alzheimer's association

AAIC 16

DATABLITZ

RESERVE, RESILIENCE AND PROTECTIVE FACTORS PIA MEETING

JULY 23 2016, TORONTO

alzheimer's association
AAIC 16

Research criteria and approaches to test reserve in aging and Alzheimer's disease

Michael Ewers	**"Research criteria to identify the neural substrate of reserve in Alzheimer's disease"**
Prashanthi Vemuri	**"Reserve and Resilience in the Mayo Clinic Study of Aging"**
Brian Gold	**"Developing neuroimaging tools to assess cognitive reserve"**
Anita Loenhoud	**"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

MAYO CLINIC

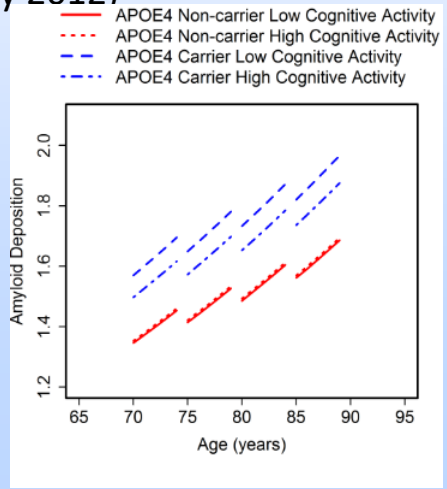
"SHIFT" of the cognition trajectory

- *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*

MAYO CLINIC

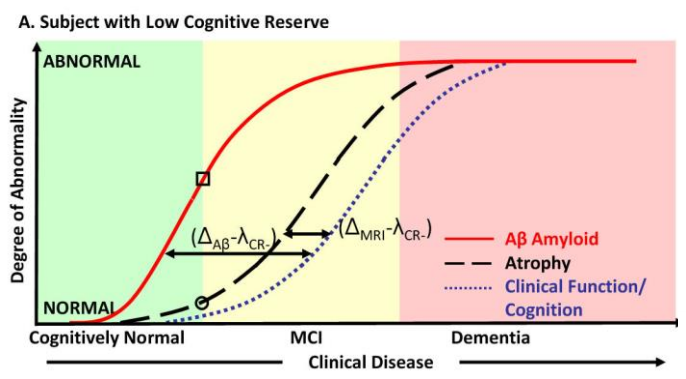
Impact on AD Biomarker Trajectories

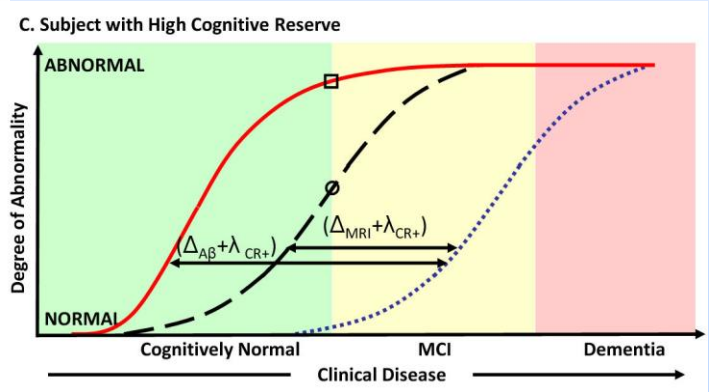
- *Two cross-sectional studies did not detect any effect of CR on AD biomarker trajectories*
  - AMNART IQ as CR proxy and CSF Biomarkers as AD Biomarker Outcomes (Vemuri et. al. Brain 2011)
  - Education/Occupation/Cognitive Activities as a CR proxy and Amyloid PET, FDG PET, MRI as AD Biomarker Outcomes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



MAYO CLINIC

Summary: Larger shifts to cognition trajectories compared to pathology trajectories





Vemuri et al. Brain 2011

Neuroimaging Tools to Assess Cognitive Reserve

Alzheimer's Association ISTAART

PIA: Reserve, Resilience and Protective Factors

Summer 2016

Brian T. Gold, PhD
Dept. of Neuroscience,
University of Kentucky
Lexington, KY

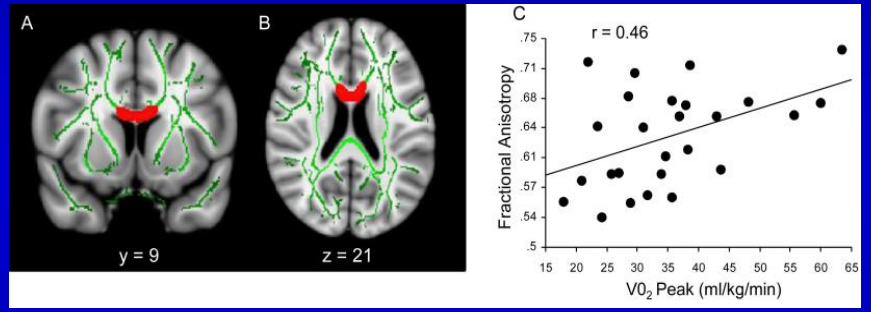
Lab Interests

- 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.

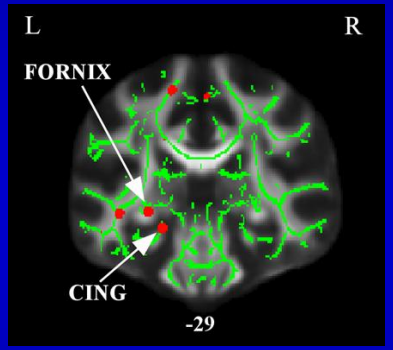
• Aerobic fitness has been linked with higher FA in the corpus callosum.



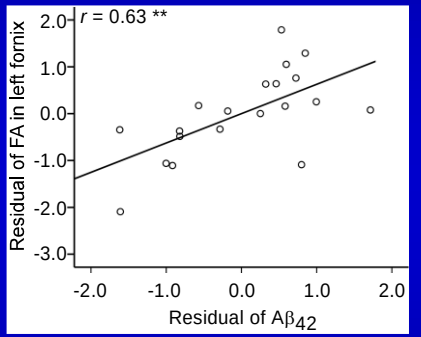
Johnson et al. (2012) NeuroImage

White Matter and AD Risk

- Alterations in fornix microstructure (e.g, fractional anisotropy) has been linked with:
- AD-risk based on genetics or family history
- AD pathology in CSF



Gold et al. (2010) NeuroImage.

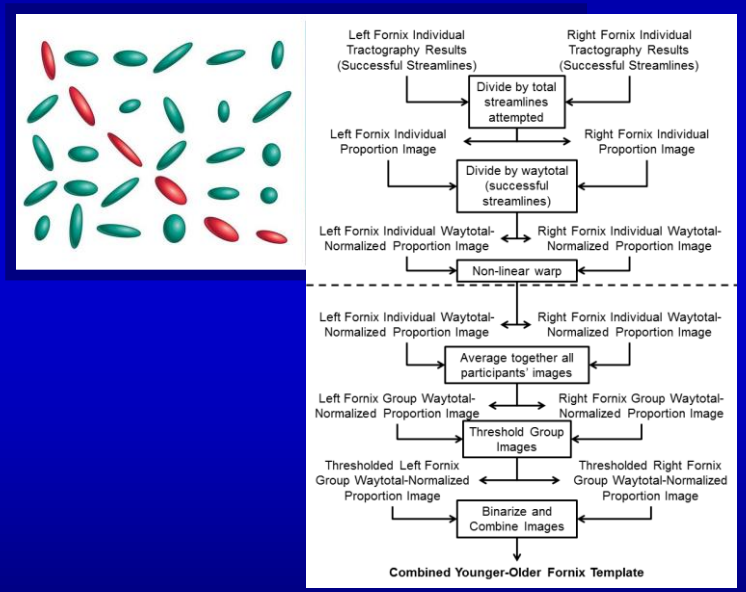


Gold et al. (2014) NBA.

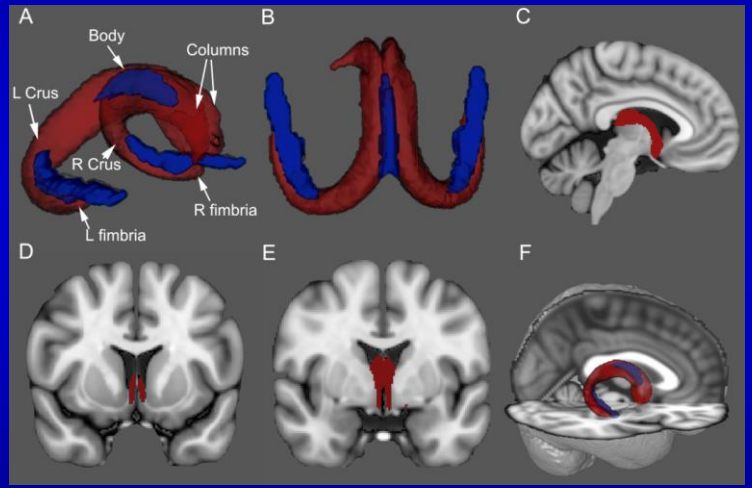
Probabilistic Tractography

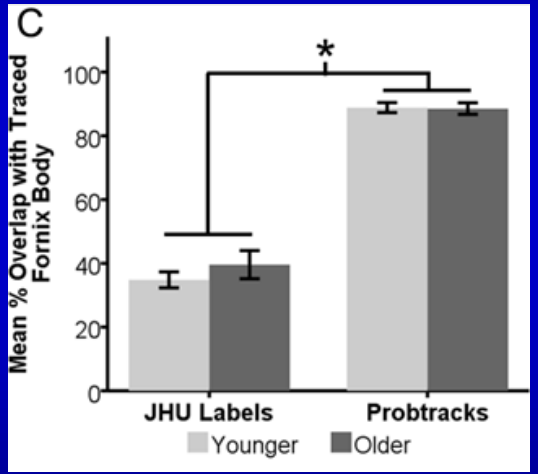
- 49 younger adults (mean = 32.5 ± 4.04 years) and 46 older adults (mean = 65.3 ± 4.55 years).

- 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.



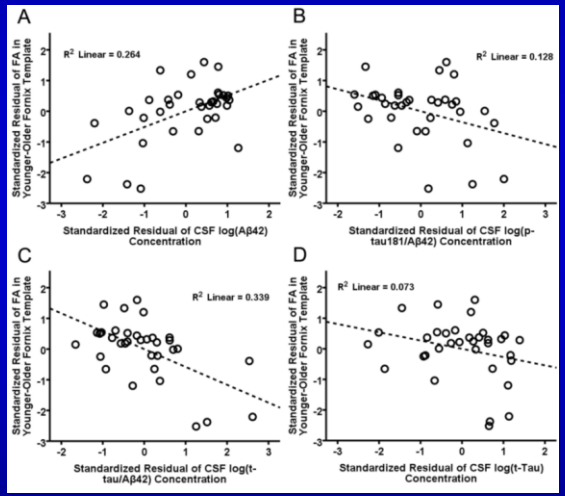
Younger-Older Comparison

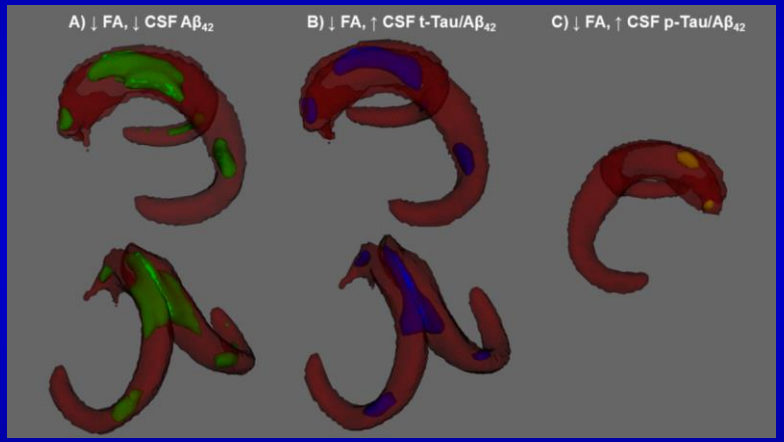




Our new younger-older adult DTI template of the fornix accommodates anatomical variability associated with human aging.

Associations with AD Pathology





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

July 23th 2016 - **PIA meeting Toronto**

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

Neuroscience Campus Amsterdam

VUmc VU University Alzheimer Center Amsterdam

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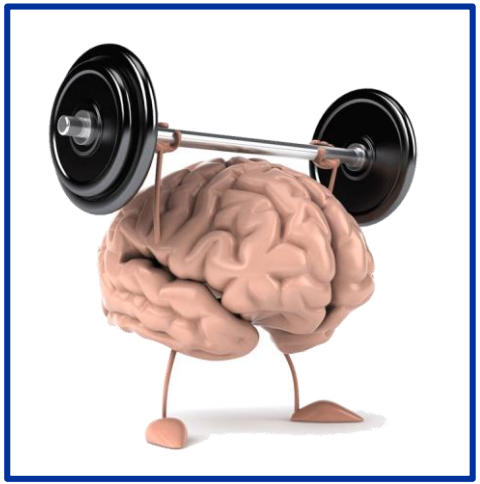
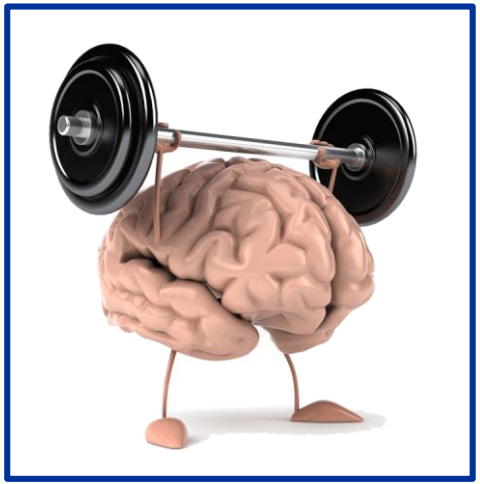
Introduction



Cognitive reserve

Introduction



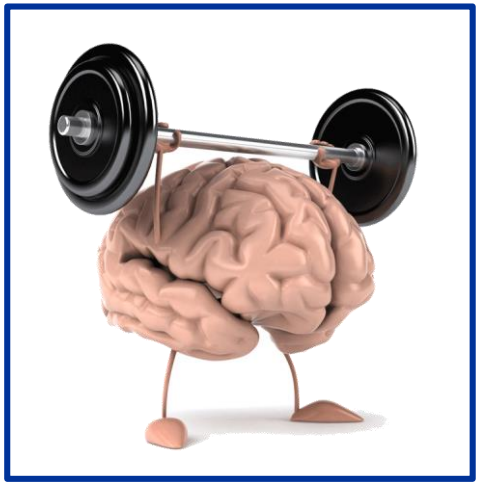
Cognitive reserve

Introduction

Education

Cognitive activity

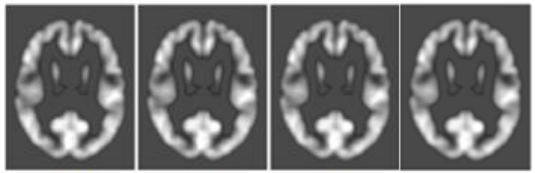
Physical activity



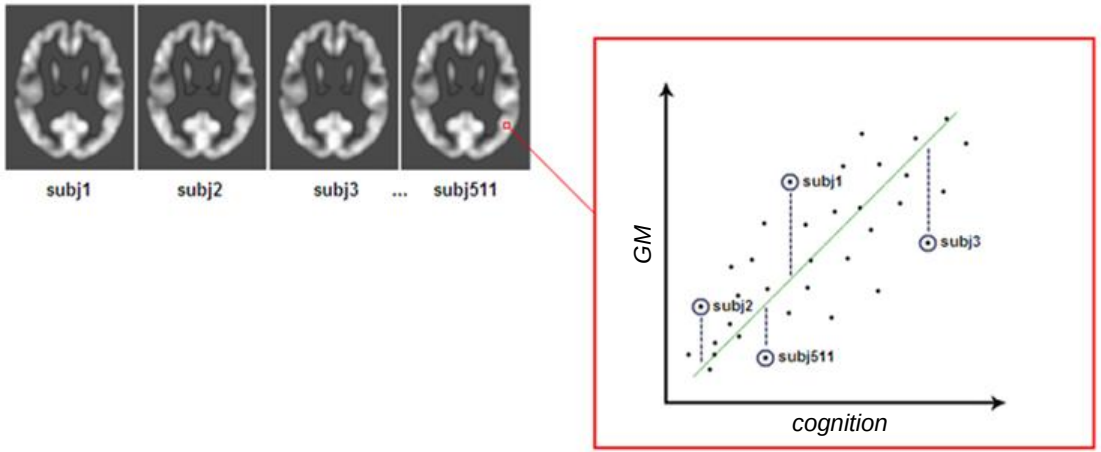
Cognitive reserve

Our approach

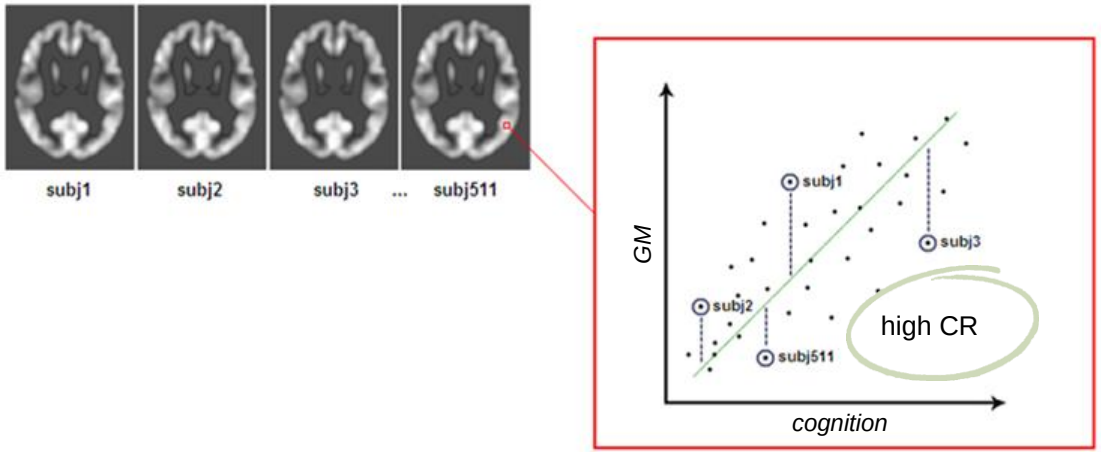
structural 3T MRI



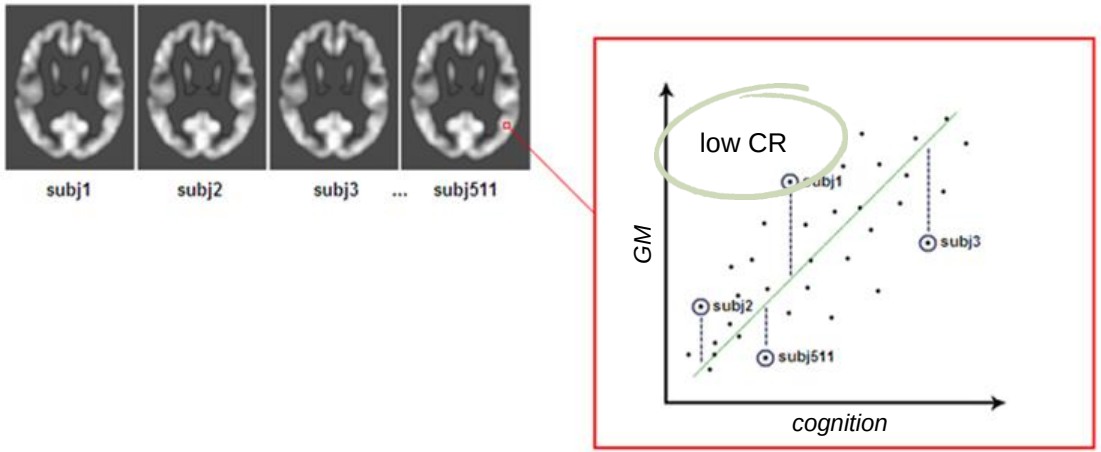
Our approach



Our approach



Our approach



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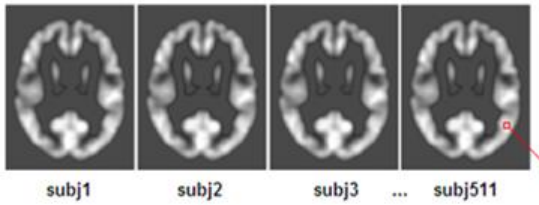
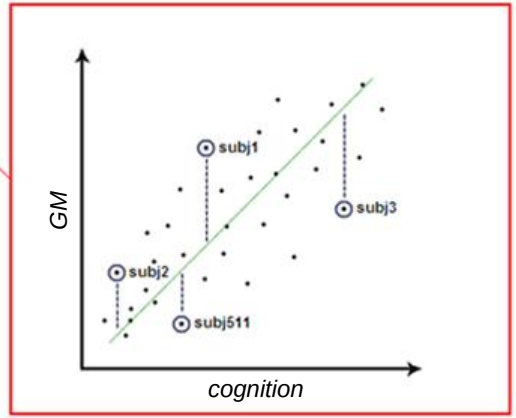


La Joie et al, J. of Neuroscience (2012)

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



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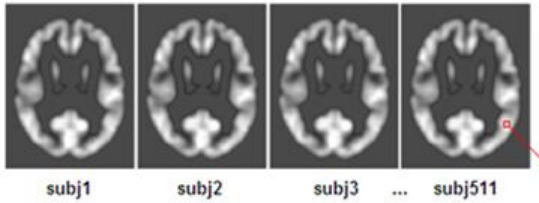

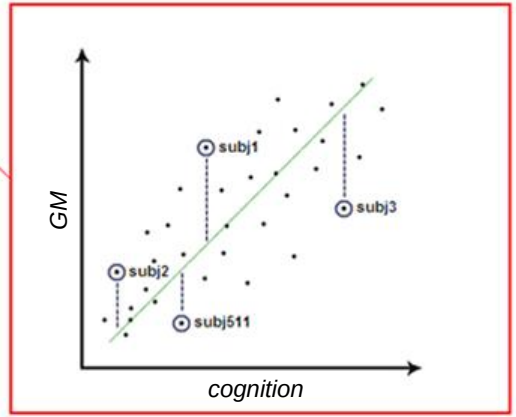

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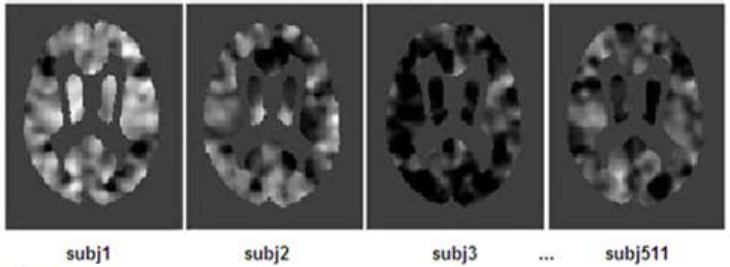

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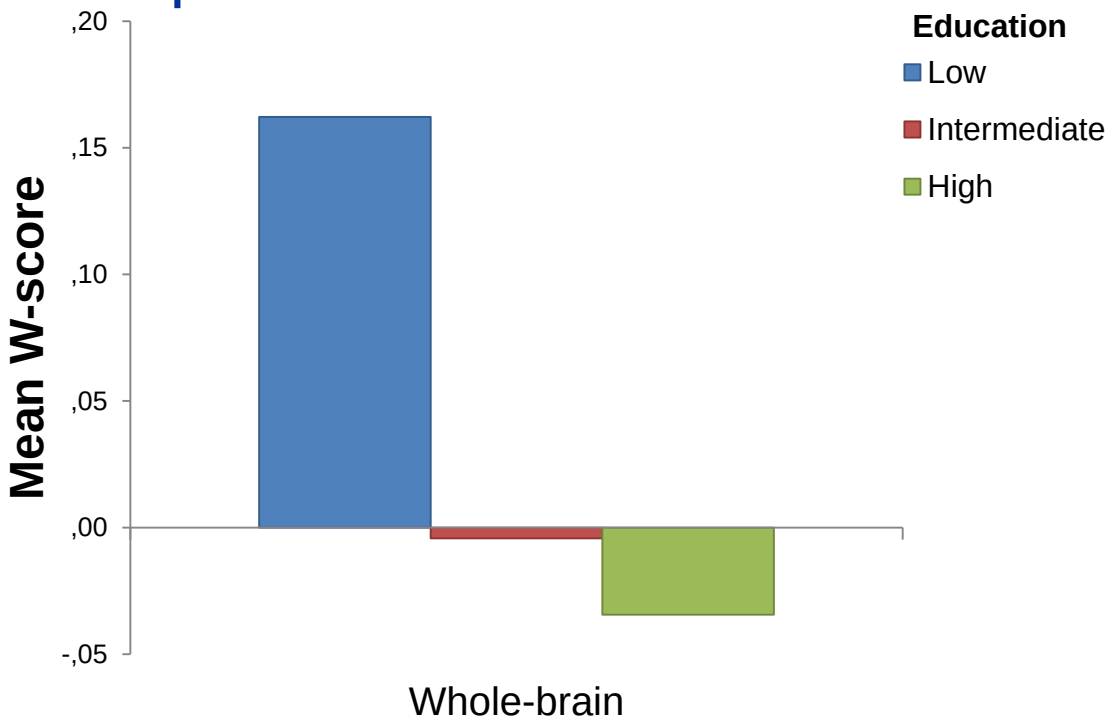
Results



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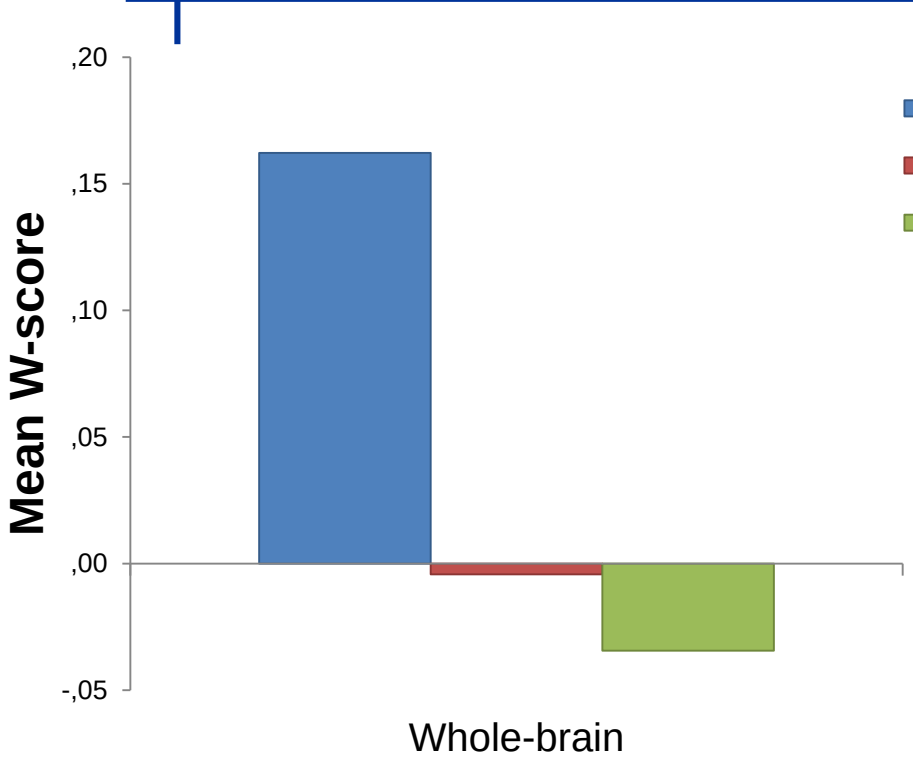
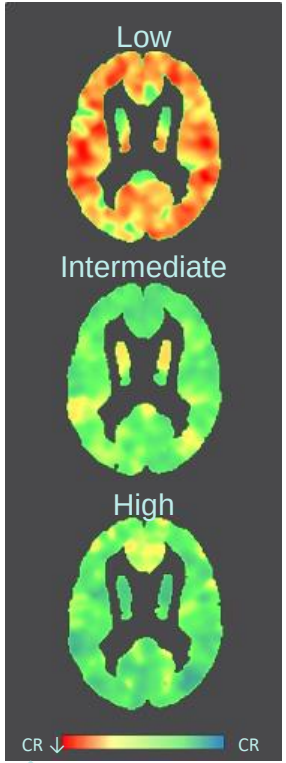
Results





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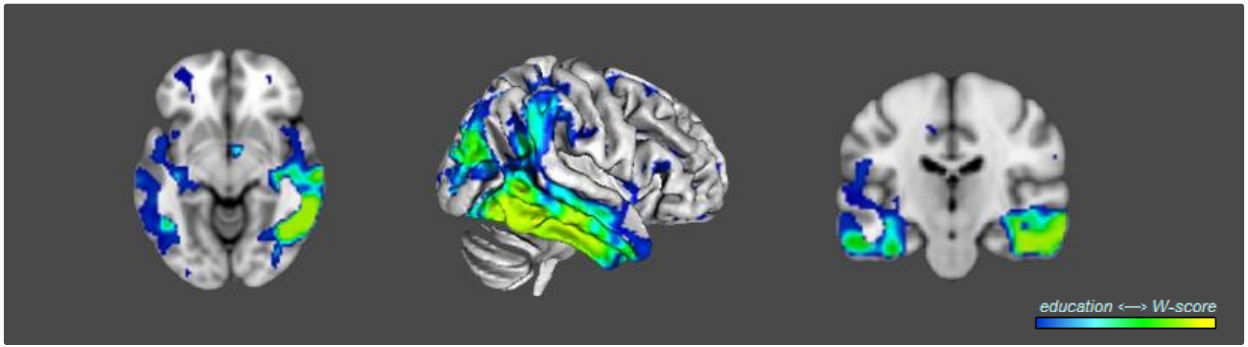
Results

- **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):



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AAIC 16

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

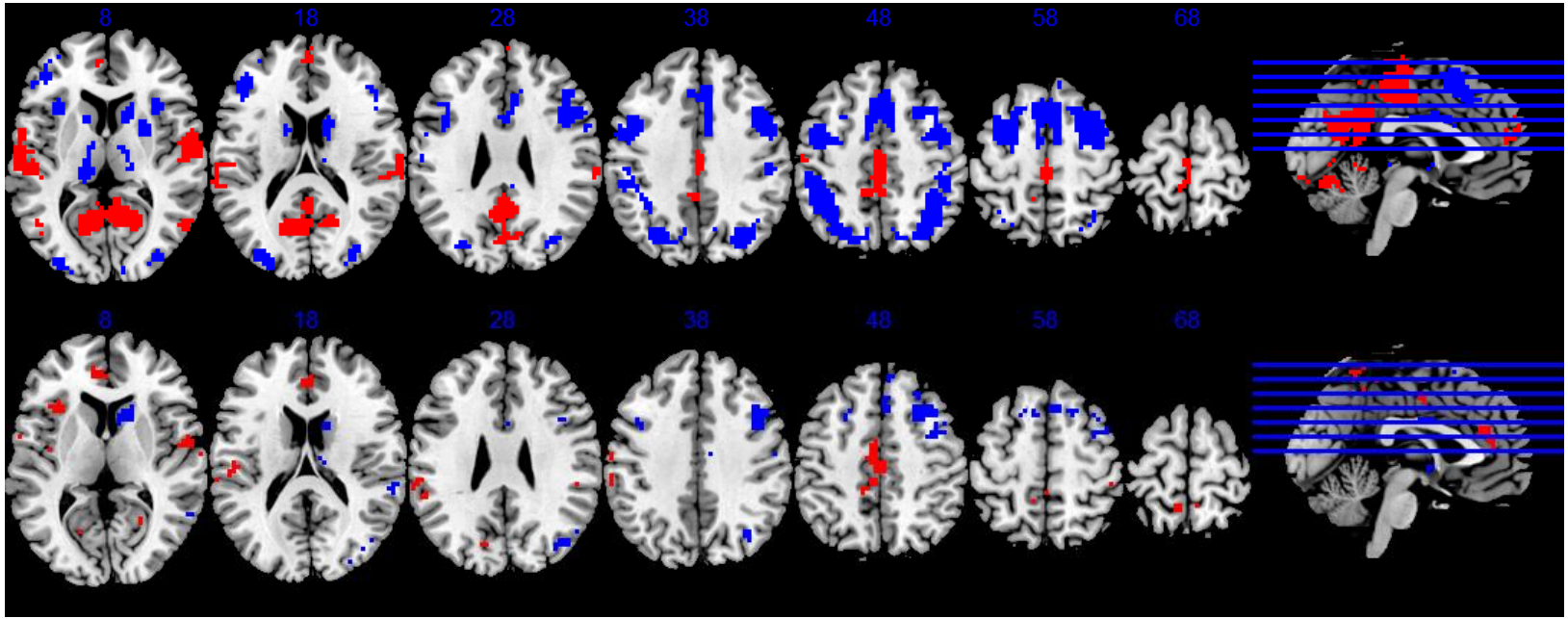
A **Generalized** Neural Representation Of Cognitive Reserve

- 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 ne 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

Task invariant CR Networks



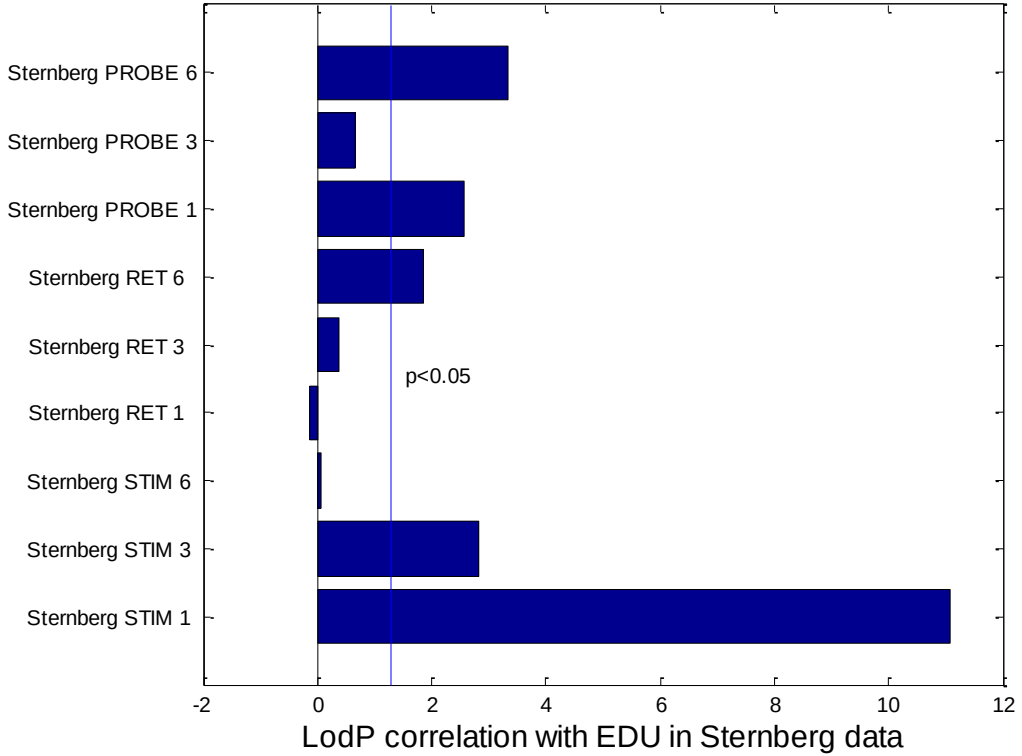
NART

EDUC

- 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

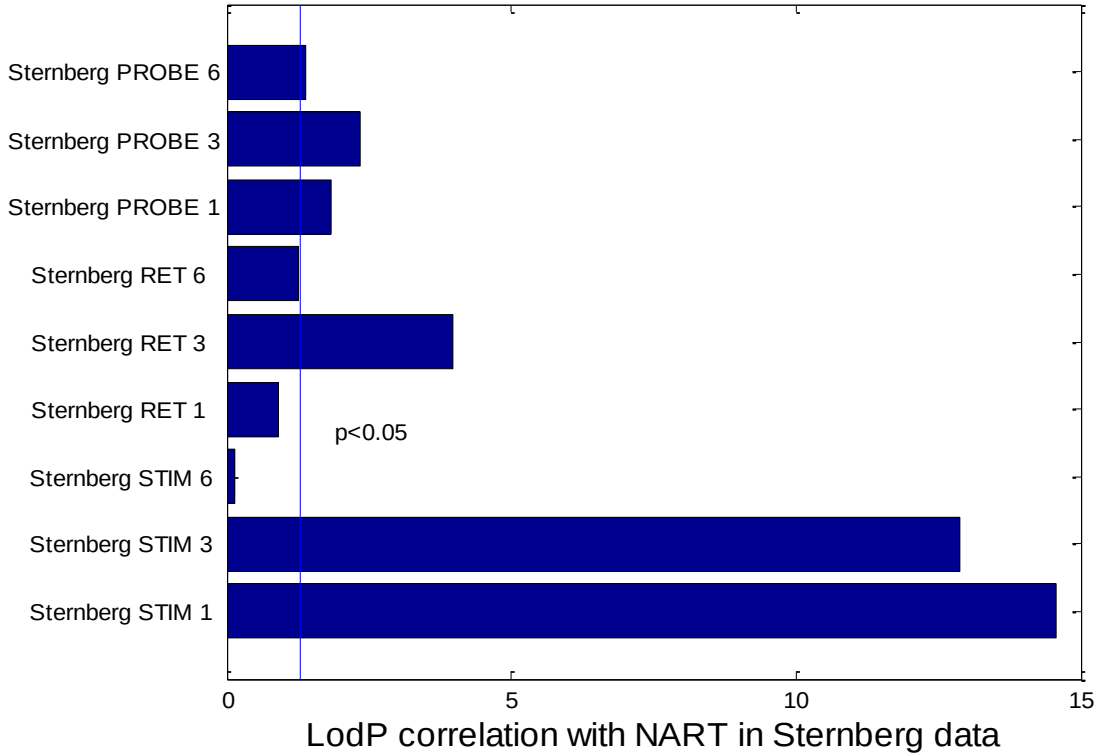
Apply EDU pattern to letter Sternberg data from 123 subjects: does subject expression correlate with EDU?

➔ 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**



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Data-Blitz

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

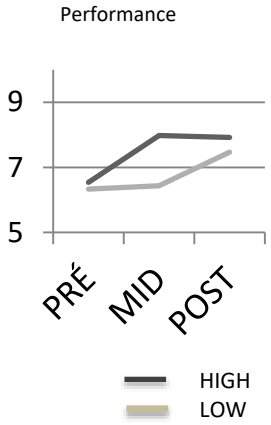
Centre de recherche iugm Institut universitaire de gériatrie de Montréal

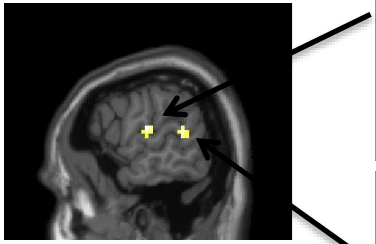
AFFILIÉ À Université de Montréal

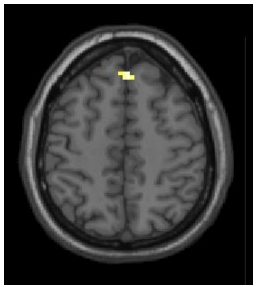
Main interests

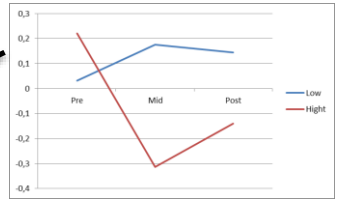
- **Use longitudinal design to identify the effect of different reserve proxies on working memory**
- **Identify functional and structural brain differences related to different reserve proxies**
- **Develop cognitive training programs to promote cognitive and brain health in aging and in the early stages 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**

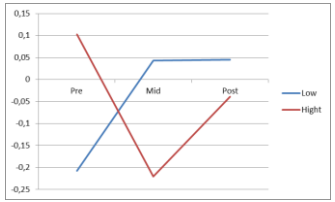
Impact of education on training-induced changes in individuals with SCD

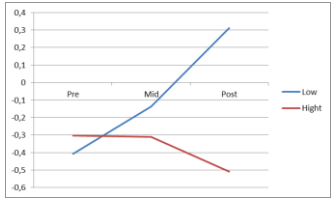












Left superior temporal gyrus

Bilateral superior and medial frontal giri

AAIC 2016

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

Centre de recherche iugm Institut universitaire de gériatrie de Montréal

benjamin.boller@umontreal.ca

Affilié à Université de Montréal

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

UNIVERSITAT DE BARCELONA

BBSLAB
BARCELONA
Brain Stimulation Lab

Former Neuroimaging studies on CR

Journal of Alzheimer's Disease 35 (2013) 715–726
DOI 10.3233/JAD-121906
IOS Press

715

Cognitive Reserve Proxies Relate to Gray Matter Loss in Cognitively Healthy Elderly with Abnormal Cerebrospinal Fluid Amyloid-β Levels

Eider M. Arenaza-Urquijo[a], José-Luis Molinuevo[c], Roser Sala-Llonch[a], Cristina Solé-Padullés[c], Mircea Balasa[c], Beatriz Bosch[c], Jaume Olives[c], Anna Antonell[c], Albert Lladó[c], Raquel Sánchez-Valle[c], Lorena Rami[c,†] and David Bartrés-Faz[a,b,†,*]

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ScienceDirect
journal homepage: www.elsevier.com/locate/cortex
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CORTEX

Special issue: Research report

Cognitive reserve modulates task-induced activations and deactivations in healthy elders, amnestic mild cognitive impairment and mild Alzheimer's disease

Beatriz Bosch[a], David Bartrés-Faz[b,c,], Lorena Rami[c,d], Eider M. Arenaza-Urquijo[b], Davinia Fernández-Espejo[b,c], Carme Junqué[b,c], Cristina Solé-Padullés[a], Raquel Sánchez-Valle[c,d], Núria Bargalló[c,d], Carles Falcón[c,e] and José Luis Molinuevo[c,d]*

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Neurobiology of Aging 30 (2009) 1114–1124

NEUROBIOLOGY OF AGING

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

Cristina Solé-Padullés[a], David Bartrés-Faz[a,b,*], Carme Junqué[a,b], Pere Vendrell[a,b], Lorena Rami[c,b], Imma C. Clemente[a], Beatriu Bosch[c,b], Amparo Villar[c,b], Núria Bargalló[d,b], M. Angeles Jurado[a], Maite Barrios[c], Jose Luis Molinuevo[c,b]

Biological Psychology 80 (2009) 256–259

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Biological Psychology

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

ELSEVIER

BIOLOGICAL PSYCHOLOGY

Brief report

Interactions of cognitive reserve with regional brain anatomy and brain function during a working memory task in healthy elders

David Bartrés-Faz[a,b,*], Cristina Solé-Padullés[c], Carme Junqué[a,b], Lorena Rami[c], Beatriz Bosch[c], Núria Bargalló[d], Carles Falcón[b,e], Raquel Sánchez-Valle[c,b], José Luis Molinuevo[c,b]

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.
Roser Sala-Llonch, M.Sc.
Cristina Solé-Padullés, Ph.D.
Carme Junqué, Ph.D.
Davinia Fernández-Espejo, M.Sc.
Núria Bargalló, M.D., Ph.D.
Lorena Rami, Ph.D.
José Luis Molinuevo, M.D., Ph.D.
David Bartrés-Faz, Ph.D.

Brain Topogr
DOI 10.1007/s10548-011-0195-9

ORIGINAL PAPER

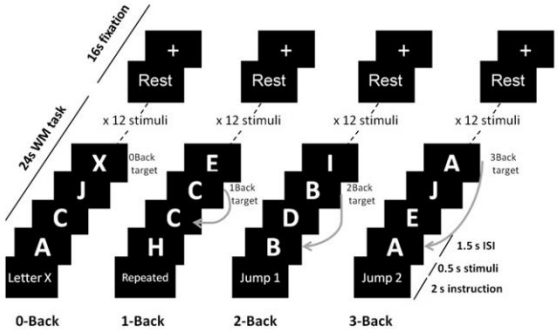
Structural and Functional Imaging Correlates of Cognitive and Brain Reserve Hypotheses in Healthy and Pathological Aging

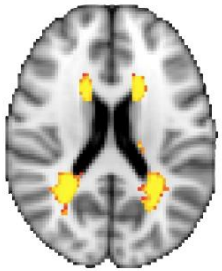
David Bartrés-Faz · Eider M. Arenaza-Urquijo

Investigate how White Matter burden interacts with Education on the expression of Working Memory networks

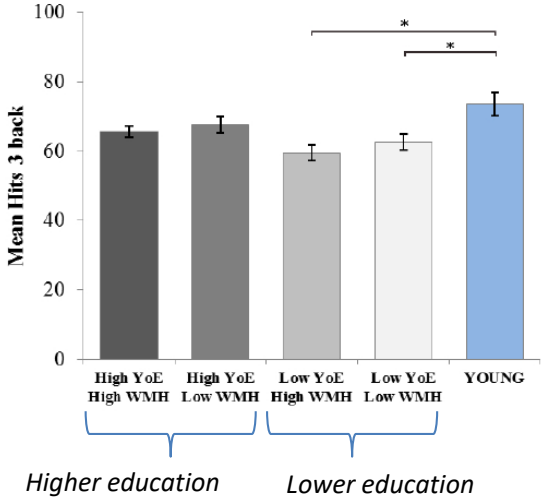
	OLD *n = 90*	YOUNG *n = 16*
Age, y	67 (2.90)	22 (1.93)
YoE	11 (4.02)	-
MMSE	29 (0.84)	-

3T Siemens Trio MRI





Automatic WMH volume segmentation



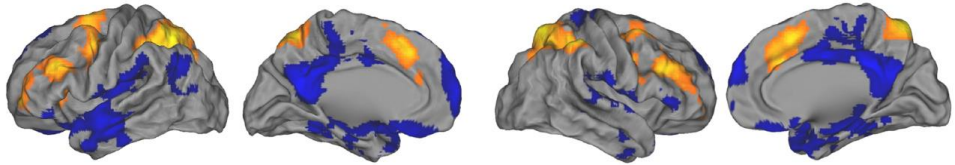
Effect of age (young vs old)
Effect of education (old)

Fernández-Cabello et al. (submitted)

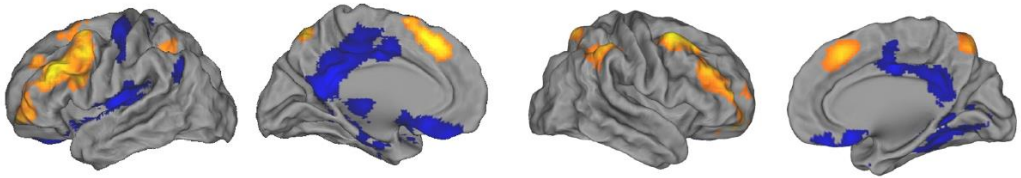
Interaction YoE x WMH effects

Cognitive Load (3>2>1>0-back)

Young
n = 16

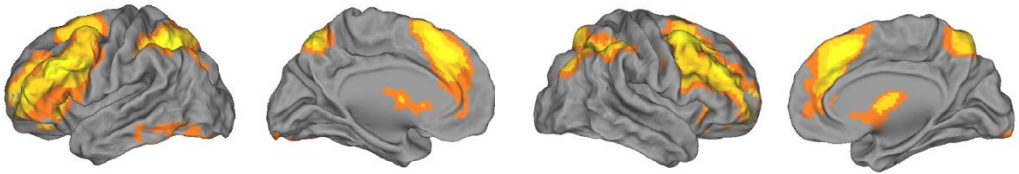


High YoE
Low WMH
n = 21



'Young like' pattern

High YoE
High WMH
n = 30



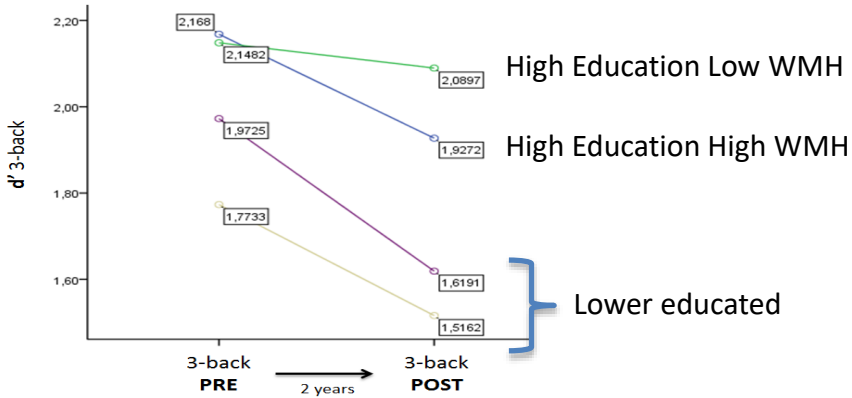
'Compensatory' pattern

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***

BBSLAB
BARCELONA
Brain Stimulation Lab

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

Thank you

UNIVERSITAT DE BARCELONA

IDIBAPS Institut D'Investigacions Biomèdiques August Pi i Sunyer

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

CLÍNIC BARCELONA Hospital Universitari

Institut de l'Envelliment UAB

José Luis Molinuevo
Beatriz Bosch
Lorena Rami

Emili Ros
Cinta Valls-Pedret

Núria Bargallo
Antoni Salvà
Sara Domènech

alzheimer's association
AAIC 16

Assessment of cognitive reserve

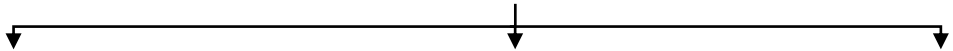
Michael Valenzuela	**“Cognitive lifestyle in different populations using Lifetime of Experiences Questionnaire”**
Robert Perneczky	**“Population-based research and cognitive reserve”**

REGENERATIVE
NEUROSCIENCE GROUP

How to Better Measure Cognitive Lifestyle?

Lifetime of Experiences Questionnaire (LEQ)

Lifespan approach



Young Adulthood (13-30 years)	Mid-Life (31-65 years)	Late Life (>65 years)
• **Educational activities** • Cognitive-loaded leisure activities • Social engagement	• **Occupational complexity** • Cognitive-loaded leisure activities • Social engagement • Educational activities	• **Cognitive-loaded leisure activities** • **Social engagement** • Ongoing work • Educational activities

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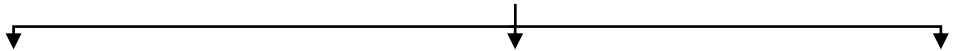
How to Better Measure Cognitive Lifestyle?

Lifetime of Experiences Questionnaire (LEQ)

Lifespan approach



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Good psychometric properties Valenzuela (2007)

Prospectively predicts cognitive decline Valenzuela (2008)

Translated into Spanish, French, German, Portugese, Greek and used by >10 groups.

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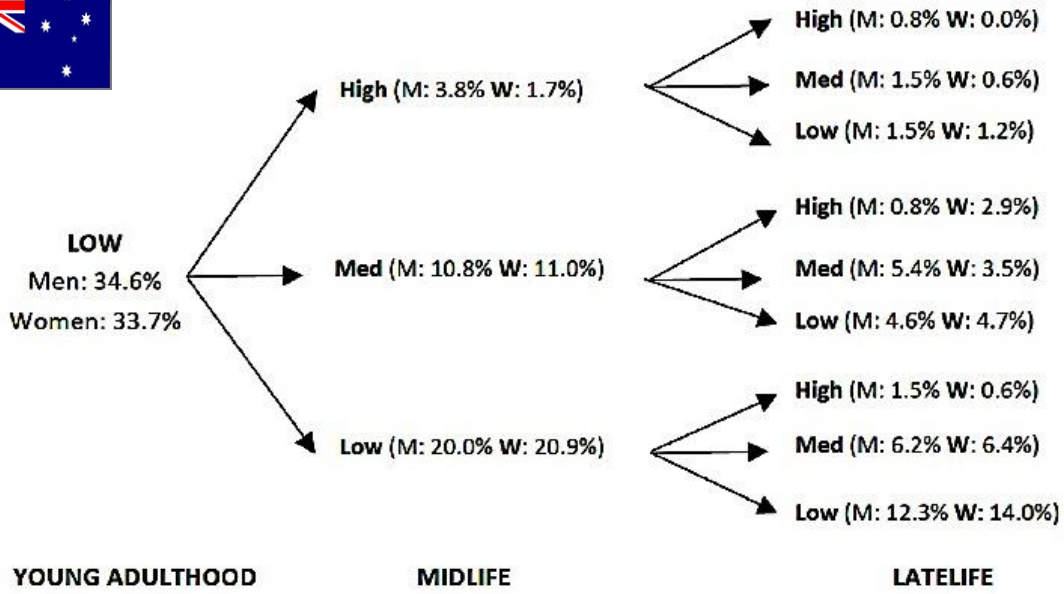
Population-based Data



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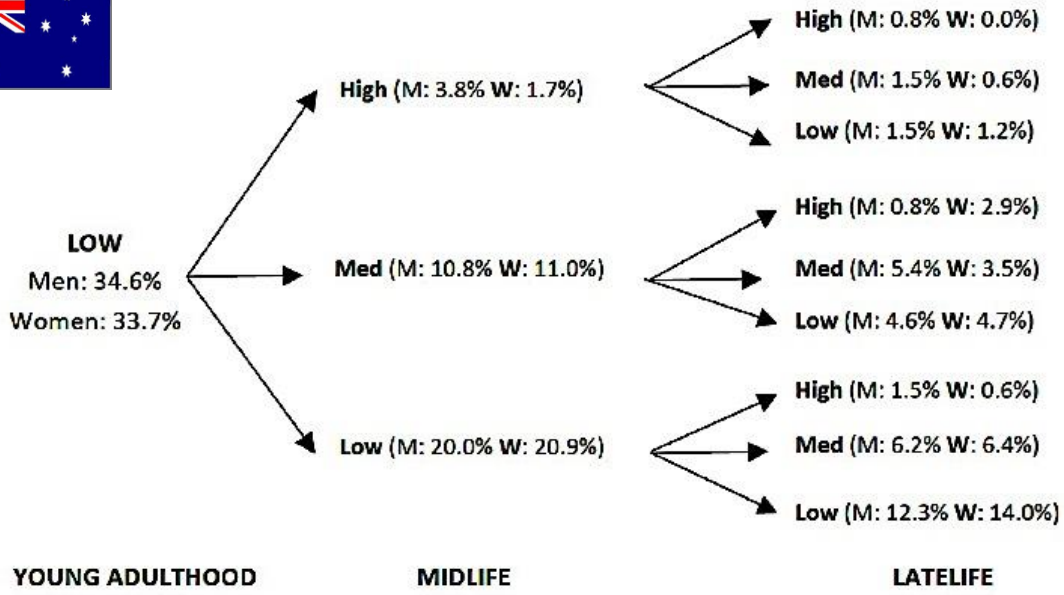
Population-based Data



Cognitive lifestyle is highly dynamic over course of lifetime. Valenzuela (2012)

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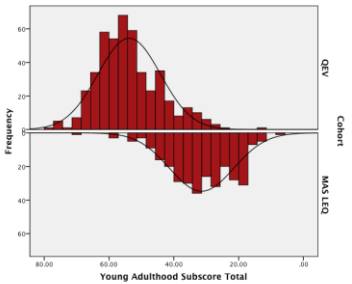
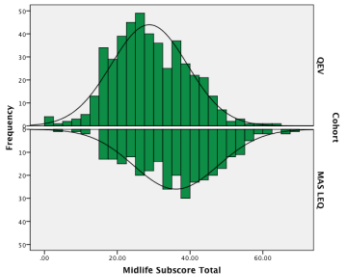
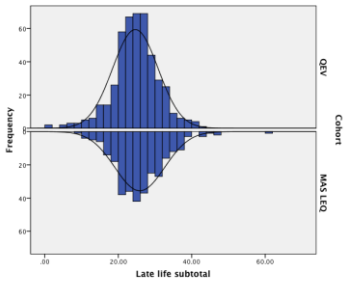
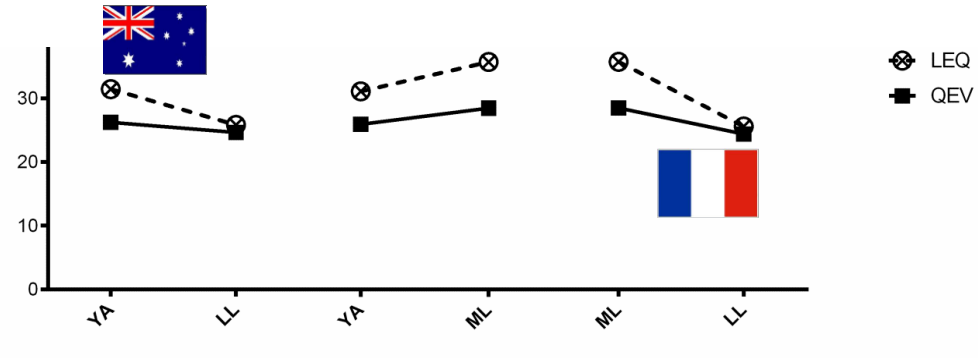
Cohort Differences Aussies vs French









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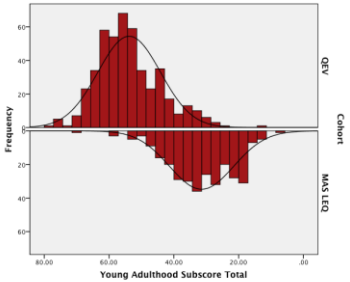
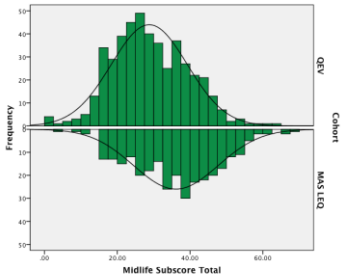
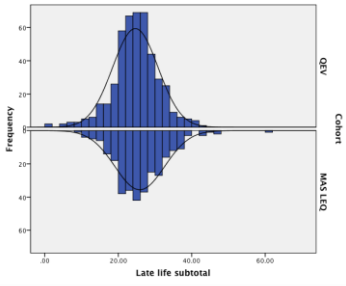
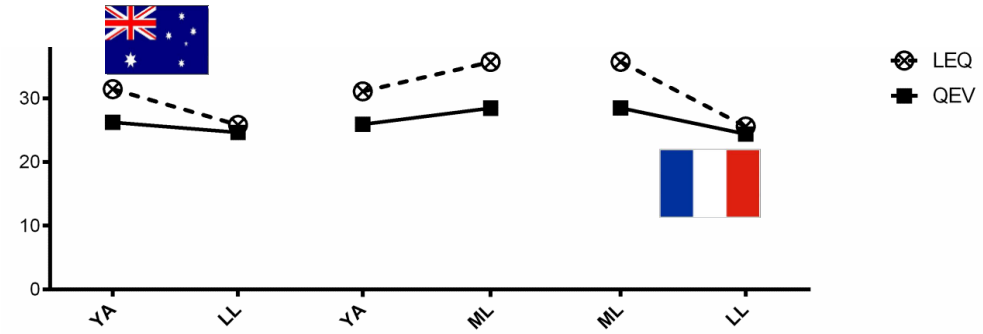
Cohort Differences Aussies vs French









What is more important? Where you end up, where you started, or how you got there?

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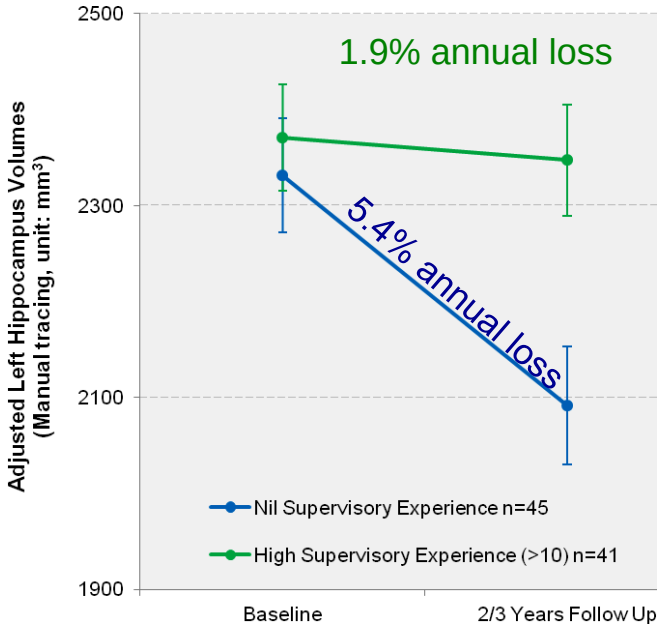
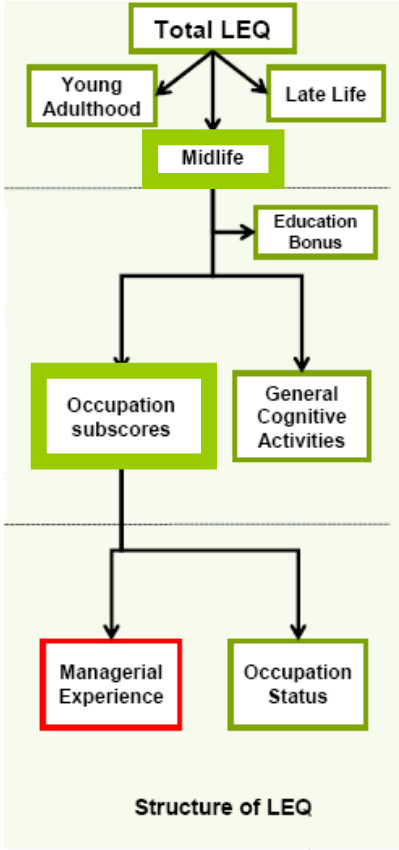
Cognitive Lifestyle & Brain Atrophy





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

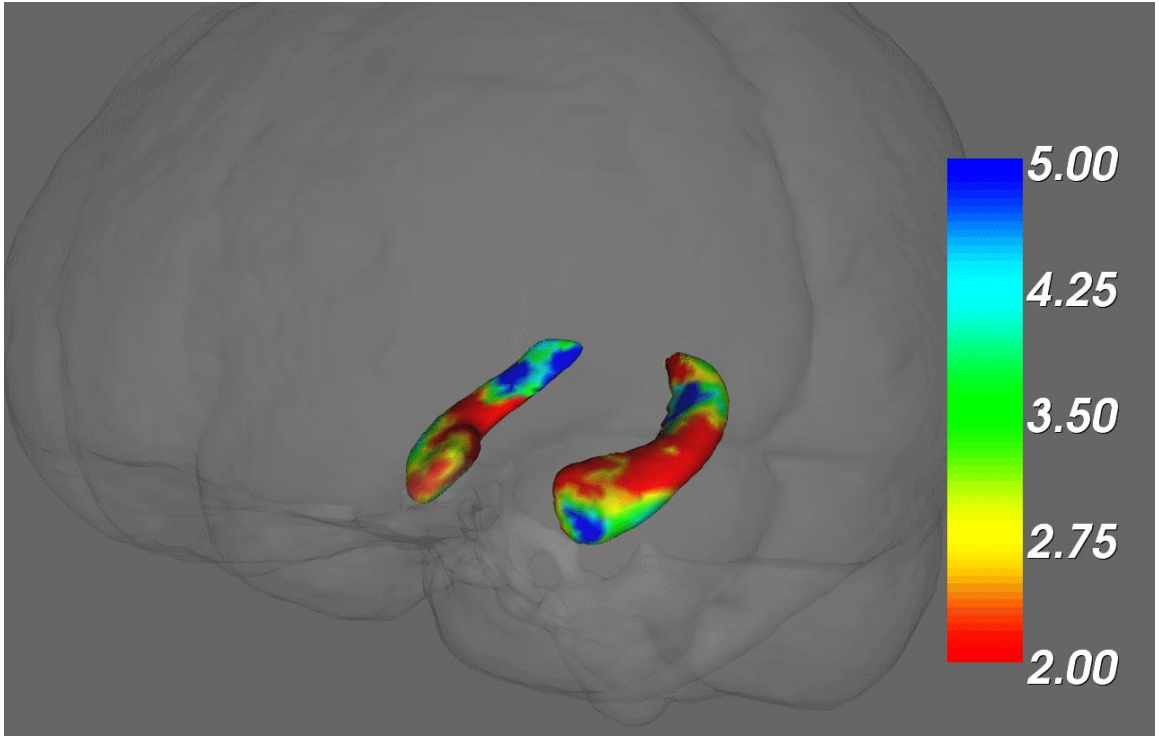
Suo et al *NeuroImage* (2012)

REGENERATIVE NEUROSCIENCE GROUP

New data!

Supervision: Hippocampus Protection

in MCI (The Sydney SMART Trial)



Suo et al Under Review

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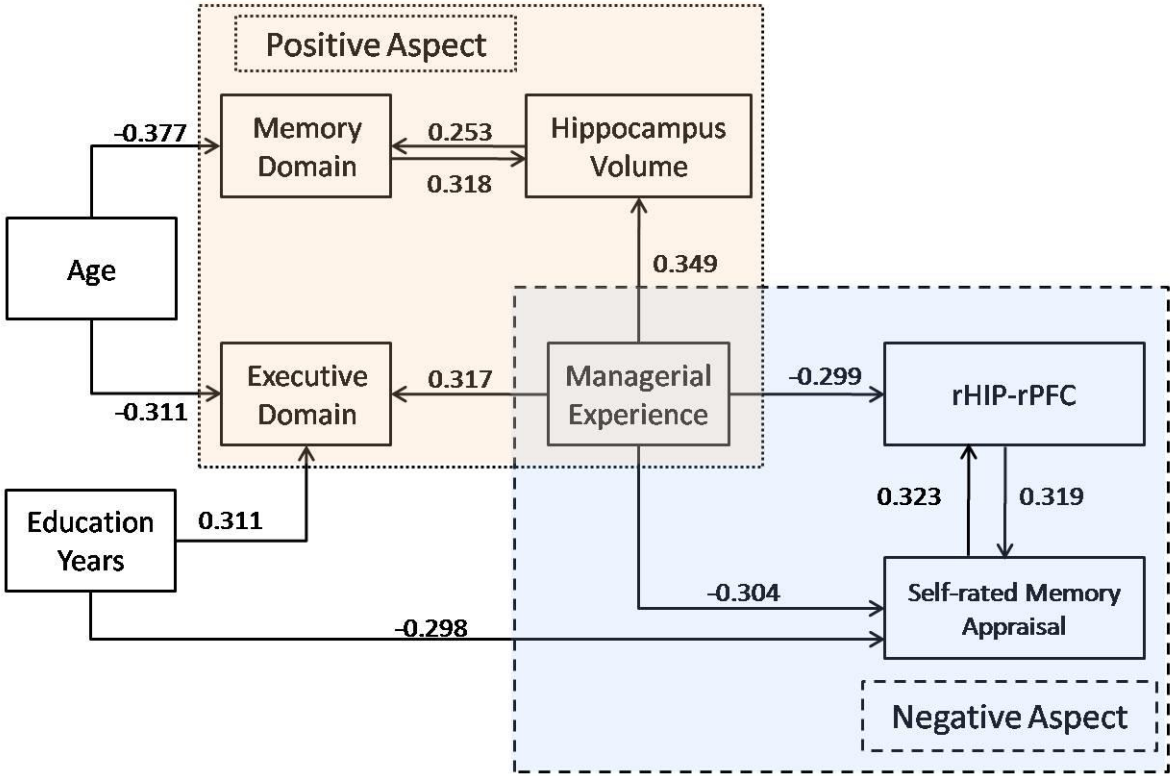
New data!

Ying & Yang of Supervision



Suo et al Under Review

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New data!

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. Jagust[1,2,3]

[1]Helen Wills Neuroscience Institute and [2]School of Public Health, University of California, Berkeley, California 94720, and [3]Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720

Carriers of the apolipoprotein E (APOE) $\varepsilon 4$ 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 $\varepsilon 4$ carriers. We therefore examined the interaction between lifetime cognitive activity and the APOE $\varepsilon 4$ allele in relation to brain Aβ burden. We obtained measures of lifetime cognitive activity in 118 cognitively normal human individuals (mean age: 76.13 $\pm$ 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 $\varepsilon 4$ carrier status, lifetime cognitive activity, and the interaction of the two factors with cortical Aβ deposition, quantified using [^{11}C] Pittsburgh-compound-B (PIB)-PET. As expected, the $\varepsilon 4$ carriers exhibited higher PIB retention compared with noncarriers. Lifetime cognitive activity moderated the APOE genotype effect such that cortical PIB retention was diminished in $\varepsilon 4$ 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.

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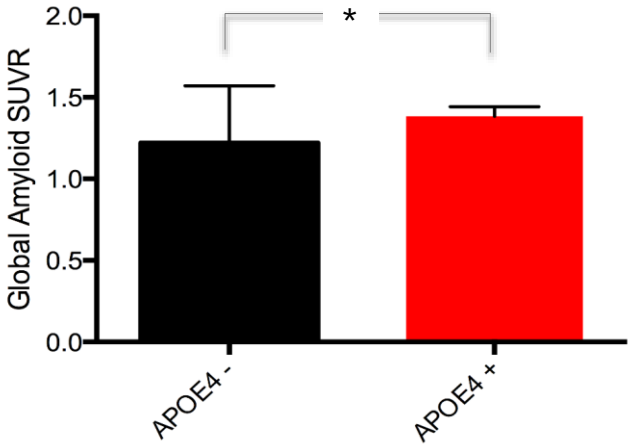
New data!

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



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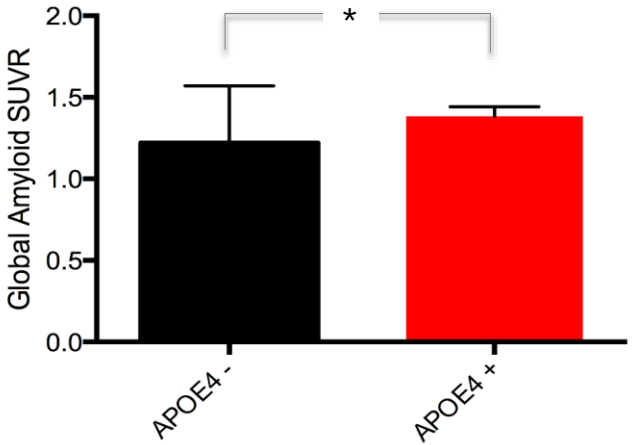

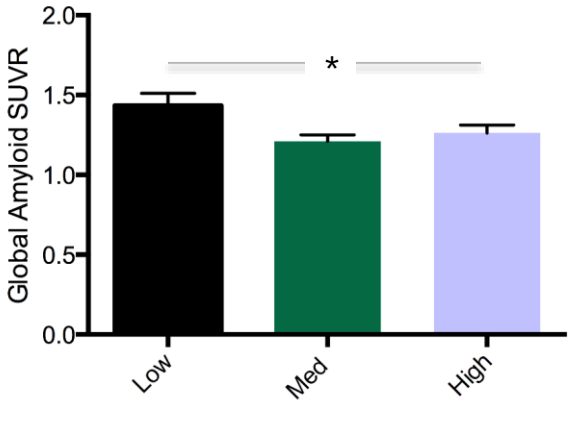

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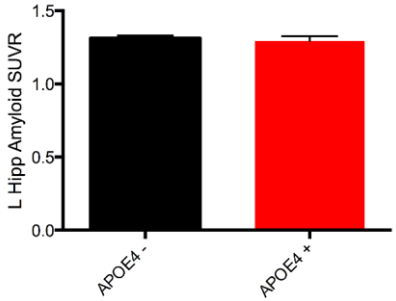
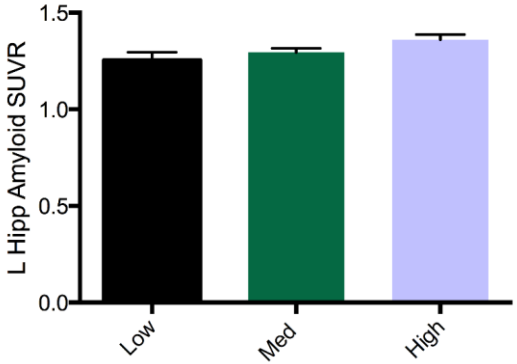
New data!

LEQ & Amyloid: Disease Modification?

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





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New data!

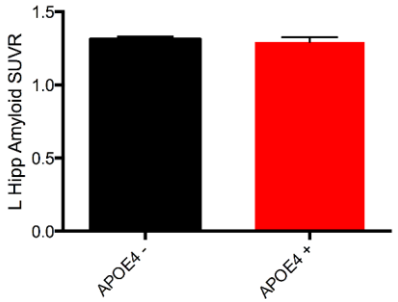
LEQ & Amyloid: Disease Modification?

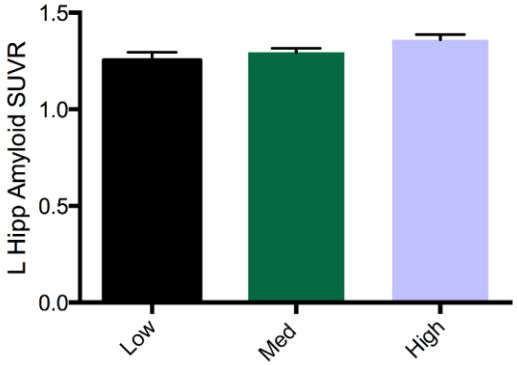
ANOVA Model

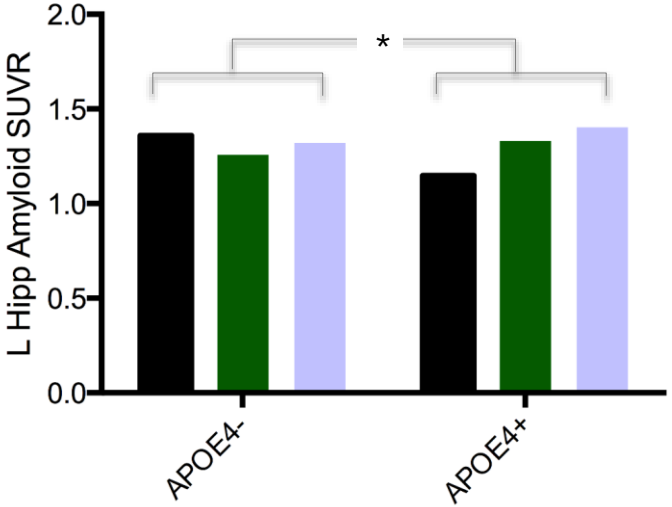
DV: Hippocampal Amyloid (^{18}F-Florbetaben)

IVs: *Covariates*: Age, sex, education *Fixed*: APOE4 (+/-), LEQ tertiles

Interaction: APOE4 X LEQ







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New data!

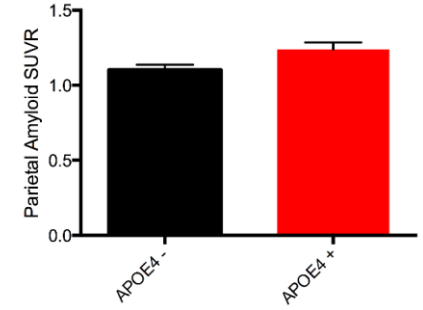
LEQ & Amyloid: Disease Modification?

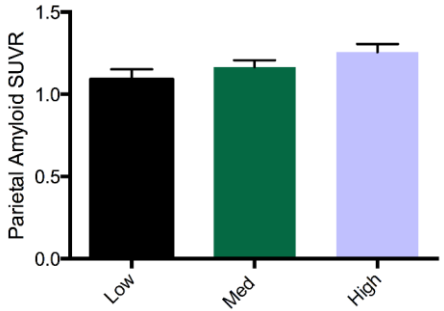
ANOVA Model

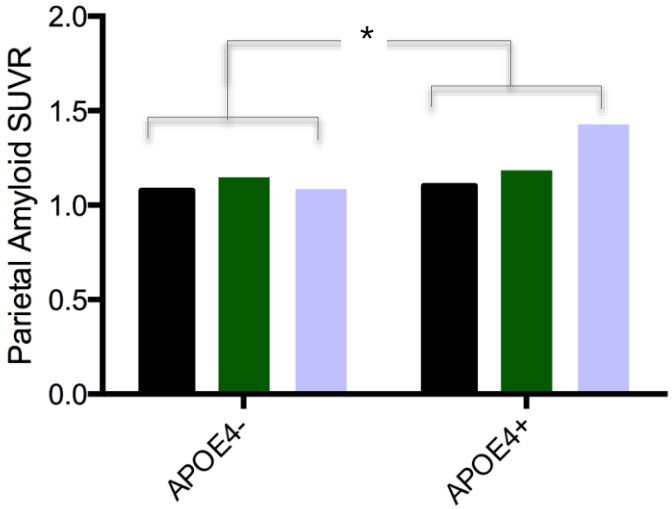
DV: Parietal Amyloid (^{18}F-Florbetaben)

IVs: *Covariates*: Age, sex, education *Fixed*: APOE4 (+/-), Late Life LEQ tertiles

Interaction: APOE4 X LEQ







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Computerised Cognitive Training Symposium

S2-01 Computerized Cognitive Training: What Works, With Whom and How? ,
Monday, July 25, 2016: 8:00 AM - 9:30 AM,
Metro Toronto Convention Centre, 105

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Imperial College London

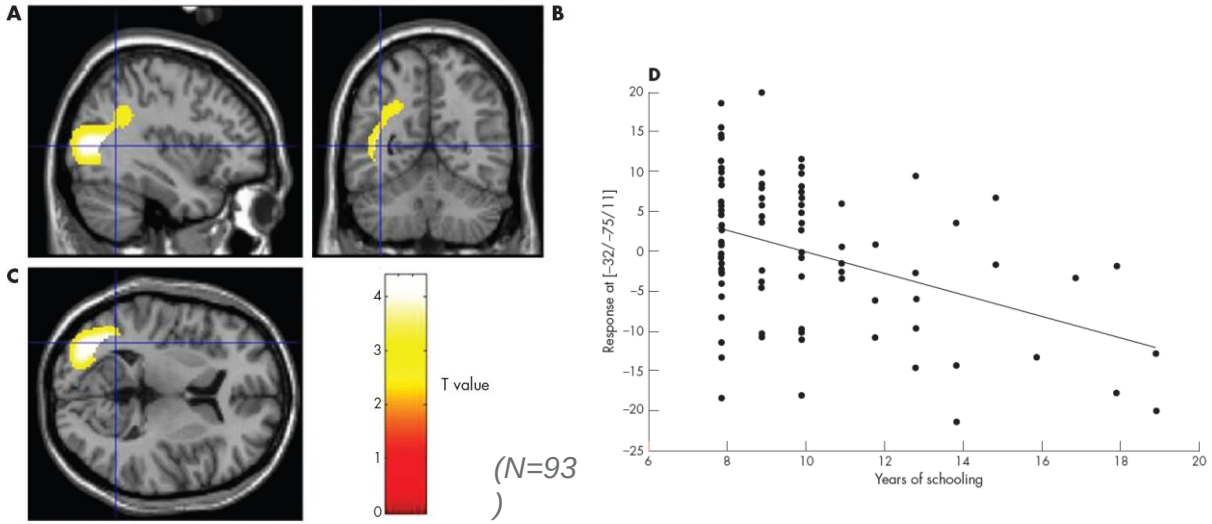
Population-based research and cognitive reserve

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

Imperial College London

The past (1)

Alzheimer's disease



(N=93)

Perneczky (J Neurol Neurosurg Psychiatry 2006)

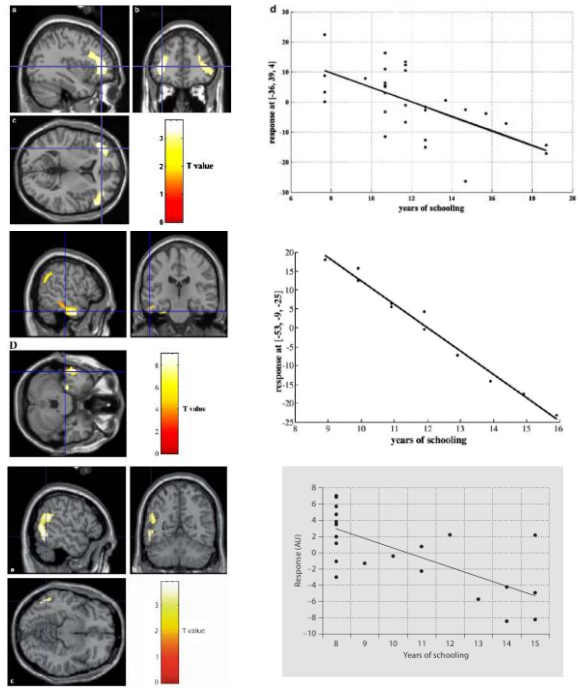
Imperial College London

The past (2)

bvFTD

NFPA

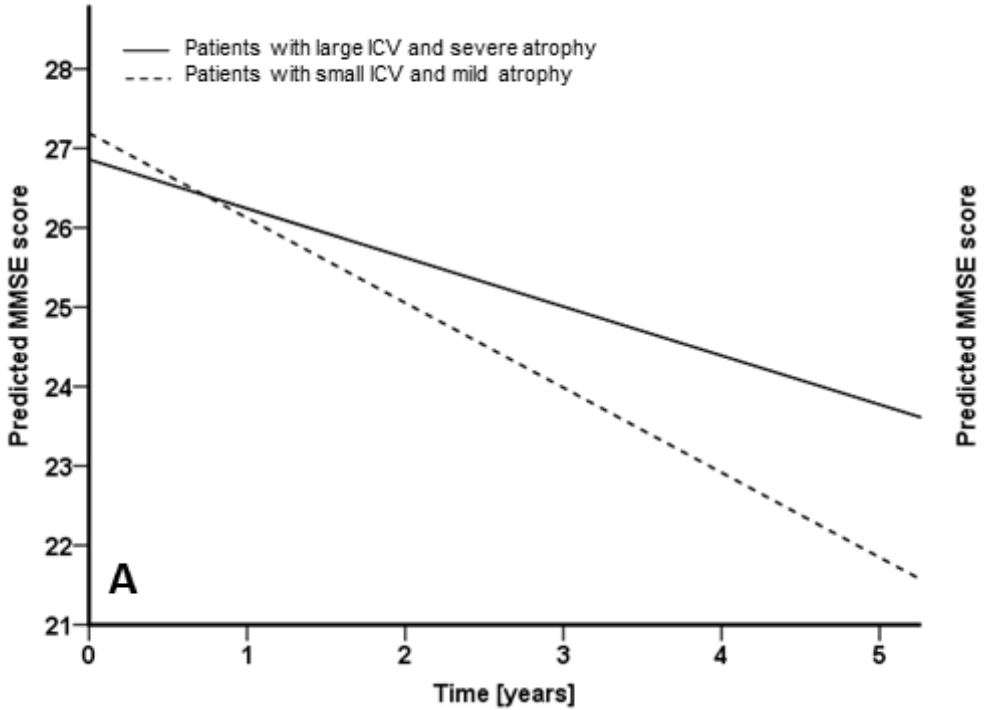
LBD



Perneczky (Eur J Nucl Med Mol Imaging 2006, Brain Res 2007, Dement Geriatr Cogn Disord 2007)

Imperial College London

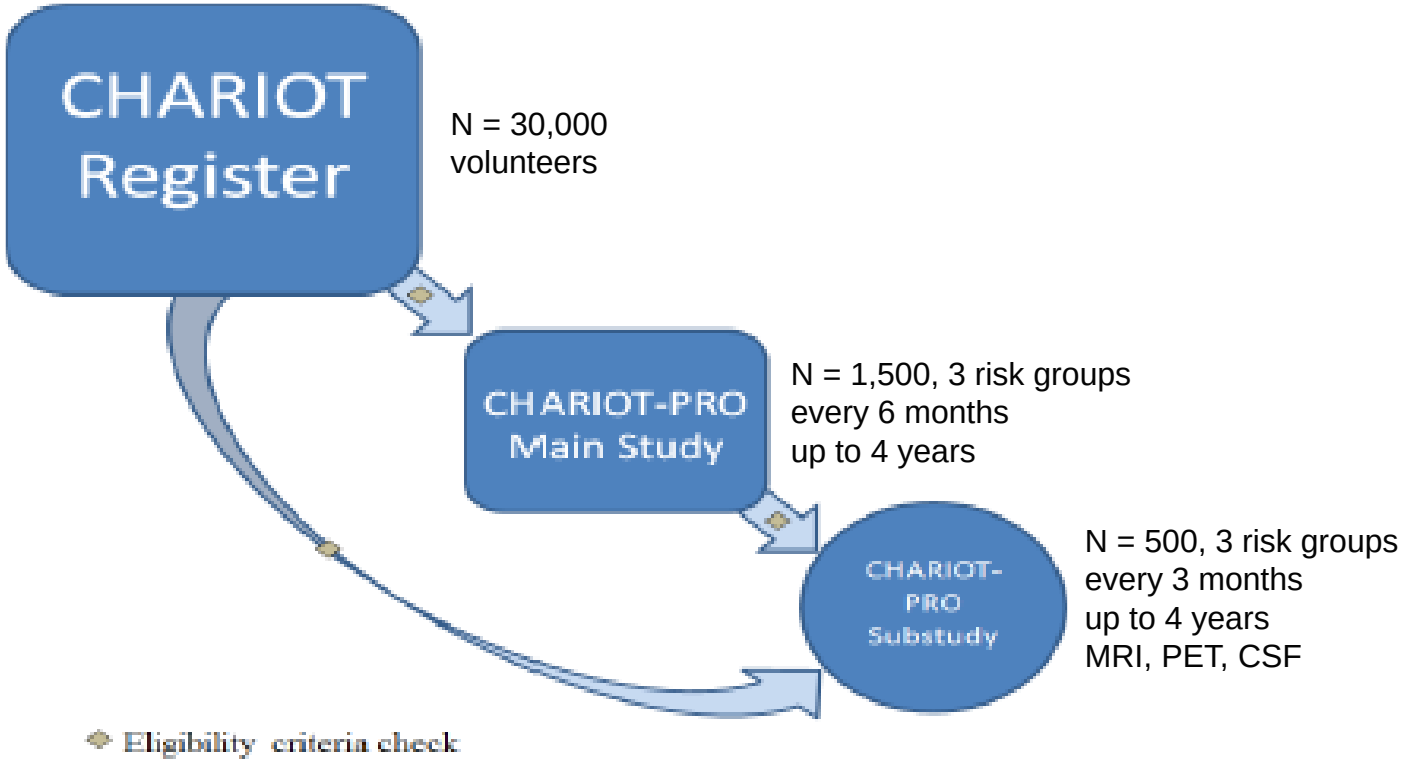
The past (3)



Guo & Perneczky (Alzheimers Dement 2013)

Imperial College London

The future (1)



Imperial College London

Population-based research and cognitive reserve

Robert Perneczky
Imperial College London
School of Public Health
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alzheimer's association
AAIC 16

Research criteria and approaches to test reserve in aging and Alzheimer's disease

Corinne Pettigrew	**"Relationships of cognitive reserve to biomarkers of neuronal injury during preclinical AD"**
José-Luis Molinuevo	**"Cognitive reserve in preclinical AD"**
Silvia Morbelli	**"Interplay between education and brain metabolic networks in normal aging and prodromal Alzheimer's disease"**

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

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MEDICINE
SCHOOL OF MEDICINE

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

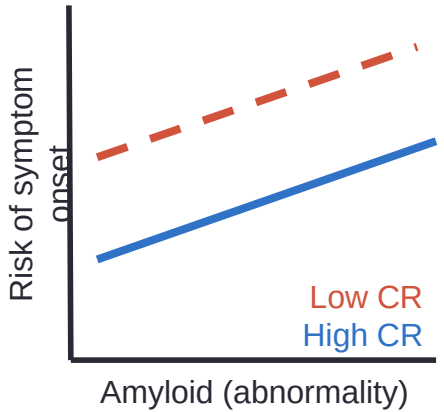
- Main effect AD biomarkers at baseline
  - *Amyloid*, CSF $A\beta_{1-42}$
  - *Neuronal injury*, CSF total tau and p-tau
    MRI cortical thickness in AD vulnerable regions
- Main effect cognitive reserve (CR)
- Biomarker x CR interaction (to determine if CR modifies relationship between biomarker and risk of symptom onset)

Covariates: age, gender

Biomarkers and CR in Relation to Onset of Symptoms

	Main Effect Biomarker		Main Effect CR		Interaction: Biomarker x CR	
Biomarker	HR	*p*	HR	*p*	HR	*p*
CSF Amyloid	0.69	.005	0.54	< .001	0.96	n.s.
CSF Tau						
CSF P-tau						
Cortical thickness						

- *Protective effects of CR on time to onset of clinical symptoms are equivalent across baseline levels of CSF amyloid*

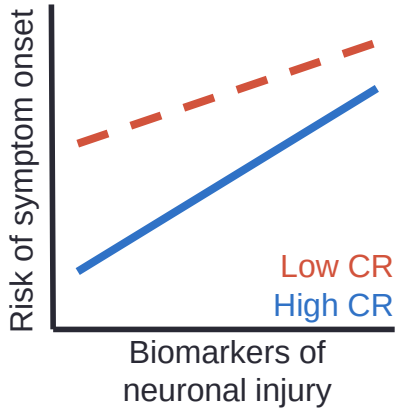


Soldan et al., 2013

Biomarkers and CR in Relation to Onset of Symptoms

	Main Effect Biomarker		Main Effect CR		Interaction: Biomarker x CR	
Biomarker	HR	*p*	HR	*p*	HR	*p*
CSF Amyloid	0.69	.005	0.54	< .001	0.96	n.s.
CSF Tau	1.17	n.s.	0.47	< .001	**1.52**	**.001**
CSF P-tau	1.50	< .001	0.51	< .001	**1.41**	**.003**
Cortical thickness	0.51	.03	0.47	< .001	**0.68**	**< .001**

- *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

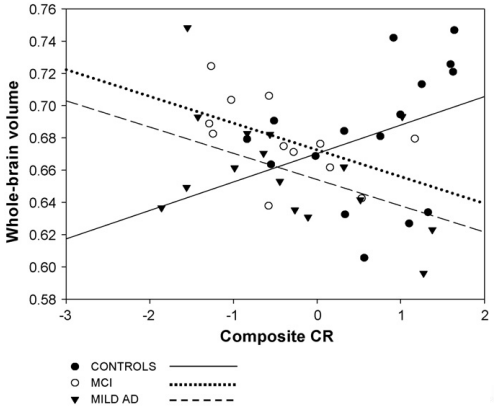
Thank *you* for your attention!

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….



ELSEVIER

Neurobiology of Aging 30 (2009) 1114–1124

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

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

Cristina Solé-Padullés [a], David Bartrés-Faz [a,b,*], Carme Junqué [a,b], Pere Vendrell [a,b], Lorena Rami [c,b], Imma C. Clemente [a], Beatriu Bosch [c,b], Amparo Villar [c,b], Núria Bargalló [d,b], M. Angeles Jurado [a], Maite Barrios [e], Jose Luis Molinuevo [c,b]

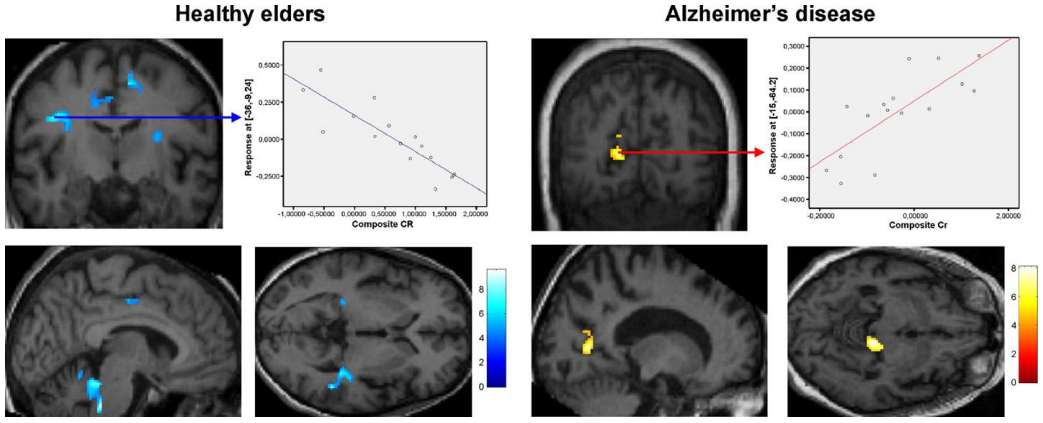


Fig. 2. Brain areas showing positive (in hot colours) and negative (in winter colours) correlations with the CR composite score in healthy controls and Alzheimer's disease patients. Scatterplots for the left precentral gyrus in the case of controls and the left lingual gyrus in AD patients are also depicted. 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

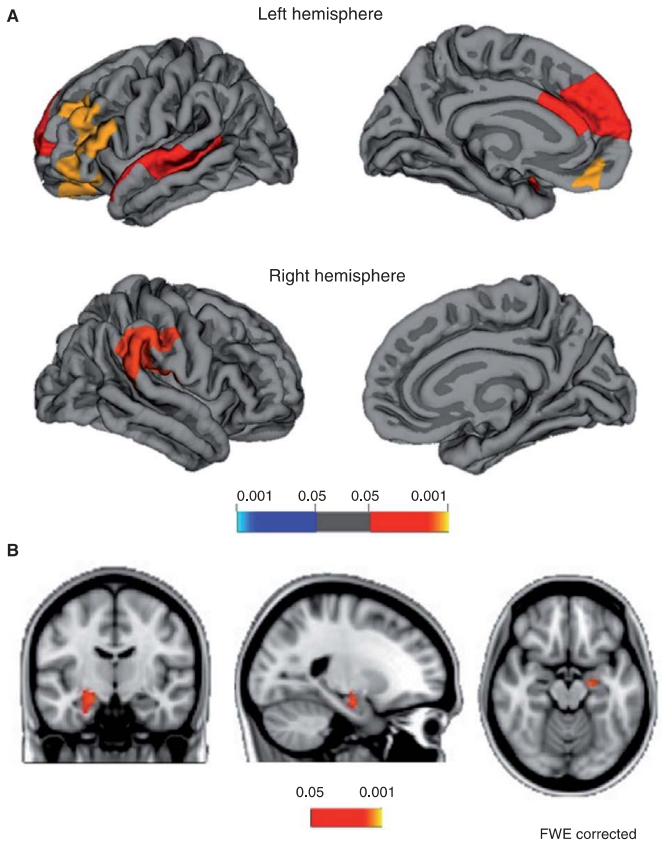
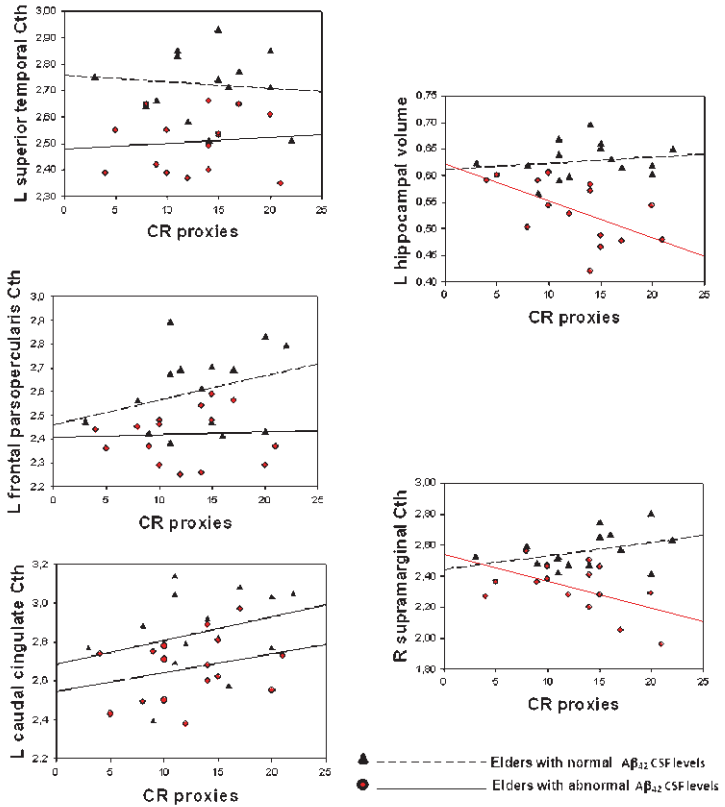


Fig. 1. Results of cortical thickness (A) and voxel-based morphometry analyses (B) showing differences between healthy elderly subjects with normal versus abnormal $A\beta_{42}$ CSF levels (abnormal < normal $A\beta_{42}$ CSF levels). All results are FWE-corrected.

Preclinical AD with high CR exhibit more gray matter loss



g. 2. Scatter plots showing interactions between cognitive reserve proxies and $A\beta_{42}$-related areas of cortical thinning or atrophy in elderly th normal versus abnormal $A\beta_{42}$ CSF levels. In red, statistically significant correlation coefficients (see Results for statistical details). Cth: rtical thickness; CR: cognitive reserve; R: right; L: left.

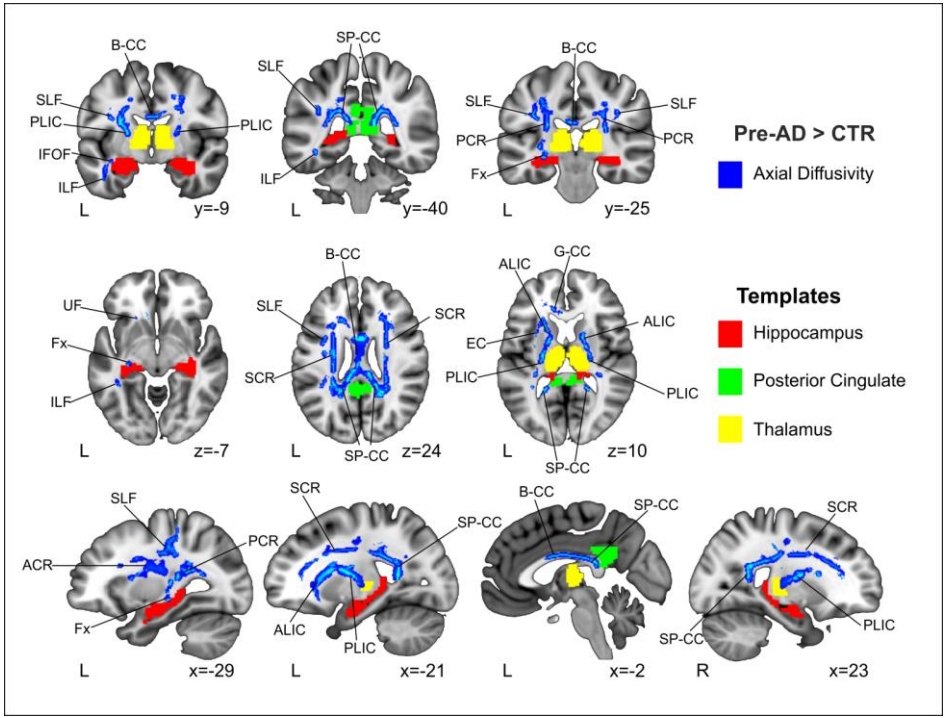
Contents lists available at ScienceDirect

Neurobiology of Aging

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

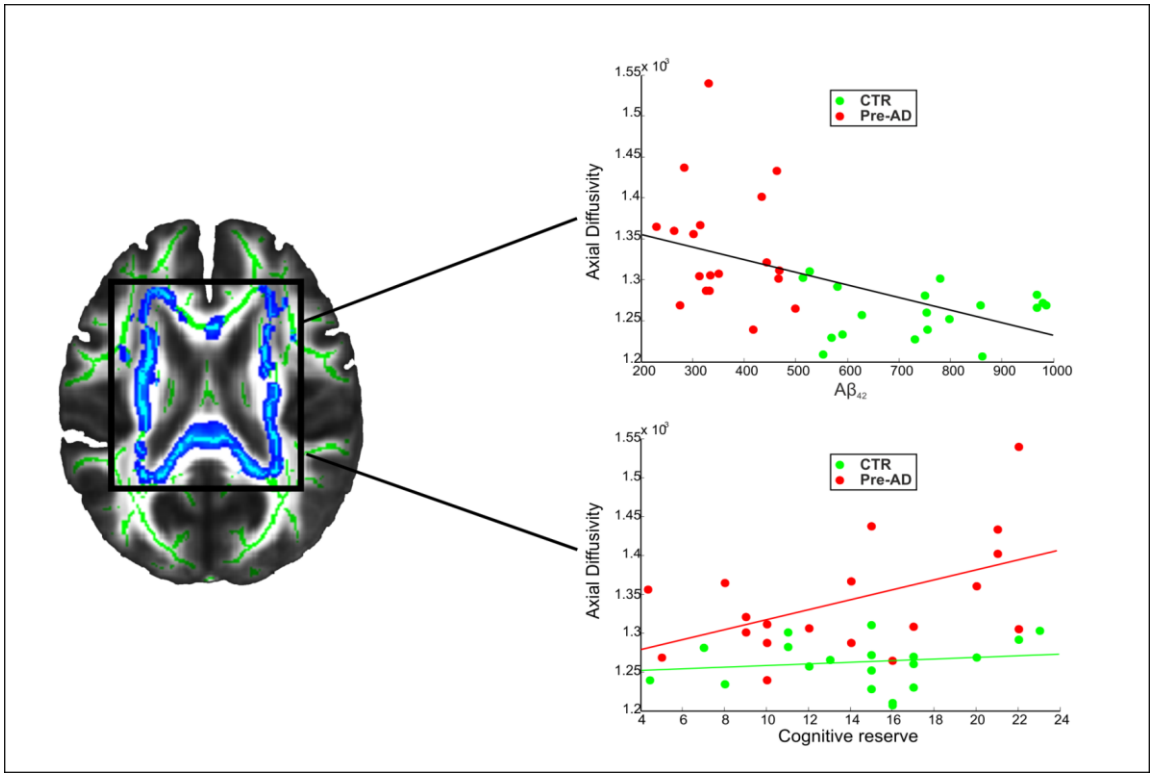
White matter changes in preclinical Alzheimer's disease: a magnetic resonance imaging-diffusion tensor imaging study on cognitively normal older people with positive amyloid β protein 42 levels

José Luis Molinuevo [a,b], Pablo Ripolles [c,d], Marta Simó [c], Albert Lladó [a,b], Jaume Olives [a,b], Mircea Balasa [a,b], Anna Antonell [a,b], Antoni Rodriguez-Fornells [c,d,e], Lorena Rami [a,b,*]



Tracts showing increased AxD in Pre-AD subjects compared with controls (blue)

Relationship between the areas showing increased AxD and the level of $A\beta_{42}$ on CSF (r=-0.52, p<0.0001) and cognitive reserve (Pre-AD group r=0.57, p<0.012).



Thank You

+100
1906 - 2006

CLÍNIC
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Hospital Universitari

barcelonaβeta
Brain Research Center

Interplay between education and brain metabolic networks in normal aging and prodromal Alzheimer's Disease (AD)

Silvia Morbelli and Flavio Nobili

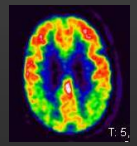
Nuclear Medicine and Clinical Neurology Units,

IRCCS San Martino – IST

University of Genoa

Dementia Research Group (University of Genoa, Italy)

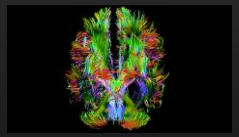
Memory Clinic



PET Center

equipped with Cyclotron and Radiopharmacy

3 Tesla MRI



Post-processing

(Connectomics,
Network and Methodological
Development on semiquantification)

EADC

European Alzheimer's Disease Consortium

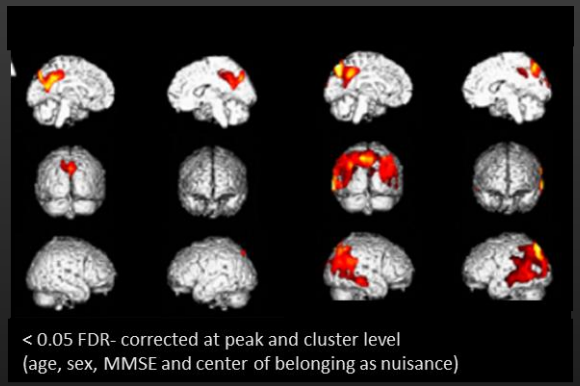
EADC 18F-FDG PET
data sharing project
(Genoa, Amsterdam, Brescia, Munich,
Marseille, Perugia)

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



< 0.05 FDR- corrected at peak and cluster level
(age, sex, MMSE and center of belonging as nuisance)

TABLE 2
Baseline Neuropsychologic *z* Scores of Patient Groups

Group	HE prodromal AD (n = 28)	LE prodromal AD (n = 36)	P
Immediate recall	−1.83 ± 1.00	−1.25 ± 0.99	NS
Delayed recall	−2.06 ± 1.07	−1.89 ± 0.74	NS
Visuoconstruction	−0.53 ± 1.94	−0.48 ± 1.76	NS
Verbal fluency	−0.16 ± 1.06	0.47 ± 1.38	NS
Attention	−0.51 ± 2.55	−0.61 ± 2.01	NS
Executive function	−1.35 ± 2.08	−1.42 ± 1.10	NS

NS = not significant.
Data are mean ± SD.

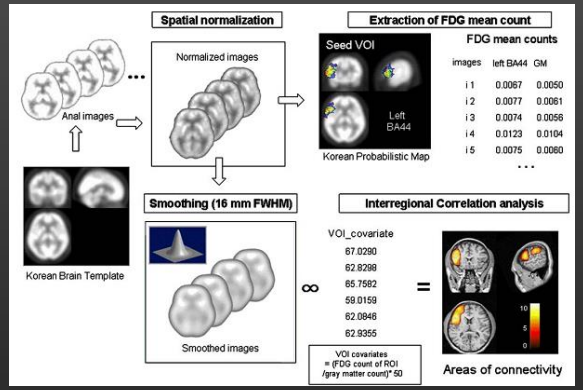
Relative preserved metabolism in R Dorsolateral Prefrontal Cortex in highly educated pAD

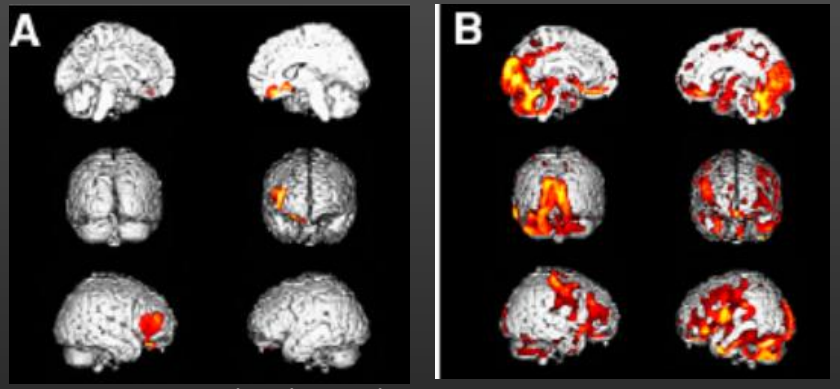
Cluster saved as seed VOI for metabolic connectivity analysis

Morbelli et al JNM 2013

Morbelli et al Clin Trans Imaging 2013

Metabolic Connectivity of right DLPFC in prodromal AD

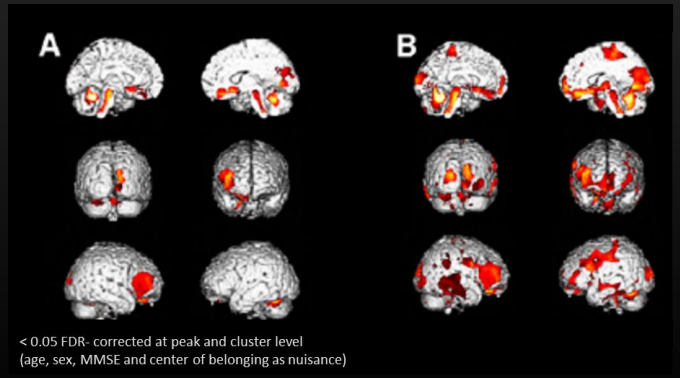




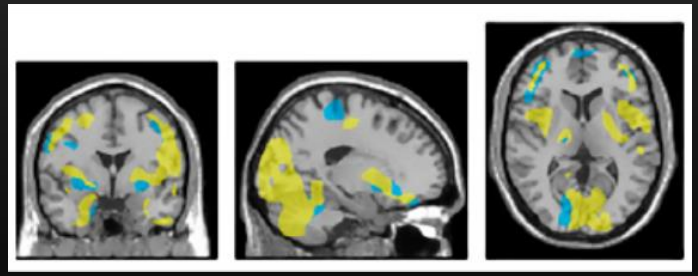
Poorly Educated pAD Highly Educated pAD

Metabolic Connectivity of right DLPFC in Healthy Elderly

Both neural reserve and neural compensation underlye this metabolic network



Poorly Educated CTR Highly Educated CTR



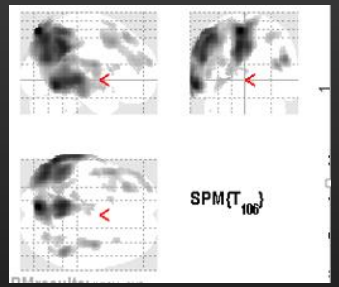
High-educ pAD

High-educ CTR

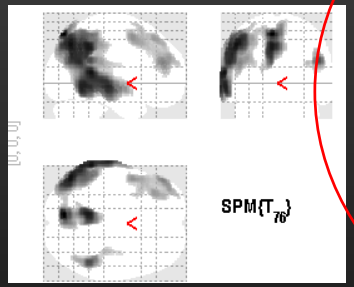
Education interacts differently with clinical expression of AD across European Countries

Hypometabolism in
CTR > Highly Educated pAD

Southern Europe

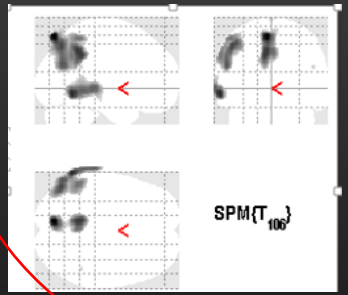


Mid Europe

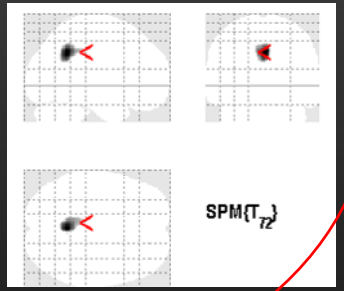


Hypometabolism in
CTR > Poorly Educated pAD

Southern Europe



Mid Europe



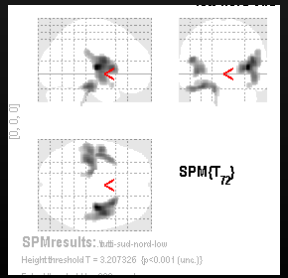
< 0.05 FDR- corrected at peak and cluster level
(age, sex, MMSE and center of belonging as nuisance)

Greater hypometabolism in Poorly Educated Southern European pAD

Mid Europe

VS

Southern Europe



Morbelli et al in preparation

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

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)

Thank you for your attention!

Camogli, Genoa, Italy

alzheimer's association
AAIC 16

From preclinical stages to dementia

Gaël Chételat	**“From observational studies to interventions: an overview of the different approaches used in the lab”**
Eider Arenaza-Urquijo	**“Cognitive reserve and lifestyle across the spectrum from normal cognition to Alzheimer‘s disease”**
Colin Groot	**“Active and passive reserve in demented an non demented stages of Alzheimer’s disease”**
Anja Soldan	**“Cognitive reserve and longitudinal cognitive change before and after onset of cognitive impairment”**

PhIND
PHYSIOPATHOLOGY & IMAGING OF NEUROLOGICAL DISORDERS

MULTIMODAL NEUROIMAGING AND LIFESTYLE IN AGEING AND ALZHEIMER'S DISEASE

Gaël Chételat, INSERM,
Centre d'imagerie Cyceron, Caen

Instituts thématiques
Inserm
Institut national de la santé et de la recherche médicale
UNICAEN
UNIVERSITÉ CAEN NORMANDIE
Normandie Université
cyceron
Centre d'imagerie cérébrale et de recherches en neuroscience
CHUCaen
IMAP
Recherche sur la Maladie d'Alzheimer

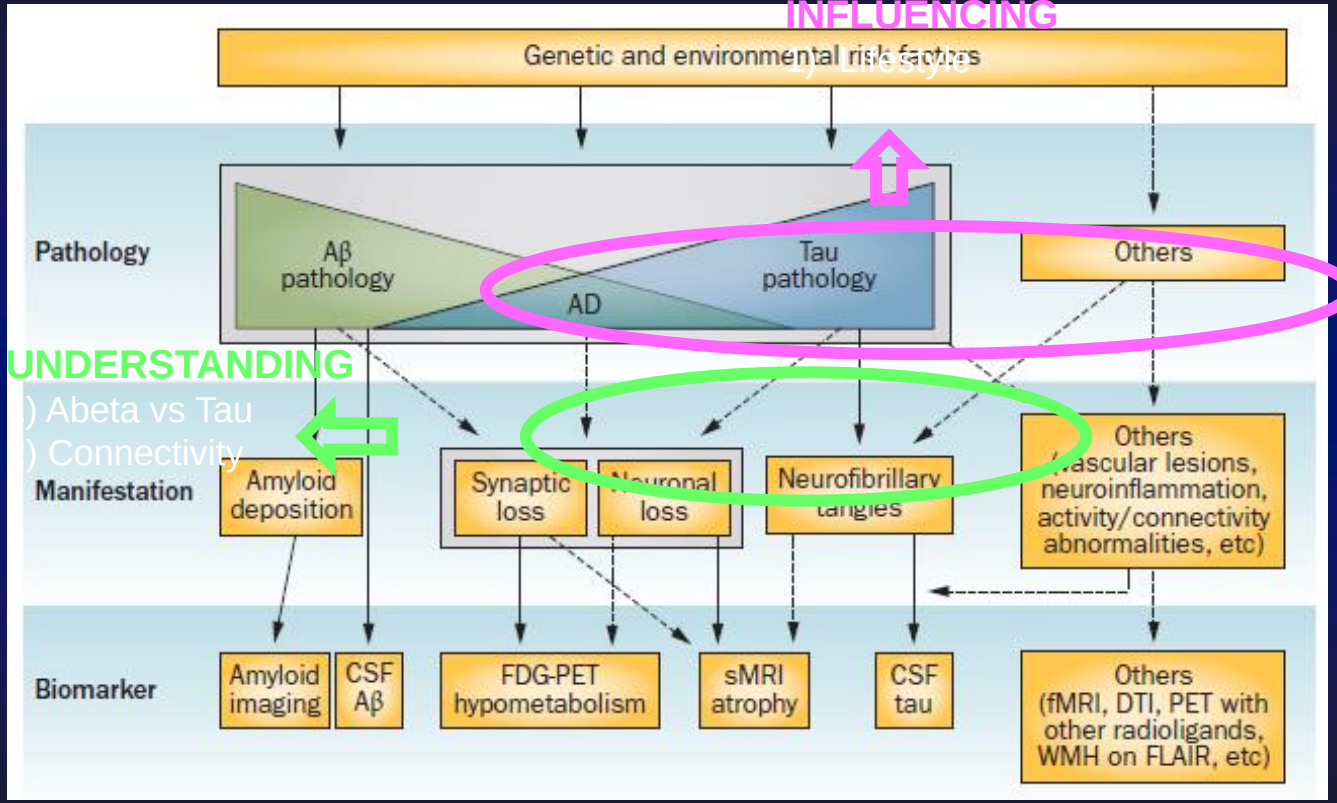
INFLUENCING

) Lifestyle

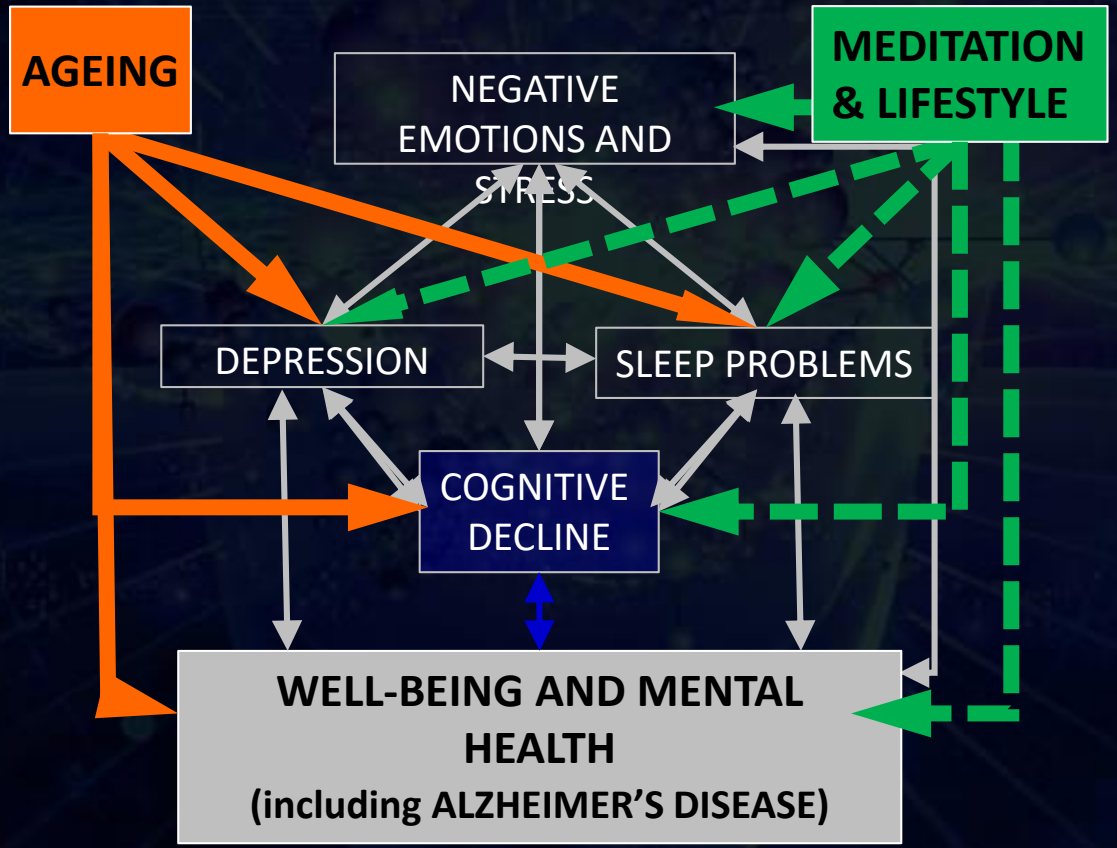
UNDERSTANDING

) Abeta vs Tau

) Connectivity



Chételat, Nat Rev Neurol, 2013


AGEING
NEGATIVE EMOTIONS AND STRESS
MEDITATION & LIFESTYLE
DEPRESSION
SLEEP PROBLEMS
COGNITIVE DECLINE
WELL-BEING AND MENTAL HEALTH
(including ALZHEIMER'S DISEASE)

INFLUENCING: 1) LIFESTYLE

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)

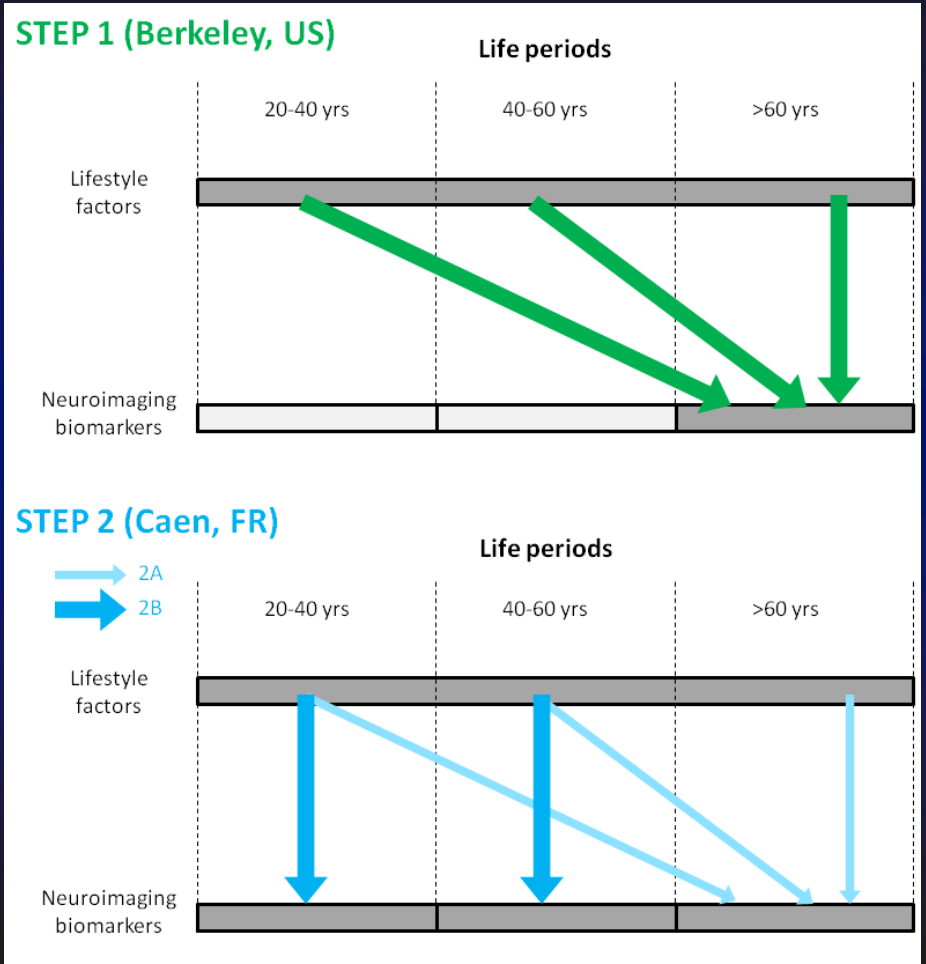
METHOD

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

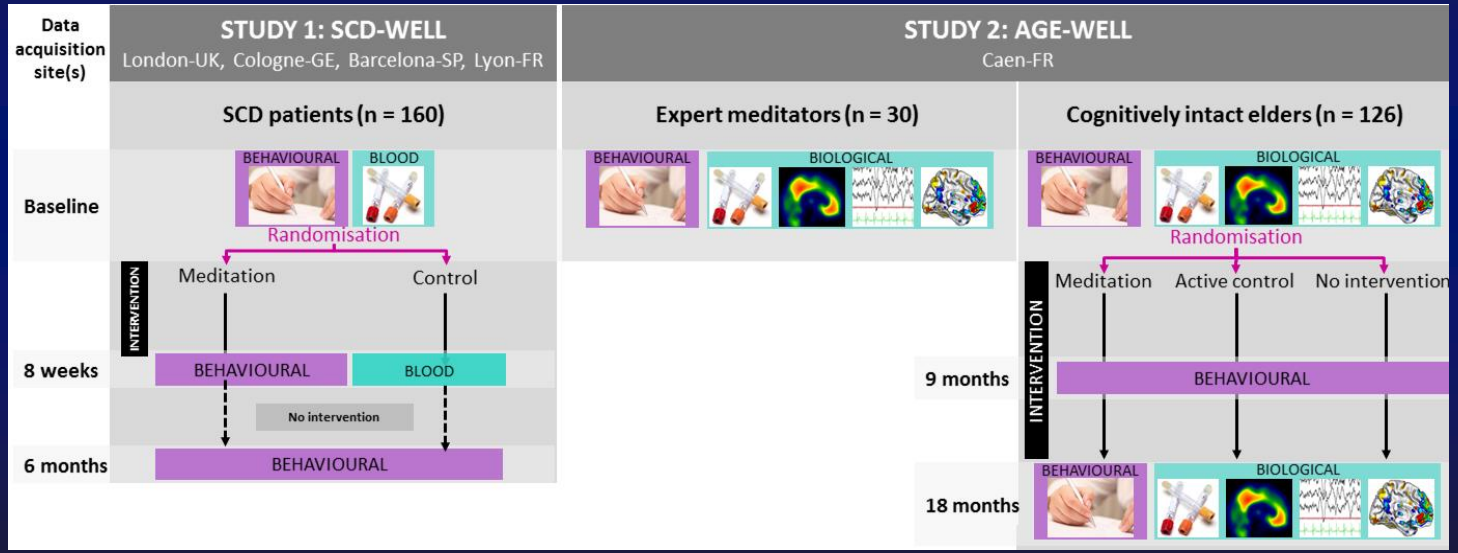
HORIZON 2020
WORK PROGRAMME 2014 – 2015
8. Health, demographic change and wellbeing
Personalising health and care

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 2B

126 healthy seniors
> 65 yrs

STUDY 2A

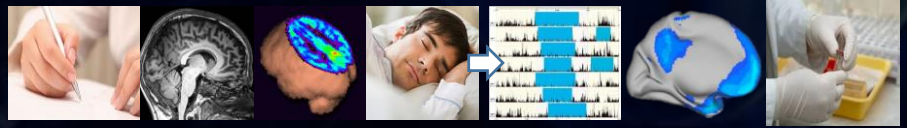
30 expert
meditators

18 mths

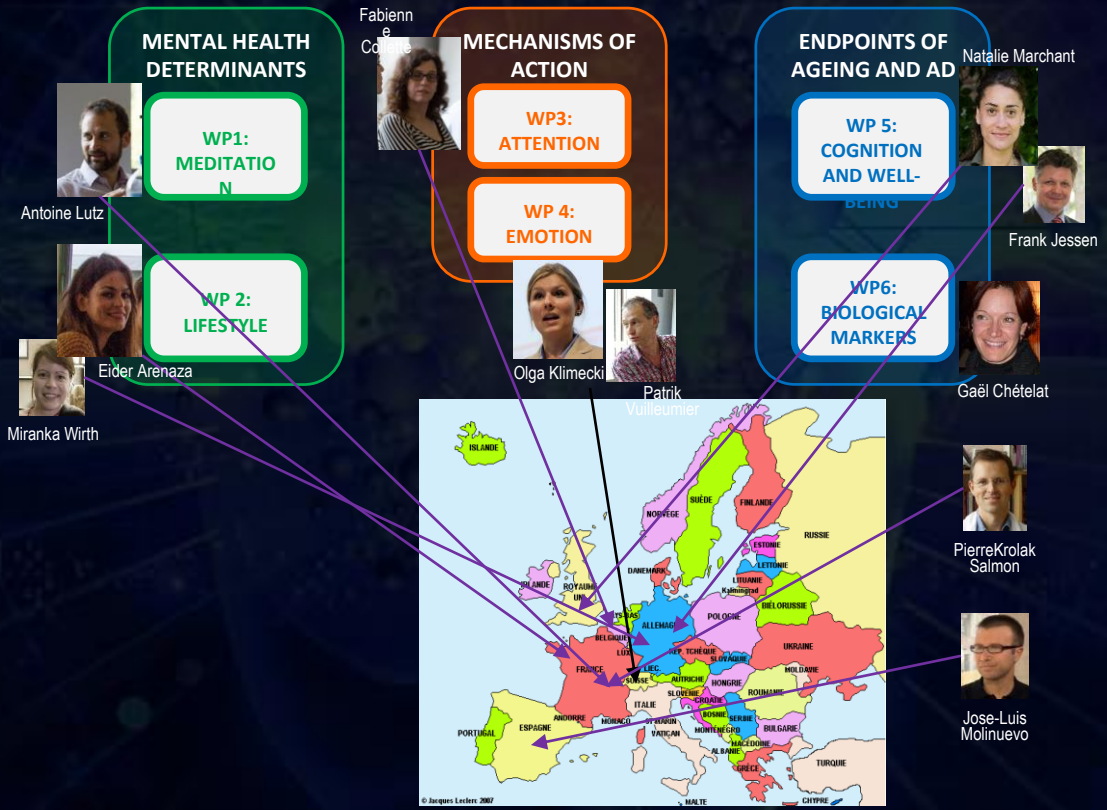
MEDITATE

NOTHING
UNUSUAL

ENGLISH
LEARNING



AGE-WELL


MENTAL HEALTH DETERMINANTS
WP1: MEDITATION
WP 2: LIFESTYLE
MECHANISMS OF ACTION
WP3: ATTENTION
WP 4: EMOTION
ENDPOINTS OF AGEING AND AD
WP 5: COGNITION AND WELL-BEING
WP6: BIOLOGICAL MARKERS
Antoine Lutz
Eider Arenaza
Miranka Wirth
Fabienne Conrod
Olga Klimecki
Patrik Vuilleumier
Natalie Marchant
Frank Jessen
Gaël Chételat
PierreKrolak Salmon
Jose-Luis Molinuevo
ISLANDE
NORVEGE
SUEDE
FINLANDE
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ESTONIE
LETTONIE
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CHYPRE
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“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

Inserm

Cyceron
PLATEFORME D'IMAGERIE BIOMÉDICALE

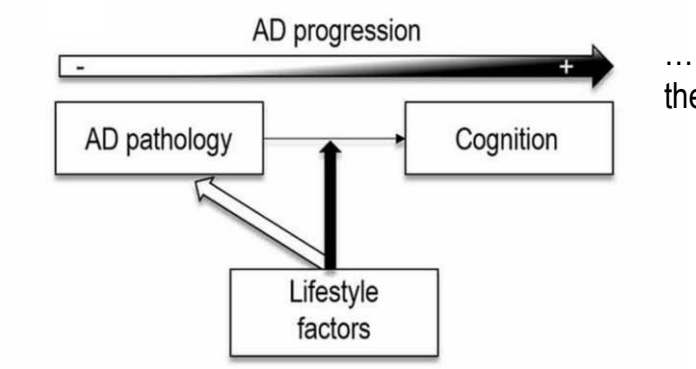
CHUCaen

École Pratique
des Hautes Études

UNICAEN
UNIVERSITÉ
CAEN
NORMANDIE

- 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)

Protective mechanisms early…

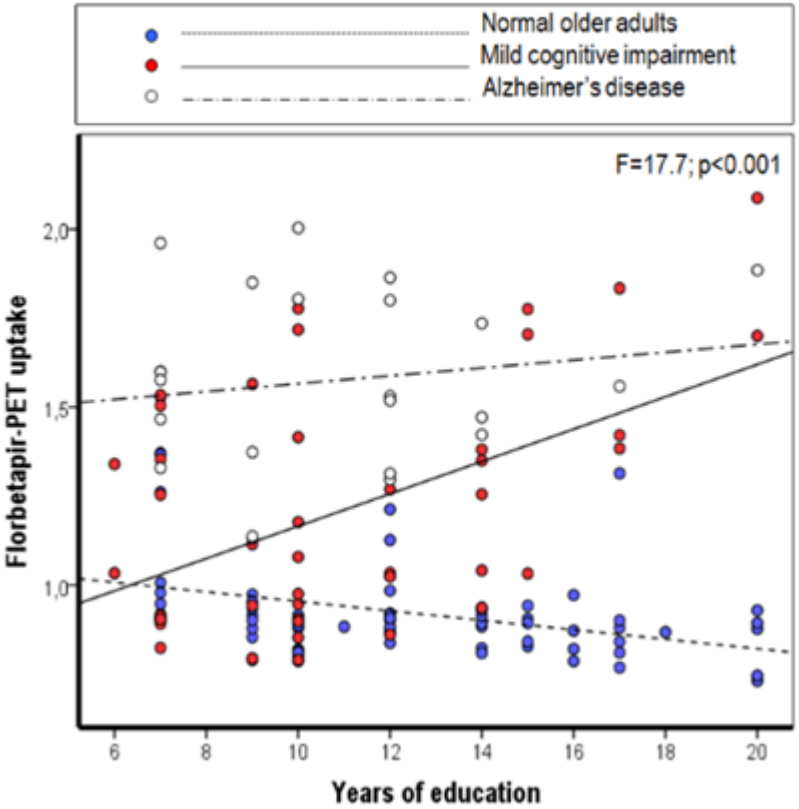


… compensatory mechanisms later as the disease progresses

- 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)

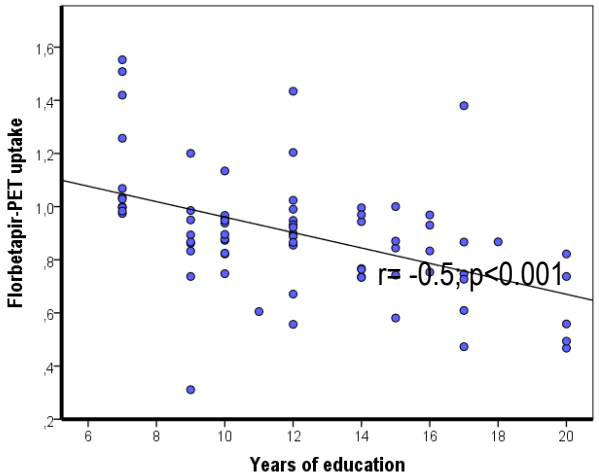
Group*education interaction on Florbetapir-PET uptake



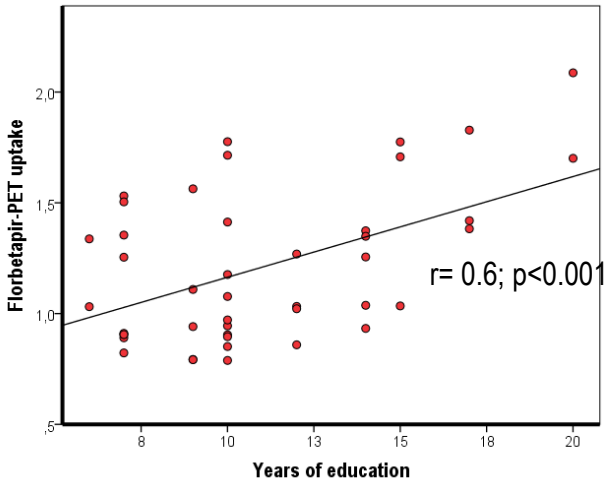
FDR corrected p<0.05, adjusted by age, sex and MMSE*group

Association between education and Florbetapir-PET uptake within each group

Cognitively normal older adults (orbitofrontal lobe)



Mild cognitive impairment (frontal,temporal and parietal áreas)



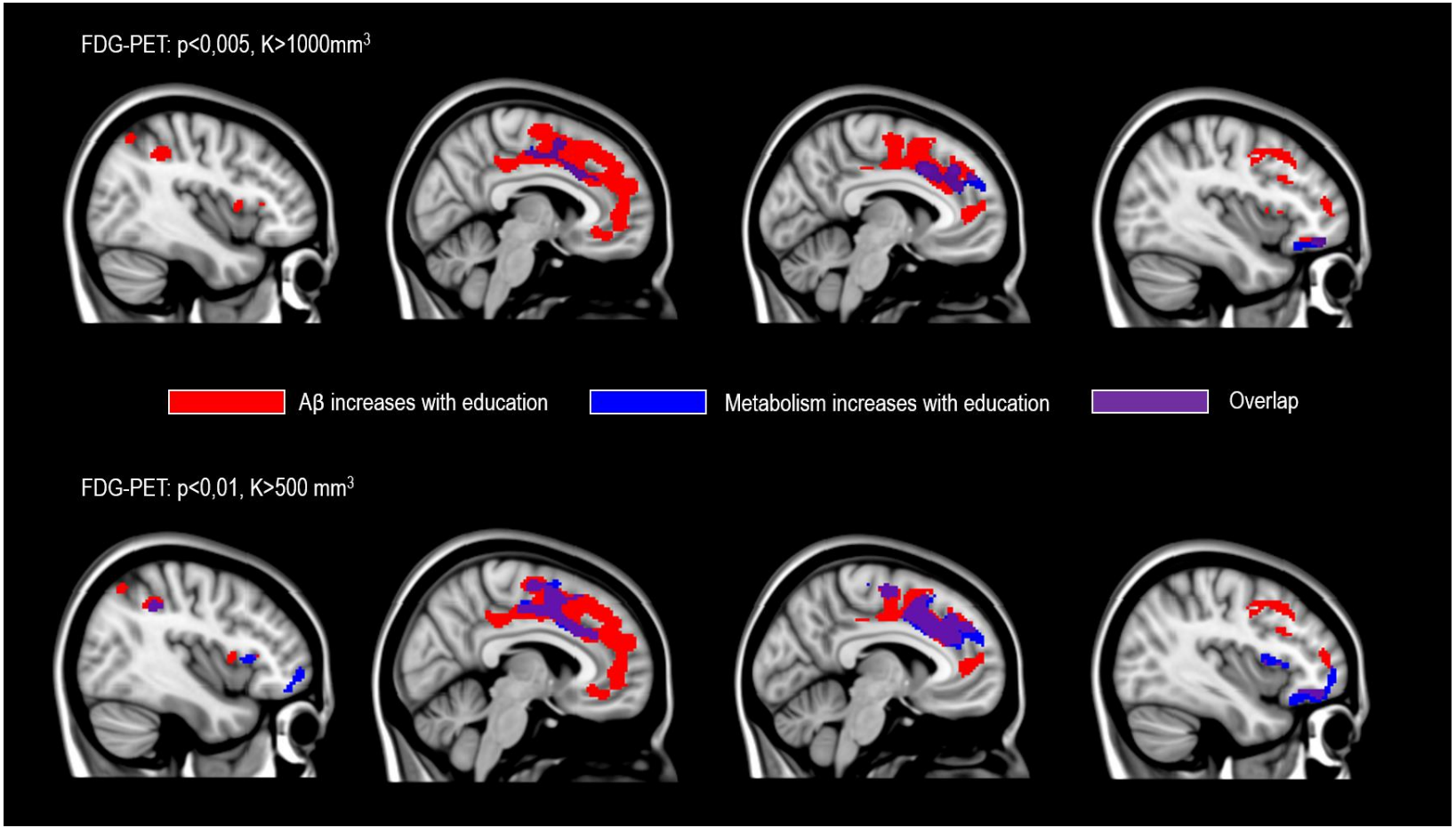
Alzheimer's disease

-

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

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PIA-meeting, July 23, 2016, Toronto

Amsterdam Neuroscience

VUmc VU University Alzheimer Center Amsterdam

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 regrssion

(age, sex, scanner-type)

- Educatio - Intracranial volum - gray matter volum - nuisance variables : Cognitior

Amsterdam Neuroscience

VUmc VU University Alzheimer Center Amsterdam

Effects education and intracranial volume

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

No dementia		
	Education	***Intracranial volume***
Memory	.03	.12
Attention	**.39***	.06
Executive	**.46***	**.18***
Language	.13	-.03
Visuospatial	.08	.14
MMSE	**.32***	.16
Dementia		
	Education	***Intracranial volume***
Memory	.08	.10
Attention	**.21***	**.14***
Executive	**.26***	**.15***
Language	.06	.05
Visuospatial	**.14***	**.13***
MMSE	**.25***	**.15***

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

Effects education and ICV

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

No dementia		
	Education	**Intracranial volume**
Memory		
Attention		
Executive		
Language		
Visuospatial		
MMSE		
Dementia		
	Education	**Intracranial volume**
Memory		
Attention		
Executive		
Language		
Visuospatial		
MMSE		

Effects education and ICV

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

No dementia				
	Education		**Intracranial volume**	
	Low ICV	*High ICV*	*Low Education*	*High Education*
Memory				
Attention				
Executive				
Language				
Visuospatial				
MMSE				

Dementia				
	Education		**Intracranial volume**	
	Low ICV	*High ICV*	*Low Education*	*High Education*
Memory				
Attention				
Executive				
Language				
Visuospatial				
MMSE				

Effects education and ICV

- **Independent positive effects**
- Effect sizes **education greater** in no dementia vs dementia
- Effect sizes **intracranial volume similar** between groups
- Effect intracranial volume **only for** patients with **low education**
- Effect education **only for** patients with **low intracranial volume**

No dementia				
	Education		**Intracranial volume**	
	Low ICV	*High ICV*	*Low Education*	*High Education*
Memory	-.04	.08	.09	.14
Attention	**.48***	**.26***	.09	.14
Executive	**.50***	**.41***	**.34***	.17
Language	.16	.08	-.05	.04
Visuospatial	.02	.14	.13	.18
MMSE	**.26***	**.39***	.20	.18
Dementia				
	Education		**Intracranial volume**	
	Low ICV	*High ICV*	*Low Education*	*High Education*
Memory	.12	.17	.12	.05
Attention	**.20***	.06	**.22***	**.21***
Executive	**.25***	.06	**.26***	**.28***
Language	.09	-.01	.09	.03
				.13*
MMSE	**.25***	.06	**.32***	**.19***

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

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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*

VUmc Alzheimer Center

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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

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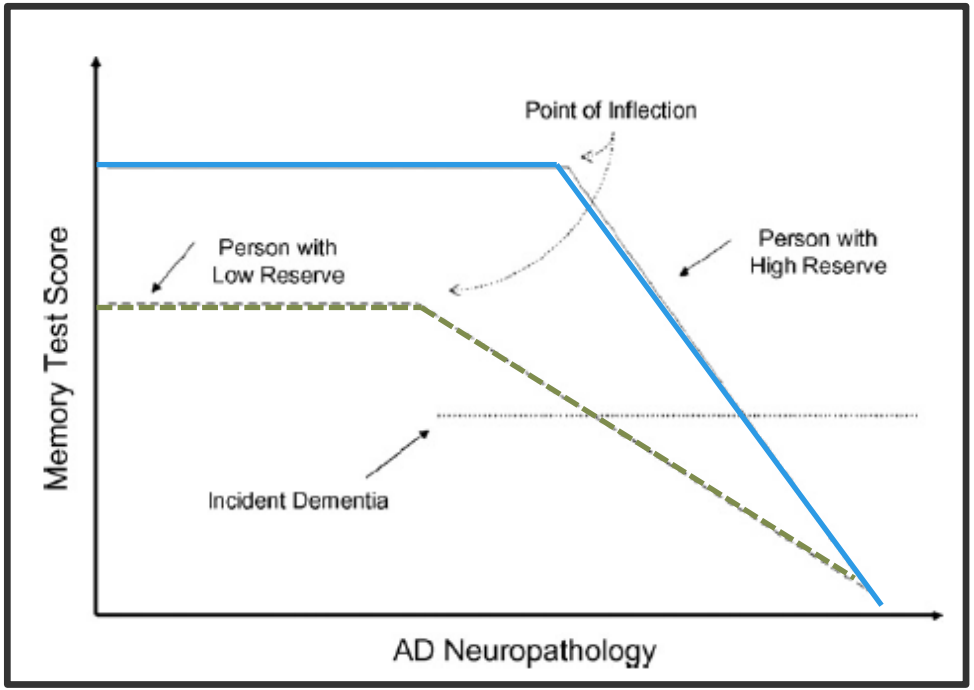
Cognitive Reserve (CR)

- Theoretical Concept



Previous work on CR, cognitive change

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

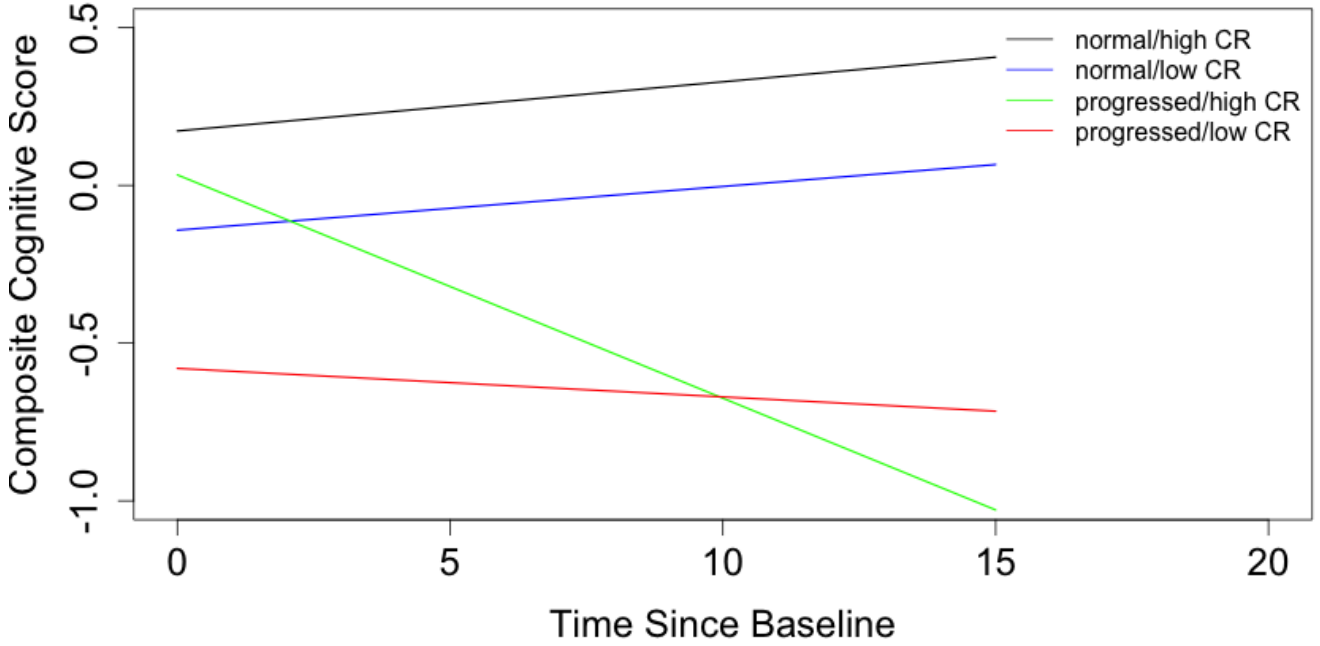
- Early Work:
  - Higher CR - reduced rates of cognitive decline
    - 12/14 studies, reviewed in Anstey and Christensen, 2000.
  - Analytical issues

- 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



Results: Impaired Subjects

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

BEFORE symptom onset

Variable	Estimate	p-value
Time	0.12	0.12
CR at baseline	**0.27**	**0.0006**
CR x time	**0.02**	**0.27**

AFTER symptom onset

t-value	p-value
0.10	0.44
0.68	**0.004**
-0.06	**0.003**

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)

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Biocard Research Team

- Marilyn Albert
- Ola Selnes
- Corinne Pettigrew
- Michael Miller
- Richard O'Brien
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- Scott Rudow

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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 *APOE*4-related amyloid deposition & cortical thinning

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University of Wisconsin School of Medicine and Public Health

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Objectives

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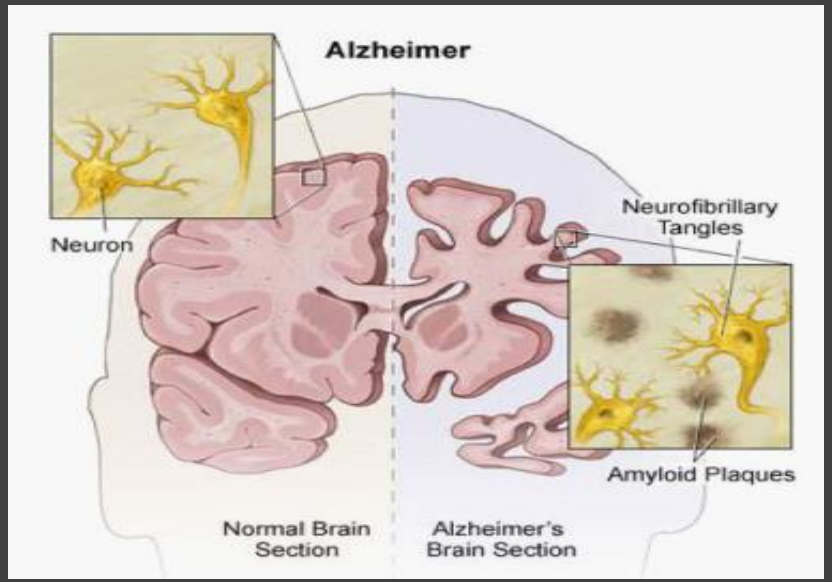
Examine whether KL-VS status modifies the association between *APOE4* and amyloid burden or cortical thickness in cognitively-normal individuals with risk factors for AD



Methods

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DNA Extraction & Genotyping

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

CSF Sampling

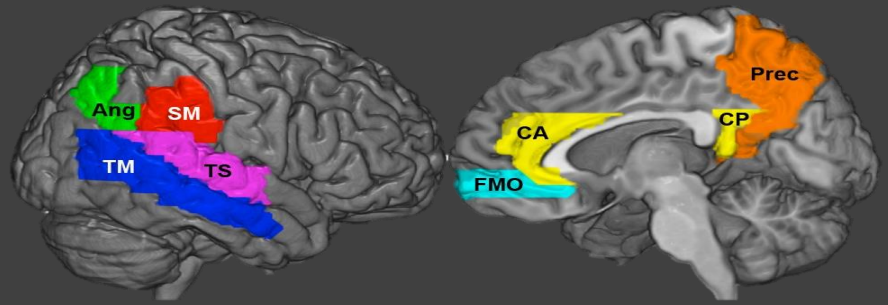
- Lumbar puncture after 12-hour fast
- Samples assayed for amyloid-β 42 (Aβ42)

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 know 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

FMO = frontal medial orbital gyrus CA = anterior cingulate
CP = posterior cingulate
Prec = precuneus

Statistics

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Linear Regressions (SPSS)

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

Characteristic	Value
Female, %	68.9
Age, years	61.39 (6.52)
Family history positive, %	69.9
Education, years	16.10 (2.42)
Mini-Mental State Exam	29.39 (.86)
APOE4 positive, %	41.1
KL-VS heterozygote, %	26.5

Results

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*APOE4*KLOTHO* on amyloid burden

Amyloid measure	KL-VS non-carrier analyses			KL-VS heterozygote analyses		
	β(SE)	t statistic	p value	β(SE)	t statistic	p value
CSF Aβ42	-162.67 (31.97)	-5.09	<.001	-52.44 (50.95)	-1.03	.308
PiB Composite	.10 (.03)	3.77	<.001	.06 (.06)	.92	.363
PiB Angular Gyrus	.10 (.03)	3.47	.001	.04 (.06)	.62	.541
PiB Anterior Cingulate	.14 (.04)	4.06	<.001	.09 (.08)	1.19	.243
PiB Posterior Cingulate	.10 (.03)	3.12	.002	.06 (.06)	1.05	.300
PiB Medial Orbitofrontal Cortex	.13 (.03)	3.83	<.001	.07 (.07)	1.07	.291
PiB Precuneus	.12 (.03)	3.79	<.001	.07 (.07)	.99	.327
PiB Supramarginal Gyrus	.07 (.02)	3.03	.003	.04 (.06)	.77	.448
PiB Middle Temporal Gyrus	.08 (.02)	3.59	<.001	.03 (.05)	.62	.541
PiB Superior Temporal Gyrus	.07 (.02)	3.29	.001	.04 (.05)	.66	.512

Statistics

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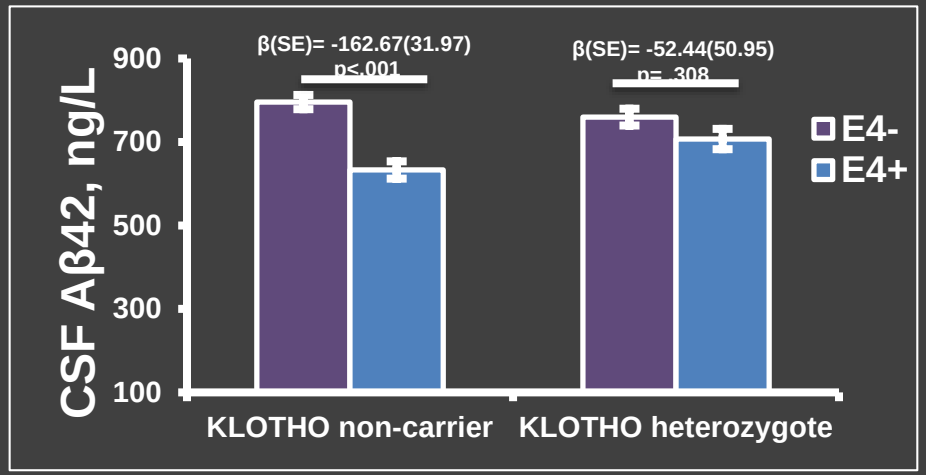
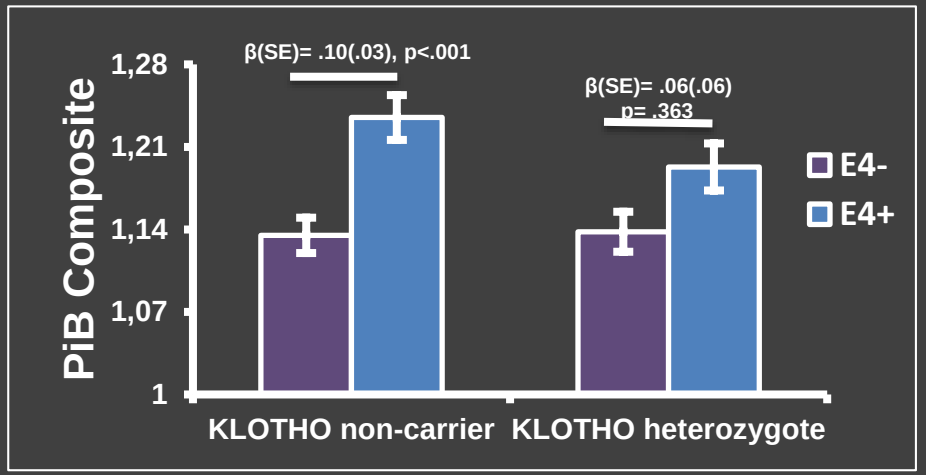
*APOE4*KLOTHO* on amyloid burden





Results

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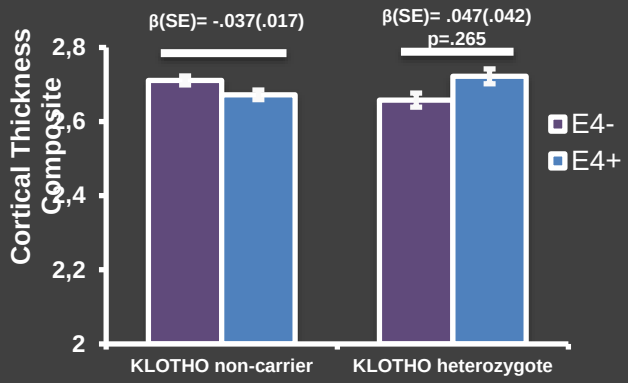
*APOE4*KLOTHO* on cortical thickness

Cortical thickness measure	KL-VS non-carrier analyses			KL-VS heterozygote analyses		
	β(SE)	t statistic	p value	β(SE)	t statistic	p value
Composite	-.037 (.017)	-2.125	.036	.047 (.042)	1.135	.265
Entorhinal	-.067 (.047)	-1.440	.152	.062 (.077)	.806	.426
Fusiform gyrus	-.022 (.021)	-1.039	.301	.038 (.049)	.773	.445
Inferior parietal	-.039 (.017)	-2.290	.024	.077 (.044)	1.757	.089
Isthmus cingulate	.025 (.030)	.817	.415	.007 (.075)	.098	.923
Parahippocampal	-.029 (.037)	-.796	.428	.080 (.084)	.951	.349
Posterior cingulate	-.051 (.023)	-2.179	.031	.039 (.060)	.656	.516
Precuneus	-.054 (.019)	-2.909	.004	.019 (.038)	.517	.609
Supramarginal gyrus	-.054 (.019)	-2.843	.005	.056 (.060)	.938	.355



Conclusions

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- *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

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NIH R01 AG021155 (PREDICT, PI: S. Johnson)
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Fitness modifies the association between a polygenic risk score and cerebrospinal fluid biomarkers

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Thank you WRAP study participants!

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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

CRF = Male(2.77) – Age(0.10) – BMI(0.17) – RHR(0.03) + 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**

$$PRS_i = \sum_{n=l}^{k} \ln(OR_n) * C_n$$

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

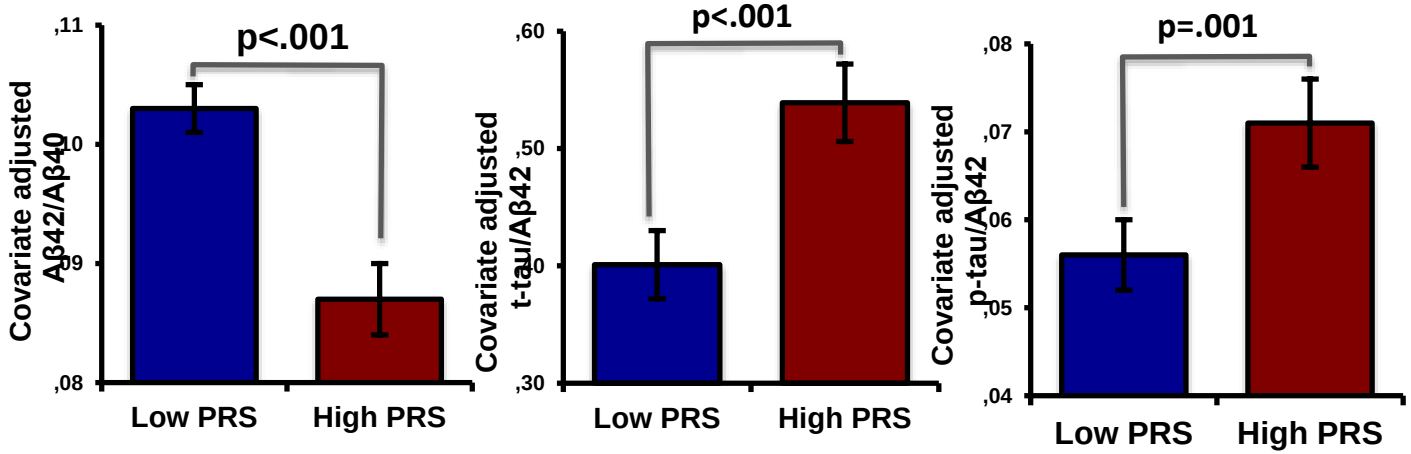
Background Characteristics

Characteristic	Value
Age at CSF sampling, years	61.2 (6.0)
Education, years	16.3 (2.2)
Female, n (%)	64 (67.4)
FH positive, n (%)	71 (74.7)
Body mass index, kg/m^2	28.9 (5.6)
Resting heart rate, beats/min	64.1 (9.1)
Amount of moderate exercise, min/week	52.3 (70.8)
Total cholesterol, mg/dL	197.7 (35.7)
HDL cholesterol, mg/dL	59.0 (16.1)
Mini-Mental State Examination	29.3 (0.8)

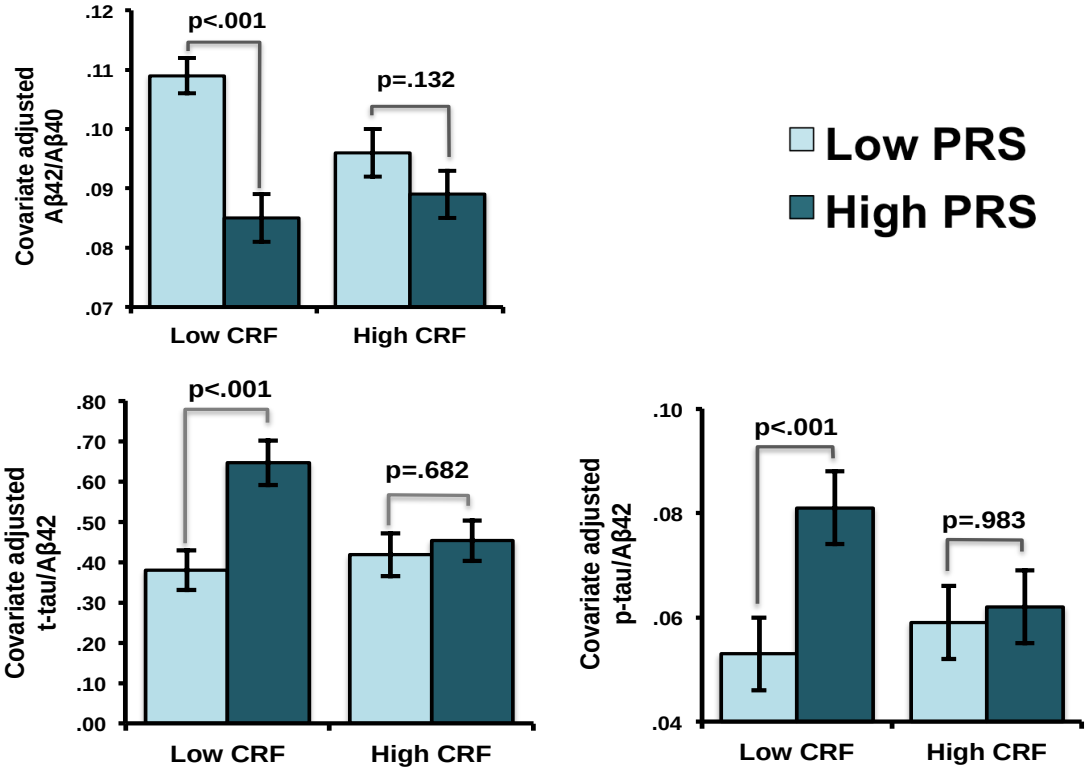
Characteristic	Value
APOE4 (rs429358, rs7412), n (%)	
0 ε4 alleles	62 (65.3)
1 ε4 alleles	31 (32.6)
2 ε4 alleles	2 (2.1)
ABCA7 (rs4147929), n (%)	
G/G	62 (65.3)
G/A*	30 (31.6)
A/A	3 (3.2)
CLU (rs9331896), n (%)	
C/C	14 (14.7)
T*/C	36 (37.9)
T/T	45 (47.4)

* Asterisk indicates risk allele

Association between the polygenic risk score and CSF biomarkers of AD



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

Washington University in St. Louis
School of Medicine

Knight ADRC
Alzheimer's Disease Research Center
Washington University St. Louis

Question/Clarification - Messa...

File | Message

Follow up.

From: Adam Ingber <ingbera@ByramHills.org> Sent: Mon 4/9/2012 1:40 PM

To: cathyr@wus

Cc: Stephanie G

Subject: Question/C

Dear Dr. Roe,

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Click on a photo to see

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

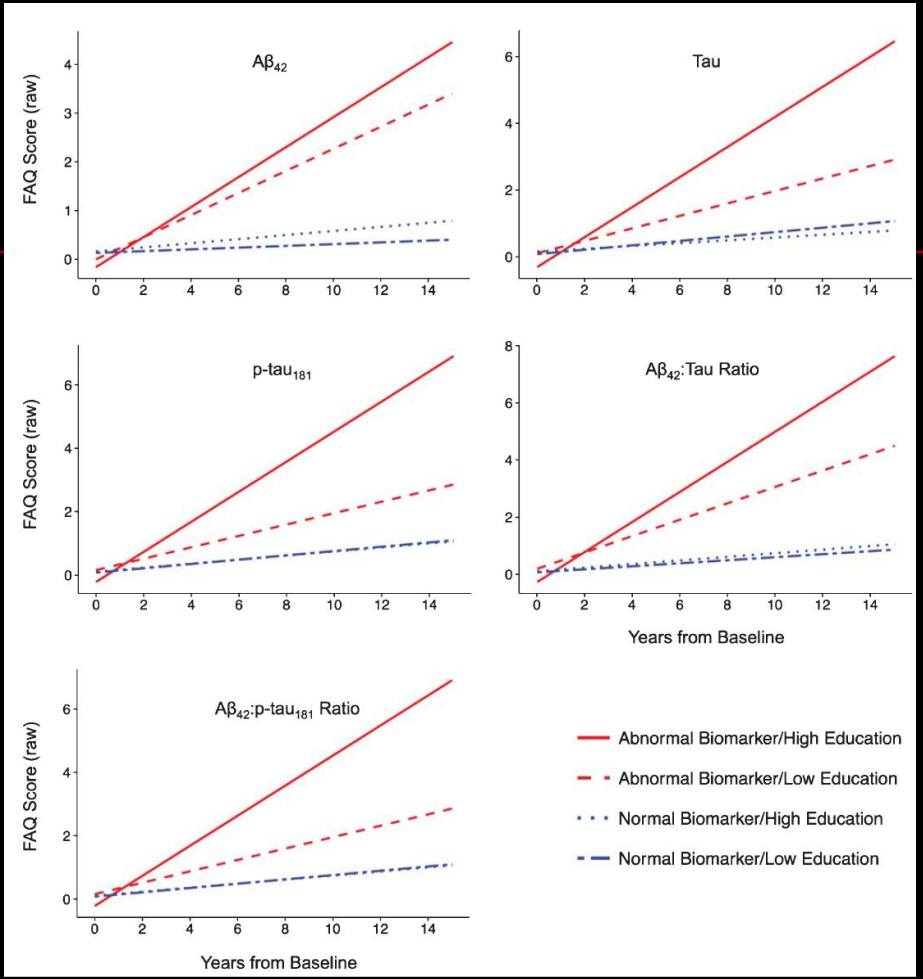
Methods

- 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

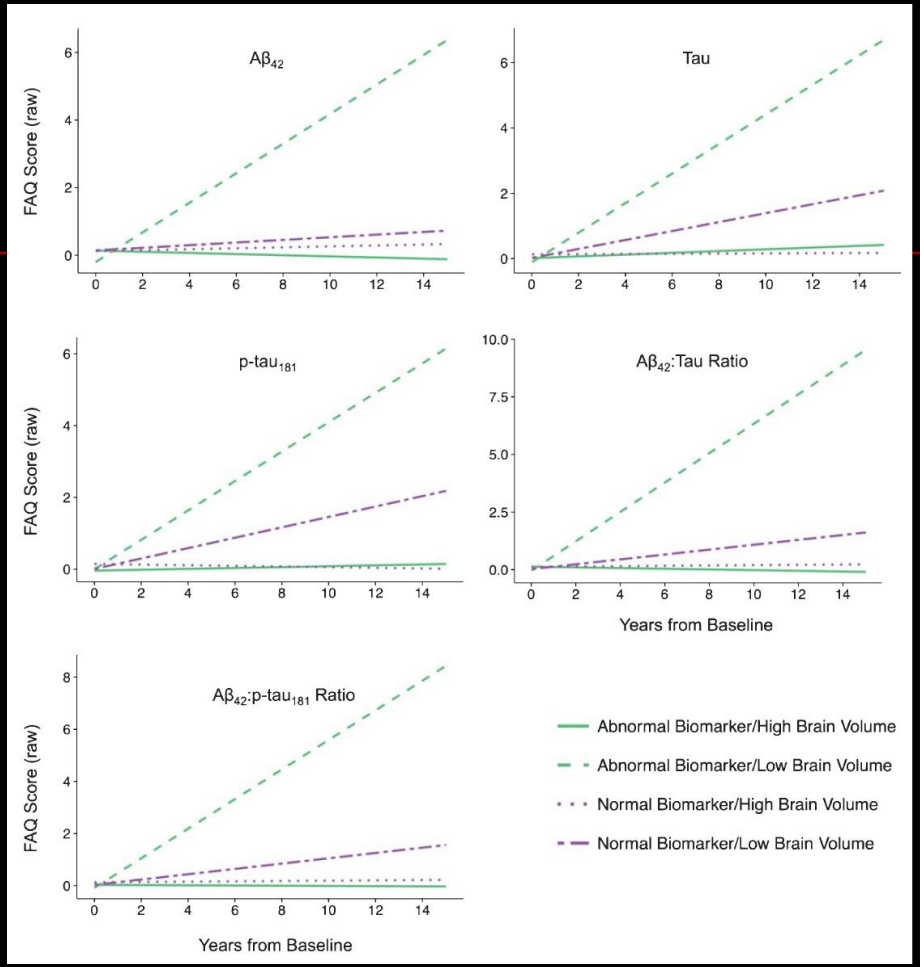
- Dichotomization
  - Education: Low (≤16y) vs. High (>16y)
  - Brain volume: Low vs. High using median split
  - CSF biomarker values: For each, Normal vs. Abnormal, based on cutoffs used previously
- Creation of four-level variables
  - Biomarkers ($A\beta_{42}$, tau, $ptau_{181}$, tau/$A\beta_{42}$, and $ptau_{181}/A\beta_{42}$) X education
  - Biomarkers ($A\beta_{42}$, tau, $ptau_{181}$, tau/$A\beta_{42}$, and $ptau_{181}/A\beta_{42}$) 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 sxs with time
  - Sometimes (approx ½) Normal CSF/Low BV more rapid sxs ↑ 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

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Cerebrospinal Fluid Biomarkers and Reserve Variables as Predictors of Future "Non-Cognitive" Outcomes of Alzheimer's Disease

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Elizabeth A. Grant[b,l], David M. Holtzman[b,c,d,h], John C. Morris[b,d,g,i,j] and Catherine
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[k]*Department of Neurol*

Handling Associate Ed

Accepted 23 February 2016

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 [2-5] and other type of dementia independently of gender, years of education, socioeconomic status and immigration [6]

- 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 [11, 12]

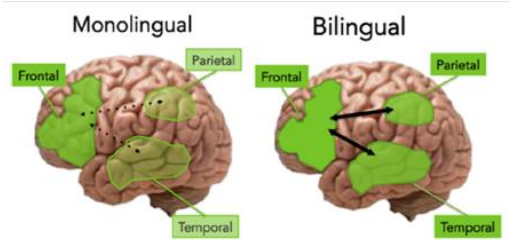
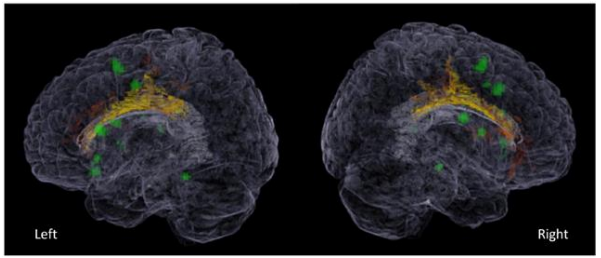


FIGURE 2 | An illustration of the monolingual vs. bilingual aging brain.



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)

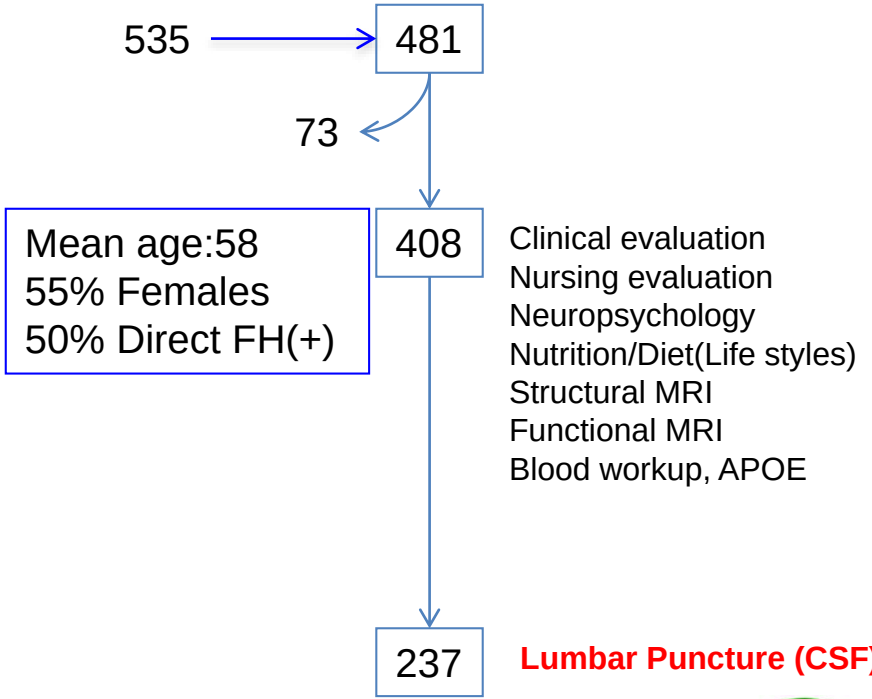
Fundación
CITA.alzhéimer
Fundazioa

The GAP study

Baseline visit (june 2011-Jan 2012)

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

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.



Subjects

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

Bilingualism study participants inclusion criteria:

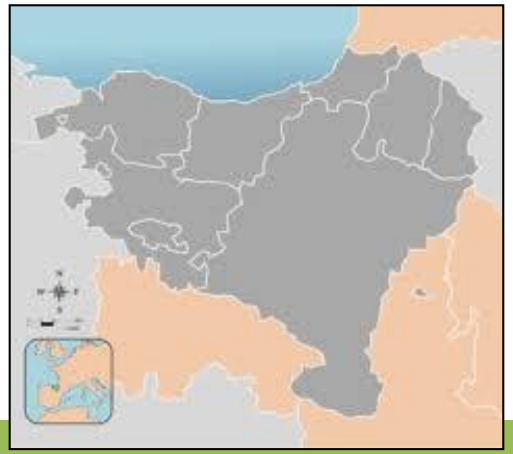
- Without cognitive impairment with a CDR=0 and MMSE ≥25

-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)

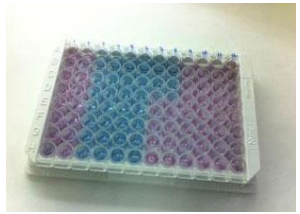


Table 1. Demographic and other characteristics

	Monolinguals n= 100	Late Bilinguals n=97	Early Bilinguals n= 81
Age, mean (SD)	57.82(6.42)	57.56(6.57)	56.82(6.48)
Gender (Male, %)	42(42%)	38(39.2%)	37(45.7%)
Years of education, mean (SD)	12.33(3.37)	14.35 (3.76) [a]	14.98(3.77) [a]
Occupation, No. (%)			
Unskilled workers	25(25%)	15(15.5%)	7(8.6%) [b]
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) [c]
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%) [d]

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

[a] $p<.001$ compared to monolinguals; [b] $p=.007$, 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

	Descriptive data			Generalized linear models			
	Monolinguals	Late Bilinguals	Early Bilinguals	Monolinguals vs. Late Bilinguals		Monolinguals vs. EarlyBilinguals	
	n= 100	n=97	n= 81	B	*p* [a]	B	*p* [a]
Digits backwards	6.01(1.72)	6.74(1.78)	7.31(2.09)	0.45	0.07	0.79	0.003[c]
TMT-A	37.05(16.27)	33.05(11.28)	33.72(11.78)	-1.79	0.32	-0.53	0.78
TMT-B	89.48(57.76)	70.4(27.95)	67.64(22.82)	-10.33	0.047 [b]	-10.20	0.06
Stroop WC	38.32(10.47)	42.81(10.82)	41.95(12.37)	2.34	0.09	0.49	0.73
Semantic VF	22.38(5.72)	24.32(5.96)	23.94(6.12)	1.14	0.15	0.30	0.71
Phonetic VF	16.5(5.03)	18.69(5.66)	17.98(4.27)	1.29	0.05	0.18	0.80
Boston Naming	54.7(3.84)	55.04(3.88)	54.56(3.95)	-0.40	0.41	-1.29	0.011[b]
15 Object Test	12.97(1.78)	12.92(1.67)	13.21(1.80)	-0.31	0.17	-0.17	0.45
JLO	23.65(4.27)	25.53(4.09)	26.01(3.88)	1.38	0.006 [b]	1.25	0.017[b]
ROCF Copy	31.39(4)	32.31(2.87)	32.42(2.73)	0.44	0.32	0.30	0.53
FCSRT Delayed Free	11.70(2.28)	11.86(2.18)	11.83(2.36)	-0.14	0.64	-0.26	0.42

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).

[a] 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.

[b] $p<.05$; [c] $p<.005$

Table 3. CSF biomarkers results comparison between monolinguals and early and late bilinguals

	Descriptives data			Generalized models			
	Monolinguals n= 59	Late Bilinguals n= 52	Early Bilinguals n= 55	Monolinguals vs. Late Bilinguals		Monolinguals vs. Early Bilinguals	
				B	*p* [a]	B	*p* [a]
Aβ1-42 pg/ml	853.39 (252.94)	846.03(239.62)	819.70 (176.94)	-46.25	.26	-60.38	.14
total-tau pg/ml	240.49 (104.29)	237.10(82.71)	198.18 (66.22)	0.23	.99	-35.15	.019[b]
p-tau pg/ml	45.49 (16.15)	45.69(13.25)	40.64 (11.64)	-0.60	.81	-3.88	.11
t-tau/ Aβ1-42 ratio	0.31(0.22)	0.31(0.18)	0.25(0.12)	0.02	.37	-0.03	.24
p-tau/ Aβ1-42 ratio	0.06(0.03)	0.06(0.03)	0.05(0.02)	0.006	.19	-0.002	.65
Pre-clinical AD CSF stage, No. (%)							
Normal	44(74.6%)	35(67.3%)	51(92.7%)	0.51	.27	-1.63	.02[b]
Stage 1	7(11.9%)	9(17.3%)	2(3.6%)				
Stage 2	4(6.8%)	1(1.9%)	1(1.8%)				
SNAP	4(6.8%)	7(13.5%)	1(1.8%)				

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

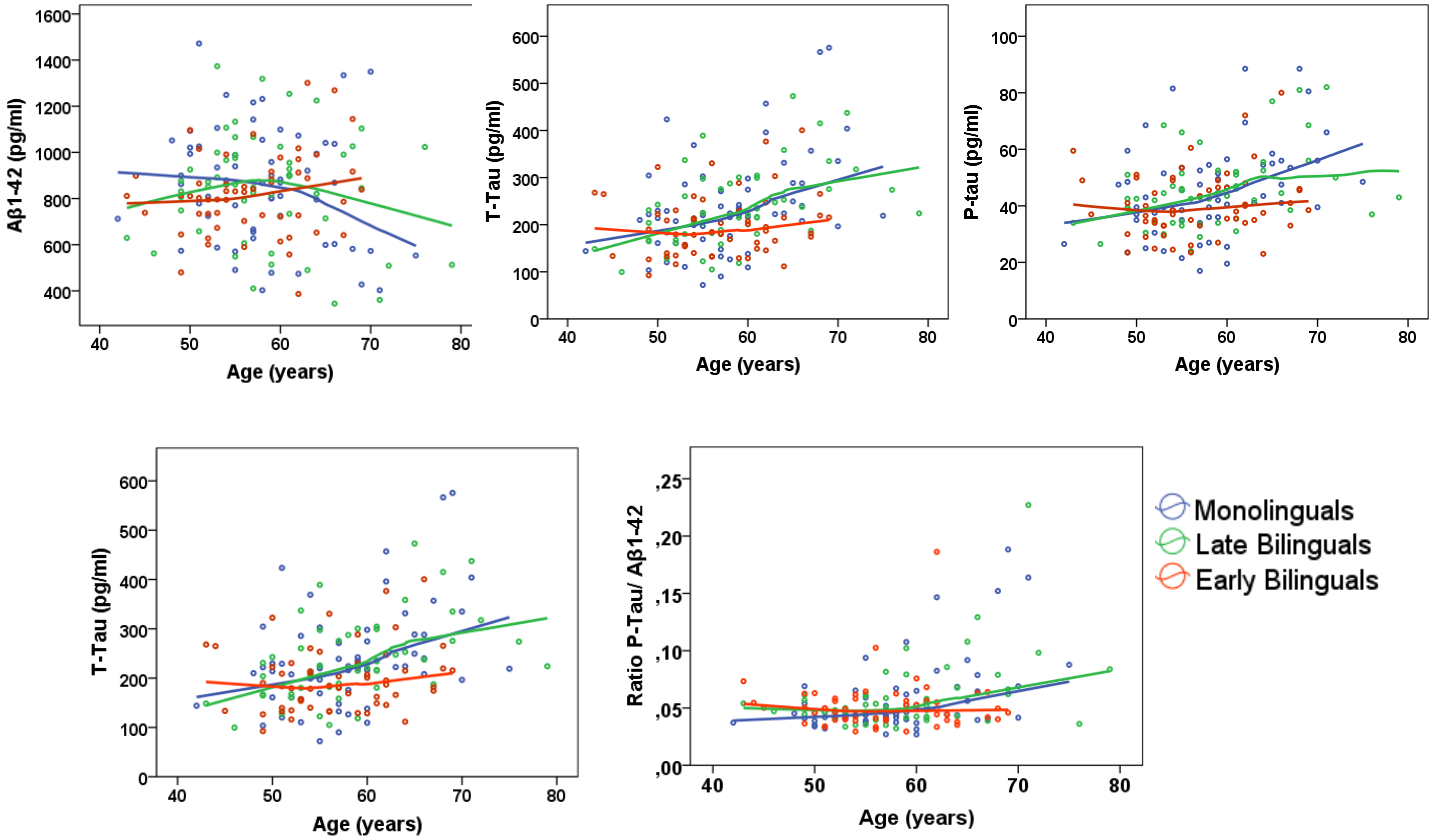
t-tau (B=15.25; *p*=.016)
p-tau (B=2.28; *p*=.03)
t-tau/$A\beta_{1-42}$ ratio (B=0.03; *p*<.001)
p-tau/$A\beta_{1-42}$ ratio (B=0.008; *p*<.001).

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

Table 4. Linear regression between age and CSF biomarkers

	Monolinguals		Late bilinguals		Early Bilinguals	
	B	*p*	B	*p*	B	*p*
$A\beta_{1-42}$ pg/ml	-7.08	.15	-3.28	0.47	5.75	.13
t-tau pg/ml	6.70	.001[a]	5.55	<.001[a]	1.88	.19
p-tau pg/ml	0.94	.002[a]	0.71	.003[a]	0.26	.29
t-tau/$A\beta_{1-42}$	0.01	<.001[a]	0.012	<.001[a]	0.002	.52
p-tau/$A\beta_{1-42}$	0.002	<.001[a]	0.002	.001[a]	<0.001	.73

Abbreviations: B= Beta coefficient
[a] p<.005


Aβ1-42 (pg/ml)
Age (years)
T-Tau (pg/ml)
Age (years)
P-tau (pg/ml)
Age (years)
T-Tau (pg/ml)
Age (years)
Ratio P-Tau/ Aβ1-42
Age (years)
Monolinguals
Late Bilinguals
Early Bilinguals

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

Gobierno Vasco / Gobierno de España / Diputación de Gipuzkoa
Kutxabank / Mecenazgo-Donaciones particulares / Ayudas de investigación

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