterogeneity in Cognitive Trajectories
Asymptomatic Alzheimer’s Disease

- Resilient v. Susceptible

All Participants:
- Amyloid$^+$
- Tau$^+$
- APOE $\varepsilon 4^+$
Asymptomatic Alzheimer’s Disease

• Reported by Braak & Braak (1997)

• Approximately 10% of NACC autopsy cases

• Approximately 30% in cohort studies (BLSA, ROS/MAP)
### Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ACT</th>
<th>ADNI</th>
<th>ADCs</th>
<th>ROSMAP</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Neuropathological AD, N</td>
<td>99</td>
<td>262</td>
<td>2842</td>
<td>407</td>
<td>3610</td>
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<tr>
<td>AD Cases</td>
<td>57</td>
<td>80</td>
<td>2764</td>
<td>263</td>
<td>3164</td>
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<tr>
<td>AD Controls</td>
<td>42</td>
<td>182</td>
<td>78</td>
<td>144</td>
<td>446</td>
</tr>
<tr>
<td>Female, %</td>
<td>68</td>
<td>49</td>
<td>51</td>
<td>70</td>
<td>54</td>
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<tr>
<td>Age, years</td>
<td>85 ± 5</td>
<td>74 ± 7</td>
<td>80 ± 9</td>
<td>90 ± 6</td>
<td>81 ± 9</td>
</tr>
</tbody>
</table>

- Neuropathological AD defined using Reagan Criteria
  - CERAD ≥ moderate
  - Braak Stage ≥ III/IV
- Genotyping QC
  - Combined ADGC Phase 1 + Phase 2 Dataset (1000 Genomes)
  - MAF = .01
  - GENO = .01
  - HWE p<.000001
  - 3,199,840 variants brought to analysis

(Hohman et al., In Preparation)
Heritability Results

\[ h^2 = 0.18 \pm 0.07, \quad p=0.002 \]

(Hohman et al., In Preparation)
Outline

• Asymptomatic Alzheimer’s Disease
• Heritability of Asymptomatic AD
• Continuous Measure of Resilience
• Heritability of Resilience
Building a Better Phenotype

Goodness of Fit = 0.76
Cross-loadings < 0.30
Dillon-Goldstein > 0.80

(Hohman et al., Neurology, 2016)
Building a Better Phenotype

(Hohman et al., Neurology, 2016)
Building a Better Phenotype

(Hohman et al., Neurology, 2016)
## Genetic Resilience to Alzheimer’s Disease

<table>
<thead>
<tr>
<th></th>
<th>ROS/MAP</th>
<th>ADNI</th>
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</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>954</td>
<td>624</td>
</tr>
<tr>
<td>Female (%)</td>
<td>614 (64%)</td>
<td>286 (46%)</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>80 (7)</td>
<td>73 (7)</td>
</tr>
<tr>
<td>CDR=0 (%)</td>
<td>556 (58%)</td>
<td>208 (33%)</td>
</tr>
<tr>
<td>APOE-ε4 (%)</td>
<td>249 (26%)</td>
<td>244 (39%)</td>
</tr>
</tbody>
</table>
Heritability Results

\[ h^2 = 0.71 \ (SE=0.34), \ p=0.034 \]

(Hohman et al., In Preparation)
Acknowledgements

Vanderbilt Memory & Alzheimer’s Center
• Angela Jefferson, PhD
• Katherine Gifford, PsyD
• Logan Dumitrescu, PhD
• Mary Ellen Koran, MD, PhD

Vanderbilt Genetics Institute
• Nancy Cox, PhD

Biospective Inc
• Donald McLaren, PhD

Harvard Medical School
• Elizabeth Mormino, PhD

Collaborators

Novartis Institute for Biomedical Research
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• William Bush, PhD

Rush University Medical Center
• David Bennett, MD
• Julie Schneider, MD

University of Miami
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• Eden Martin, PhD
• Brian Kunkle, PhD

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• David Libon, PhD

Funding:
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• Alzheimer’s Association IIRG-08-88733
• K24-AG046373, R01-AG034962, R01-HL111516
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<th>CHR</th>
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<th>MAF</th>
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Loenhoud

Genetic Risk Profile for Prediction of Cognitive Decline in Pre-Symptomatic Alzheimer’s Disease

Laws

Heritability of Asymptomatic Alzheimer’s Disease

Hohman

**Discriminating and Predicting Cognitive Exceptionality and Resilience: A Roadmap for Trajectory and Interaction Analyses with Risk and Protective Factors**

Dixon

Investigating protective factors for amyloid and AD pattern neurodegeneration to discover paths to "Exceptional Aging" without AD

Vemuri
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Vemuri
Discovering pathways to “Exceptional Aging” without AD

Prashanthi Vemuri, Ph.D.
Associate Professor of Radiology
Mayo Clinic Rochester

19th July 2017, London, UK

Nothing to disclose
Oldest-old individuals and APOE

- The association between APOE genotype and risk of AD in the oldest old individuals is greatly attenuated

Nelson et al. 2011
The central idea

- A combination of environmental, lifestyle, and genetic factors trigger the onset of AD in the *majority* of individuals as they age = *Average Trajectories*
The central idea

- A combination of environmental, lifestyle, and genetic factors trigger the onset of AD in the majority of individuals as they age = *Average Trajectories*

- A fraction of oldest old individuals have protection or resistance against AD despite the aging process = *Exceptional Agers (partying outliers)*
The central idea

- A combination of environmental, lifestyle, and genetic factors trigger the onset of AD in the majority of individuals as they age = Average Trajectories

- A fraction of oldest old individuals have protection or resistance against AD despite the aging process = Exceptional Agers (partying outliers)
Framework for discovering exceptional agers

EARLY LIFE | MIDLIFE | LATELIFE

AGE
Framework for discovering exceptional agers

EARLY LIFE

MIDLIFE

AMYLOID

LATELIFE

TAU

NEURODEGENERATION

AGE

COGNITIVE IMPAIRMENT
Framework for discovering exceptional agers

Each component of the biomarker cascade has different triggers, accelerators, and decelerators.
Evidence from Previous work on Intellectual Enrichment and Cognitive Function (Resilience)

Intellectual Enrichment - Larger shifts to cognitive trajectories compared to pathological changes trajectories

Vemuri et al. Brain 2011
Further Evidence based on Current Work (Protection/Resistance)

942 Population based sample of 70+ individuals from Mayo Clinic Study of Aging (Amyloid and Neurodegeneration)
Further Evidence based on Current Work (Protection/Resistance)

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Vemuri et al. JAMA Neurology 2017
Investigating Independent and Combined Protective Factors for Amyloid and Neurodegeneration

Vemuri et al. JAMA Neurology 2017
Investigating Independent and Combined Protective Factors for Amyloid and Neurodegeneration

APOE

MIDLIFE

Dyslipidemia

Obesity, Diabetes, Hypertension, Smoking

LATELIFE

Amyloid Deposition

Chronic Conditions

Neurodegeneration in AD signature regions

Cognitive Impairment

AGE

Vemuri et al. JAMA Neurology 2017
Investigating Independent and Combined Protective Factors for Amyloid and Neurodegeneration

Vemuri et al. JAMA Neurology 2017
Evidence for Exceptional Aging

- 85+ year old CN A-N- (N=35) vs. A+ or N+ (N=185)
- The Cohen $d$ results showed small to moderate effects (effect sizes $> 0.2$) for several variables in predicting exceptional aging without ADP

Vemuri et al. JAMA Neurology 2017
Current ongoing work - Mechanisms

- Mechanisms underlying these changes (Sleep as a protective factor) – Longitudinal amyloid deposition

Carvalho et. al. Under Review
Thanks to these amazing people...
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Study participants and staff in the Mayo Clinic Study of Aging, Mayo Alzheimer’s Disease Research Center, and Aging Dementia Imaging Research laboratory
Cross-network coupling of the fronto-parietal control network during memory performance supports protective effects of education in aging

Education can strengthen the role of the left hippocampus in episodic memory performance

Working memory and brain maintenance: A longitudinal study

Neurofunctional activation associated with early and lifelong cognitively stimulating activities moderates working memory differences in normal aging

Beta-Amyloid Accumulation Hurts and Crystallized Knowledge Helps Brain Modulatory Capacity
Cross-network coupling of the fronto-parietal control network during memory performance supports protective effects of education in aging

Nico Franzmeier & Michael Ewers
Fronto-parietal control network hubs as a potential substrate of reserve

Resting-state fMRI global connectivity of a fronto-parietal control network hub is associated with
1) greater education
2) attenuated effects of AD pathology on cognition

Greater resting-state global connectivity of fronto-parietal hubs is thought to reflect their ability to exert control on other networks during cognitive demands

Hypotheses:
1. Education is associated with more efficient network topology (i.e. small-worldness) in core memory networks during memory task fMRI
2. Higher network efficiency is mediated by the level FPCN connectivity to a network
3. More efficient network topology is linked to better memory performance
Memory task-related connectivity

Networks defined based on 264 spherical ROIs with 5 mm radius based on a widely used brain parcellation (Power et al., Neuron, 2011)

Task-related functional connectivity assessment via conditional psychophysiological interaction (cPPI)

Sample: 26 cognitively normal elderly that underwent face-name learning task-fMRI
Greater education is associated with higher small-worldness of core memory networks

All models controlled for age, gender, APOE genotype and whole brain grey matter volume; *FDR-corrected $p<0.05$, **FDR-corrected $p<0.01$
The effect of education on network small-worldness is mediated via FPCN cross-network coupling

<table>
<thead>
<tr>
<th></th>
<th>Successful encoding</th>
<th>Successful recognition</th>
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</thead>
<tbody>
<tr>
<td><strong>Fit indices</strong></td>
<td></td>
<td></td>
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<tr>
<td>Global Fit index (GFI)</td>
<td>0.983</td>
<td>Mediation n.s.</td>
</tr>
<tr>
<td>Root mean square error of approximation (RMSEA)</td>
<td>&lt;0.001</td>
<td>Mediation n.s.</td>
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<tr>
<td>Standardized root mean square residual (SRMR)</td>
<td>0.023</td>
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Summary: Fronto-parietal control network hubs as a substrate of reserve

Education: protective factor in aging

Memory performance

FPCN hubs

Efficient functional network topology
Thank you

1ST INTERNATIONAL CONFERENCE ON COGNITIVE RESERVE IN THE DEMENTIAS

Department of Psychiatry and Psychotherapy
Ludwig-Maximilians-University Munich
Nussbaumstraße 7 • 80336 Munich • Germany

24-25 November 2017
Cross-network coupling of the fronto-parietal control network during memory performance supports protective effects of education in aging

**Education can strengthen the role of the left hippocampus in episodic memory performance**

Working memory and brain maintenance: A longitudinal study

Neurofunctional activation associated with early and lifelong cognitively stimulating activities moderates working memory differences in normal aging

Beta-Amyloid Accumulation Hurts and Crystallized Knowledge Helps Brain Modulatory Capacity
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Working memory and brain maintenance: 
A longitudinal study

Lídia Vaqué-Alcázar, Cinta Valls-Pedret, Roser Sala-Llonch, Sara Pudas, Kilian Abellaneda-Pérez, Núria Bargalló, Emilio Ros, Lars Nyberg, David Bartrés-Faz

Lídia Vaqué-Alcázar
PhD student
Medical Psychology Unit. Department of Medicine
Faculty of Medicine and Health Sciences
University of Barcelona

http://www.ub.edu/bbslab/
There are different cognitive trajectories in aging

**BRAIN MAINTENANCE**

‘Individual differences in the manifestation of age-related brain changes and pathology allow some people to show little or no age-related cognitive decline’


We aimed to characterize the **functional changes** of a group of healthy elders showing **stability of working memory** function (**stables**) during a **2-year follow-up**, as compared to those showing some level of age-related cognitive decline (**decliners**).
Forty-seven healthy aged subjects, mean age: 68.4 ± 2.85 (70.47 ± 2.97 at follow-up) underwent magnetic resonance imaging (MRI) acquisition and a neuropsychological assessment (NPS) at two time points (2-year follow-up).

**MRI**

Functional MRI (fMRI)

N-Back task

FEAT-FSL software

Contrast of interest:
cognitive load (3>2>1>0-Back)

FLAME (FMRIB's Local Analysis of Mixed Effects). General Linear Models (GLM) matrices.
The statistical significance was set at p<0.05 and z>2.3 (cluster wise corrected).

**NPS**

d’ 2 and 3-Back
Backward digits
TMTB-TMTA

\[ \text{POMP} = \left( \frac{\text{observed} - \text{minimum}}{\text{maximum} - \text{minimum}} \right) \times 100 \]

Moeller J, Front Psychol (2015)

Working Memory factor (WMF)

Sala-Llonch R, Cortex (2012)
RESULTS

Stables vs Decliners

CLASSIFICATION CRITERIA:

The whole sample WMf performance significantly decline after 2 years (t=2.983 / p=0.005)

Significant decline:
t=6.335 / p<0.001

Rate of change above the group mean (-4.38)

DECLINERS N=22

STABLES N=25

Mean activation

STABLES: pre>post

DECLINERS: pre<post

R

Z=32

Z=52

Z=57

L

Baseline
Follow-up

BOLD signal Cluster
Decliners: pre>post +/− 1 SEM

t=2.162
p=0.036

Baseline
Follow-up

BOLD signal Cluster
Stables: pre>post +/− 1 SEM

t=3.592
p=0.001

Stables
Decliners
RESULTS

Stables vs Decliners

CLASSIFICATION CRITERIA:
The whole sample WMf performance significantly decline after 2 years (t=2.983 / p=0.005)

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DECLINERS  
N=22

STABLES  
N=25

Rate of change above the group mean (-4.38)

Mean activation
STABLES: pre>post
DECLINERS: pre<post

Z=32  
Z=52  
Z=57

Baseline  
Follow-up

BOLD signal Cluster  
Decliners:pre-post  
+/- 1 SEM

t=4.203  
p<0.001

BOLD signal Cluster  
Stables:pre>post  
+/- 1 SEM

t=2.162  
p=0.036

t=2.162  
p=0.036

BOLD signal Cluster  
Stables:pre>post  
+/- 1 SEM

t=3.592  
p=0.001

\( r=0.454 \ / \ p=0.002 \)
RESULTS

S vs D - Performance

STABLES
N=25

DECLINERS
N=22

SHP N=9
STABLES high performers

SLP N=16
STABLES low performers

baseline performance above the group mean (46.95)
RESULTS

S vs D - Performance

<table>
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<th>N</th>
<th>Description</th>
<th>Baseline Performance</th>
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<td>25</td>
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</tr>
<tr>
<td>SHP</td>
<td>9</td>
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No significant differences

Mean activation

Z-scores:
- SLP: pre < post, Z=30, Z=36
- SHP: pre < post, Z=Z

BOLD signal changes:
- Cluster SLP: pre < post, +/− 1 SEM

Statistical tests:
- t=2.123, p=0.045
- t=2.492, p=0.020
- t=6.412, p<0.001
• **WM function stability** in aging could be related to **more efficient WM network activation**.

• Decliners’ group recruited brain regions from other non-related WM systems during the cognitively demanding task.

• For the stables’ group, the **baseline WM performance seems to predict different age-related changes at a functional level.**

  > Stables with low performance at baseline show a brain pattern of change similar to the decliners’ group.
THANK YOU

P3-351
Structural and Functional Correlates of Brain Maintenance during a Working Memory Task
Tuesday, July 18

http://www.ub.edu/bbslab/

Lídia Vaqué-Alcázar

@bbs_lab
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Neurofunctional activation associated with early and lifelong cognitively stimulating activities moderates working memory differences in normal aging

Gabriel Ducharme-Laliberté Ph. D. (c), Samira Mellah, Ph. D., Benjamin Boller, Ph. D., & Sylvie Belleville, Ph. D.

Department of Psychology, Université de Montréal
Research Center of the Institut Universitaire de Gériatrie de Montréal
What neurobiological mechanisms underlie reserve?

- Age has a deleterious effect on working memory (WM)
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- Reserve differences might intervene to buffer, or moderate, those effects
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  - Neural efficiency / compensation?
  - Load-dependent mechanisms?
What neurobiological mechanisms underlie reserve?

• Age has a deleterious effect on working memory (WM)

• Reserve differences might intervene to buffer, or moderate, those effects

• How?
  • Neural efficiency / compensation?
  • Load-dependent mechanisms?

1) What functional activations are associated with reserve proxies?
2) Do they moderate the impact of age on WM?
Methods
Methods

• 37 older adults without cognitive impairment
  • 65-88 years old
  • 9-22 years of education
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• fMRI – n-back task (0, 1 & 2)
  • Manipulation of task load
Methods

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  • 65-88 years old
  • 9-22 years of education

• **fMRI – n-back task (0, 1 & 2)**
  • Manipulation of task load

• **Whole brain multiple regressions:**
  • Years of formal education
  • PCA-based composite reserve score
    • Years of formal education
    • Vocabulary (WAIS-IV)
    • Educational-occupational attainment
      • Social, physical & leisure activities
    • New information processing (VLS; Hultsch et al., 1999)

I + W + C + W + K + ...

500 ms

1 500 ms

e.g. 2-back condition
Methods

- **37 older adults without cognitive impairment**
  - 65-88 years old
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- **Moderation analyses:**
  - Hierarchical multiple regressions (age*β-value → WM performance)
1-back condition: neural efficiency in a specialized region attenuates the age effect on WM
1-back condition: neural efficiency in a specialized region attenuates the age effect on WM

**PROXY EFFECT**

Better reserve proxy = Lower activation in the left medial superior frontal gyrus (BA8)

Composite: [x: −9, y: 47 z: 47]; $p < 0.001$ uncorr.; $k = 43$

Education: [x: −9, y: 44, z: 50]; $p < 0.001$ uncorr.; $k = 37$
1-back condition: neural efficiency in a specialized region attenuates the age effect on WM

**PROXY EFFECT**

Better reserve proxy = Lower activation in the left medial superior frontal gyrus (BA8)

**MODERATION EFFECT**

Low activators show a smaller age effect on WM performance than High activators

Composite: [x: −9, y: 47, z: 47]; p < 0.001 uncorr.; k = 43

Education: [x: −9, y: 44, z: 50]; p < 0.001 uncorr.; k = 37

Composite: \( F(3, 33) = 6.69, p = 0.001; \beta = 0.31, p = 0.037 \)

Education: \( F(3, 33) = 5.91, p = 0.002; \beta = 0.27, p = 0.073 \)
2-back condition: compensatory activation in an alternative region attenuates the age effect on WM
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PROXY EFFECT

Better reserve proxy = Higher activation in the right caudate body

Education: [x: 15, y: -13, z: 23]; $p < 0.001$ uncorr.; $k = 126$
2-back condition: compensatory activation in an alternative region attenuates the age effect on WM

**PROXY EFFECT**
Better reserve proxy = Higher activation in the right caudate body

**MODERATION EFFECT**
High activators show no age effect on WM performance whereas Low activators do

Education: \(x: 15, y: -13, z: 23\); \(p < 0.001\) uncorr.; \(k = 126\)

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Beta-Amyloid Accumulation Hurts and Crystallized Knowledge Helps Brain Modulatory Capacity
Beta-Amyloid Deposition Hurts and Crystallized Knowledge Helps Brain Modulation: An fMRI Study

Zhang Jingting¹, Zhuang Song¹, Michelle Farrell¹
Patricia A. Reuter-Lorenz² & Denise C. Park¹

¹University of Texas at Dallas
²University of Michigan
MODULATION IS AN IMPORTANT BRAIN FUNCTION
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- What is **Brain Modulation**?
  - The ability to increase brain activity to **task difficulty** (e.g., **Hard > Easy**), primarily in the fronto-parietal control network (Braver et al., 2012; Braver, 2009; Turner & Spreng, 2015)
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    - **Modulation = Hard > Easy**
  - Higher modulation relates to better cognition (e.g., Rieck et al., 2017)
Modulation is an important brain function

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- Older adults, compared to young, are less able to modulate brain activity to task difficulty (Kennedy et al., 2015; Rieck et al., 2017; Reuter-Lorenz, 2008)
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![Graphs showing modulation and age](image-url)
CURRENT STUDY: HOW DO BRAIN DEPLETION & ENRICHMENT FACTORS AFFECT MODULATION?

- **Depletion**
  - Does amyloid deposition impair the ability to modulate?

- **Enrichment (Cognitive Reserve)**
  - Does crystallized knowledge benefit modulation and modify the relationship between amyloid and modulation?

- The lifespan perspective is key for understanding depletion & enrichment effects in aging
OVERVIEW OF DESIGNS

- **Participants: cognitively normal** (MMSE > 26)
  - 40-89 years (N=274) Dallas Lifespan Brain Study
    - Middle-age (40-59 years, M = 52.66 years, SD = 5.0);
    - Older (60-89 years, M = 72.5 years, SD = 7.6)

- **Depletion factor – Beta Amyloid in PET scan**
  - F-18 Florbetapir: standardized to the whole cerebellum to compute the Mean Cortical Standardized Uptake Value Ratio (SUVR).

- **Enrichment factor - Crystallized knowledge**
  - Shipley vocabulary
  - ETS vocabulary
  - CANTAB Graded Naming task

- **Outcome measure – Brain modulation in an fMRI task**
  - Semantic judgement: living/non-living
  - Unambiguous (Easy): LION or RADIO
  - Ambiguous (Hard): VIRUS or ZOMBIE
  - Modulation = Hard > Easy
MODULATION DECLINES WITH AGE
Contrasting Hard vs. Easy
**Amyloid Deposition Impairs Brain Modulation but Only in Middle-aged Adults**

- Significant **Age x Amyloid** Interactions ($p$'s = 0.021 ~ 0.049)
- **Higher amyloid predicted lower modulation for middle-aged adults** (40 – 59 years) **but not older adults** (60 – 89 years):

![Graphs showing modulation against mean cortical SUVR (centered) for middle-aged and older adults](image-url)
CRystallized Knowledge benefits Modulation

After controlling for Age and Amyloid, participants with better crystallized knowledge showed higher modulation.

No interactions: Age x Crystallized; Amyloid x Crystallized
SUMMARY

- Depletion: Amyloid deposition impairs brain modulation in middle-aged adults, showing some of the earliest evidence of amyloid toxicity on the brain.
  - There is no effect on the older adults (60 – 89 years)

- Enrichment: Crystallized knowledge benefits modulation independent of both age and amyloid burden.
  - May reflect cognitive reserve

AIC  Poster #18769 (Sat, July 15, 12:15 PM - 1:30 PM, S9)
AAIC  Poster #16632 (Tue, July 18, 9:30 AM - 4:15 PM, S8)
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AAIC  Poster #16632 (Tue, July 18, 9:30 AM - 4:15 PM, S8)
THANK YOU FOR YOUR ATTENTION!
After controlling for age, higher modulation predicted better fluid abilities

Significant in all 4 ROIs
Example plot: Left med sup frontal
Higher modulatory capacity predicted better working memory in left med sup frontal across all ages
HIGHER MODULATORY CAPACITY PREDICTED BETTER WORKING MEMORY, AGE DIFFERENCES VARY ACROSS REGIONS

Right angular

Young

R² = 0.013

Middle-age

R² = 0.028

Old

R² = 0.008

Very Old

R² = 0.006

Working memory

Modulatory capacity
Higher modulatory capacity predicted better working memory, age differences vary across regions.

Right cerebellum

Young

\[ R^2 = 0.001 \]

Middle-age

\[ R^2 = 0.046^* \]

Old

\[ R^2 = 0.028^* \]

Very Old

\[ R^2 = 0.015 \]
For age-related neural deterioration, crystallized knowledge as a type of reserve

- What is reserve?
  - Life experiences help older adults to become less vulnerable to neural deterioration (Stern 2002, 2016; Reuter-Lorenz & Park, 2014)

- High level of crystallized knowledge, as a type of reserve, is particularly important for older adults’ cognition
  - Crystallized knowledge is highly preserved with age