The challenge of preventing Alzheimer's disease: the BBRC experience

Dr. José Luis Molinuevo

Alzheimer Europe Foundation

barcelonaβeta
BRAIN RESEARCH CENTER

Disclosures

barcelonaβeta
BRAIN RESEARCH CENTER

José Luis Molinuevo has provided scientific advice, been data-monitoring board member or symposium chair/speaker receiving fees from: Novartis, Biogen, Roche Pharma, MSD, Genentech, Lundbeck, Lilly, Axovant, Merz, Boehringer Ingelheim, GE Healthcare, Roche Diagnostics, Biocross, IBL, Raman Health.

The research leading to these results has received support from “la Caixa” Banking Foundation (Alfa Project) and the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115736, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

Fundación Bancaria "la Caixa"

efpia

imi innovative medicines initiative

Index

barcelonaβeta
BRAIN RESEARCH CENTER

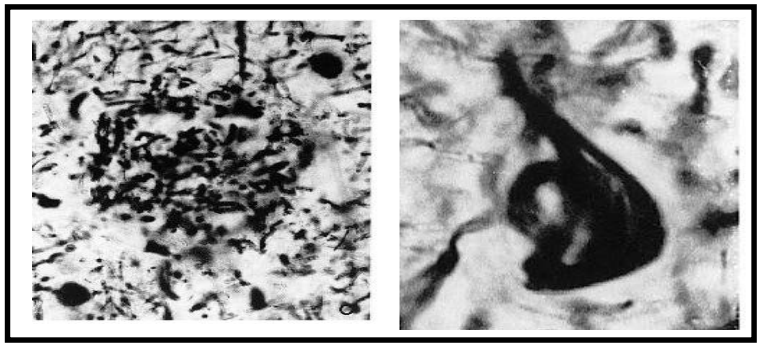
- The new conceptualization of AD: the rationale for prevention
- Research on risk factors on AD
- Prevention initiatives
- Addressing the challenges for preventing AD: BarcelonaBeta Brain Research Center experience

The starting point

barcelonaβeta
BRAIN RESEARCH CENTER

Clinic pathological dual diagnosis:[1]

- Definitive AD diagnosis:
  - Dementia + pathological lesions on postmortem exam
- Probable AD diagnosis
- Possible AD diagnosis



Dr Alzheimer's original publication (Bielchowsky's technique)

Current clinical AD diagnostic methods shows much variability among studies.

General impression that clinical diagnosis is accurate.

NINCDS-ADRDA CRITERIA are considered the "Gold Standard"[2]

AD, Alzheimer's disease, NINCDS-ADRDA, Mational Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; 1. McKhann G, et al. Neurology 1984;34:939–44; 2. Beach TG, et al. J Neuropathol Exp Neurol 2012;71(4):266–73.

Assessing the accuracy of the diagnosis

barcelonaβeta
BRAIN RESEARCH CENTER

Study performed on US-NACC data 2005–2010:

- N = 919 demented with neuropathological diagnosis
- Mean age: 79
- Gender: 368 women, 551 male
- Clinical diagnoses prob/poss AD: 70.5%
- Pathological diagnoses: AD in 67.2%

Non AD pathological diagnosis (clinical diagnosis AD): tauopathies (15), other FTLD (16), CVD (11), LBD (9), hippocampal sclerosis (9) Hallervorden-Spatz (2), amyloid angiopathy (2), limbic encephalities, no pathology

	No AD pathology	Yes AD pathology	
No probable AD (clinical)	213	180	NPV=54%
Probable AD (clinical)	88	438	PPV=83%
	Specificity = 70.8%	Sensitivity = 70.9%	

Pathological diagnosis:
moderate or frequent plaques AND Braak* IV–VI

*Braak IV-VI it is the needed pathological threshold to make the pathological diagnosis of AD
AD, Alzheimer's disease, NINCDS-ADRDA, Mational Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association;
1. Beach TG, et al. J Neuropathol Exp Neurol 2012;71(4):266–73; Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. Neurobiol Aging 1997;18:S1–S2

barcelonaβeta
BRAIN RESEARCH CENTER

Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

Bruno Dubois, Howard H Feldman, Claudia Jacova, Harald Hampel, José Luis Molinuevo, Kaj Blennow, Steven T DeKosky, Serge Gauthier, Dennis Selkoe, Randall Bateman, Stefano Cappa, Sebastian Crutch, Sebastiaan Engelborghs, Giovanni B Frisoni, Nick C Fox, Douglas Galasko, Marie-Odile Habert, Gregory A Jicha, Agneta Nordberg, Florence Pasquier, Gil Rabinovici, Philippe Robert, Christopher Rowe, Stephen Salloway, Marie Sarazin, Stéphane Epelbaum, Leonardo C de Souza, Bruno Vellas, Pieter J Visser, Lon Schneider, Yaakov Stern, Philip Scheltens, Jeffrey L Cummings

ELSEVIER

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

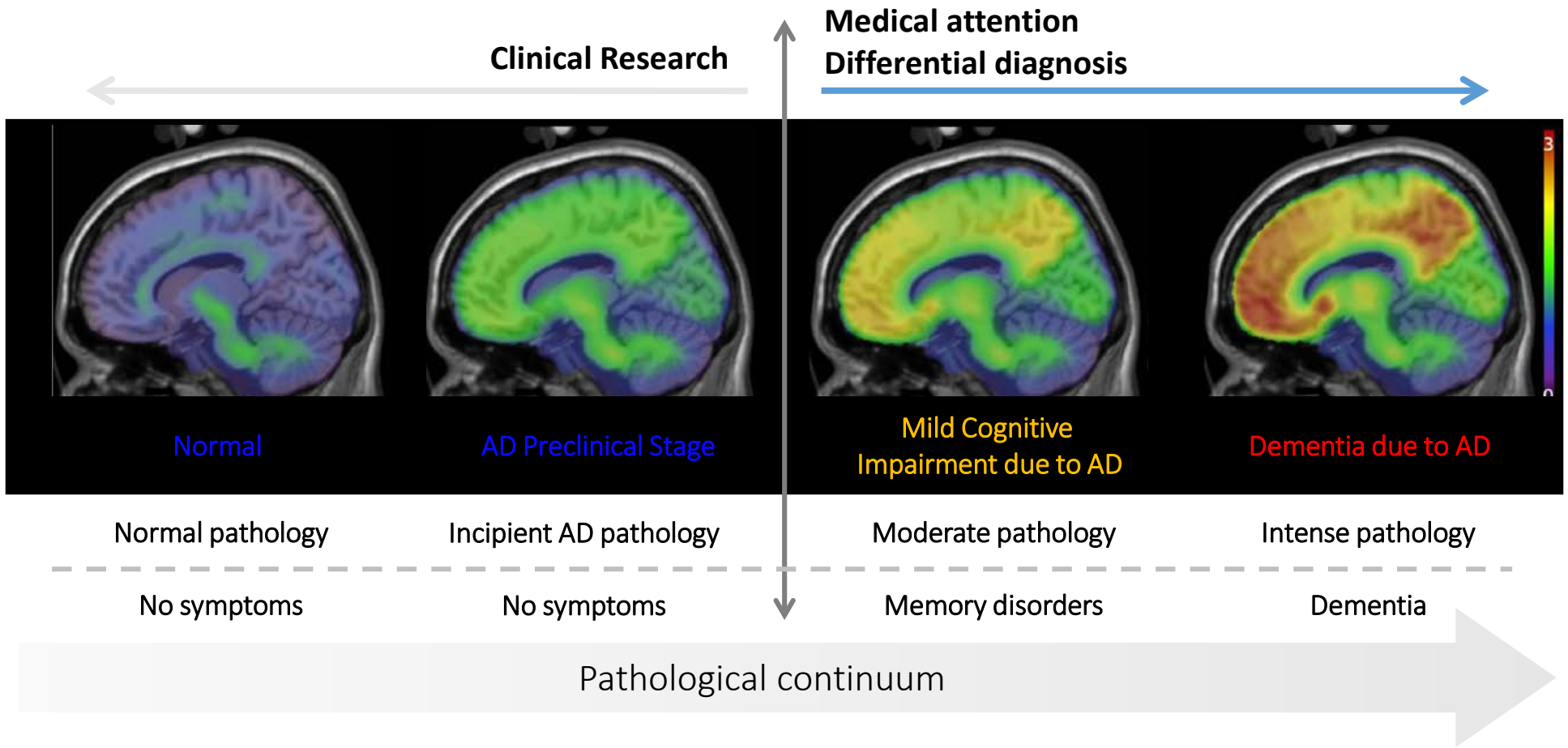
Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[†]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

- The diagnosis is not based on the clinical consequences of the disease (i.e.symptoms/signs)
- The definition of AD shifts **from a syndromic to a biological construct** and is based on presence of both biomarkers proxies of pathology (amyloid and tau).

barcelonaβeta
BRAIN RESEARCH CENTER

"Since a cure for dementia is not yet available, finding effective preventive strategies is essential for a sustainable society in an aging world"

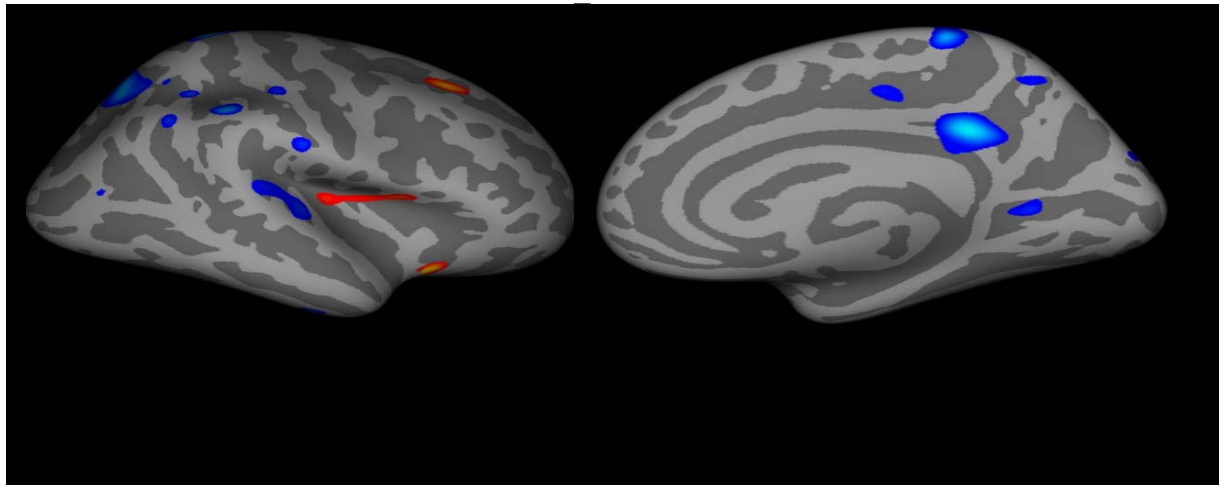


Mangialasche et al. Alzheimers Res Ther 2012; 4 (1): 6
Cummings J, Dubois B, Molinuevo JL, Scheltens P. IWG criteria for the diagnosis of Alzheimer disease Med Clin North Am;97:363-8.

ARCHIVAL REPORT

Cognitively Preserved Subjects with Transitional Cerebrospinal Fluid ß-Amyloid 1-42 Values Have Thicker Cortex in Alzheimer's Disease Vulnerable Areas

Juan Fortea, Roser Sala-Llonch, David Bartrés-Faz, Albert Lladó, Cristina Solé-Padullés, Beatriz Bosch, Anna Antonell, Jaume Olives, Raquel Sanchez-Valle, Jose L. Molinuevo, and Lorena Rami



Increased cortical thickness in AD areas in subjects with ß-amyloid levels in the middle tertiles (transitional levels) respect those with normal levels

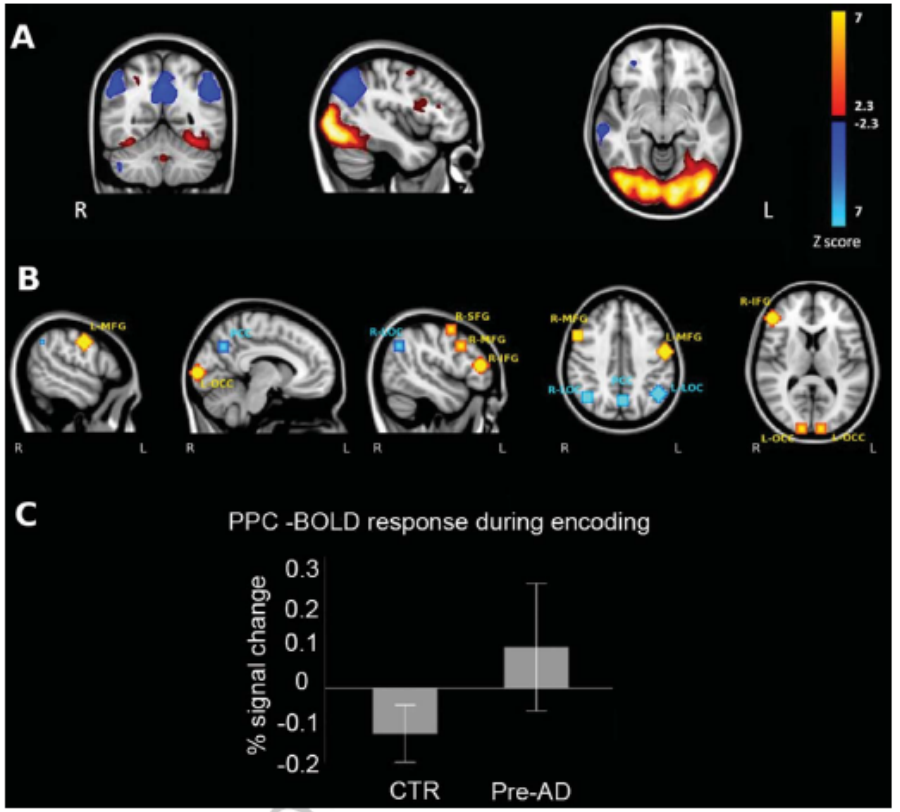
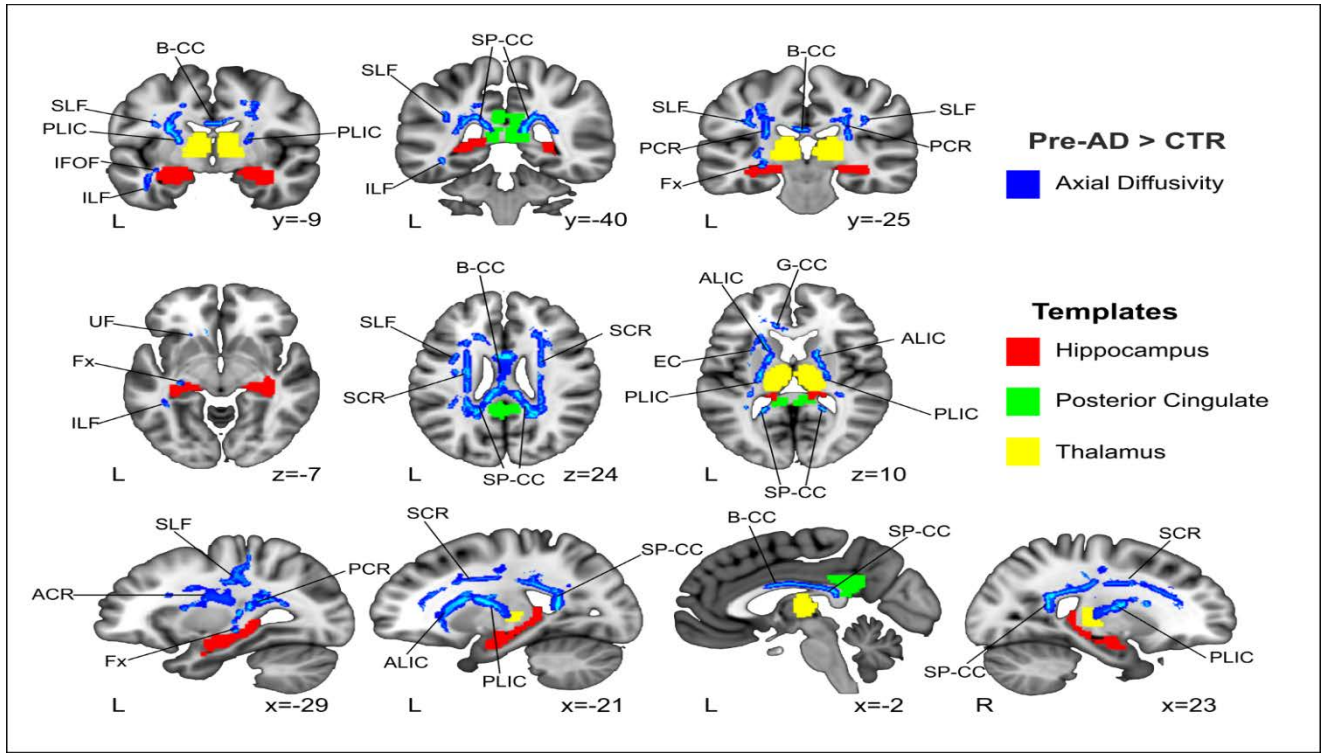
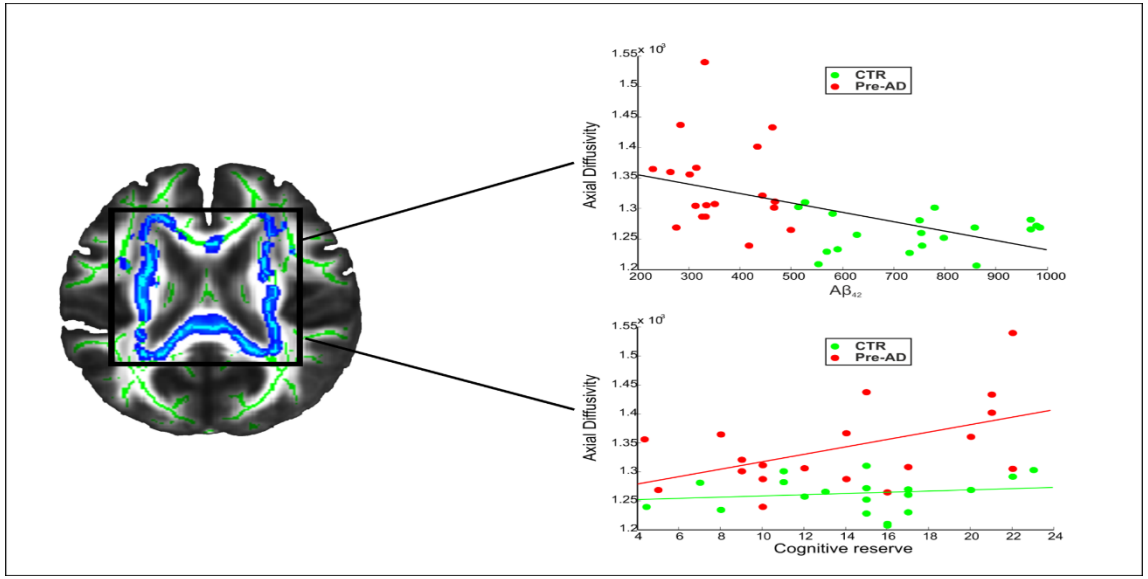


Fig. 1. A) Spatial map of the main independent component associated with the encoding condition. Positive (activated) areas are shown in red-yellow colors and negative (deactivated areas) in blue. B) Spherical ROIs created from the map above. C) Boxplot showing the mean activation (averaged BOLD response) in the precuneus and posterior cingulate cortex (PCC) for the two groups during encoding and (D) scatter plot of the same score and the performance in the task.

Preclinical AD exhibit increased activation of precuneus





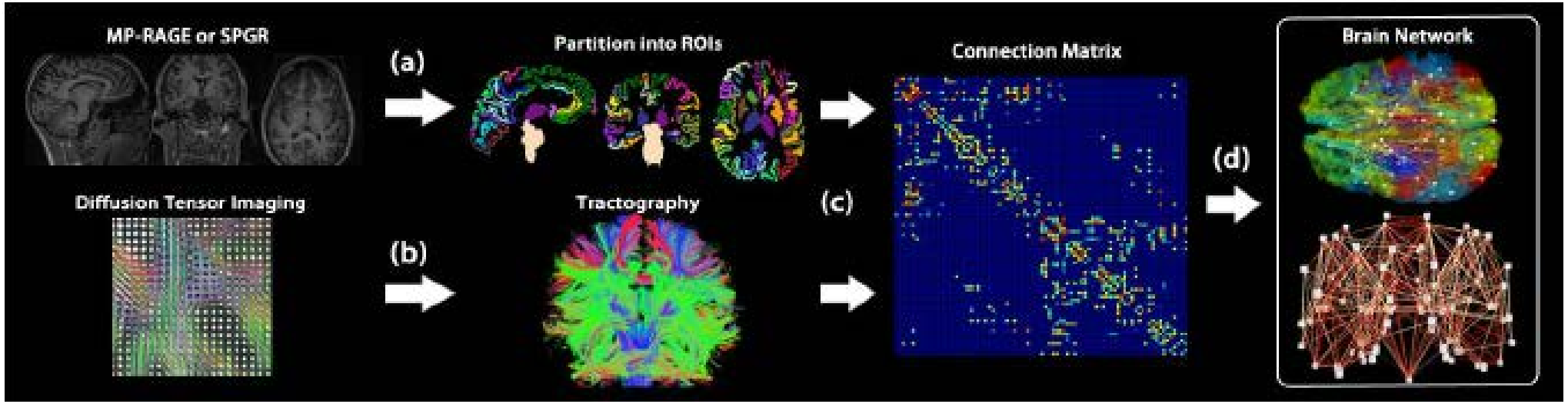
Tracts showing increased AxD in Pre-AD subjects compared with controls (blue)

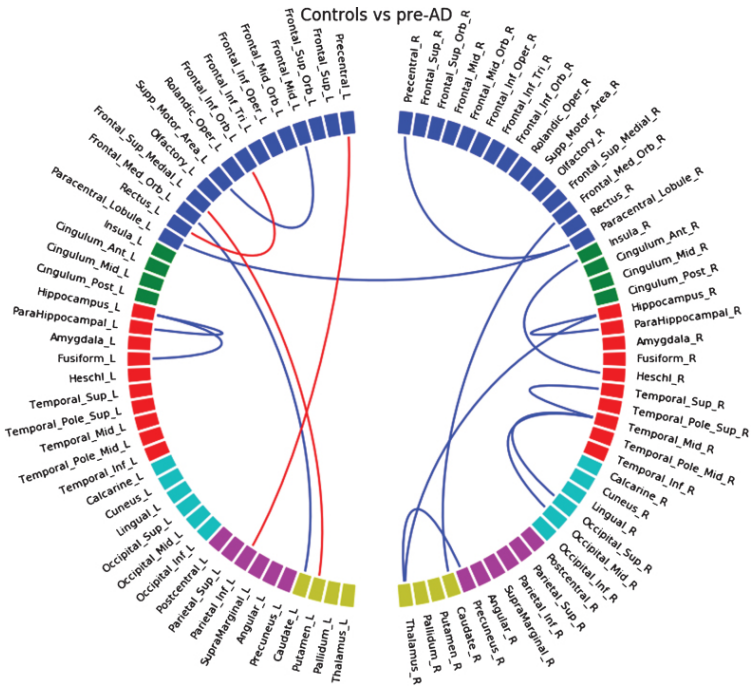
Relationship between the areas showing increased AxD and the level of $A\beta_{42}$ on CSF (r=-0.52, p<0.0001) and cognitive reserve (Pre-AD group r=0.57, p<0.012).

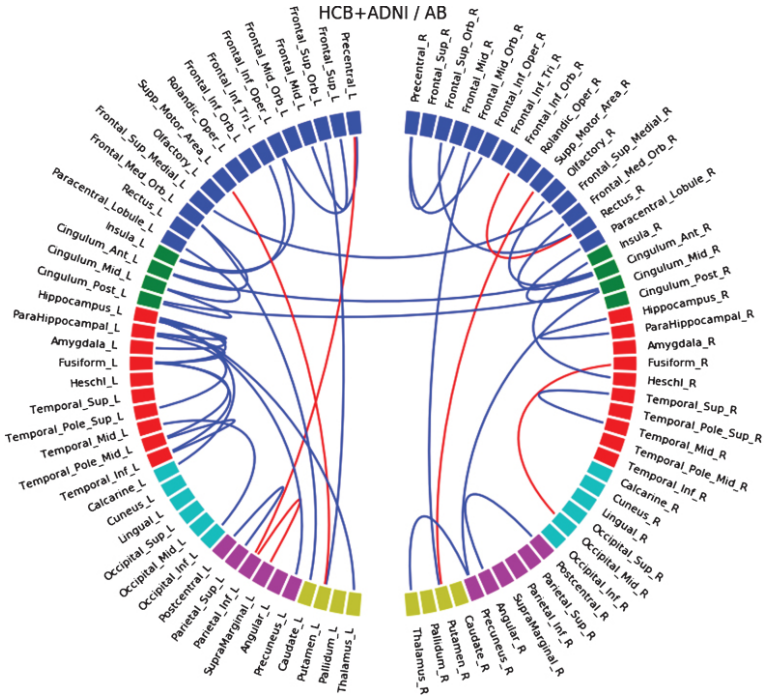
Molinuevo et al. Neurobiol Aging 2014

Structural connectivity alterations in PRE-AD

barcelonaβeta
BRAIN RESEARCH CENTER



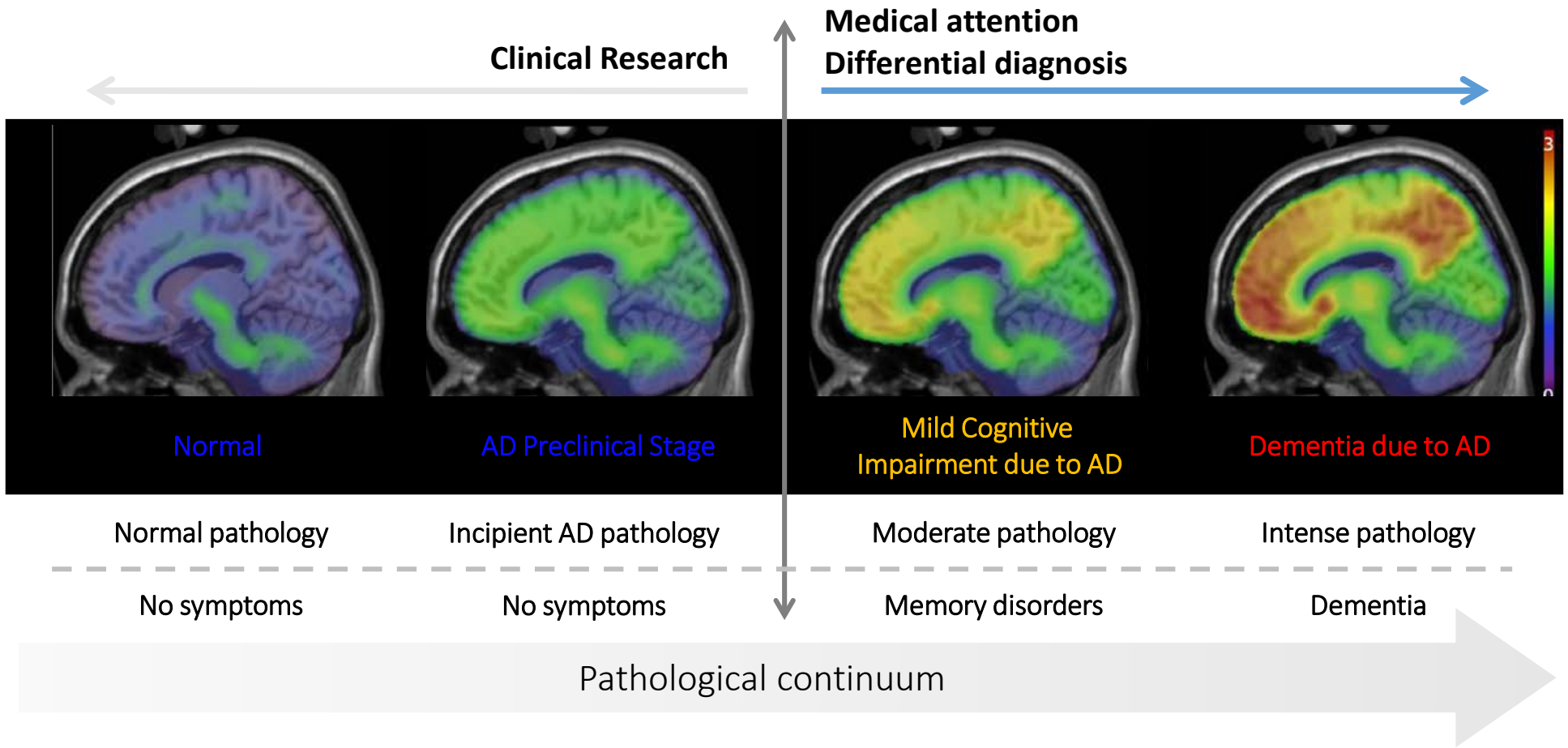




Tucholka et al. JAD. 2018

barcelonaβeta
BRAIN RESEARCH CENTER

"Since a cure for dementia is not yet available, finding effective preventive strategies is essential for a sustainable society in an aging world"



Mangialasche et al. Alzheimers Res Ther 2012; 4 (1): 6
Cummings J, Dubois B, Molinuevo JL, Scheltens P. IWG criteria for the diagnosis of Alzheimer disease Med Clin North Am;97:363-8.

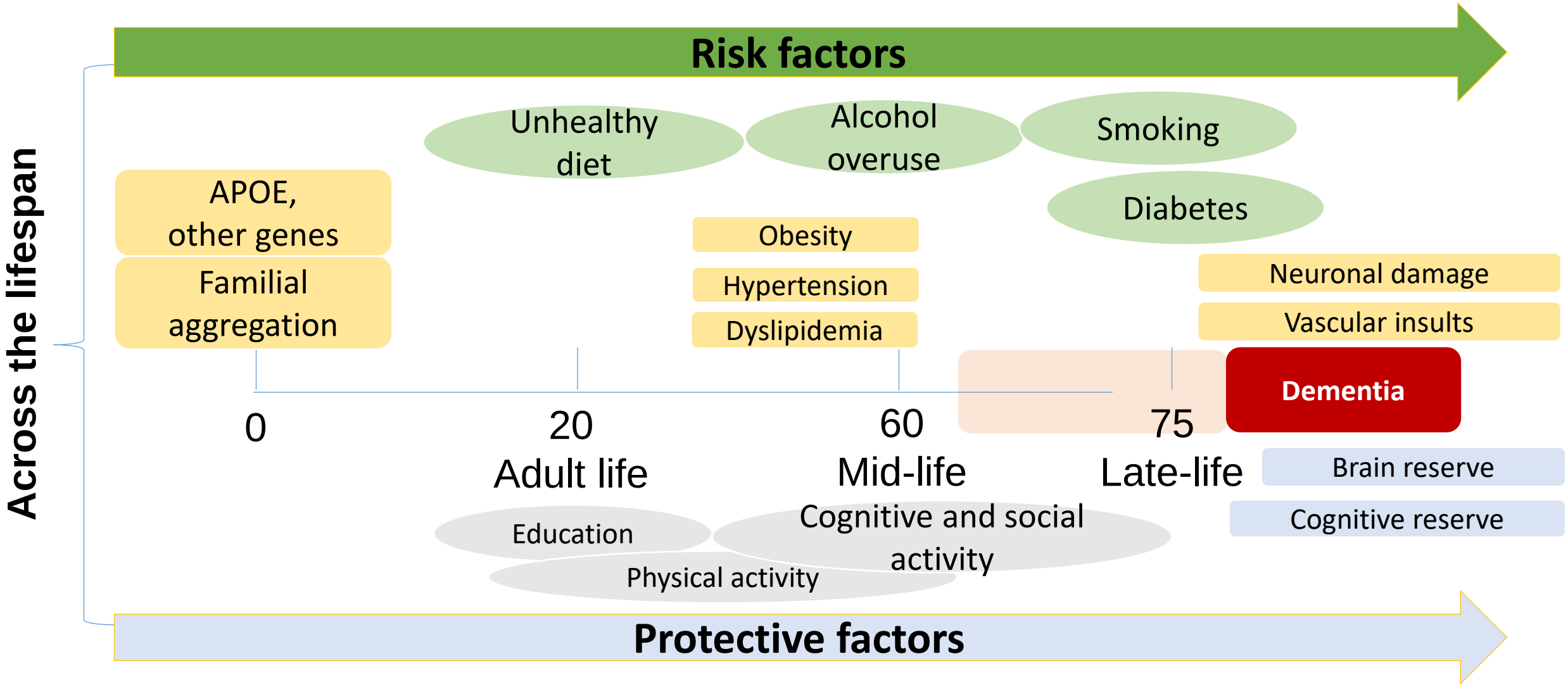


Figure adapted from Sindi S , et al. F1000Prime Rep. 2015;7:50.

WILEY

RESEARCH ARTICLE

Episodic memory and executive functions in cognitively healthy individuals display distinct neuroanatomical correlates which are differentially modulated by aging

Raffaele Cacciaglia[1] | José Luis Molinuevo[1,2,3] | Gonzalo Sánchez-Benavides[1] | Carles Falcón[1,4] | Nina Gramunt[1,3] | Anna Brugulat-Serrat[1] | Oriol Grau[1] | Juan Domingo Gispert[1,4,5] | for the ALFA Study

HUMAN BRAIN MAPPING

MAIN OBJECTIVE

To explore the cerebral morphological properties underlying episodic memory (EM) and executive functions in cognitively healthy individuals.

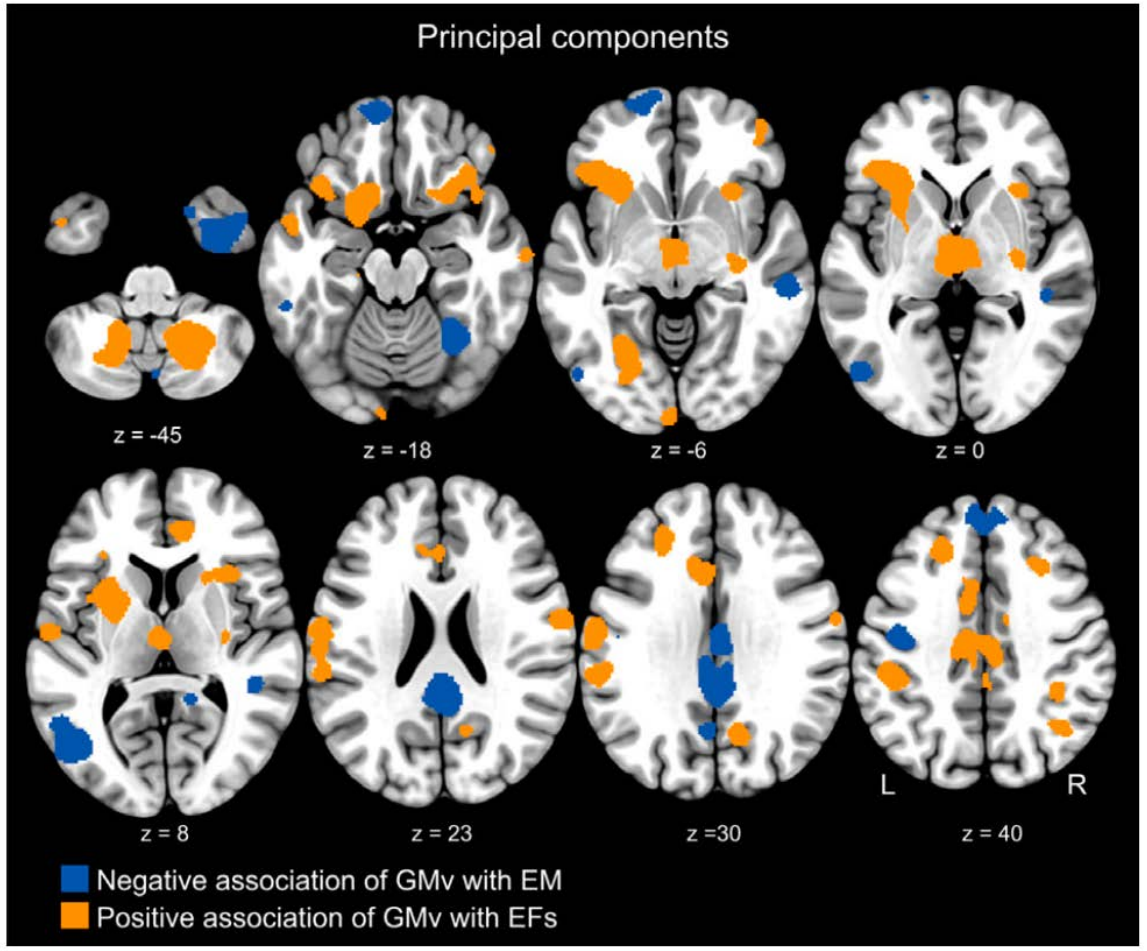


Figure 4. The cerebral morphological correlates underlying EM and EFs are spatially segregated

MAIN CONCLUSIONS

EM and EFs rely on distinct brain neuroanatomical patterns that closely resemble the DMN and the ECN, respectively. The opposite direction of the observed relationships with regional GMv underscores that EM and EFs belong to two different global cognitive processes.

Aging differentially modulates these associations, exerting opposite modulatory roles in the relationship between regional GMv and the two cognitive domains.

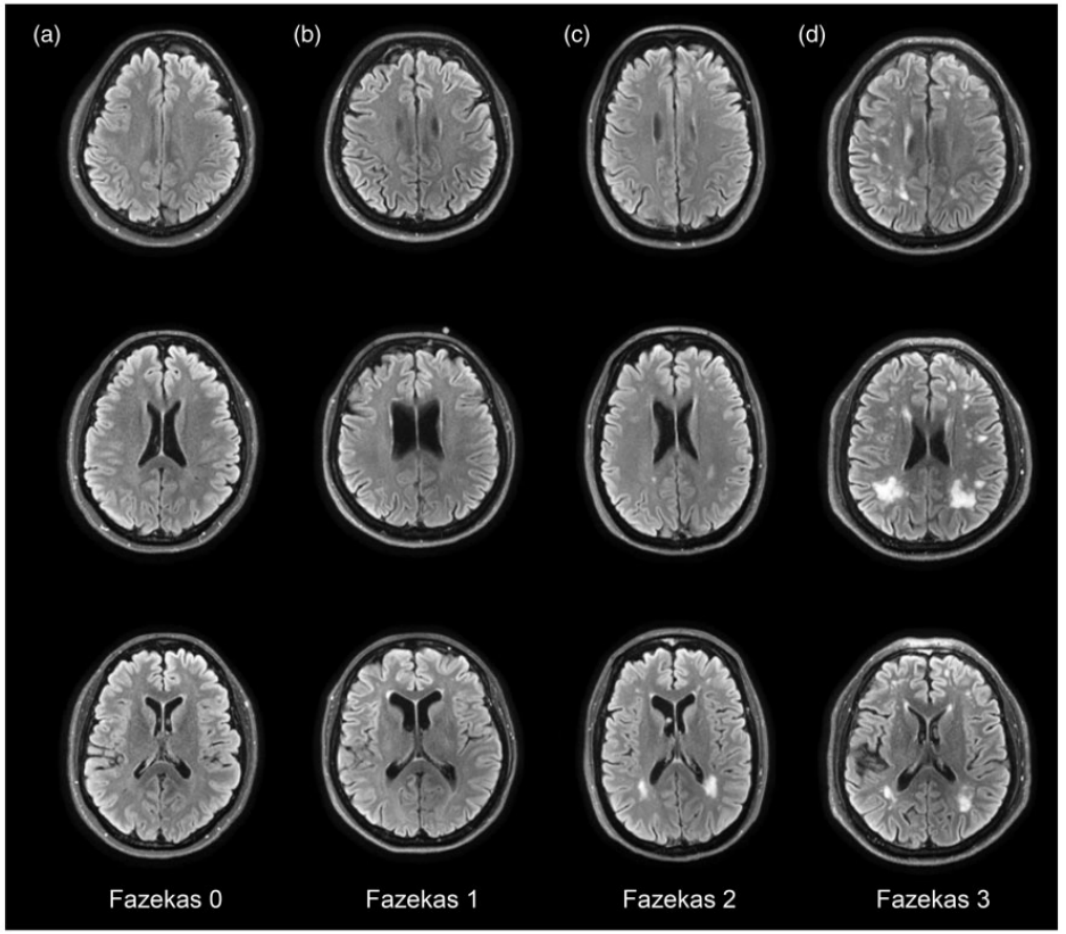
Original Article

JCBFM

Journal of Cerebral Blood Flow & Metabolism
0(00) 1–12
© Author(s) 2017
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0271678X17707397
journals.sagepub.com/home/jcbfm
SAGE

Higher prevalence of cerebral white matter hyperintensities in homozygous *APOE-ε4* allele carriers aged 45–75: Results from the ALFA study

Santiago Rojas[1,2,*], Anna Brugulat-Serrat[1,*], Nuria Bargalló[3,4], Carolina Minguillón[1], Alan Tucholka[1], Carles Falcon[1,5], Andreia Carvalho[1,6], Sebastian Morán[7], Manel Esteller[7,8,9], Nina Gramunt[1], Karine Fauria[1], Jordi Camí[1,10], José L Molinuevo[1,11] and Juan D Gispert[1,5,10]



MAIN OBJECTIVE

To investigate the association between the *APOE-ε4* allele and vascular risk factors with white matter hyperintensities, and explore their interactions, in a cohort of cognitively healthy adults (575 Alfa Study participants).

MAIN CONCLUSIONS

APOE-ε4 homozygotes, but not heterozygotes, bear higher risk of displaying pathological white matter hyperintensities. Aging, hypertension and cardiovascular and dementia risk scales were also positively associated but did not modulate the effect of *APOE-ε4/ε4*.

In subjects at genetic risk of developing Alzheimer's disease, the control of modifiable risk factors of white matter hyperintensities is of particular relevance to reduce or delay dementia's onset.

ELSEVIER

Check for updates

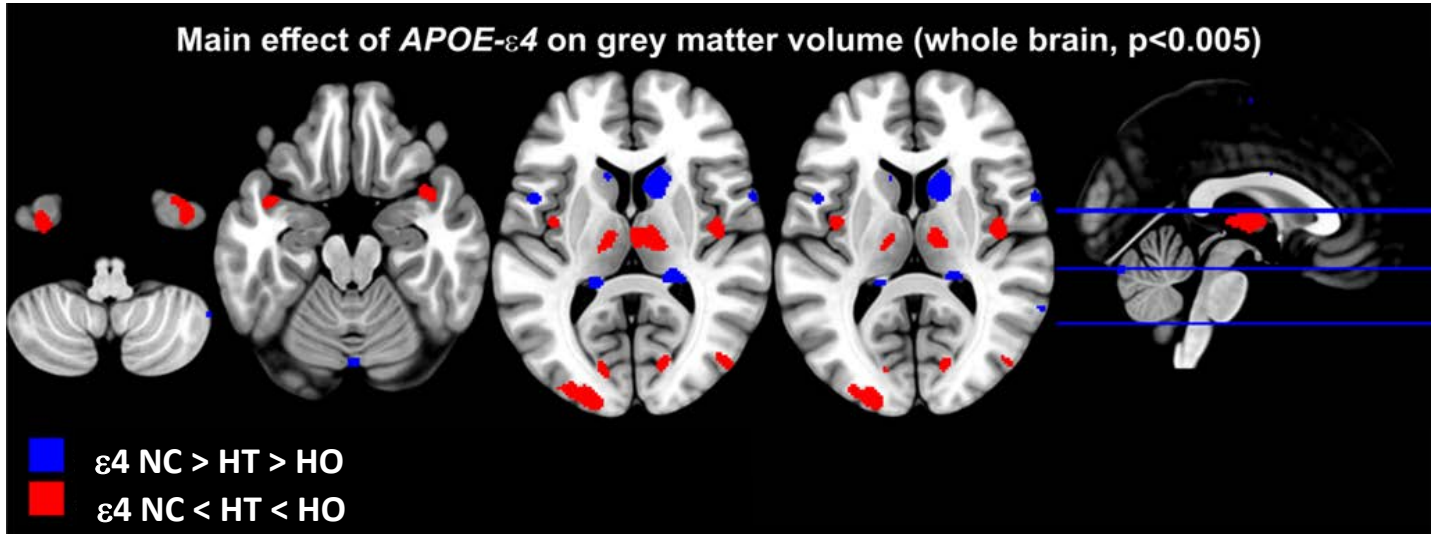
Alzheimer's & Dementia 14 (2018) 902-912

Alzheimer's & Dementia

Featured Article

Effects of *APOE*-ε4 allele load on brain morphology in a cohort of middle-aged healthy individuals with enriched genetic risk for Alzheimer's disease

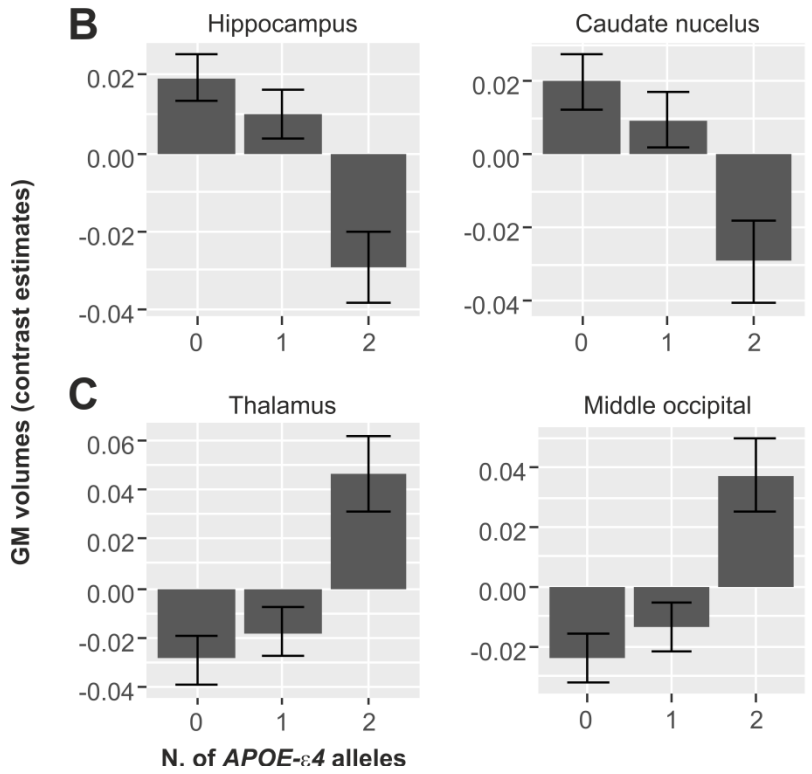
Raffaele Cacciaglia[a], José Luis Molinuevo[a,b,c,*], Carles Falcón[a,d], Anna Brugulat-Serrat[a], Gonzalo Sánchez-Benavides[a], Nina Gramunt[a,c], Manel Esteller[e,f,g], Sebastián Morán[e], Carolina Minguillón[a], Karine Fauria[a], Juan Domingo Gispert[a,d,*], for the ALFA study



MAIN OBJECTIVE

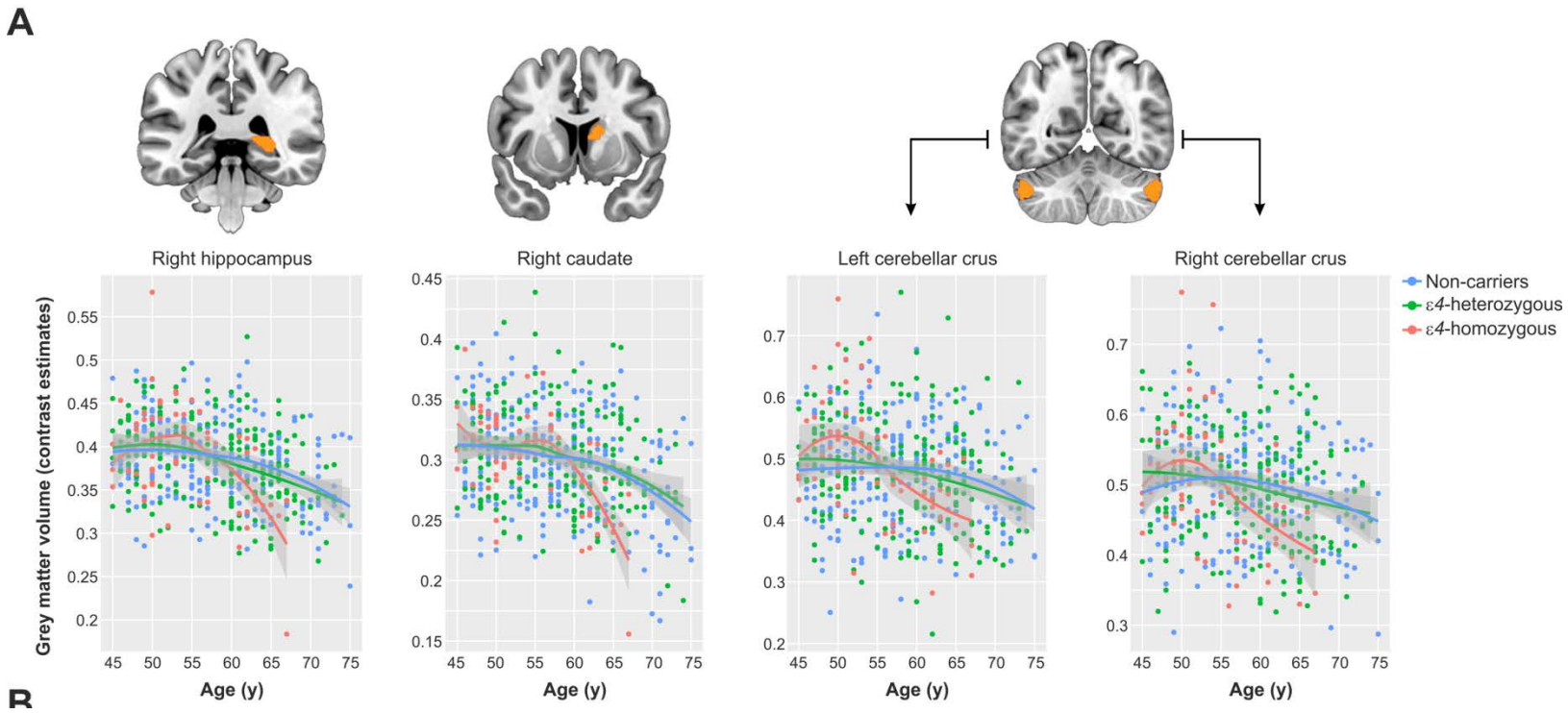
barcelonaβeta BRAIN RESEARCH CENTER

To determine the effects of *APOE-ε4* allele load on brain morphology to better characterize the mechanisms through which *APOE-ε4* confers an increased risk to develop AD in a cognitively healthy population.



Interactions of grey matter volume, genotype and age

barcelonaβeta
BRAIN RESEARCH CENTER



MAIN CONCLUSIONS

We found additive effects of *APOE-ε4* determining lower gray matter volume in the R hippocampus, caudate, precentral gyrus, and cerebellar crus and greater gray matter volume in the right thalamus, left occipital gyrus, and Rfrontal cortex. Our data suggest that the dose-dependent vulnerability induced by *APOE-ε4* may be reflected on the brain morphological level in regions that are critical for AD pathophysiology.

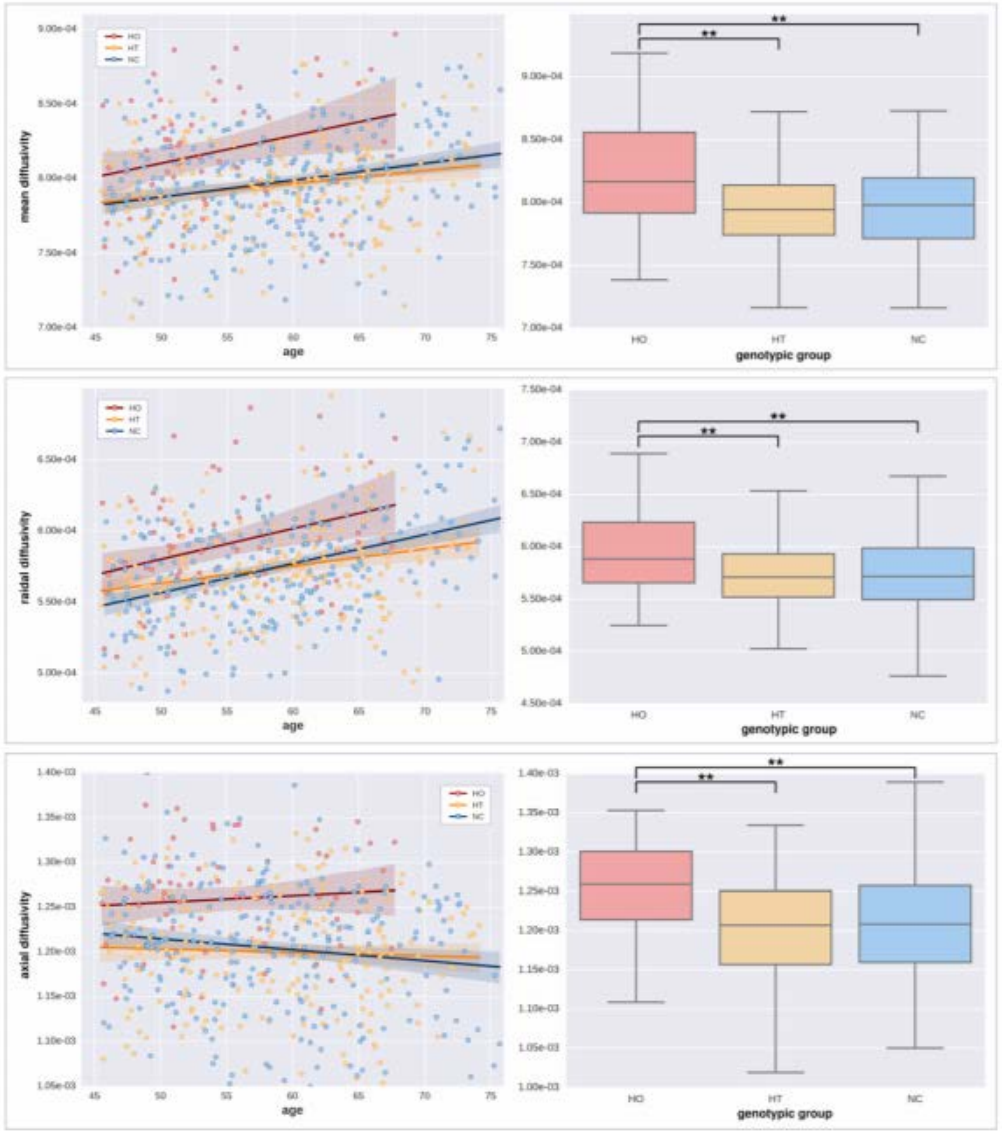


Figure 5. Effect of aging and APOE genotype on diffusion parameters (in seconds per mm2) on significant voxels in the additive contrast

Operto *et al. Alzheimer's Research & Therapy* (2018) 10:48
https://doi.org/10.1186/s13195-018-0375-x

Alzheimer's Research & Therapy

RESEARCH Open Access

White matter microstructure is altered in cognitively normal middle-aged *APOE*-ε4 homozygotes

Grégory Operto[1], Raffaele Cacciaglia[1], Oriol Grau-Rivera[1], Carles Falcon[1,2], Anna Brugulat-Serrat[1], Pablo Ródenas[3], Rubén Ramos[3], Sebastián Morán[4], Manel Esteller[4,5,6], Nuria Bargalló[7,8], José Luis Molinuevo[1,7,9], Juan Domingo Gispert[1,2*] and for the ALFA Study

MAIN CONCLUSIONS

Carrying the *APOE-ε4* allele confers an additional burden to the normal age-related changes observed in regions affected by AD pathology. This burden emerges as differential changes in

dMRI parameters, essentially in diffusivity, suggesting

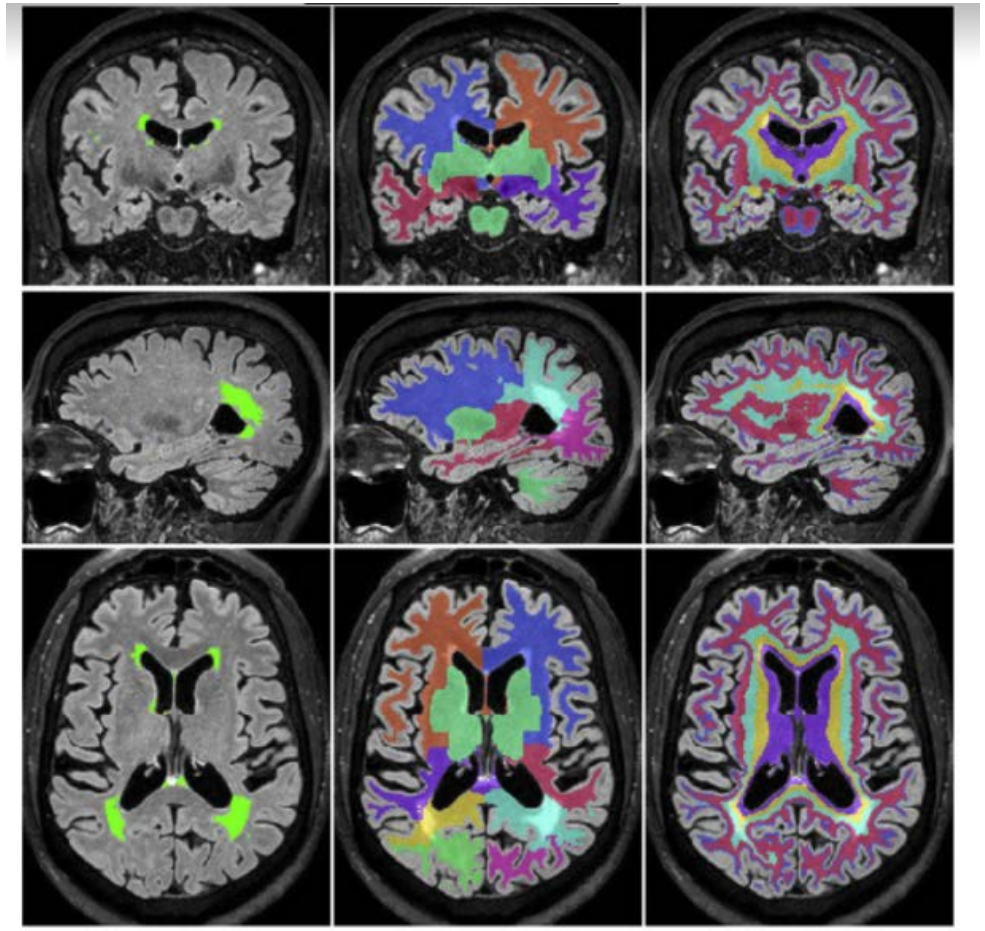
early affection of the fibers of the myelin sheath at a

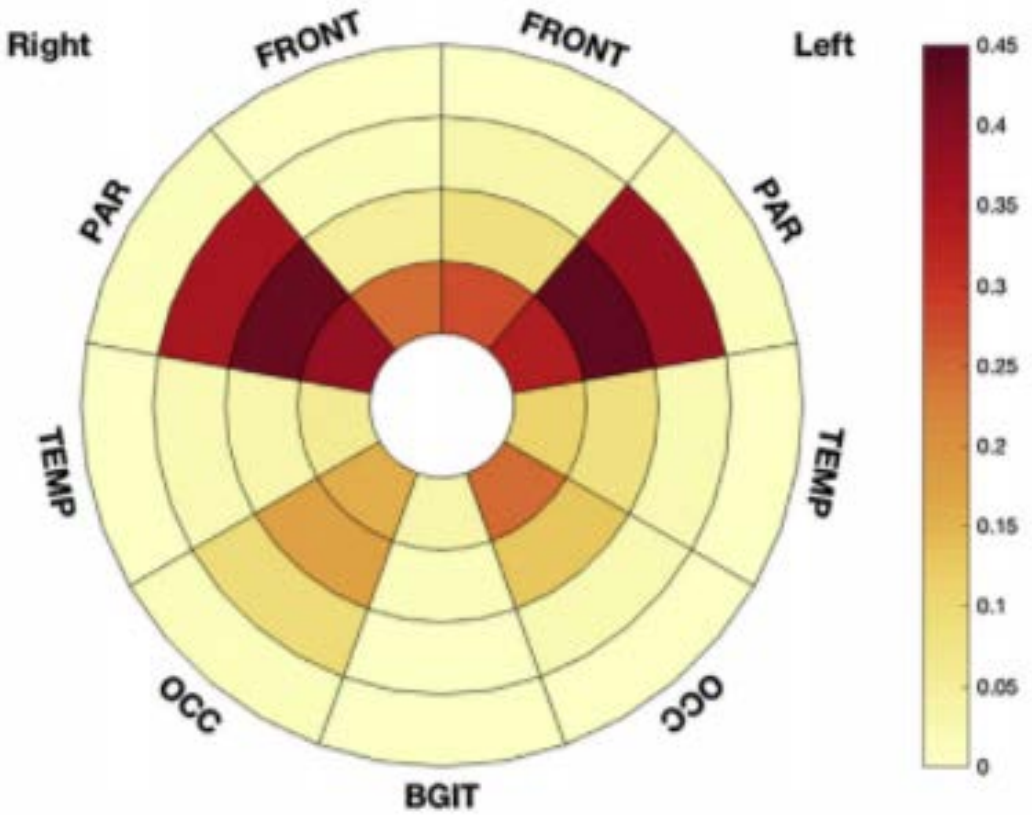
stage predating axonal loss and typically resulting in decreases of anisotropy. With the uniquely high number of homozygotes in our dataset, our study showed that carrying two copies of the ε4 allele is also associated with a significantly higher impact on the WM microstructure.

Regional WMH load

barcelonaβeta
BRAIN RESEARCH CENTER

Method:

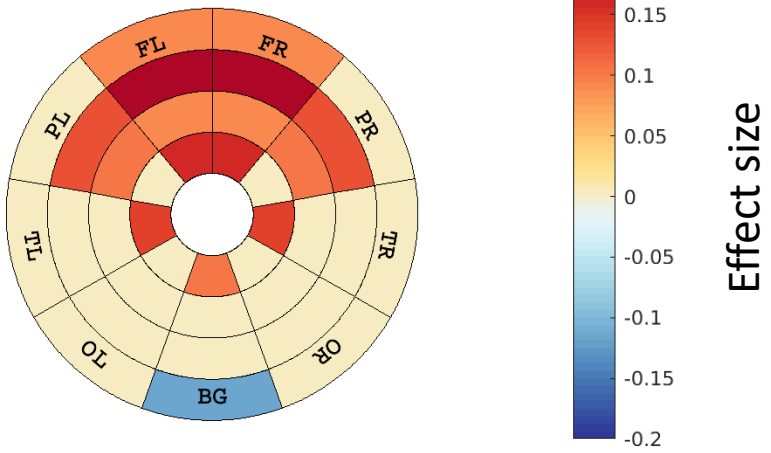




Results: Association between regional WMH burden and CAIDE

barcelonaβeta
BRAIN RESEARCH CENTER

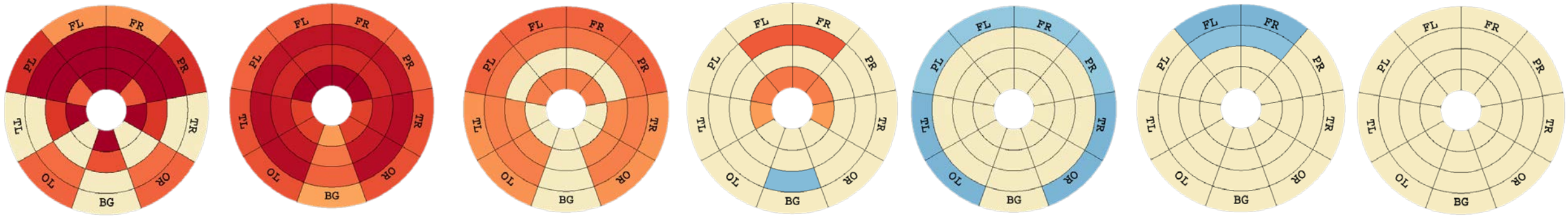
CAIDE-I



WMH increased in

- Older persons
- Hypertensive
- Hypercholesterolemic
- High/Low BMI
- Women
- Low education

Age | **Hypertension** | **Hypercholesterolemia** | **BMI** | **Sex** | **Education** | **Physical exercise**

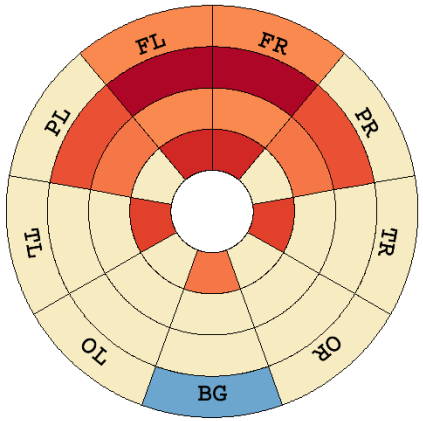


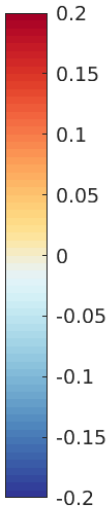
Salvadó et al. submitted

Results: Association between regional WMH burden and CAIDE

barcelonaβeta
BRAIN RESEARCH CENTER

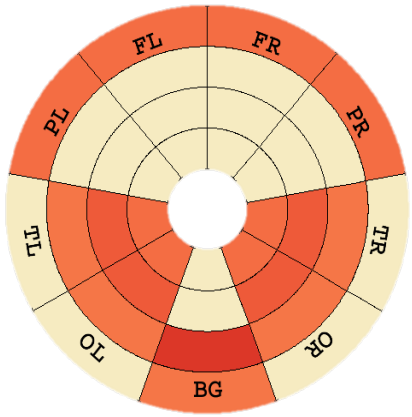
CAIDE-I



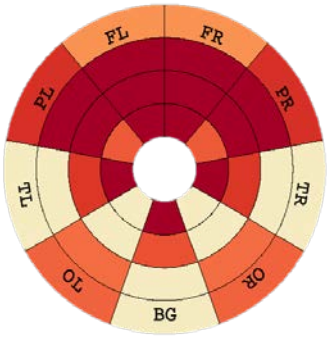


Effect size

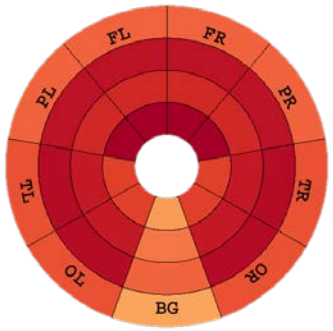
Higher WMH load in subjects with maternal family history



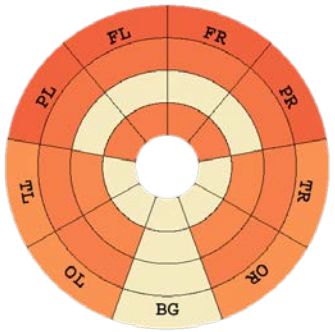
Age



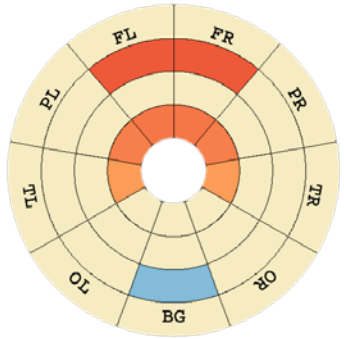
Hypertension



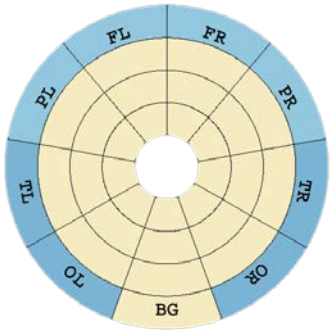
Hypercholesterolemia



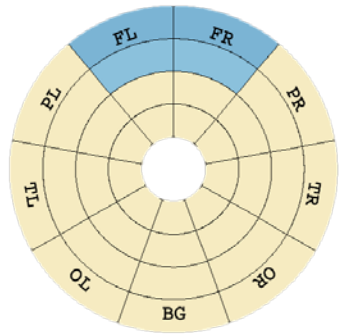
BMI



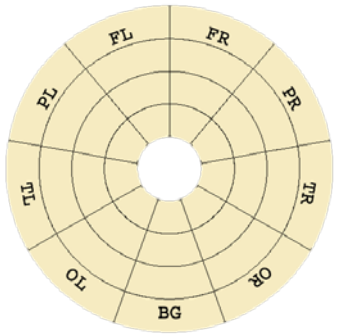
Sex



Education



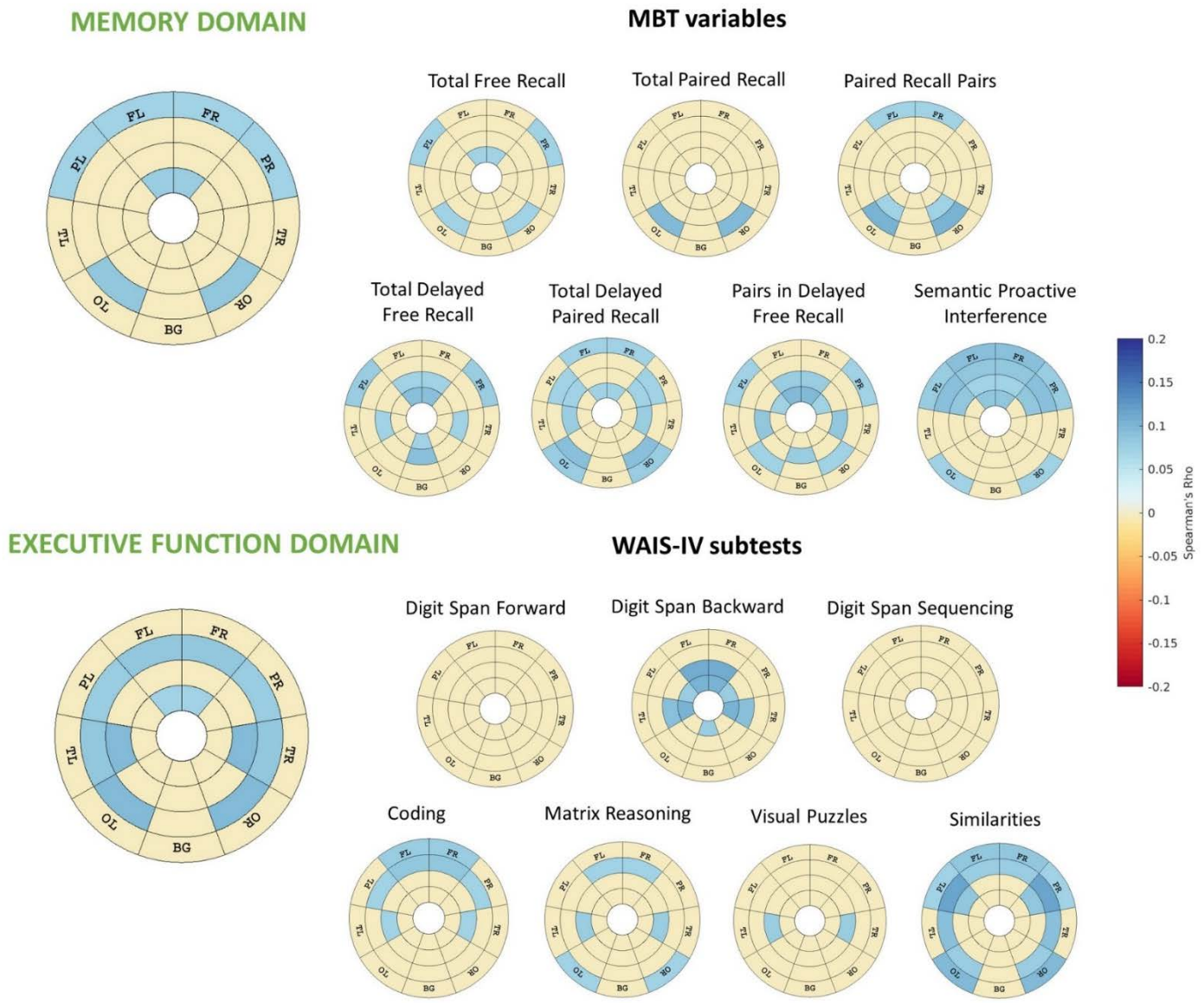
Physical exercise



Salvadó et al. submitted

Patterns of WMH correlate with cognition

barcelonaβeta
BRAIN RESEARCH CENTER



*Corrected by age, sex, education and number of *APOE*-ε4 alleles. WMH also corrected by TIV.
R: Right, L: Left, F: Frontal lobe, T: Temporal lobe, P: Parietal lobe, O: Occipital lobe and BG: Basal ganglia

Brugulat-Serrat et al. submitted

Contents lists available at ScienceDirect

Environmental Research

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

Long-term exposure to residential green and blue spaces and anxiety and depression in adults: A cross-sectional study

Mireia Gascon[a,b,c,*], Gonzalo Sánchez-Benavides[d,e], Payam Dadvand[a,b,c], David Martínez[a,b,c], Nina Gramunt[d,e], Xavier Gotsens[d], Marta Cirach[a,b,c], Cristina Vert[a,b,c], José Luis Molinuevo[d,e], Marta Crous-Bou[d,f,**], Mark Nieuwenhuijsen[a,b,c]

Association between access to major green and blue spaces and self-reported history of anxiety and depression disorders and medication use.

Outcomes (Ncases/Ntotal study population)	Access to major green spaces 300 m		Access to blue spaces 300 m		Access to blue spaces 500 m	
	N (%) of cases among exposed[a]	OR (95%CI)	N (%) of cases among exposed[b]	OR (95%CI)	N (%) of cases among exposed[c]	OR (95%CI)
Self-reported history of:						
Anxiety (21/905)	15 (2.2)	0.95 (0.35, 2.55)	2 (1.2)	0.45 (0.10, 1.98)	6 (1.7)	0.65 (0.25, 1.73)
Depression (13/874)	5 (0.8)	0.18 (0.06, 0.58)	3 (1.8)	1.28 (0.34, 4.83)	5 (1.5)	0.99 (0.32, 3.12)
Self-reported history of medication with:						
Benzodiazepines (49/916)	35 (5.1)	0.80 (0.41, 1.53)	8 (4.7)	0.82 (0.37, 1.82)	13 (3.7)	0.53 (0.28, 1.03)
Antidepressants (54/926)	38 (5.5)	0.73 (0.39, 1.36)	10 (5.7)	0.87 (0.42, 1.80)	18 (4.9)	0.68 (0.37, 1.23)
Any self-reported disorder or medication (112/958)	76 (10.6)	0.66 (0.43, 1.03)	20 (11.2)	0.92 (0.54, 1.55)	36 (9.7)	0.70 (0.46, 1.08)

Models adjusted for gender, age, education, living alone, BMI, smoking status, sleep difficulties, and caregivers' burden.

[a] 828 (86.4%) study participants had access to major green spaces within a buffer of 300 m.

[b] 178 (18.6%) study participants had access to blue spaces within a buffer of 300 m.

[c] 370 (38.6%) study participants had access to blue spaces within a buffer of 500 m.

MAIN CONCLUSIONS

Potential protective role of greenspaces on mental health (depression and anxiety) in adults. These associations are partly mediated by air pollution and in a lesser extent noise, whereas physical activity and social support seem to play a minor role.

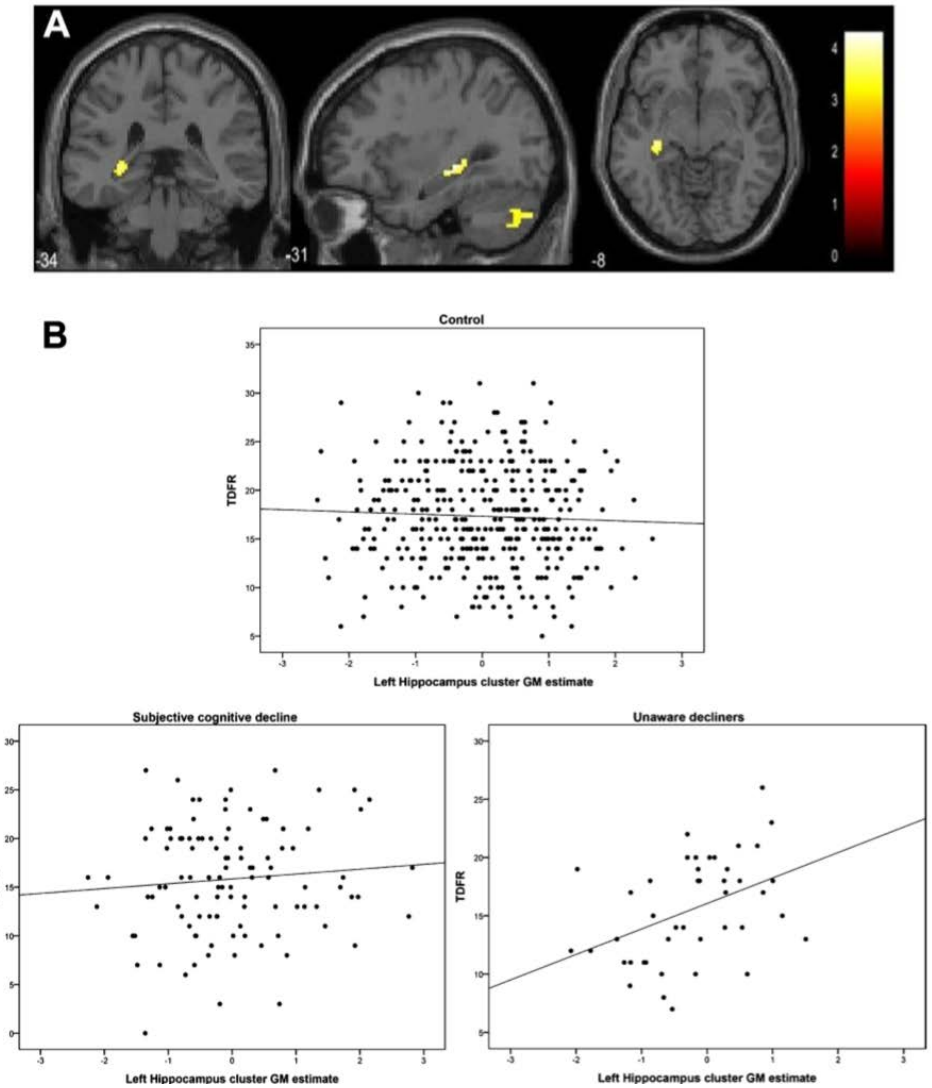


Figure 3. Main effect of positive informant report of decline in decrements of GM volumes (A) and within group associations between memory and GM in the hippocampal cluster (B).

Journal of Alzheimer's Disease 65 (2018) 181–191
DOI 10.3233/JAD-180378
IOS Press

Distinct Cognitive and Brain Morphological Features in Healthy Subjects Unaware of Informant-Reported Cognitive Decline

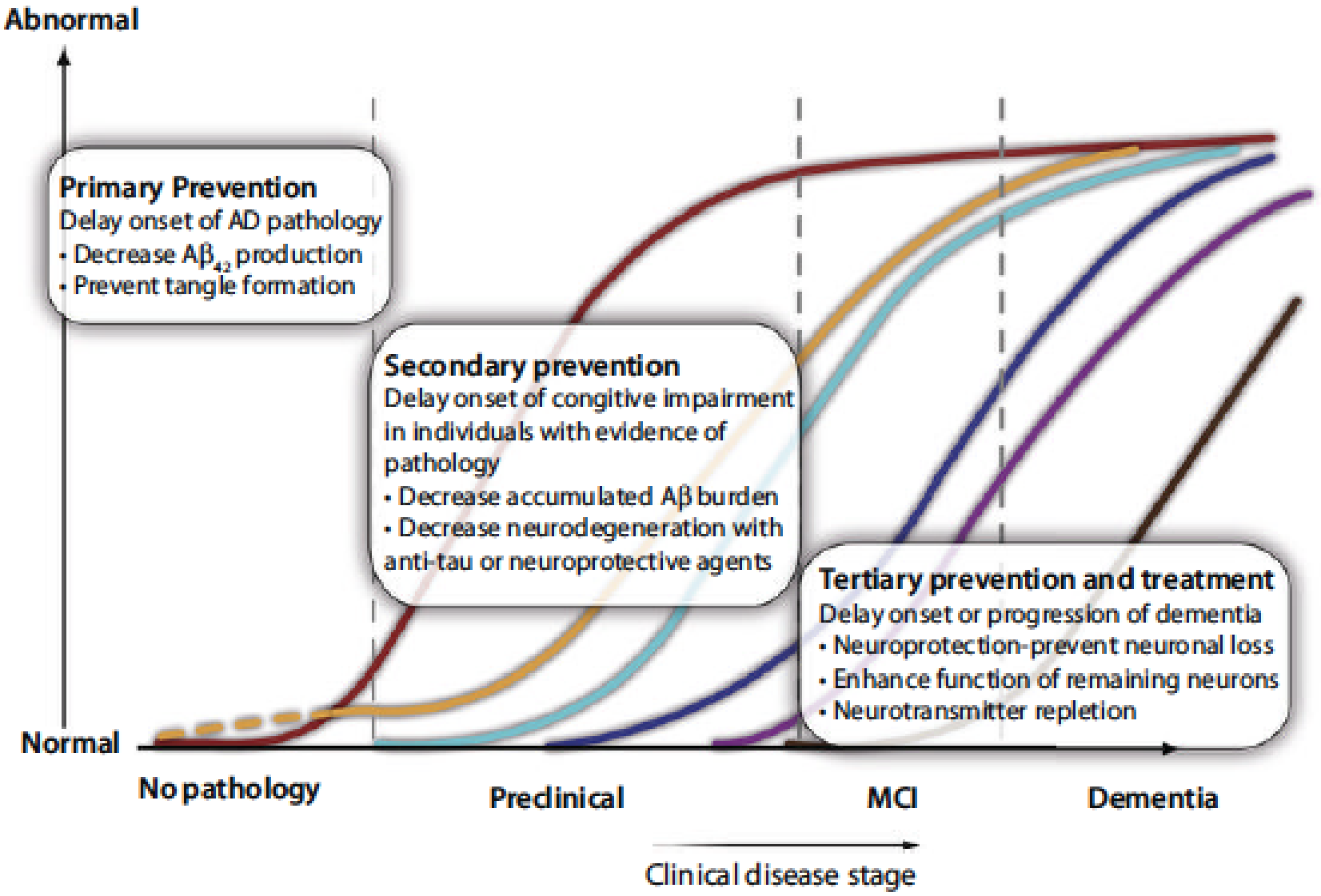
Gonzalo Sánchez-Benavides[a,b], Oriol Grau-Rivera[a], Raffaele Cacciaglia[a], Marc Suárez-Calvet[a], Carles Falcon[a,c], Carolina Minguillon[a,b], Nina Gramunt[a,b], Aleix Sala-Vila[d], ALFAstudy[†], Juan Domingo Gispert[a,c,e] and José Luis Molinuevo[a,b,*]

MAIN CONCLUSIONS

Middle-aged normal subjects unaware cognitive decline display lower memory scores that are related to hippocampal volume and additional brain differences in areas involved in processing self-referential information. Our results suggest that unaware decliners may represent a distinct clinical group at risk of cognitive impairment. Longitudinal studies will be of value to understand the rate of objective cognitive decline of this proposed new group of healthy participants.

Delaying the beginning of AD by 5 years will impact its prevalence

barcelonaβeta
BRAIN RESEARCH CENTER



NEW MULTIMODAL INTERVENTION STUDY

Prevention of cognitive decline after a multimodal intervention combined with EGCG in *ApoE4* carriers with subjective cognitive decline (PENSA Study)

PENSA Study

Study sites:

barcelonaβeta BRAIN RESEARCH CENTER

IMIM Parc de Salut MAR Barcelona
Institut Hospital del Mar d'Investigacions Mèdiques

Funded by:

alzheimer's association

ISC Instituto de Salud Carlos III

barcelonaβeta
BRAIN RESEARCH CENTER

AIM

To evaluate the efficacy of **epigallocatechin gallate** (EGCG) combined with a multicomponent intervention (dietary, cognition and physical activity) in **slowing down cognitive decline and improving brain connectivity** in a population of subjects with SCD.

INTERVENTIONS

- Patients carrying an *ApoE4* allele recently diagnosed of SCD will be randomized to a **multiarm trial in which two interventions will be tested**. The primary end point is a cognitive composite (ADCS-PACC-Plus-exe) and the secondary is based on fMRI.
- An OLE period is also being considered

The EPAD Consortium

Academia

THE UNIVERSITY of EDINBURGH
UNIVERSITY OF OXFORD
barcelonaβeta Brain Research Center
Karolinska Institutet
VUmc VU University Medical Center Amsterdam
UNIVERSITY OF CAMBRIDGE
MRC Biostatistics Unit
UNIVERSITÉ DE GENÈVE
Radboudumc
CARDIFF UNIVERSITY PRIFYSGOL CAERDYDD
Hôpitaux de Toulouse
Erasmus MC
Inserm
University of Leicester
Fraunhofer FHR
UNIKLINIK KÖLN

SMEs

SYNAPSE
Berry Consultants Statistical Innovation
aridhia
IXICO

Patient Organisation

Alzheimer Europe

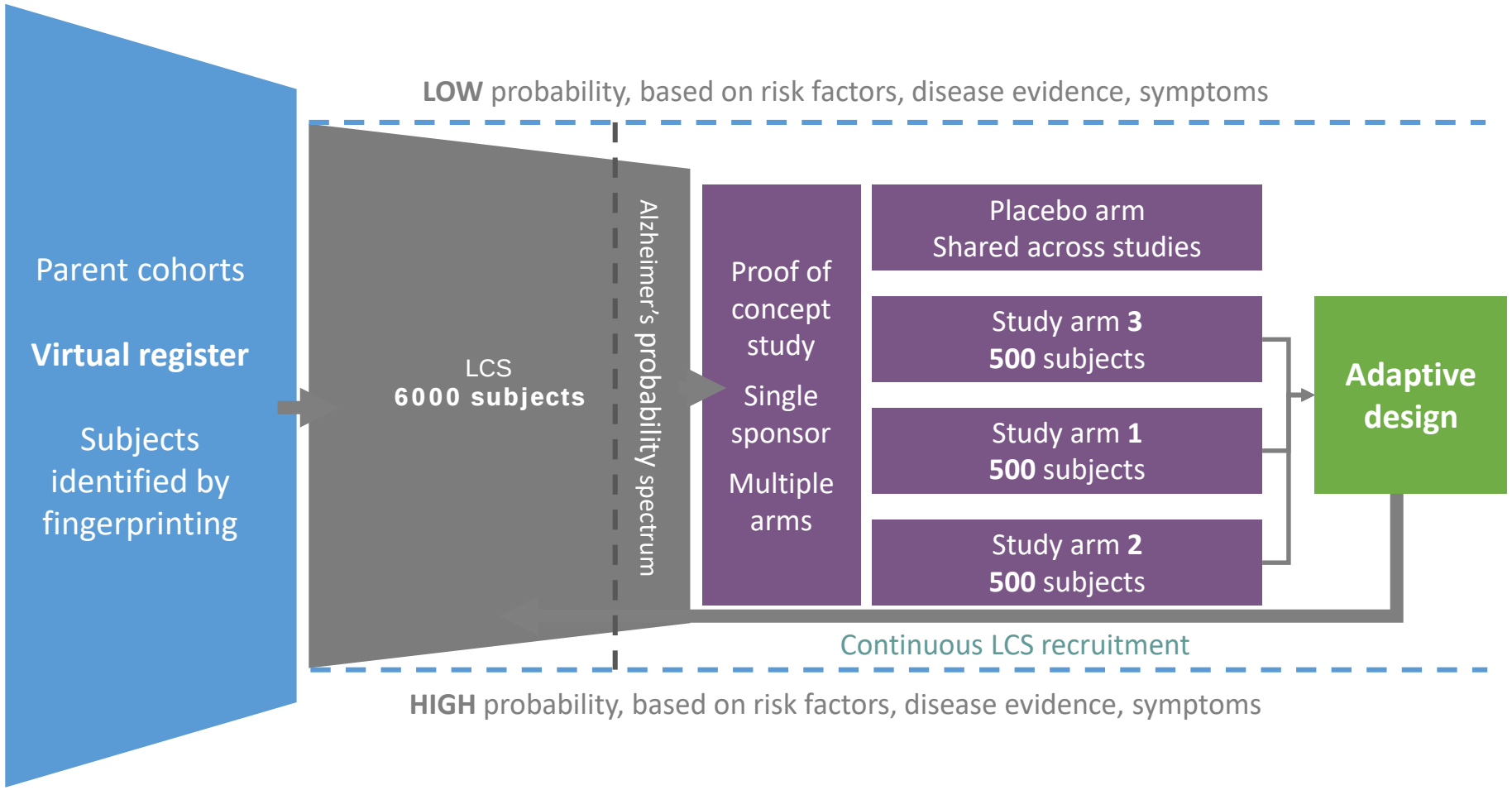
Other industry

IQVIA
Araclon Biotech GRIFOLS

EFPIA

janssen
Eisai
SANOFI
NOVARTIS
Boehringer Ingelheim
Lilly
Lundbeck
Takeda
Roche
AC IMMUNE
Biogen
AMGEN
Pfizer
Inspired by patients. Driven by science.

EPAD flow: the trial “machine”



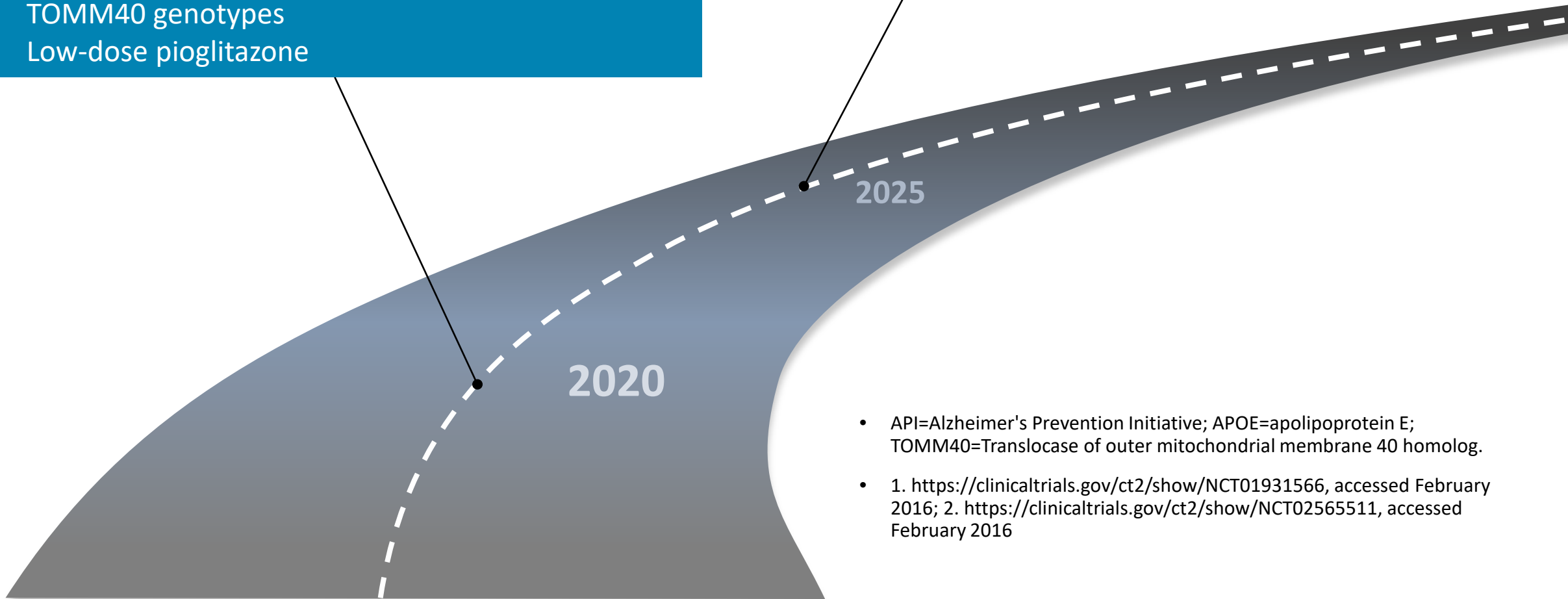
Adapted from ALZ Forum. Coming to a Center Near You: GAP and EPAD to Revamp Alzheimer’s Trials. 2016. Available at: http://www.alzforum.org/news/conference-coverage/coming-center-near-you-gap-and-epad-revamp-alzheimers-trials (accessed January 2017). EPAD, European Prevention of Alzheimer’s Dementia Consortium; LCS, longitudinal cohort study

AD Prevention Studies: Genetically Defined Risk

barcelonaβeta
BRAIN RESEARCH CENTER

TOMMORROW Study (normals)[1]
- Defines a high-risk group based upon age, APOE and TOMM40 genotypes
- Low-dose pioglitazone

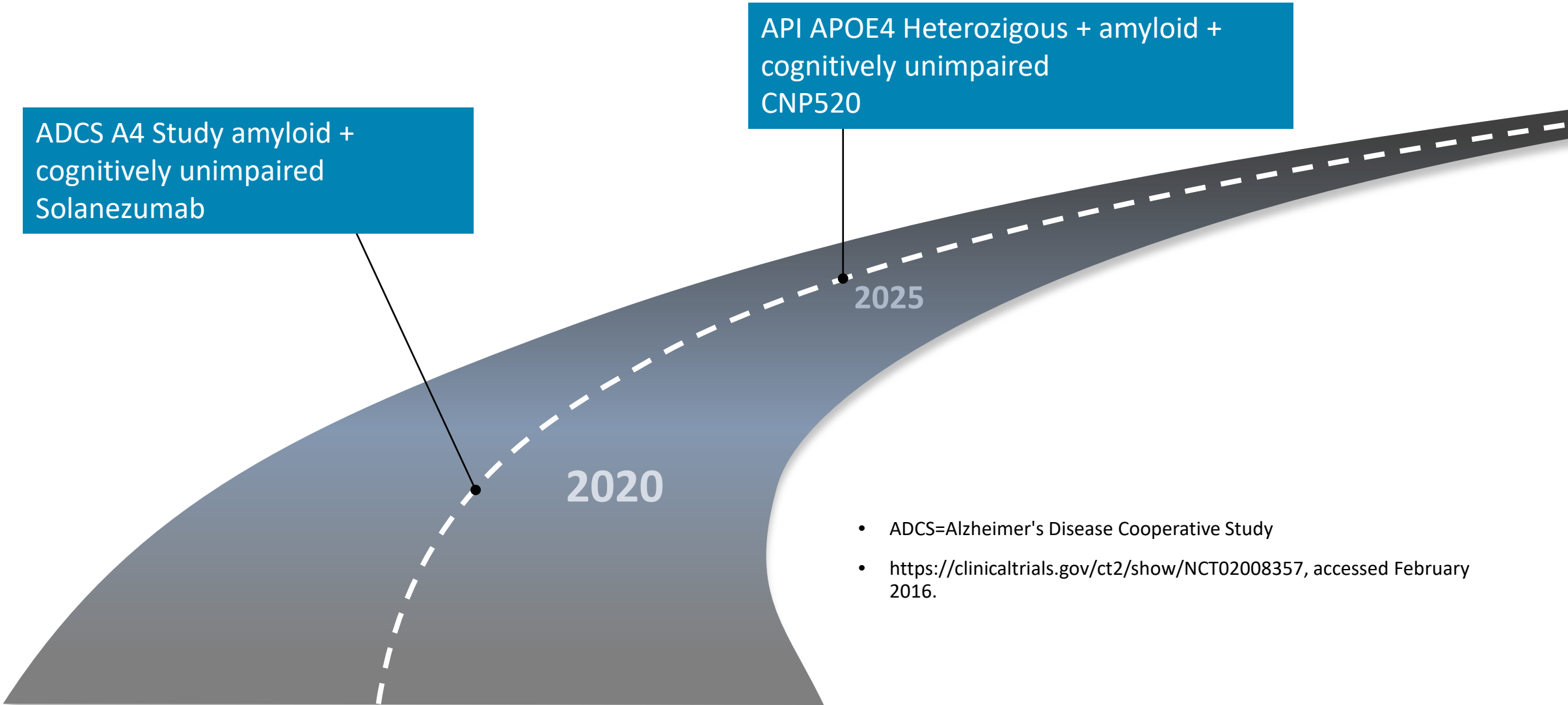
API APOE4 Homozygous Study (normals)[2]
- CAD106 and CNP520



- API=Alzheimer's Prevention Initiative; APOE=apolipoprotein E; TOMM40=Translocase of outer mitochondrial membrane 40 homolog.
- 1. https://clinicaltrials.gov/ct2/show/NCT01931566, accessed February 2016; 2. https://clinicaltrials.gov/ct2/show/NCT02565511, accessed February 2016

AD Prevention Studies: Biomarker Defined Risk

barcelonaβeta
BRAIN RESEARCH CENTER



- ADCS=Alzheimer's Disease Cooperative Study
- https://clinicaltrials.gov/ct2/show/NCT02008357, accessed February 2016.

The challenges of prevention

barcelonaβeta
BRAIN RESEARCH CENTER

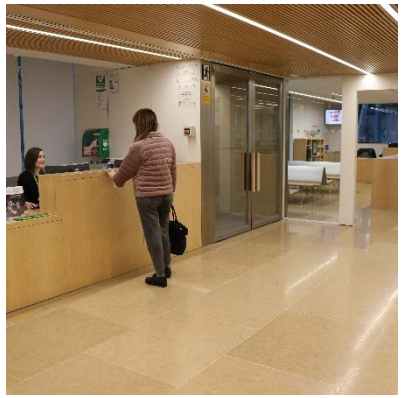
Challenges

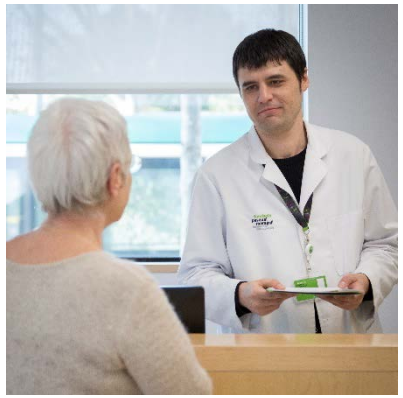
- New target population
- New recruitment strategies
  - Registries
  - Readiness cohort
- Longer phase 3 trials
- Ethical challenges
- New cognitive endpoints: role of composites and continuous measures
- Time-to-event endpoints (agencies favorite)

barcelonaβeta
BRAIN RESEARCH CENTER

Solutions

- Population Based Recruitment
- Healthy aging programs
- Primary & secondary prevention
- Risk disclosure approach
- Personalized medicine approach





barcelonaβeta
BRAIN RESEARCH CENTER

ELSEVIER

Alzheimer's & Dementia: Translational Research & Clinical Interventions ■ (2016) 1-11

Alzheimer's & Dementia

Featured Article

The ALFA project: A research platform to identify early pathophysiological features of Alzheimer's disease

José Luis Molinuevo[a,*], Nina Gramunt[a], Juan Domingo Gispert[a], Karine Fauria[a], Manel Esteller[b,c,d], Carolina Minguillon[a], Gonzalo Sánchez-Benavides[a], Gema Huesa[a], Sebastián Morán[b,c], Rafael Dal-Ré[a], Jordi Camí[e,f,**]

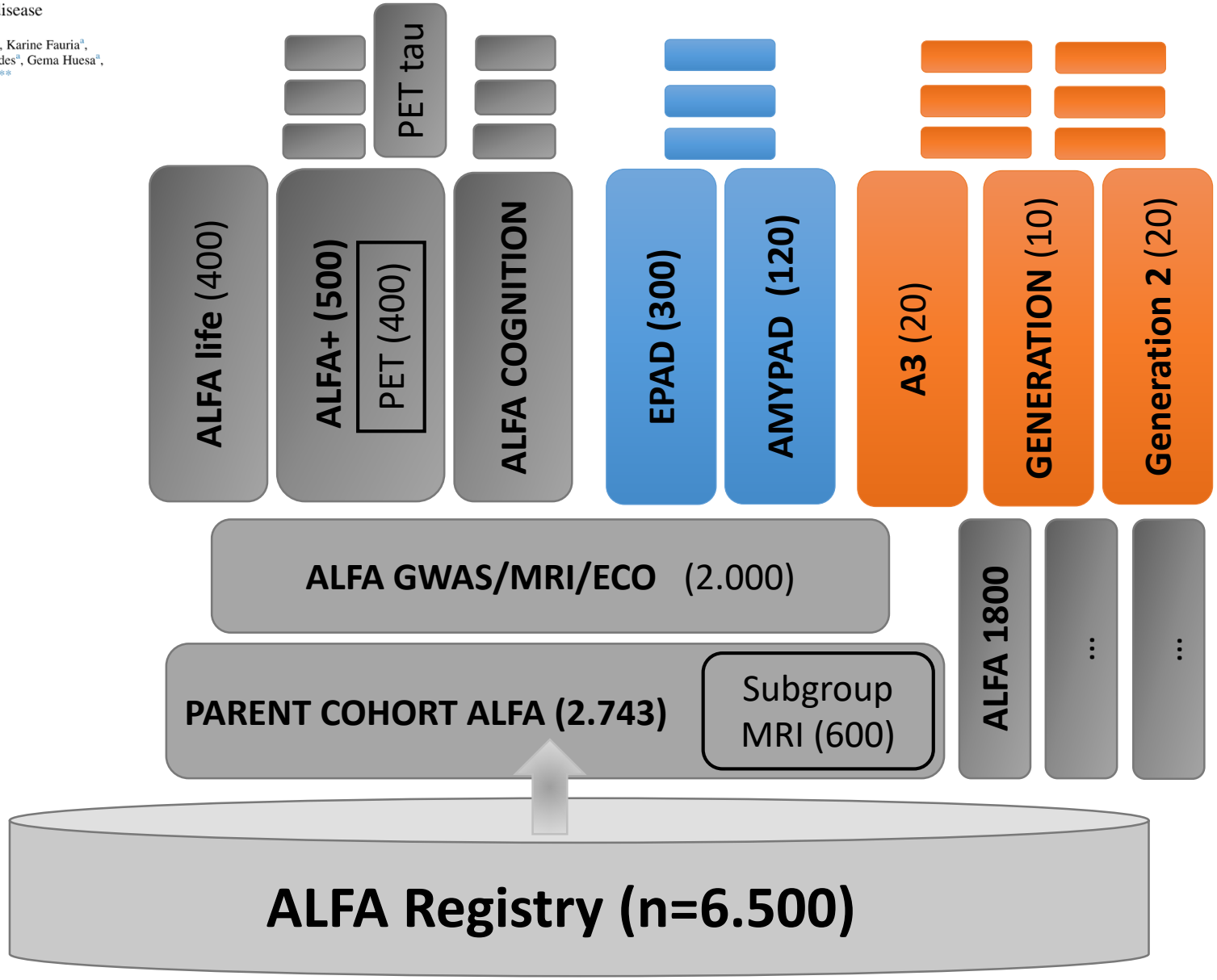
ELSEVIER
Alzheimer's & Dementia: Translational Research & Clinical Interventions ■ (2016) 1-11
Alzheimer's & Dementia

Featured Article

The ALFA project: A research platform to identify early pathophysiological features of Alzheimer's disease

José Luis Molinuevo[a,*], Nina Gramunt[a], Juan Domingo Gispert[a], Karine Fauria[a], Manel Esteller[b,c,d], Carolina Minguillon[a], Gonzalo Sánchez-Benavides[a], Gema Huesa[a], Sebastián Morán[b,c], Rafael Dal-Ré[e], Jordi Camí[e,f,**]

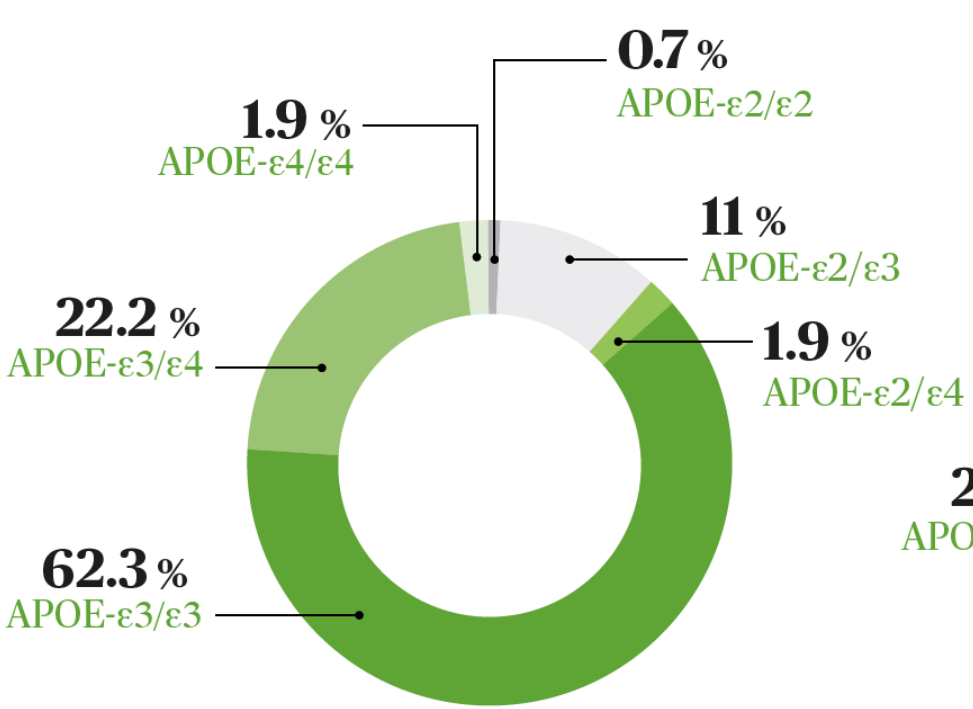
barcelonaβeta
BRAIN RESEARCH CENTER



Alfa population description

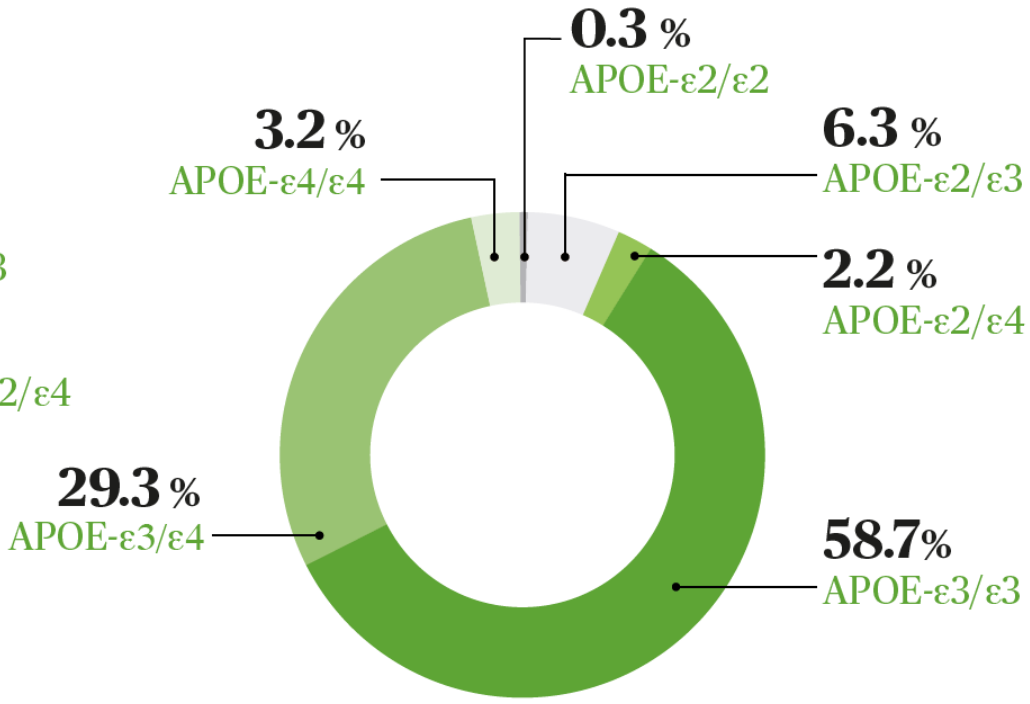
barcelonaβeta
BRAIN RESEARCH CENTER

Enriched for AD genetic risk factors



Control, AlzGene

(N=7094)



ALFA parent cohort

(N=2670)

barcelonaβeta
BRAIN RESEARCH CENTER

UNMET NEEDS

for dementia prevention

- The value of prevention: engaging the population
- Finding the right population
- Optimizing recruitment methods
- Cost-efficient methods
- Addressing the risk of dementia in cognitively unimpaired
- Optimal way for disclosing risk estimates
- Impact of disclosing risk is unknown
- Biological correlates of risk estimates are unknown

barcelonaβeta
BRAIN RESEARCH CENTER

OBJECTIVES

- To develop a **web based recruitment method** that targets the optimal population for dementia prevention.
- To disclose individual's risk estimates of dementia with a **personalized** approach.
- To assess the **risk/benefit of disclosing** risk estimates of dementia.
- To present a personalized action plan, based on the individual's risk profile, including but not limited to **primary prevention advice** and **secondary prevention** approach.
- To assess the individual benefit of the program in order to advocate on the need of creating **Dementia Prevention Clinics** within the healthcare system.
- To **correlate the risk estimate algorithm with amyloid** measures and to test its accuracy to detect amyloid.

STUDY FLOW CHART

SELECTION

- **Web-based algorithm** results in a **registry of *a priori* eligible** persons that are interested in the study

INVITATION

- **Phone-based communication** and invitation of a priori eligible candidates from the study registry

BASELINE VISIT

CLINICAL SESSION

- PIS/ICF
- Sociodemographic information
- Medical history
- Lifestyle habits
- Clinical evaluation: cognition, anxiety, depression…
- Blood sample

EXCLUSION

COGNITIVE SESSION

Neuropsychological tests and scales

EXCLUSION

MRI SESSION

REVISION OF DATA

- Revision of all data gathered to **ensure compliance** with eligibility criteria

EXCLUSION

INDIVIDUAL'S RISK CALCULATION

- Estimation of individual's risk
- Determination of **personalized prevention plan**

DISCLOSURE OF RISK

- Disclosure of individual's risk
- Explanation of personalized primary **prevention advice**

FOLLOW-UP
~2-7 days post-disclosure

- Assessment of emotional impact **by phone**

FOLLOW-UP
~6 weeks post-disclosure

- Assessment of emotional impact
- Assessment of QoL
- Life habits questionnaires
- Presentation of secondary prevention studies (observational and/or clinical trials)

FOLLOW-UP
~6 months post-disclosure

- Assessment of emotional impact **by phone**

FOLLOW-UP
~1 year post-disclosure

- Assessment of emotional impact
- Assessment of potential benefits
- Life habits questionnaires
- Study wrap-up and satisfaction

Take home message

barcelonaβeta
BRAIN RESEARCH CENTER

- AD is now defined as a biological construct that reflects the underlying pathology manifesting through a clinical continuum ranging from normal cognition to dementia
- Imaging and biomarkers research are shedding light on risk factors pathophysiology
- Current understanding of AD has allowed the design of prevention trials
  - EPAD represents the first step of a global initiative
  - Clinical trials are on the way for sporadic AD
- We need to create newly designed infrastructures (structural and research ones) to defeat AD

There is a huge need for a COMMON UNITED APPROACH


Thank You!!

barcelonaβeta

BRAIN RESEARCH CENTER