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

Dr. José Luis Molinuevo
Disclosures

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• 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

Clinic pathological dual diagnosis:¹

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

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
Assessing the accuracy of the diagnosis

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

<table>
<thead>
<tr>
<th>Pathological diagnosis: moderate or frequent plaques AND Braak* IV–VI</th>
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<tr>
<td>**</td>
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<tr>
<td>No AD pathology</td>
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<tr>
<td>No probable AD (clinical)</td>
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<tr>
<td>Probable AD (clinical)</td>
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<td>Specificity = 70.8%</td>
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* Braak IV-VI it is the needed pathological threshold to make the pathological diagnosis of AD

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).
“Since a cure for dementia is not yet available, finding effective preventive strategies is essential for a sustainable society in an aging world.”
Increased cortical thickness in AD areas in subjects with ß-amyloid levels in the middle tertiles (transitional levels) respect those with normal levels

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 $r=0.57$, $p<0.012$).
Structural connectivity alterations in PRE-AD
“Since a cure for dementia is not yet available, finding effective preventive strategies is essential for a sustainable society in an aging world.”
Dementia
Familial aggregation
APOE, other genes
Dyslipidemia
Hypertension
Obesity
Dyslipidemia
Smoking
Diabetes
Neuronal damage
Vascular insults
Brain reserve
Cognitive reserve

Across the lifespan

Risk factors

0
Adult life

20

Education
Physical activity

60
Mid-life

Cognitive and social activity

75
Late-life

Dementia

Protective factors

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

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

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

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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.
MAIN OBJECTIVE

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.
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 R frontal 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.
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.

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

Method:
Results: Association between regional WMH burden and CAIDE

CAIDE-I

Effect size

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

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

*Corrected by age, sex, education and number of APOE-ε4 alleles. WMH also corrected by TIV.
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.
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
NEW MULTIMODAL INTERVENTION STUDY

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

Study sites:

Funded by:

PENSA Study
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 **multiarmed 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
EPAD flow: the trial “machine”

- Parent cohorts
- Virtual register
- Subjects identified by fingerprinting

**LCS 6000 subjects**

- **Alzheimer’s probability spectrum**
  - LOW probability, based on risk factors, disease evidence, symptoms
  - HIGH probability, based on risk factors, disease evidence, symptoms

- **Proof of concept study**
  - Placebo arm
    - Shared across studies
  - Single sponsor
  - Multiple arms
    - Study arm 1: 500 subjects
    - Study arm 2: 500 subjects
    - Study arm 3: 500 subjects

**Adaptive design**

AD Prevention Studies: Genetically Defined Risk

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.

AD Prevention Studies: Biomarker Defined Risk

- ADCS=Alzheimer’s Disease Cooperative Study

ADCS A4 Study amyloid + cognitively unimpaired
Solanezumab

API APOE4 Heterozygous + amyloid + cognitively unimpaired
CNP520

- ADCS=Alzheimer's Disease Cooperative Study
The challenges of prevention

Challenges

- New target population
- Longer phase 3 trials
- Population Based Recruitment
- Primary & secondary prevention
- Risk disclosure approach
- Personalized medicine approach
- Healthy aging programs

Solutions

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

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Featured Article

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

José Luis Molinuevo\textsuperscript{a,*}, Nina Gramunt\textsuperscript{a}, Juan Domingo Gispert\textsuperscript{a}, Karine Fauria\textsuperscript{a}, Manel Esteller\textsuperscript{b,c,d}, Carolina Minguillon\textsuperscript{a}, Gonzalo Sánchez-Benavides\textsuperscript{a}, Gema Huesa\textsuperscript{a}, Sebastián Morán\textsuperscript{b,c}, Rafael Dal-Re\textsuperscript{a}, Jordi Camí*\textsuperscript{a,**}
Featured Article
The ALFA project: A research platform to identify early pathophysiological features of Alzheimer’s disease

José Luis Molinuevo1,2,3, Nina Gersten, Juan Domingo Gómez, Kajsa Forss1, Manuel Estefan1,2,3, Carolina Mangillon, Gonzalo Sánchez-Benavides, Gerda Haan, Sebastian Modin1, Rafael Del Re, Jordi Cinca2,3,4
Alfa population description

Enriched for AD genetic risk factors

Control, AlzGene
(N=7094)

ALFA parent cohort
(N=2670)
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
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.
**Barcelonaβeta Dementia Prevention Research Clinic**

**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 all data gathered to ensure compliance with eligibility criteria
- Estimation of individual's risk
- Determination of personalized prevention plan
- Disclosure of individual's risk
- Explanation of personalized primary prevention advice

EXCLUSION
Barcelonaβeta Dementia Prevention Research Clinic

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

Follow-up: ~2-7 days post-disclosure

Follow-up: ~6 weeks post-disclosure

Follow-up: ~6 months post-disclosure

Follow-up: ~1 year post-disclosure

- Assessment of emotional impact by phone
- Assessment of potential benefits
- Life habits questionnaires
- Study wrap-up and satisfaction
Take home message

• 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!!