“Research criteria to identify the neural substrate of reserve in Alzheimer’s disease”

“Reserve and Resilience in the Mayo Clinic Study of Aging”

“Developing neuroimaging tools to assess cognitive reserve”

“A neuroimaging method to capture cognitive reserve”
Reserve and Resilience Research in Mayo Clinic Study of Aging

Prashanthi Vemuri, Ph.D.: Unable to present due to AIC conflict
Assistant Professor of Radiology,
Mayo Clinic Rochester

Presented by: Eider M. Arenaza-Urquijo, Ph.D.

Data Blitz, 23rd July 2016
Mayo Clinic Study of Aging and work on Reserve

Study (PI: Ron Petersen): Population based sample of non-demented elderly between 50-90 ages with extensive longitudinal clinical and imaging follow-up.

*Mayo Clinic Study of Aging Studies have investigated the impact of CR on:*

*Cognition as an Outcome*

*Alzheimer’s Disease Biomarkers as an Outcome*
“SHIFT” of the cognition trajectory

- **Study 1**: Intellectual Enrichment delays the onset of cognitive impairment (Vemuri et al. JAMA Neurology 2014)
  - E.g. In an 80 year old APOE4 cognitively normal, delay is in the order of 3-8 years based on male vs. female, education level - occupation complexity (low, medium, high), midlife cognitive activities (low, medium, high)

- **Study 2**: Shifts in longitudinal cognitive trajectories irrespective of Amyloid (A) vs. Vascular (V) Pathologies (Vemuri et al. Brain 2015)
  - E.g. A 81 year old A+V+ at 75th percentile of education/occupation will perform cognitively similar to a 81 year old A-V- at 25th percentile
Impact on AD Biomarker Trajectories

- Two cross-sectional studies did not detect any effect of CR on AD biomarker trajectories
  - AMNART IQ as CR proxy and CSF Biomarkers as AD Biomarker Outcomes (Vemuri et al. Brain 2011)
  - Education/Occupation/Cognitive Activities as a CR proxy and Amyloid PET, FDG PET, MRI as AD Biomarker Outcomes (Vemuri et al. Annals of Neurology 2012)

- Longitudinal imaging study found evidence for “early brain reserve or protection” but found no impact on rate of AD biomarker changes (Vemuri et al. Neurology 2016)
Summary: Larger shifts to cognition trajectories compared to pathology trajectories

Vemuri et al. Brain 2011
Lab Interests

• How reserve factors such as physical exercise and cognitive stimulation may delay cognitive declines in individuals harboring AD pathology.

• Neuroimaging region of interest (ROI) analyses have many advantages, but most available ROI templates were developed solely on younger adults.

• ROI templates including older adults better control for volumetric differences, and improve sensitivity of statistical analyses (Thompson et al., 2001; Smith et al., 2006).
White Matter and Reserve

- White matter microstructure assessed with DTI is increasingly being studied in aging and reserve.

- Aerobic fitness has been linked with higher FA in the corpus callosum.

Johnson et al. (2012) *NeuroImage*
Alterations in fornix microstructure (e.g., fractional anisotropy) has been linked with:

- AD-risk based on genetics or family history
- AD pathology in CSF
• 49 younger adults (mean = 32.5 ± 4.04 years) and 46 older adults (mean = 65.3 ± 4.55 years).

• BEDPOSTX (Behrens et al., 2003)] was run using a 2-fiber model, curvature threshold of 0.2 (approximately ± 80°), a step length of 0.5mm with maximum of 2000 steps.
Younger-Older Comparison

Our new younger-older adult DTI template of the fornix accommodates anatomical variability associated with human aging.
Associations with AD Pathology

A) FA, CSF Aβ42
B) FA, CSF t-Tau/Aβ42
C) FA, CSF p-Tau/Aβ42
Acknowledgements

Lab Members: Christopher Brown (Grad Student), Jon Hakun (Postdoc), Zude Zhu (Postdoc).

Collaborators at Sanders-Brown Center on Aging: Profs. Charles Smith, Gregory Jicha, Fred Schmitt.

Funding: NIA R01 Grant AG033036, NSF BCS-0814302
A neuroimaging approach to capture cognitive reserve

Anita van Loenhoud, Alle Meije Wink, Colin Groot, Sander Verfaillie, Jos Twisk,
Frederik Barkhof, Bart van Berckel, Philip Scheltens, Wiesje van der Flier, Rik Ossenkoppele

July 23th 2016 - PIA meeting Toronto
A neuroimaging approach to capture cognitive reserve

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Introduction

Cognitive reserve
Introduction

Cognitive reserve
Introduction

- Education
- Cognitive activity
- Physical activity

Cognitive reserve
Our approach

structural 3T MRI

subj1  subj2  subj3  ...  subj511
Our approach
Our approach
Our approach
Our approach

\[ W\text{-score} = \frac{GM_{\text{obs}} - GM_{\text{pred}}}{SD_{\text{res}}} \]

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

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

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

Education
- Low
- Intermediate
- High

Mean W-score vs Whole-brain
Results

Mean W-score

Whole-brain

Education
- Low
- Intermediate
- High

Low
Intermediate
High

Neuroscience Campus Amsterdam
VUmc
VU University Alzheimer Center Amsterdam
Results

• **Validation**: correlation with education (adjusted for disease stage)
Results

• **Validation**: correlation with education (adjusted for disease stage)
  - Education ↔ W-score on voxel level (tfce-corr, p < .05):
Insights from functional neuroimaging

Yaakov Stern and Christian Habeck
“Identification of a task-invariant cognitive reserve network”

Benjamin Boller
“Impact of education on training-induced changes in brain activity in individuals with subjective cognitive decline“

David Bartrés-Faz
“Education and fMRI activity patterns during working memory load in cognitively preserved elders”
Identification of a task-invariant cognitive reserve network

Yaakov Stern and Christian Habeck
Cognitive Neuroscience Division, Department of Neurology
Columbia University College of Physicians and Surgeons
A Generalized Neural Representation Of Cognitive Reserve

- CR allows people to better maintain function in multiple activities and cognitive domains in the face of brain changes or pathology.
- This suggests CR might be subserved by one or more task-invariant brain networks that are active across tasks with varying processing demands.
- Goal: Can we identify a task-invariant pattern of CR-related brain activity, defined as:
  - common to task-related activation across 12 different tasks
  - can estimate a CR proxy measure in out-of-sample data using different activation tasks
Approach

• 255 subjects from RANN study, age 20-80, with complete neuroimaging for 12 different tasks – age has not been considered explicitly
• Randomly divide data into training sample of 200 observations and test sample of 41 observations for NART (200/55 for education)
• In derivation sample, use scaled Subprofile modeling (SSM) to derive best-fit NARY and education patterns according to AIC criterion
• Project derived pattern into test sample and obtain pattern scores for each subject in all 12 tasks
• Estimate NART and education using training sample model; record p-level and sign of association between NART/Education; and average subject pattern scores with sign-weighted lodP value
• Repeat steps 100 times, each time storing the derived patterns and the test prediction quality
• Compute Z-map of pattern loadings for the 100 patterns
• The education pattern contains a subset of the NART pattern
• The default-mode network is shown as de-activating with increasing NART, while the task-positive network appears in the regions that increase in activation
Apply EDU pattern to letter Sternberg data from 123 subjects: does subject expression correlate with EDU?

Derived education value shows correlation with actual education at p<0.05 in 5 out of 9 task conditions.
Apply NART pattern to Letter Sternberg data from 123 subjects: does subject expression correlate with NART?

Derived NART value shows correlation with actual NART at $p<0.05$ in 7 out of 9 task conditions.
PIA Reserve, resilience and protective factors

The impact of cognitive reserve on training-induced changes in individuals with subjective cognitive decline

Benjamin BOLLER, Ph.D.
Research center of the Institut universitaire de gériatrie de Montréal
Main interests

- Use longitudinal design to identify the effect of different reserve proxies on working memory
- Identify functional and structural brain differences related to different reserve proxies
- Develop cognitive training programs to promote cognitive and brain health in aging and in the early stages of AD
- Identify the brain mechanisms underlying cognitive training and compare them with those associated with more traditional reserve proxies
- Evaluate the impact of reserve proxies on the response to cognitive training, on the brain changes resulting from training and on the dose-response relationship
Impact of education on training-induced changes in individuals with SCD

Performance

Left superior temporal gyrus

Bilateral superior and medial frontal giri
Two presentations of interest:

Session: Computerized Cognitive Training: What Works, With Whom and How?  
**Monday, July 25, 2016: 8:00 AM, Room 105**

“**Functional Neuroimaging in Trials of Cognition Focused Interventions**”  
Belleville, Bier, Boller, Mellah & Ouellet

Session: Non-Pharmacological Interventions and Meaningfulness of Risk Factors  
**Tuesday, July 26, 2016 at 2:00 PM, Room 105**

“**Cognitive reserve modulates encoding related neural response after memory training in individuals with Subjective Cognitive Decline**”  
Boller, Ouellet, Mellah, Gauthier & Belleville

benjamin.boller@umontreal.ca
Education and fMRI activity patterns during working memory load in cognitively preserved elders

David Bartrés-Faz
Department of Medicine
Faculty of Medicine and Health Sciences
University of Barcelona
Former Neuroimaging studies on CR

Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer’s disease

Cristina Solé-Padullés*, David Bartrés-Faz*, Lorenz Rahm*, Lorena Ramí*, Juan C. Clemente, Beatriz Bosch*, Antonio Villar*, María Bargallo*, M. Angeles Jurado, M. M. Barrios, José Luis Molinuevo

Specific Anatomic Associations Between White Matter Integrity and Cognitive Reserve in Normal and Cognitively Impaired Elders

Eider M. Arenaza-Urquijo, M.Sc., Beatriz Bosch, M.Sc., Rosa Sola-Bruch, M.Sc., Cristina Solé-Padullés, Ph.D., Carmen Jusquí, Ph.D., Daria Fernández-Espejo, M.Sc., María Bargallo, M.D., Ph.D., Lorena Ramí, Ph.D., José Luis Molinuevo, M.D., Ph.D., David Bartrés-Faz, Ph.D.

Structural and Functional Imaging Correlates of Cognitive and Brain Reserve Hypotheses in Healthy and Pathological Aging

David Bartrés-Faz · Eider M. Arenaza-Urquijo
Investigate how White Matter burden interacts with Education on the expression of Working Memory networks

<table>
<thead>
<tr>
<th></th>
<th>OLD ( n = 90 )</th>
<th>YOUNG ( n = 16 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67 (2.90)</td>
<td>22 (1.93)</td>
</tr>
<tr>
<td>YoE</td>
<td>11 (4.02)</td>
<td>-</td>
</tr>
<tr>
<td>MMSE</td>
<td>29 (0.84)</td>
<td>-</td>
</tr>
</tbody>
</table>

3T Siemens Trio MRI

Effect of age (young vs old)
Effect of education (old)

Automatic WMH volume segmentation

Fernández-Cabello et al. (submitted)
Interaction YoE x WMH effects
Cognitive Load (3>2>1>0-back)

Young
\(n = 16\)

High YoE
Low WMH
\(n = 21\)

‘Young like’ pattern

High YoE
High WMH
\(n = 30\)

‘Compensatory’ pattern

No age and gender adjusted differences in cortical thickness

Fernández-Cabello et al. (submitted)
Ongoing in our lab.....

- Study of fMRI patterns (maintenance or change) at 2-year follow-up.

- Modulation of ‘reserve networks’ through non-invasive brain stimulation.

[Graph showing data points for different education levels and WMH status over a 2-year period.]
Thank you

Special thanks

Eider M. Arenaza-Urquijo
INSERM – Univ. Caen

Cristina Solé-Padullés
Univ. de Barcelona

Sara Fernández-Cabello
University of Salzburg

Dídac Vidal-Piñeiro
Oslo University

Roser Sala-Llonch
Oslo University

Lídia Vaqué-Alcázar
Univ. de Barcelona

Collaborations

José Luis Molinuevo
Beatriz Bosch
Lorena Rami

Emili Ros
Cinta Valls-Pedret

Núria Bargallo
Antoni Salvà
Sara Domènech
<table>
<thead>
<tr>
<th>Michael Valenzuela</th>
<th>“Cognitive lifestyle in different populations using Lifetime of Experiences Questionnaire”</th>
</tr>
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<tr>
<td>Robert Perneczky</td>
<td>“Population-based research and cognitive reserve”</td>
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</table>
How to Better Measure Cognitive Lifestyle?

Lifespan approach

Lifetime of Experiences Questionnaire (LEQ)

- Educational activities
- Cognitive-loaded leisure activities
- Social engagement

Young Adulthood
(13-30 years)

- Occupational complexity
- Cognitive-loaded leisure activities
- Social engagement
- Educational activities

Mid-Life
(31-65 years)

- Cognitive-loaded leisure activities
- Social engagement
- Ongoing work
- Educational activities

Late Life
(>65 years)
How to Better Measure Cognitive Lifestyle?

Lifetime of Experiences Questionnaire (LEQ)

*Lifespan approach*

- **Young Adulthood** (13-30 years)
  - Educational activities
  - Cognitive-loaded leisure activities
  - Social engagement

- **Mid-Life** (31-65 years)
  - Occupational complexity
  - Cognitive-loaded leisure activities
  - Social engagement
  - Educational activities

- **Late Life** (>65 years)
  - Cognitive-loaded leisure activities
  - Social engagement
  - Ongoing work
  - Educational activities

Good psychometric properties  Valenzuela (2007)

Prospectively predicts cognitive decline  Valenzuela (2008)

Translated into Spanish, French, German, Portuguese, Greek and used by >10 groups.
Cognitive lifestyle is highly dynamic over course of lifetime. Valenzuela (2012)
Cohort Differences Aussies vs French
Cohort Differences Aussies vs French

What is more important? Where you end up, where you started, or how you got there?
Cognitive Lifestyle & Brain Atrophy

1.9% annual loss


Adjusting for background variables of age, intracranial volume, sex, vascular risk factors, APOE4, physical activity (past and present), current mood, NART-IQ and current cognitive lifestyle.

Supervision: Hippocampus Protection in MCI (The Sydney SMART Trial)

Suo et al Under Review
Ying & Yang of Supervision

New data!

Suo et al Under Review
LEQ & Amyloid: Disease Modification?

Gene–Environment Interactions: Lifetime Cognitive Activity, APOE Genotype, and Beta-Amyloid Burden

Miranka Wirth,1 Sylvia Villeneuve,1 Renaud La Joie,1 Shawn M. Marks,1 and William J. Jagust1,2,3
1Helen Wills Neuroscience Institute and 2School of Public Health, University of California, Berkeley, California 94720, and 3Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720

Carriers of the apolipoprotein E (APOE) ε4 allele, the major genetic risk for Alzheimer’s disease (AD), harbor an increased load of β-amyloid (Aβ) plaque burden that is felt to be a major instigator of AD development. Data has suggested that lifestyle factors may reduce AD risk by directly mitigating Aβ pathology, which could be particularly beneficial in APOE ε4 carriers. We therefore examined the interaction between lifetime cognitive activity and the APOE ε4 allele in relation to brain Aβ burden. We obtained measures of lifetime cognitive activity in 118 cognitively normal human individuals (mean age: 76.13 ± 5.56 years, 70 women) using a validated questionnaire that included measures over early, middle, and current age epochs. Hierarchical regression models (adjusted for age, gender, and years of education) were conducted to examine effects of APOE ε4 carrier status, lifetime cognitive activity, and the interaction of the two factors with cortical Aβ deposition, quantified using [11C] Pittsburgh-compound-B (PIB)-PET. As expected, the ε4 carriers exhibited higher PIB retention compared with noncarriers. Lifetime cognitive activity moderated the APOE genotype effect such that cortical PIB retention was diminished in ε4 carriers that reported higher cognitive activity over the life course. The findings suggest that greater lifetime cognitive activity may forestall AD pathology, specifically in genetically susceptible individuals. The effect could imply that cognitive training promotes increased neural efficiency that might retard the lifelong neurally mediated deposition of Aβ.
LEQ & Amyloid: Disease Modification?

ANOVA Model
DV: Whole brain Amyloid (\(^{18}\)F-Florbetaben)
IVs: Covariates: Age, sex, education  Fixed: APOE4 (+/-), LEQ tertiles
Interaction: APOE4 X LEQ

![Global Amyloid SUVR](image)
LEQ & Amyloid: Disease Modification?

ANOVA Model
DV: Whole brain Amyloid ($^{18}$F-Florbetaben)
IVs: Covariates: Age, sex, education  
Fixed: APOE4 (+/-), LEQ tertiles  
Interaction: APOE4 X LEQ

New data!
LEQ & Amyloid: Disease Modification?

ANOVA Model
DV: Hippocampal Amyloid (¹⁸F-Florbetaben)
IVs: Covariates: Age, sex, education  
     Fixed: APOE4 (+/-), LEQ tertiles
     Interaction: APOE4 X LEQ

New data!
LEQ & Amyloid: Disease Modification?

ANOVA Model
DV: Hippocampal Amyloid (¹⁸F-Florbetaben)
IVs: Covariates: Age, sex, education  Fixed: APOE4 (+/-), LEQ tertiles
Interaction: APOE4 X LEQ
LEQ & Amyloid: Disease Modification?

ANOVA Model
DV: Parietal Amyloid (18F-Florbetaben)
IVs: Covariates: Age, sex, education
Fixed: APOE4 (+/-), Late Life LEQ tertiles
Interaction: APOE4 X LEQ

New data!
Computerised Cognitive Training: What Works, With Whom and How?, Monday, July 25, 2016: 8:00 AM - 9:30 AM, Metro Toronto Convention Centre, 105
Population-based research and cognitive reserve

Robert Perneczky
Imperial College London
School of Public Health
r.perneczky@imperial.ac.uk
Alzheimer's disease

(N=93)

Pernecky (J Neurol Neurosurg Psychiatry 2006)
The past (2)

The past (3)

Guo & Perneczky (Alzheimers Dement 2013)
The future (1)

- CHARIOT Register
  - N = 30,000 volunteers

- CHARIOT-PRO Main Study
  - N = 1,500, 3 risk groups every 6 months up to 4 years

- CHARIOT-PRO Substudy
  - N = 500, 3 risk groups every 3 months up to 4 years
  - MRI, PET, CSF
Population-based research and cognitive reserve

Robert Perneczky
Imperial College London
School of Public Health
r.perneczky@imperial.ac.uk
## Research criteria and approaches to test reserve in aging and Alzheimer’s disease

<table>
<thead>
<tr>
<th>Speaker</th>
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<tbody>
<tr>
<td>Corinne Pettigrew</td>
<td>“Relationships of cognitive reserve to biomarkers of neuronal injury during preclinical AD”</td>
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<tr>
<td>José-Luis Molinuevo</td>
<td>“Cognitive reserve in preclinical AD”</td>
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<td>Silvia Morbelli</td>
<td>“Interplay between education and brain metabolic networks in normal aging and prodromal Alzheimer’s disease”</td>
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</table>
Relationship of cognitive reserve to biomarkers of neuronal injury during preclinical AD

Corinne Pettigrew, PhD
Research Associate, Department of Neurology
Johns Hopkins School of Medicine

Reserve, Resilience and Protective Factors PIA Data Blitz
AAIC 2016, Toronto, Canada
Background

• Biomarkers in preclinical AD
  • ↑ abnormality of AD biomarkers is associated with an ↑ risk of progression from normal cognition to MCI/dementia (e.g., Moghekar et al., 2013; Soldan et al., 2015; Pettigrew et al., 2016)

• Models of cognitive reserve (CR) suggest CR reduces the impact of pathology on cognitive and clinical outcomes (e.g., Stern, 2009)

• Research question: does CR modify the relationship between AD biomarkers and risk of clinical symptom onset?
The BIOCARD study

• Overarching goal of study
  • Examine predictors of progression from normal cognitive status to mild impairment and/or dementia

• Longitudinally followed cohort ($M_{fup} = 12y$, up to 20y)

• At baseline, $N = 349$ enrolled
  • Cognitively normal
  • Primarily middle age ($M_{baseline\ age} = 57.2y$, $SD = 10.3$)
  • Over time, $n = 64$ have progressed to clinical symptoms of MCI
Analyses: Cox regression models

- Effect of risk factors on time to onset of clinical symptoms

- Main effect AD biomarkers at baseline
  - *Amyloid*, CSF Aβ\textsubscript{1-42}
  - *Neuronal injury*, CSF total tau and p-tau
    - MRI cortical thickness in AD vulnerable regions

- Main effect cognitive reserve (CR)
  - **Biomarker x CR interaction** (to determine if CR modifies relationship between biomarker and risk of symptom onset)

Covariates: age, gender
### Biomarkers and CR in Relation to Onset of Symptoms

<table>
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<tr>
<th>Biomarker</th>
<th>Main Effect Biomarker</th>
<th>Main Effect CR</th>
<th>Interaction: Biomarker x CR</th>
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<tbody>
<tr>
<td>CSF Amyloid</td>
<td>HR 0.69, p = 0.005</td>
<td>HR 0.54, p &lt; 0.001</td>
<td>HR 0.96, p = n.s.</td>
</tr>
<tr>
<td>CSF Tau</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF P-tau</td>
<td></td>
<td></td>
<td></td>
</tr>
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- **Protective effects of CR on time to onset of clinical symptoms are equivalent across baseline levels of CSF amyloid**

*Soldan et al., 2013*
### Biomarkers and CR in Relation to Onset of Symptoms

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<td>1.17</td>
<td>n.s.</td>
<td>0.47</td>
</tr>
<tr>
<td>CSF P-tau</td>
<td>1.50</td>
<td>&lt; .001</td>
<td>0.51</td>
</tr>
<tr>
<td>Cortical thickness</td>
<td>0.51</td>
<td>.03</td>
<td>0.47</td>
</tr>
</tbody>
</table>

- **Protective effects of CR on time to onset of clinical symptoms are different if baseline levels of neuronal injury are high vs. low**
- **CR more protective at low levels of neuronal injury**

*Soldan et al., 2013; Pettigrew et al., under review*
Summary and Conclusions

- Multiple AD biomarkers associated with risk of clinical symptom onset during preclinical AD
- CR reduces risk of clinical symptom onset
- Effect of CR equivalent across levels of CSF amyloid
- Effect of CR differs depending on level of neuronal injury
  - Greater benefit of CR at low levels of neuronal injury
- CN individuals with high CR may be better able to compensate for low levels of neuronal injury
  - Reduced effectiveness of CR higher levels of neuronal injury may be due to more advanced neurodegeneration
Acknowledgments

Co-authors

• Cognitive & clinical
  • Marilyn Albert
  • Ola Selnes
  • Anja Soldan

• Biostatistics
  • Shanshan Li
  • Mei-Cheng Wang
  • Yuxin (Daisy) Zhu

• CSF
  • Abhay Moghekar
  • Richard O’Brien

• MRI
  • Timothy Brown
  • Mike Miller

• BIOCARD Research Team

BIOCARD participants and study partners
Supported by grants from the NIA
Thank you for your attention!
Cognitive reserve in preclinical Alzheimer’s disease

Dr. José L Molinuevo

Alzheimer’s disease and other cognitive disorders unit
ICN, Hospital Clinic I Universitari, Barcelona
BarcelonaBeta Brain Research Centre
Fundació Pasqual Maragall
Previously....

Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer’s disease

Cristina Salvi-Paladini, David Batres-For, Carmen Jacques, Perch Vondra, Lorena Rami, Emma C. Clemente, Beatriz Bocch, Amparo Villas, Nieves Bajo, M. Angeles Jurado, Maite Barrios, Jose Luis Molinuevo

Fig. 2. Brain areas showing positive (in hot colour) and negative (in winter colour) correlations with the CR composite score in healthy controls and Alzheimer’s disease patients. Scatterplots for the left precentral gyrus in the case of controls and the left lingual gyrus in AD patients are also depicted. For a precise localization of the cerebral regions, see Table 3.
Preclinical AD

- The preclinical stage has been postulated to be a long asymptomatic period during which the pathophysiological process is progressing.

- Preclinical AD subjects have been defined as individuals who have evidence of early AD pathological changes but do not meet clinical criteria for MCI or dementia (Sperling et al., 2011).

- Presymptomatic subjects: this state applies to individuals who will develop AD (monogenic AD)

- Asymptomatic at risk state for AD: this state can be identified in vivo by evidence of amyloidosis of the brain (PET or CSF).
Cortical thickness and VBM in preclinical AD

Fig. 1. Results of cortical thickness (A) and voxel-based morphometry analyses (B) showing differences between healthy elderly subjects with normal versus abnormal Aβ42 CSF levels (abnormal < normal Aβ42 CSF levels). All results are FWE-corrected.
Preclinical AD with high CR exhibit more gray matter loss.
Tracts showing increased AxD in Pre-AD subjects compared with controls (blue)
Relationship between the areas showing increased AxD and the level of Aβ_{42} on CSF (r=-0.52, p<0.0001) and cognitive reserve (Pre-AD group r=0.57, p<0.012).
Thank You
Interplay between education and brain metabolic networks in normal aging and prodromal Alzheimer’s Disease (AD)

Silvia Morbelli and Flavio Nobili

Nuclear Medicine and Clinical Neurology Units,
IRCCS San Martino – IST
University of Genoa
Dementia Research Group
(University of Genoa, Italy)

Memory Clinic

PET Center
equipped with Cyclotron and Radiopharmacy

3 Tesla MRI

Post-processing
(Connectomics,
Network and Methodological Development on semiquantification)

EADC 18F-FDG PET data sharing project
(Genoa, Amsterdam, Brescia, Munich, Marseille, Perugia)

EADC Amyloid PET data sharing project
(to date 11 centers across Europe)
Cognitive Reserve mediates functional compensation in highly educated prodromal AD

Hypometabolism in Poorly Educated pAD

Hypometabolism in Highly Educated pAD

Relative preserved metabolism in R Dorsolateral Prefrontal Cortex in highly educated pAD

Morbelli et al JNM 2013

Cluster saved as seed VOI for metabolic connectivity analysis

Morbelli et al Clin Trans Imaging 2013

< 0.05 FDR- corrected at peak and cluster level (age, sex, MMSE and center of belonging as nuisance)
Metabolic Connectivity of right DLPFC in prodromal AD

Both neural reserve and neural compensation underlye this metabolic network

Metabolic Connectivity of right DLPFC in Healthy Elderly

< 0.05 FDR: corrected at peak and cluster level (age, sex, MMSE and center of belonging as nuisance)
Education interacts differently with clinical expression of AD across European Countries

Hypometabolism in CTR > Highly Educated pAD

Southern Europe

Mid Europe

Hypometabolism in CTR > Poorly Educated pAD

Southern Europe

Mid Europe

Greater hypometabolism in Poorly Educated Southern European pAD

Mid Europe

VS

Southern Europe

Poorly educated AD from Countries with Lower Educational gradient have greater CR

Hp

- different association between formal education and occupational complexity/mid life intellectual enrichment

- To be evaluated: effect of different frequency of ApoE ε4

Morbelli et al in preparation
Thank you for your attention!

**Neurology**
Flavio Nobili
Matteo Pardini
Dario Arnaldi
Michela Ferrara
Agnese Picco
Andrea Brugnolo
Nicola Girtler
Jennifer Accardo

**Nuclear Medicine**
Gianmario Sambuceti
Matteo Bauckneht
Ambra Buschiazzo
Alessia Democrito
Chiara Ghersi
Lucia Garaboldi

**Post-processing and Statistics**
Andrea Chincarini (INFN)
Fabrizio De Carli (CNR)
Marco Pagani (CNR)
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<tr>
<th>Name</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaël Chételat</td>
<td>“From observational studies to interventions: an overview of the different approaches used in the lab”</td>
</tr>
<tr>
<td>Eider Arenaza-Urquijo</td>
<td>“Cognitive reserve and lifestyle across the spectrum from normal cognition to Alzheimer’s disease”</td>
</tr>
<tr>
<td>Colin Groot</td>
<td>“Active and passive reserve in demented an non demented stages of Alzheimer’s disease”</td>
</tr>
<tr>
<td>Anja Soldan</td>
<td>“Cognitive reserve and longitudinal cognitive change before and after onset of cognitive impairment”</td>
</tr>
</tbody>
</table>
Multimodal neuroimaging and lifestyle in ageing and Alzheimer’s disease

Gaël Chételat, INSERM,
Centre d’imagerie Cyceron, Caen
UNDERSTANDING

1) Abeta vs Tau
2) Connectivity

INFLUENCING

Chételat, Nat Rev Neurol, 2013
AGEING

NEGATIVE EMOTIONS AND STRESS

DEPRESSION

SLEEP PROBLEMS

COGNITIVE DECLINE

MEDITATION & LIFESTYLE

WELL-BEING AND MENTAL HEALTH (including ALZHEIMER’S DISEASE)
OBJECTIVE:
Better understand the relative influence of different lifestyle factors (cognitive activity, physical activity, diet) on different neuroimaging markers (structural, functional and molecular) in different life periods (young, middle age, old).

METHOD
Questionnaires x Multimodal neuroimaging data from already acquired data (IMAP + Berkeley) and new data (UP-AD)
Intervention on cognitive activity (new language learning)
INFLUENCING: 1) LIFESTYLE

Funded by
the France-Berkeley
Programme
(Coll. W Jagust)
INFLUENCING: 2) MEDITATION

HORIZON 2020
WORK PROGRAMME 2014 – 2015
8. Health, demographic change and wellbeing
   Personalising health and care

PHC 22 – 2015: Promoting mental wellbeing in the ageing population

SILVER SANTÉ STUDY
MEDIT-AGEING

Investigating the impact of meditation training on mental health and wellbeing in the ageing population
MEDIT-AGEING / SILVER SANTÉ
STUDY: DESIGN

STUDY 1: SCD- WELL
London-UK, Cologne-GE, Barcelona-SP, Lyon-FR

SCD patients (n = 160)

Baseline

Meditation
Control

Randomisation

8 weeks

Meditation
Control

No Intervention

6 months

Meditation

STUDY 2: AGE- WELL
Caen-FR

Expert meditators (n = 30)

Randomisation

9 months

Meditation
Active control
No intervention

Cognitively intact elders (n = 126)

18 months

Meditation

BIOLOGICAL

BEHAVIOURAL
30 expert meditators

126 healthy seniors
> 65 yrs

18 mths

MEDITATE

ENGLISH LEARNING

NOTHING UNUSUAL

AGE-WELL

STUDY 2B

STUDY 2A
MENTAL HEALTH DETERMINANTS
WP1: MEDITATION
WP2: LIFESTYLE

MECHANISMS OF ACTION
WP3: ATTENTION
WP4: EMOTION

ENDPOINTS OF AGEING AND AD
WP5: COGNITION AND WELL-BEING
WP6: BIOLOGICAL MARKERS

Antoine Lutz
Eider Arenaza
Miranka Wirth
Fabienn
Patriz
Olga Klimecki
Gael Chetelat
Patrik Vuilleumier
Natalie Marchant
Frank Jessen
Jose Luis Molinuevo
Miranka Wirth
“Cognitive reserve and lifestyle across the spectrum from normal cognition to dementia”

Eider M. Arenaza-Urquijo
Reserve, resilience and protective factors PIA meeting
July 23, 2016
In a previous work, we proposed that there might be an interplay between lifestyle-related protective and compensatory mechanisms across the spectrum from normal cognition to AD dementia. (Arenaza-Urquijo, Wirth and Chételat, 2015)

We test this hypothesis with a cross-sectional design: we test the association between years of education and amyloid deposition (Florbetapir-PET) in:

- Cognitively normal older adults (n=74)
- Mild cognitive impairment (n=44)
- Alzheimer’s patients (n=23)
Group*education interaction on Florbetapir-PET uptake

FDR corrected p<0.05, adjusted by age, sex and MMSE*group
Association between education and Florbetapir-PET uptake within each group

Cognitively normal older adults (orbitofrontal lobe)

Mild cognitive impairment (frontal, temporal and parietal areas)

Alzheimer's disease

How are higher educated MCI patients able to tolerate greater amyloid deposition?

FDR corrected p<0.05, adjusted by age, sex and MMSE
MCI: FDG increases with education in same areas where Florbetapir increases with education

Adjusted by age, sex and MMSE
Conclusions

• There might be an interplay between amyloid-related protective and compensatory mechanisms before the onset of dementia in higher educated individuals:
  
  • A protective influence of education on amyloid may occur before cognitive impairment.
  
  • At the MCI stage, however, education may rather help tolerate greater Aβ deposition, probably thanks to an increased local FDG-PET metabolism.
Thank you for your attention
Cognitive and Brain Reserve Mitigate Cognitive Symptoms in Alzheimer’s Disease Patients

Colin Groot\textsuperscript{1,2}, Anita C van Loenhoud\textsuperscript{1,2}, Bart NM van Berckel\textsuperscript{2}, Frederik Barkhof\textsuperscript{2}, Teddy Koene\textsuperscript{3}, Charlotte E Teunissen\textsuperscript{4}, Philip Scheltens\textsuperscript{1}, Wiesje M van der Flier\textsuperscript{1,5}, Rik Ossenkoppele\textsuperscript{1,2}

\textit{Department of Neurology and Alzheimer Center\textsuperscript{1}/Radiology and Nuclear Medicine\textsuperscript{2}/Medical Psychology\textsuperscript{2}/Clinical Chemistry\textsuperscript{4}/Epidemiology and Biostatistics\textsuperscript{5}, VU University Medical Center, Amsterdam, the Netherlands}

\textit{PIA-meeting, July 23, 2016, Toronto}
Research question

Are there independent effects of cognitive and brain reserve on cognition in AD patients with and without dementia?
Methods

Subjects
• COgnitive Brain Reserve in Alzheimer’s disease (COBRA) cohort
• 663 AD-biomarker positive (CSF/PET)
• Dementia (prob. AD, n=462), no dementia (SCD/MCI, n=201)

Measures
• Cognitive reserve: Education (Verhage, 1964; range 1-7)
• Brain reserve: Intracranial volume (3T; T1 MRI; SPM 12)
• Cerebral atrophy: Gray matter (GM) volume (adjusted for ICV)
• Cognition: MMSE and 5 cognitive domains (memory; attention; executive; language; visuospatial)

Multiple linear regression
• education - Intracranial volume - gray matter volume - nuisance variables - Cognition (age, sex, scanner-type)
**Effects education and intracranial volume**

- Independent positive effects
- Effect sizes **education greater** in no dementia vs dementia
- Effect sizes **intracranial volume similar** between groups

### RESULTS

**No dementia**

<table>
<thead>
<tr>
<th></th>
<th>Education</th>
<th>Intracranial volume</th>
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<tbody>
<tr>
<td>Memory</td>
<td>.03</td>
<td>.12</td>
</tr>
<tr>
<td>Attention</td>
<td>.39*</td>
<td>.06</td>
</tr>
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<td>Executive</td>
<td>.46*</td>
<td>.18*</td>
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<tr>
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<td>.13</td>
<td>-.03</td>
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<tr>
<td>MMSE</td>
<td>.32*</td>
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**Dementia**

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<tr>
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<td>.21*</td>
<td>.14*</td>
</tr>
<tr>
<td>Executive</td>
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<td>.15*</td>
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* Significant effect, controlling for GM, age, sex and scanner
## EFFECTS EDITION AND ICV

- **Independent positive effects**
- Effect sizes **education greater** in no dementia vs dementia
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<tr>
<td>Memory</td>
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</table>

|                   | Dementia    |                                           |                                           |
|                   | Education   | Intracranial volume                        |                                           |
|                   |             | Low ICV | High ICV | Low Education | High Education |
| Memory            |             |         |          |               |                |
| Attention         |             |         |          |               |                |
| Executive         |             |         |          |               |                |
| Language          |             |         |          |               |                |
| Visuospatial      |             |         |          |               |                |
| MMSE              |             |         |          |               |                |
### RESULTS

**Effects education and ICV**

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<tr>
<td></td>
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<tr>
<td>Attention</td>
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<td>Language</td>
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#### Dementia

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<td>-.01</td>
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<tr>
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<td>.06</td>
</tr>
</tbody>
</table>

* Significant effect, controlling for GM, age, sex and scanner

- Effect intracranial volume only for patients with **low education**
- Effect education only for patients with **low intracranial volume**
Conclusions

- Independent positive effects on cognition in AD patients
- Effects of cognitive reserve seem to diminish in dementia
- Effects of cognitive reserve are more pronounced in patients who are vulnerable due to low brain reserve, and vice versa
Cognitive reserve and longitudinal cognitive change before and after onset of cognitive impairment

Anja Soldan, PhD
Department of Neurology
Johns Hopkins School of Medicine

Reserve, Resilience and Protective Factors PIA Data Blitz
AAIC 2016, Toronto, Canada
Cognitive Reserve (CR)

- Theoretical Concept

![Graph showing the relationship between Memory Test Score and AD Neuropathology for Person with Low Reserve, Person with High Reserve, and Incident Dementia. The graph illustrates the point of inflection where the cognitive reserve affects the progression of AD neuropathology.]
Previous work on CR, cognitive change

**Question:** Does CR modify rate of change in cognition or only baseline cognitive performance?

**Early Work:**
- Higher CR - reduced rates of cognitive decline
  - 12/14 studies, reviewed in Anstey and Christensen, 2000.
  - Analytical issues

**Later work:**
- Higher CR - greater baseline cognitive performance but NOT with rate of change
  - e.g., Zahodne et al., 2011; Christensen et al., 2001; Karlamangla et al., 2009; Wilson et al., 2009; Piccinin et al., 2013
Goals of the current study

- Examine association between baseline CR and longitudinal cognitive performance:
  - In primarily middle-aged (57 years) subjects, N=293
  - All subjects were cognitively normal at baseline
  - Long follow-up: M=12 years (max=20 years)
  - Separately by diagnostic outcome
    - N=58 progressed to MCI/ Dementia
    - Before and after symptom onset
Results: All subjects

![Graph showing the relationship between composite cognitive score and time since baseline for subjects with different cognitive reserve (CR) levels. The graph includes lines for normal/high CR, normal/low CR, progressed/high CR, and progressed/low CR.](image-url)
Results: Impaired Subjects

Greater decline among high CR than low CR subjects **AFTER**, but not before symptom onset
Summary & Conclusions

- Higher CR associated with higher cognitive performance.
- CR did not modify cognitive trajectories of cognitively normal individuals.
- CR did not modify cognitive trajectories PRIOR to symptom onset in those who progress.
- CR associated with faster decline AFTER symptom onset.
- Consistent with hypothetical model of CR (e.g., Stern, 2009).
Acknowledgments

Biocard Research Team

- Marilyn Albert
- Ola Selnes
- Corinne Pettigrew
- Michael Miller
- Richard O’Brien
- Abhay Moghekar
- Roberta Scherer
- Mei-Chang Wang
- Qing Cai
- Juan Troncoso
- Sosumo Mori
- Tilak Ratnanather
- Timothy Brown
- Guy McKhann
- Leonie Farrington
- Rebecca Gottesman
- Maura Grega
- Gay Rudow
- Dan D’Agostino
- Scott Rudow

- BIOCARD participants and study partners
- Supported by a grant from the NIA, U01-AG033655
Cognitive reserve and AD biomarkers

Karly Cody

“Longevity gene KLOTHO alters APOE4-related cortical thinning”

Stephanie Schultz

“Cardiorespiratory fitness alters the association between a polygenic risk score and biomarkers of AD”

Catherine Roe

“Cerebrospinal fluid biomarkers and reserve variables as predictors of future “non-cognitive” outcomes of Alzheimer’s disease”

Pablo Martinez-Lague

“Beneficial effect of bilingualism on Alzheimer’s disease CSF biomarkers and cognition”
Longevity gene *KLOTHO* alters *APOE4*-related amyloid deposition & cortical thinning

Karly Cody, BS
Stephanie Schultz, BS
Wisconsin Alzheimer’s Disease Research Center
Wisconsin Alzheimer’s Institute
University of Wisconsin School of Medicine and Public Health
Objectives

Examine whether KL-VS status modifies the association between \textit{APOE4} and amyloid burden or cortical thickness in cognitively-normal individuals with risk factors for AD
Methods

DNA Extraction & Genotyping
- DNA extracted from whole blood samples and quantified via UV spectrophotometry
- KLOTHO – rs9536314 and rs9527025
- APOE – rs429358 and rs7412

CSF Sampling
- Lumbar puncture after 12-hour fast
- Samples assayed for amyloid-β 42 (Aβ42)

PiB-PET Imaging
- 70 min dynamic scan post bolus injection
- Focused on 8 bilateral ROIs sensitive to Aβ accumulation
- Composite measure of global Aβ load

MRI Imaging
- Acquired on GE x750 3T
- Cortical reconstruction/segmentation done with FreeSurfer software
- Focused on 8 bilateral ROIs known to be affected early in AD cascade
- Composite measure of cortical thickness

Ang = angular gyrus
SM = supramarginal gyrus
TS = superior temporal gyrus
TM = middle temporal gyrus
CA = anterior cingulate
CP = posterior cingulate
Prec = precuneus
FMO = frontal medial orbital gyrus
Statistics

Linear Regressions (SPSS)

- Included terms for age, sex, family history, and APOE4
- Stratified by KL-VS status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Female, %</td>
<td>68.9</td>
</tr>
<tr>
<td>Age, years</td>
<td>61.39 (6.52)</td>
</tr>
<tr>
<td>Family history positive, %</td>
<td>69.9</td>
</tr>
<tr>
<td>Education, years</td>
<td>16.10 (2.42)</td>
</tr>
<tr>
<td>Mini-Mental State Exam</td>
<td>29.39 (.86)</td>
</tr>
<tr>
<td>APOE4 positive, %</td>
<td>41.1</td>
</tr>
<tr>
<td>KL-VS heterozygote, %</td>
<td>26.5</td>
</tr>
</tbody>
</table>
## Results

**APOE4*KLOTHO** on amyloid burden

<table>
<thead>
<tr>
<th>Amyloid measure</th>
<th>KL-VS non-carrier analyses</th>
<th>KL-VS heterozygote analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β(SE)</td>
<td>t statistic</td>
</tr>
<tr>
<td>CSF Aβ42</td>
<td>-162.67 (31.97)</td>
<td>-5.09</td>
</tr>
<tr>
<td>PIB Composite</td>
<td>.10 (.03)</td>
<td>3.77</td>
</tr>
<tr>
<td>PIB Angular Gyrus</td>
<td>.10 (.03)</td>
<td>3.47</td>
</tr>
<tr>
<td>PIB Anterior Cingulate</td>
<td>.14 (.04)</td>
<td>4.06</td>
</tr>
<tr>
<td>PIB Posterior Cingulate</td>
<td>.10 (.03)</td>
<td>3.12</td>
</tr>
<tr>
<td>PIB Medial Orbitofrontal Cortex</td>
<td>.13 (.03)</td>
<td>3.83</td>
</tr>
<tr>
<td>PIB Precuneus</td>
<td>.12 (.03)</td>
<td>3.79</td>
</tr>
<tr>
<td>PIB Supramarginal Gyrus</td>
<td>.07 (.02)</td>
<td>3.03</td>
</tr>
<tr>
<td>PIB Middle Temporal Gyrus</td>
<td>.08 (.02)</td>
<td>3.59</td>
</tr>
<tr>
<td>PIB Superior Temporal Gyrus</td>
<td>.07 (.02)</td>
<td>3.29</td>
</tr>
</tbody>
</table>
**APOE4** KLOTHO on amyloid burden

**CSF Aβ42, ng/L**
- KLOTHO non-carrier: β(SE) = -162.67(31.97), p < .001
- KLOTHO heterozygote: β(SE) = -52.44(50.95), p = .308

**PiB Composite**
- KLOTHO non-carrier: β(SE) = .10(.03), p < .001
- KLOTHO heterozygote: β(SE) = .06(.06), p = .363
### Results

**APOE4*KLOTHO** on cortical thickness

<table>
<thead>
<tr>
<th>Cortical thickness measure</th>
<th>KL-VS non-carrier analyses</th>
<th>KL-VS heterozygote analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta (SE) )</td>
<td>t statistic</td>
</tr>
<tr>
<td>Composite</td>
<td>(-.037 (.017))</td>
<td>-2.125</td>
</tr>
<tr>
<td>Entorhinal</td>
<td>(-.067 (.047))</td>
<td>-1.440</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>(-.022 (.021))</td>
<td>-1.039</td>
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<tr>
<td>Inferior parietal</td>
<td>(-.039 (.017))</td>
<td>-2.290</td>
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<tr>
<td>Isthmus cingulate</td>
<td>(.025 (.030))</td>
<td>.817</td>
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<tr>
<td>Parahippocampal</td>
<td>(-.029 (.037))</td>
<td>-.796</td>
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<tr>
<td>Posterior cingulate</td>
<td>(-.051 (.023))</td>
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<tr>
<td>Precuneus</td>
<td>(-.054 (.019))</td>
<td>-2.909</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>(-.054 (.019))</td>
<td>-2.843</td>
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Conclusions

- *APOE4*-associated amyloid accumulation was attenuated in KL-VS heterozygotes

- KL-VS heterozygotes showed a diminution of *APOE4*-related alterations in cortical thickness in select regions associated with AD

- These findings support the notion that carrying the longevity-promoting haplotype of *KLOTHO* may provide resilience to amyloid accumulation and cortical thinning, specifically in those at increased risk for AD
Acknowledgements

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Alzheimer’s Assoc. N1R1D (PI: O. Okonkwo)
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Wisconsin ADRC Imaging Group

http://www.brainmap.wisc.edu

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Siobhan Hoscheidt, PhD
Sterling Johnson, PhD
Sanjay Asthana, MD
Ozioma Okonkwo, MD

WRAP Study Participants

Contact:
ozioma@medicine.wisc.edu
Fitness modifies the association between a polygenic risk score and cerebrospinal fluid biomarkers

Stephanie Schultz, BS
Ozioma Okonkwo, PhD

Wisconsin Alzheimer’s Disease Research Center
Wisconsin Alzheimer’s Institute
University of Wisconsin School of Medicine and Public Health
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Extendicare Foundation (PI: O. Okonkwo)
NIH Beeson K23 AG045957 (PI: O. Okonkwo)
NIH R21 AG051858 (PI: O. Okonkwo)
NIH R01 AG027161 (WRAP, PI: S. Johnson)
NIH R01 AG021155 (PREDICT, PI: S. Johnson)
NIH P50 AG033514 (WADRC, PI: S. Asthana)

Wisconsin ADRC Imaging Group

http://www.brainmap.wisc.edu/

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Wisconsin Registry for Alzheimer's Prevention

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Dorothy Edwards, PhD
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No conflicts of interest.

Thank you WRAP study participants!

Contact: ozioma@medicine.wisc.edu
Objectives

In a late-middle-aged cohort of at-risk cognitively-normal individuals:

- Examine whether a PRS derived from CLU, ABCA7, and APOE4 is associated with CSF biomarkers of AD

- Examine whether higher CRF modifies the association between a PRS and CSF biomarkers
Methods

• 95 participants enrolled in the Wisconsin Registry for Alzheimer’s Prevention (WRAP)

• CRF estimate
  ➢ Jurca et al 2005
  
  \[
  \text{CRF} = \text{Male}(2.77) - \text{Age}(0.10) - \text{BMI}(0.17) - \text{RHR}(0.03) + \text{Self-reported PA} + 18.07
  \]

• CSF Sampling
  ➢ Lumbar puncture after 12-hour fast
  ➢ Samples assayed for amyloid-β 42 (Aβ42), amyloid-β 40 (Aβ40), total tau (t-tau), and phosphorylated tau (p-tau)
  ➢ Additionally computed Aβ42/Aβ40, t-tau/Aβ42, and p-tau/Aβ42 ratios

• Genotyped for APOE, CLU, and ABCA7

\[
\text{PRS}_i = \sum_{n=1}^{k} \ln(\text{OR}_n) \times C_n
\]

i=individual
n=SNP
OR= odds ratio of SNP n
C= individual’s count of risk alleles for SNP n
Statistical Analyses

“Lead in” Analyses
- Test the influence of the PRS on CSF biomarkers
- Linear regressions
- Included terms for age, sex, and PRS
- **Term of interest:** PRS

Primary Analyses
- Interactive effect of CRF and PRS on CSF biomarkers
- Linear regressions
- Included terms for age, sex, CRF, PRS, and a CRF*PRS interaction
- **Term of interest:** CRF*PRS interaction
## Background Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at CSF sampling, years</td>
<td>61.2 (6.0)</td>
</tr>
<tr>
<td>Education, years</td>
<td>16.3 (2.2)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>64 (67.4)</td>
</tr>
<tr>
<td>FH positive, n (%)</td>
<td>71 (74.7)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.9 (5.6)</td>
</tr>
<tr>
<td>Resting heart rate, beats/min</td>
<td>64.1 (9.1)</td>
</tr>
<tr>
<td>Amount of moderate exercise, min/week</td>
<td>52.3 (70.8)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>197.7 (35.7)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>59.0 (16.1)</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>29.3 (0.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOE4 (rs429358, rs7412), n (%)</td>
<td></td>
</tr>
<tr>
<td>0 ε4 alleles</td>
<td>62 (65.3)</td>
</tr>
<tr>
<td>1 ε4 alleles</td>
<td>31 (32.6)</td>
</tr>
<tr>
<td>2 ε4 alleles</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>ABCA7 (rs4147929), n (%)</td>
<td></td>
</tr>
<tr>
<td>G/G</td>
<td>62 (65.3)</td>
</tr>
<tr>
<td>G/A*</td>
<td>30 (31.6)</td>
</tr>
<tr>
<td>A/A</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>CLU (rs9331896), n (%)</td>
<td></td>
</tr>
<tr>
<td>C/C</td>
<td>14 (14.7)</td>
</tr>
<tr>
<td>T*/C</td>
<td>36 (37.9)</td>
</tr>
<tr>
<td>T/T</td>
<td>45 (47.4)</td>
</tr>
</tbody>
</table>

* Asterisk indicates risk allele
Association between the polygenic risk score and CSF biomarkers of AD

- Covariate adjusted 
- Low PRS vs. High PRS
  - Aβ42/Aβ40
    - p<.001

  - t-tau/Aβ42
    - p<.001

  - p-tau/Aβ42
    - p=.001
CRF modifies the association between the PRS and CSF biomarkers of AD
Summary

- A PRS was associated with CSF biomarkers
  - Better predictor than APOE4 alone

- The adverse influence of the genetic polymorphisms on CSF biomarkers was diminished in those with high CRF
  - Influenced by sex, BMI, and SR-PA

- These findings suggest that a physically-fit lifestyle may play an important role in the prevention of AD
CSF Biomarkers and Reserve Variables as Predictors of Future “Non-cognitive” AD Outcomes

Catherine M. Roe, PhD
July 23, 2016
Reserve, Resilience and Protective Factors PIA meeting
Dear Dr. Roe,

My name is Adam Ingber and I am a senior at Yorba Linda High School. I am currently an honors student and have been selected for the Authentic Science Program at Yorba Linda College. I am writing to express my concern with the decision of the faculty to place me on academic probation. I believe this is not fair and I wish to appeal the decision.

I have been attending Yorba Linda High School for four years and have maintained a 4.0 GPA throughout my time here. I have always been a hard worker and have never had any issues with my academic performance. I believe that the faculty has made a mistake in their decision and I would like to have the opportunity to prove my case.

Sincerely,

Adam Ingber

---

THE SECOND CHOICE

Theodore Dreiser
“Non-cognitive” outcomes

- Does cognitive, brain reserve mediate relationships between AD biomarker levels in cognitively normal persons and future changes in
  - Function - Functional Activities Questionnaire (FAQ)
    - Instrumental activities of daily living
  - Mood – Geriatrics Depression Scale (GDS)
    - Depression symptoms
  - Neuropsychiatric behavior – Neuropsychiatric Inventory Questionnaire (NPI-Q)
    - Neuropsychiatric symptoms & psychopathology
Methods

- **Participants (N=328)**
  - Enrolled in Knight ARDC longitudinal studies
    - CSF and structural MRI within 1y of a clinical assessment with CDR 0 (baseline)
    - Aged 50+y at baseline
  - Followed 0.9 – 14.5y, mean(SD) = 4.9y (2.5)
  - Linear mixed models tested differences in slopes as function of the combination variables
Independent variable construction

- **Dichotomization**
  - Education: Low (≤16y) vs. High (>16y)
  - Brain volume: Low vs. High using median split
  - CSF biomarker values: For each, Normal vs. Abnormal, based on cutoffs used previously

- **Creation of four-level variables**
  - Biomarkers (Aβ$_{42}$, tau, ptau$_{181}$, tau/Aβ$_{42}$, and ptau$_{181}$/Aβ$_{42}$) X education
  - Biomarkers (Aβ$_{42}$, tau, ptau$_{181}$, tau/Aβ$_{42}$, and ptau$_{181}$/Aβ$_{42}$) X brain volume
Education & CSF biomarkers

- FAQ, NPI-Q, GDS
  - Biomarker effect, Abnormal > faster increase in symptoms
  - No effect of education
Brain volume & CSF biomarkers

- NPI-Q, GDS, FAQ
  - With few exceptions, Abnormal/CSF AND Low BV has most rapid increase in sx with time
  - Sometimes (approx ½) Normal CSF/Low BV more rapid sx ↑ than Normal CSF/High BV

- Intracranial volume: same results as education
Conclusions

- Brain volume had a pronounced effect when combined with biomarker status to predict changes in function, mood, & behavior.
- Education & maximal brain growth (intracranial volume) did not strongly affect the predictive abilities of CSF biomarkers.
Cerebrospinal Fluid Biomarkers and Reserve Variables as Predictors of Future “Non-Cognitive” Outcomes of Alzheimer’s Disease

Adam P. Ingerb, Jason Hassenstab, Anne M. Fagan, Tammie L.S. Benzinger, Elizabeth A. Grant, David M. Holtzman, John C. Morris, and Catherine

Handling Associate Editor: Michael J. Emslie

Accepted 23 February 2016
Beneficial effect of bilingualism on Alzheimer’s disease CSF biomarkers and cognition

Ainara Estanga PhD; Mirian Ecay-Torres MSc; Almudena Ibañez BSc; Andrea Izagirre RN; Jorge Villanua MD, PhD; Maite Garcia-Sebastian PhD; Ane Otaegui-Arrazola PhD; Ane Iriondo MSc; Monserrat Clerigue MD, PhD; Pablo Martinez-Lage MD, PhD

FUNDACION CITA ALZHEIMER FUNDAZIOA
Donostia / San Sebastian. Spain
BILINGUALISM

- Lifelong bilingualism may delay, by up to 5 years, the onset of symptoms of AD and other type of dementia independently of gender, years of education, socioeconomic status and immigration.

- Bilingualism may contribute to the strengthening of neural networks related to attention and executive function.

- Recent evidence has indicated that certain life habits attenuate age-related AD pathology.
Objective

- To investigate differences between monolinguals, early bilinguals, and late bilinguals in cognitive performance and CSF AD-biomarker profiles.

- To study the modulating effect of bilingualism on the association of age and CSF AD-biomarkers
Proyecto Gipuzkoa Alzheimer (PGA)
Gipuzkoa Alzheimer Project (GAP)

Fundación CITA.alzhéimer
Fundazioa
The GAP study Baseline visit (June 2011-Jan 2012)

Inclusion criteria:
- 40 to 80 years.
- Informed consent
- No dementia

Mean age: 58
55% Females
50% Direct FH(+)

Criterios de exclusión:
- Dementia (DSM-IV criteria and CDR ≥ 1)
- Any systemic, neurologic or psychiatric disorder able to cause cognitive impairment/dementia
- MRI

Contraindications
- Unable to perform neuropsychology evaluations.

Clinical evaluation
Nursing evaluation
Neuropsychology
Nutrition/Diet (Life styles)
Structural MRI
Functional MRI
Blood workup, APOE

Lumbar Puncture (CSF)
Subjects

Gipuzkoa Alzheimer Project (GAP), a longitudinal study on pre-clinical AD ongoing in the Basque Country.

Bilingualism study participants inclusion criteria:
- Without cognitive impairment with a CDR=0 and MMSE ≥25
- Bilinguals: “Subjects who were able to communicate fluently at least in two languages and made regular use for both”
  - Early bilinguals- from birth and before schooling at age 6
  - Late bilinguals- after schooling at age 6
- Monolinguals “pure”
Methods

Socio-demographics and other cognitive reserve indicators

Cardiovascular disease risk: Framingham index

APOE4 genotype

RMI White matter hyperintensities: FAZEKAS scale

Neuropsychological assessment:

-MMSE
- Attention and executive functions: TMT A y B, Stroop test
- Semantic and phonetic verbal fluency
- Memory: FCSRT
- Language: Boston naming
- Visual-spatial and visuoperceptive: Judgement Line Orientation Test, 15 Object test
- Visuoconstructive: ROCF

CSF biomarkers

AB42 pg/ml (cutoff= 580pg/ml)
Total-Tau pg/ml (cutoff= 350pg/ml)
Phospo-Tau pg/ml (cutoff= 61pg/ml)
<table>
<thead>
<tr>
<th></th>
<th>Monolinguals</th>
<th>Late Bilinguals</th>
<th>Early Bilinguals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>57.82(6.42)</td>
<td>57.56(6.57)</td>
<td>56.82(6.48)</td>
</tr>
<tr>
<td><strong>Gender (Male, %)</strong></td>
<td>42(42%)</td>
<td>38(39.2%)</td>
<td>37(45.7%)</td>
</tr>
</tbody>
</table>
| **Years of education, mean (SD)** | 12.33(3.37) | 14.35(3.76)
|                                | a            | 14.98(3.77)
| **Occupation, No. (%)**        |              |                 |                 |
| Unskilled workers              | 25(25%)      | 15(15.5%)       | 7(8.6%)          |
| Skilled workers                | 24(24%)      | 18(18.6%)       | 13(16%)          |
| Administrative                 | 33(33%)      | 35(36.1%)       | 27(33.3%)        |
| Professionals                  | 18(18%)      | 29(29.9%)       | 34(42%)          |
| **MMSE, mean (SD)**            | 28.44(1.34)  | 28.81(1.09)     | 28.59(1.26)      |
| **Leisure and Productive activities** | 51.42(9.04) | 56.24(7.93)
|                                | a            | 54.27(7.92)     |
| **Vocabulary (WAIS-III), mean (SD)** | 0.84(0.80)  | 1.08(0.77)      | 1.16(0.68)       |
| **APOE4 carrier (1 allele/2allele), No. (%)** | 26(26%)/0    | 25(26.3%)/1(1.1%) | 17(21%)/1(1.2%) |
| **Family history of AD in a direct relative, No. (%)** | 51(51%)      | 50(51.5%)       | 35(43.2%)        |
| **Framingham index**           | 6.89(6.68)   | 6.13(5.80)      | 6.84(6.76)       |
| **Fazekas scale, No. (%)**     |              |                 |                 |
| 0                              | 53(54.1%)    | 53(55.2%)       | 45(55.6%)        |
| 1                              | 38(38.8%)    | 40(41.7%)       | 34(42%)          |
| 2                              | 4(4.1%)      | 2(2.1%)         | 2(2.5%)          |
| 3                              | 3(3.1%)      | 1(1%)           | 0 (0%)           |
| **Birthplace in Basque Country, No. (%)** | 71 (71%)     | 86 (90.5%)      | 79 (97.5%)       |

Abbreviations: MMSE= Mini Mental State Examination; WAIS-III= Wechsler Adult Intelligence Scale third edition; AD= Alzheimer’s Disease.

* p<.001 compared to monolinguals; *p* =.007, significant differences on the distribution of occupation level between the three groups; c* p*.02 compared to monolinguals; *p* <.001 significant differences between the distribution of the three groups
Table 2. Neuropsychological results

<table>
<thead>
<tr>
<th></th>
<th>Descriptive data</th>
<th>Generalized linear models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monolinguals</td>
<td>Late Bilinguals</td>
</tr>
<tr>
<td></td>
<td>n= 100</td>
<td>n= 97</td>
</tr>
<tr>
<td>Digits backwards</td>
<td>6.01(1.72)</td>
<td>6.74(1.78)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT-A</td>
<td>37.05(16.27)</td>
<td>33.05(11.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT-B</td>
<td>89.48(57.76)</td>
<td>70.4(27.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop WC</td>
<td>38.32(10.47)</td>
<td>42.81(10.82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semantic VF</td>
<td>22.38(5.72)</td>
<td>24.32(5.96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phonetic VF</td>
<td>16.5(5.03)</td>
<td>18.69(5.66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston Naming</td>
<td>54.7(3.84)</td>
<td>55.04(3.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Object Test</td>
<td>12.97(1.78)</td>
<td>12.92(1.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JLO</td>
<td>23.65(4.27)</td>
<td>25.53(4.09)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCF Copy</td>
<td>31.39(4)</td>
<td>32.31(2.87)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FCSRT Delayed Free</td>
<td>11.70(2.28)</td>
<td>11.86(2.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: TMT-A= Trail Making Test A; TMT-B= Trail Making Test B; Stroop WC= Stroop Word-Color task; VF= verbal fluency; JLO= Judgement of Line Orientation; FCSRT= Free and Cued Selective Reminding test; ROCF= Rey-Osterrieth Complex Figure; B= Beta coefficient. Descriptive data are the mean (SD).

*Analyses were adjusted for age, years of education, occupation level, vocabulary subtest from WAIS-III z score, and leisure and productive activity questionnaire score; FCSRT delayed recall, Digits backwards, TMTA and B, JLO, Copy ROCF and 15 object test were also adjusted for sex; FCSRT delayed recall, verbal fluency tests, Stroop test and TMTA and B were additionally adjusted for Framingham CVD index.

* p<.05; ** p<.005
Table 3. CSF biomarkers results comparison between monolinguals and early and late bilinguals

<table>
<thead>
<tr>
<th></th>
<th>Descriptives data</th>
<th>Generalized models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monolinguals</td>
<td>Late Bilinguals</td>
</tr>
<tr>
<td></td>
<td>n= 59</td>
<td>n= 52</td>
</tr>
<tr>
<td>Aβ1-42 pg/ml</td>
<td>853.39 (252.94)</td>
<td>846.03 (239.62)</td>
</tr>
<tr>
<td>total-tau pg/ml</td>
<td>240.49 (104.29)</td>
<td>237.10 (82.71)</td>
</tr>
<tr>
<td>p-tau pg/ml</td>
<td>45.49 (16.15)</td>
<td>45.69 (13.25)</td>
</tr>
<tr>
<td>t-tau/ Aβ1-42 ratio</td>
<td>0.31 (0.22)</td>
<td>0.31 (0.18)</td>
</tr>
<tr>
<td>p-tau/ Aβ1-42 ratio</td>
<td>0.06 (0.03)</td>
<td>0.06 (0.03)</td>
</tr>
<tr>
<td>Pre-clinical AD CSF stage, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>44 (74.6%)</td>
<td>35 (67.3%)</td>
</tr>
<tr>
<td>Stage 1</td>
<td>7 (11.9%)</td>
<td>9 (17.3%)</td>
</tr>
<tr>
<td>Stage 2</td>
<td>4 (6.8%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>SNAP</td>
<td>4 (6.8%)</td>
<td>7 (13.5%)</td>
</tr>
</tbody>
</table>

Abbreviations: B= Beta coefficient; CSF= Cerebrospinal fluid; SNAP= suspected non Alzheimer pathology
Descriptive data are the mean (SD) and No. (%)

*a* Generalized linear model analyses for bilingualism status were adjusted for age, APOE-4 genotype, Fazekas scale and Framingham index. Linear model were used for scaled variables and ordinal logistic model was used to compare pre-clinical AD CSF stage classification.

b*p<.05
MODERATION EFFECT OF BILINGUALISM ON THE RELATIONSHIP BETWEEN AGE AND CSF-BIOMARKERS

“age x bilingualism” interaction adjusted by covariates

t-tau (B=15.25; \( p=0.016 \))
p-tau (B=2.28; \( p=0.03 \))
t-tau/A\( \beta_{1-42} \) ratio (B=0.03; \( p<0.01 \))
p-tau/A\( \beta_{1-42} \) ratio (B=0.008; \( p<0.01 \)).

After excluding monolinguals and late bilinguals over 70 years old, the results remained significant.

<table>
<thead>
<tr>
<th>Table 4. Linear regression between age and CSF biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Monolinguals} )</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>( A\beta_{1-42} ) pg/ml</td>
</tr>
<tr>
<td>-7.08</td>
</tr>
<tr>
<td>t-tau pg/ml</td>
</tr>
<tr>
<td>p-tau</td>
</tr>
<tr>
<td>p-tau/A( \beta_{1-42} )</td>
</tr>
</tbody>
</table>

Abbreviations: B= Beta coefficient
\( ^a \) \( p<0.005 \)
**Conclusions**

- This work adds further evidence to support the contribution of bilingualism to cognitive reserve.

- Positive impact of bilingualism on cognitive functioning in middle-aged subjects expands beyond executive function to involve also visual-spatial performance.

- Furthermore, this study reports for the first time the favorable effect of bilingualism on CSF t-tau levels, its modulating effect on the association of aging and CSF AD-biomarkers and the lower proportion of pre-clinical AD among early bilingual subjects and suggests how intellectual achievements may also contribute to brain reserve.

- Further: Neuroimaging / longitudinal follow-up
Gracias - Eskerrik asko - Thank you!

AFAGI / Instituto Biodonostia-H.U.Donostia / UPV-EHU / Biobanco Vasco BIOEF / Onkologikoa / Unidad gestión Hospital Alto Deba / Hospital Sant Pau (red CIBERNED) / VU University Amsterdam (Medical Center, Image Analysis) / Proyectos Europeos (EMIF-AD) / Alzheimer’s Association (LP Feasibility) / University of Pennsylvania / Araclon Biotech / Biocross-Raman Health Technologies / London School of Economics / Fundación Real Sociedad / Siemens