PharmaCog

Advancing science and treatment of Alzheimer's Disease

Potential use of biomarkers and their temporal relationship with the different phases of AD in different stages of drug development

Prof Olivier BLIN

Marseille

France

PharmaCog: Jill Richardson & R Bordet, Coordinators

Innovative Medicines Initiative

Personal Interests Disclosure

Available on Afssaps.fr (since 2004) and sante.gouv.fr (since 2010)

Public

- Prof & Head Pharmacology Dpt, Marseille
- VP Section X of CS for CSFRS
- Member Follow up Committee, French National Plan against NeuroDegenerative Diseases 2014-2019
- Expert EC

Private

- Non profit Association 1901
- Scientific expertise
- Industry (past)
2011-2013: GSK global SNC discovery medicine

24 nov 2014

Biomarker: Definitions

- EMA: Tests that can be used to follow body processes and diseases in humans and animals. They can be used to predict how a patient will respond to a medicine or whether they have, or are likely to develop, a certain disease.
- National Institutes of Health Biomarkers Definitions Working Group: a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention
- WHO: "almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction"

Different categories of Biomarkers according to final goal

Diagnostic
- Patients at risk
- Early Diagnosis
- Discriminate disease stages
- Topography of the neurodegenerative process

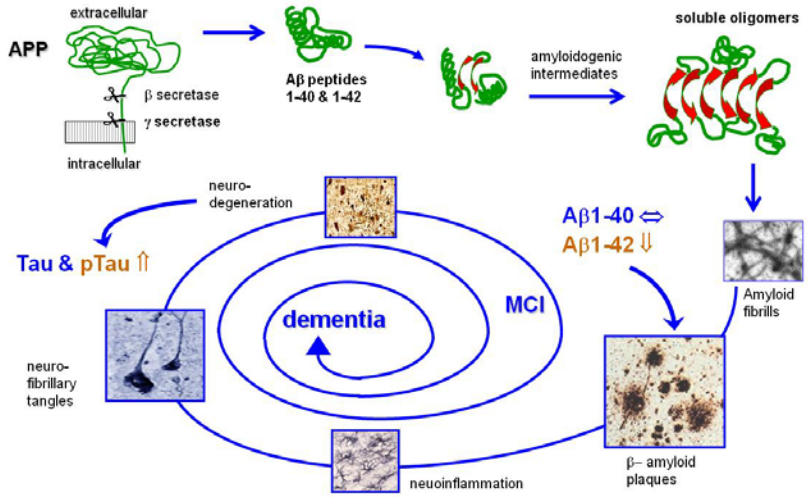
Prognosis
- Severity marker
- Intensity of underlying mechanism(s)
- Recurrence marker
- Evolution

Prediction
- Conversion
- Personalized medicine: individual target engagement
- Therapeutic Response
- Therapeutic decision tool

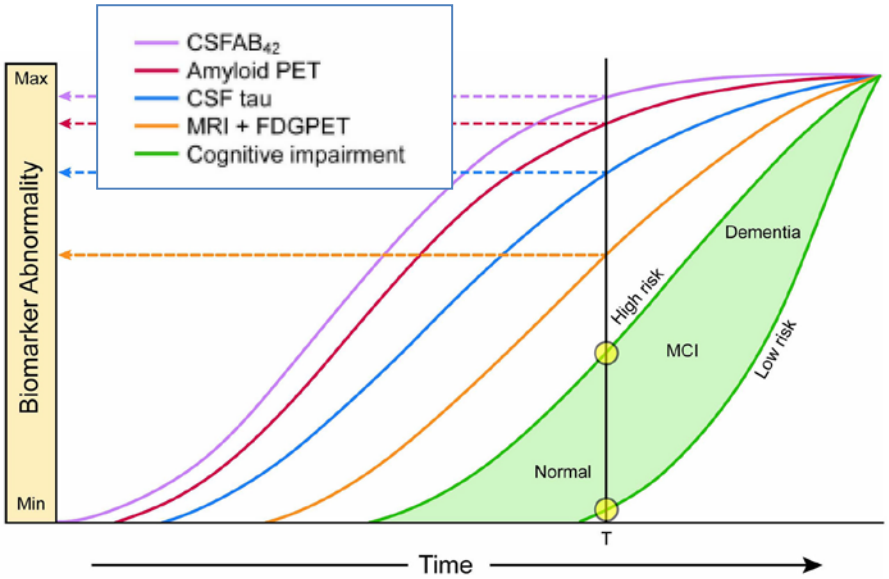
Stratification
Drug MoA
Time frame

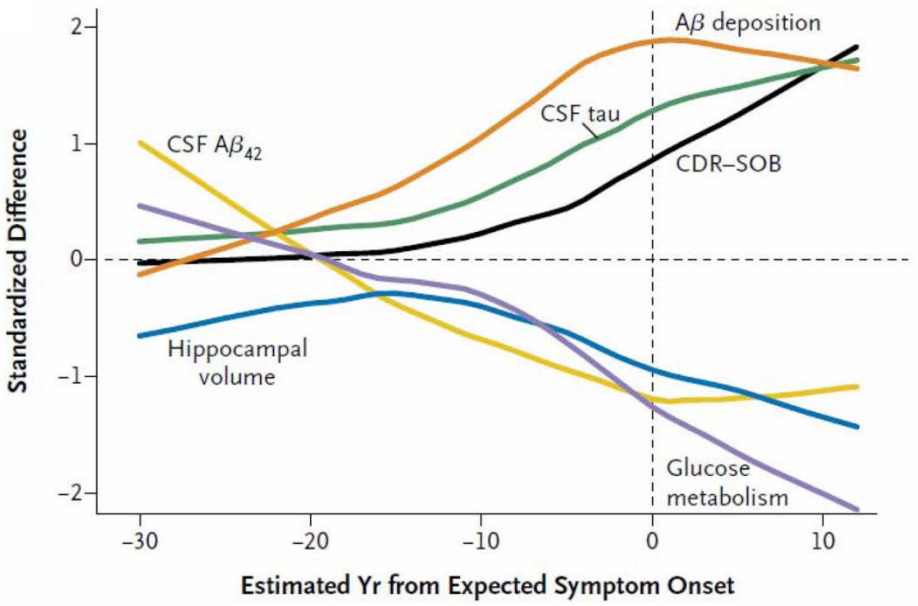
Biomarker model of the Alzheimer´s amyloid cascade

A. Alzheimer



Relation between these biomarkers and Function? Cognition?

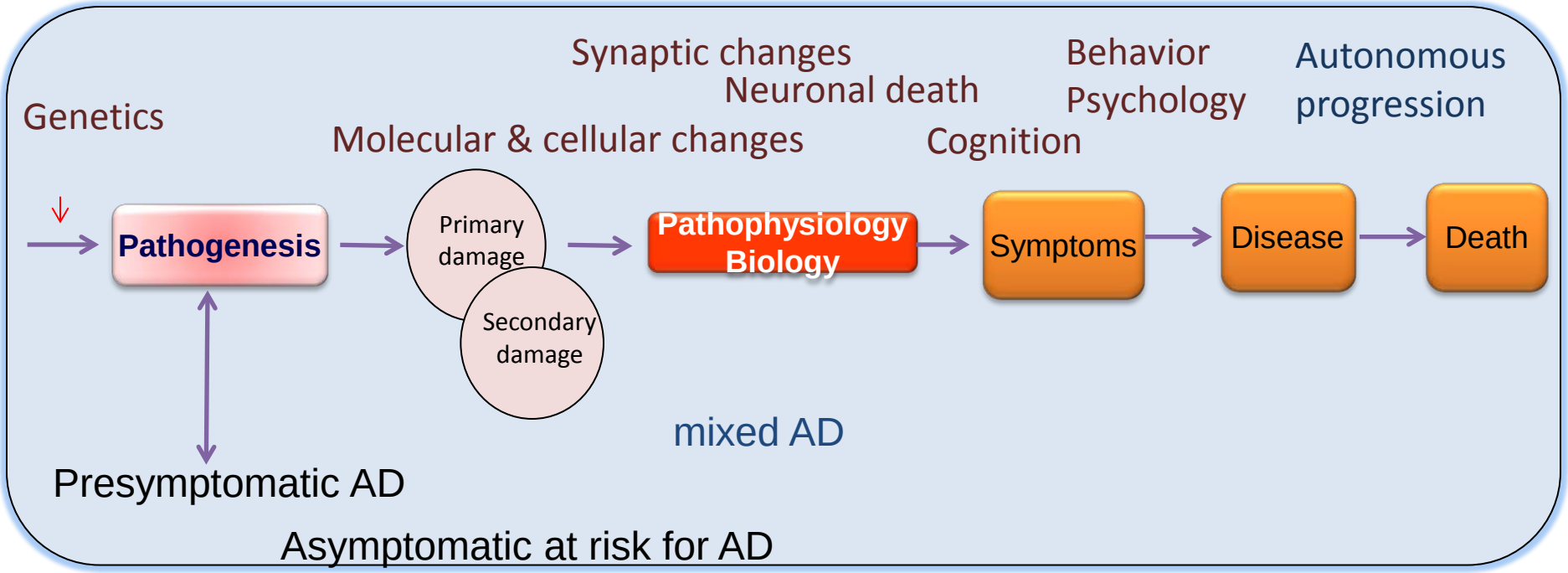




Jack et al., Lancet Neurol. 2013
Landau et al. Ann Neurol, 2013

DIAN: 40 non carriers, 88 carriers (40 *PSEN1, 3 PSEN2, and 8 APP pedigrees) Bateman et al. 2012*

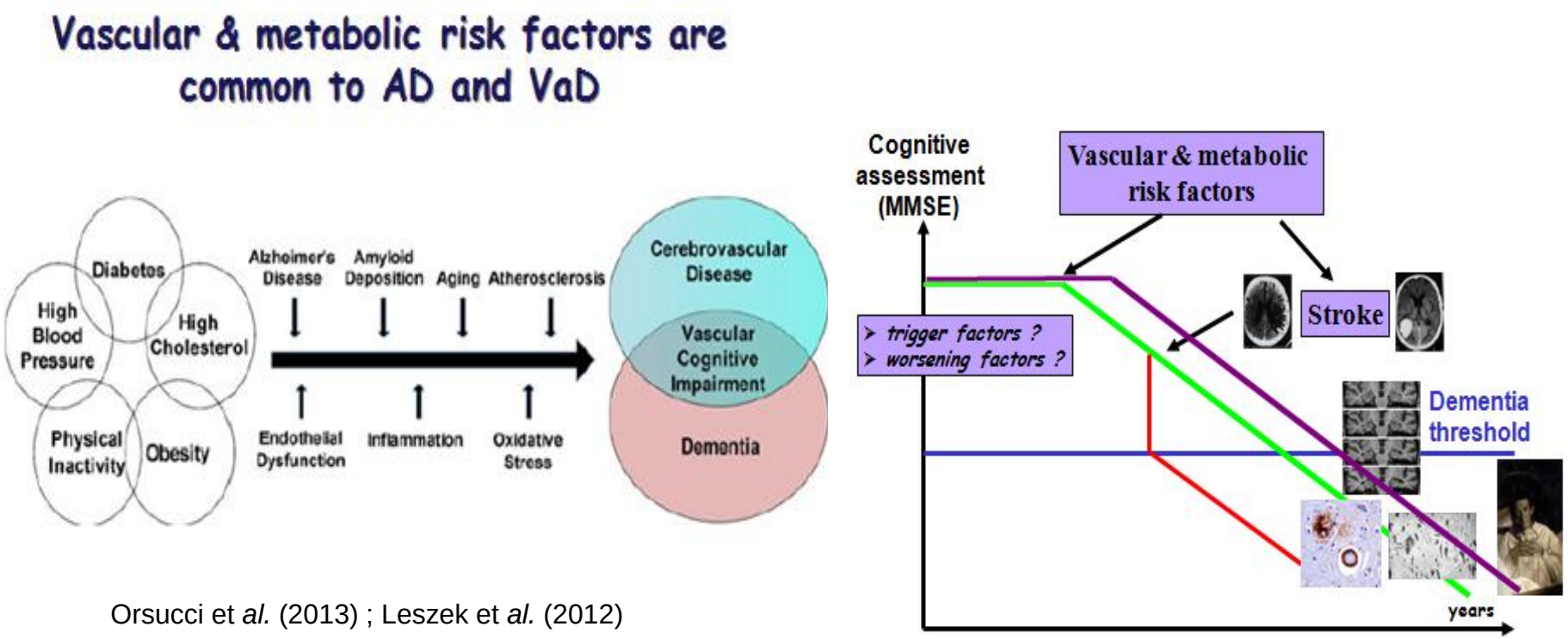
Markers for pathogenesis, pathophysiology or pharmacodynamic response?



Prevention **Disease modifier** **Symptomatic treatment**

Adapted from David Lewis, Robert Sweet: *J. Clinical Investigation* 2009.

Alzheimer's Disease: Vascular, Metabolic & Inflammatory Factors of Vulnerability

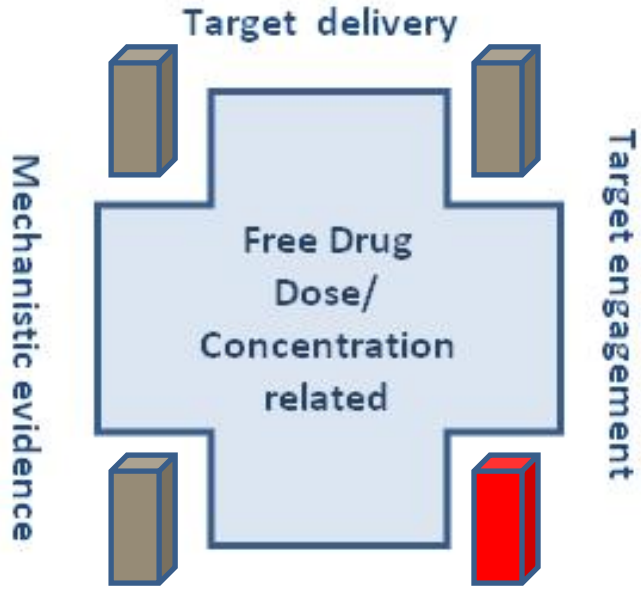


Orsucci et *al.* (2013) ; Leszek et *al.* (2012)

- **Early detection** of these risk factors as **potential targets for prevention** of the onset of cognitive disorders including degenerative ones
- **Interactions** between these factors and neurodegenerative process is also an opportunity **to better understand pathophysiological processes of AD** beyond the classical Amyloïd and Tau cascade

Pilars and Cornerstones

Mechanistic Pathophysiological approaches

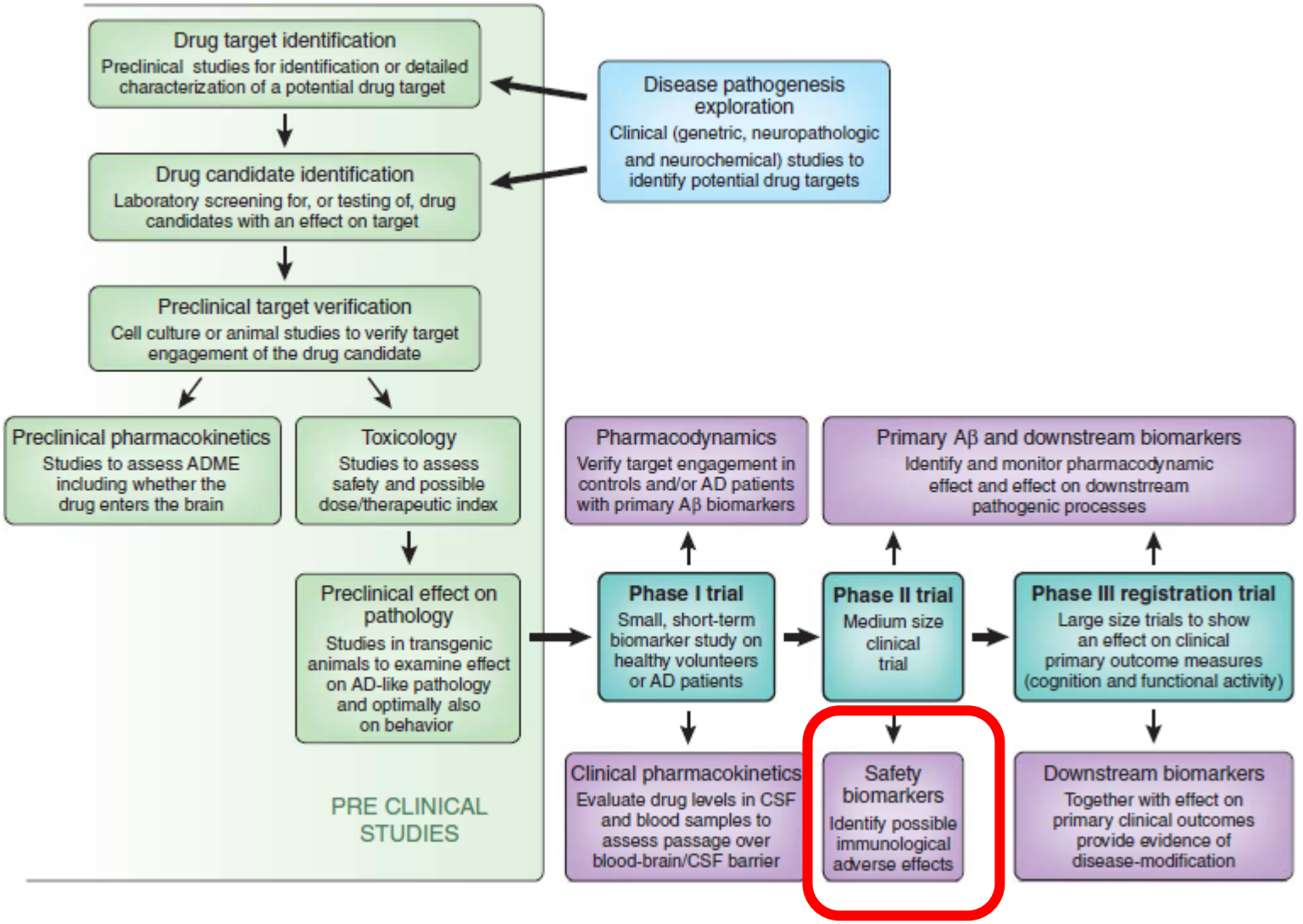


Regulatory approaches

Translatability to clinical efficacy

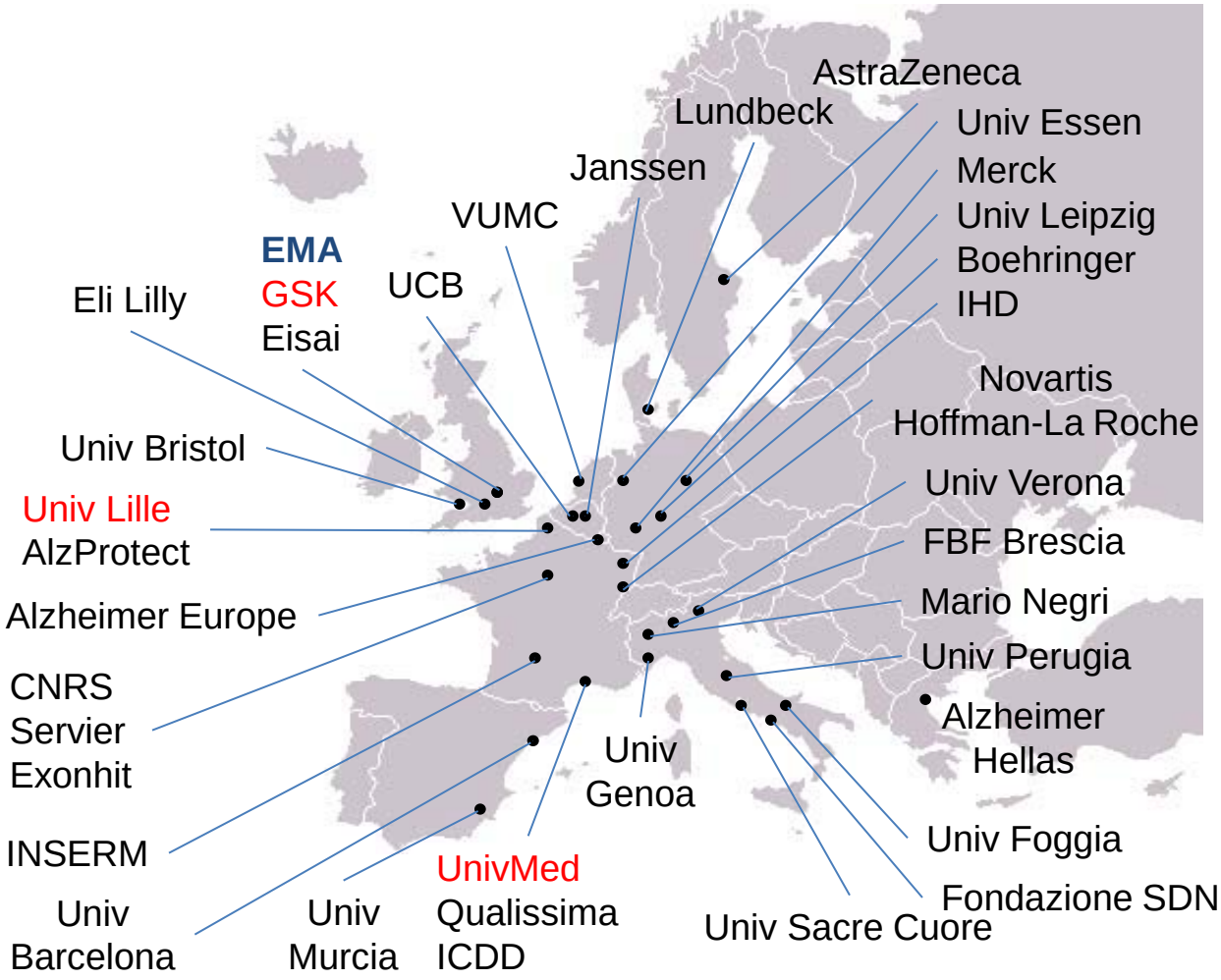
Morgan et al. Drug Discov Today. 2012 May;17(9-10):419-24
Blin et al. Clinical Investigation, 2012, 2(7): 663-665

Position of biomarkers in AD Drug development



Blennow, Neuropsychopharmacology, 2014

Public Private Partnerships are essential to addressing the high hurdles of AD Drug Discovery



Partnership between:
- Academia
- Industry
- SMEs
- Patient Groups
- EMA

Start date: 1/1/2010

Duration: 5 years

Partners: 38

Total cost: €27.7M

Advancing science and treatment of Alzheimer's Disease

Innovative Medicines Initiative

IMI - PharmaCog

Objectives

Develop pre-clinical and clinical models with greater predictive value to support early hint of efficacy studies

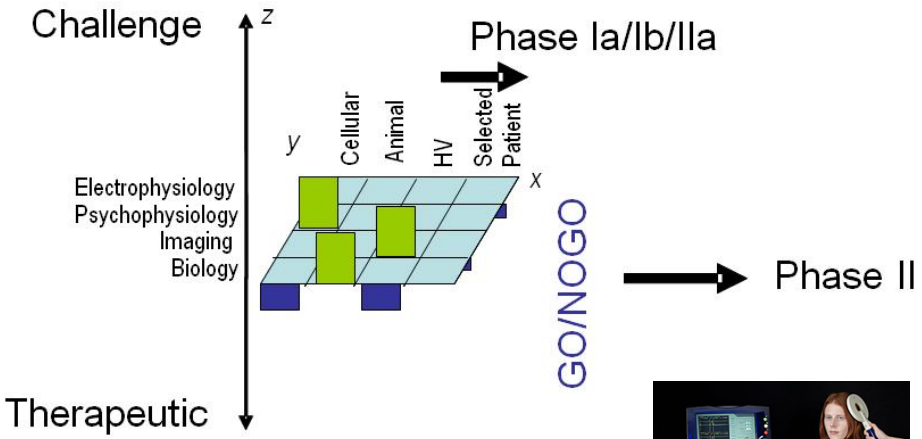
Develop and validate translatable pharmacodynamic markers to support dose selection

Identify and validate markers of disease progression and patient stratification

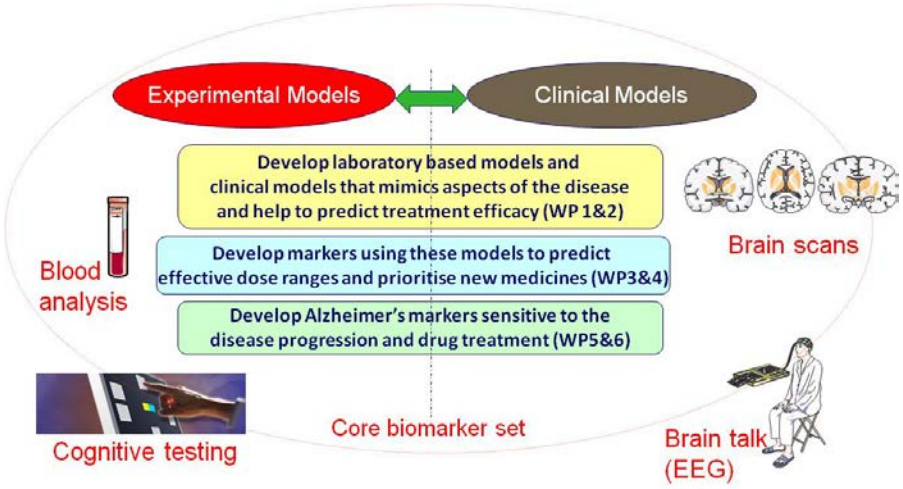
Gain industry and regulatory acceptance of models and markers

Develop pan European network of experts

Matrix development strategy



Selected challenges
rTMS
Sleep Deprivation
Hypoxia

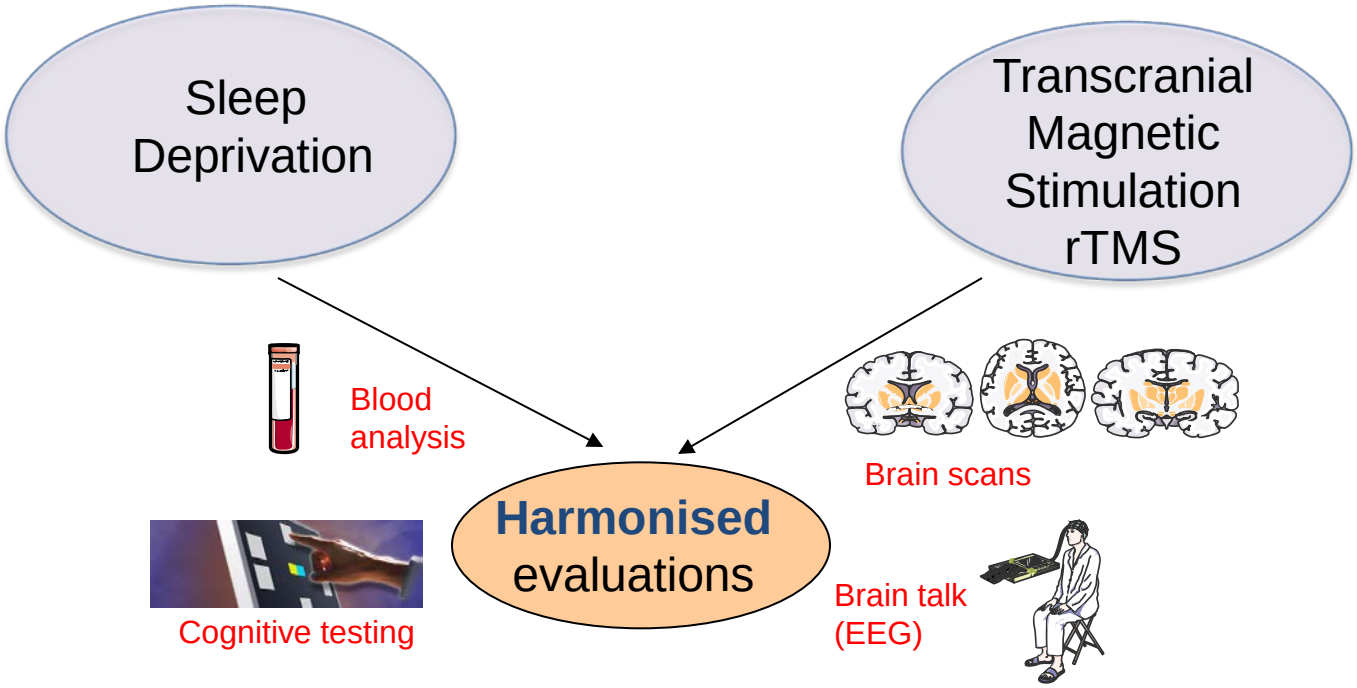


Advancing science and treatment of Alzheimer's Disease

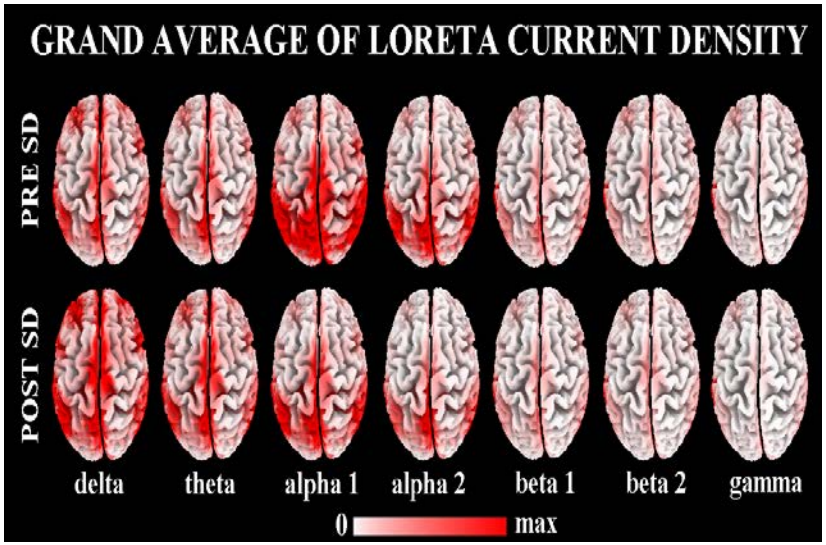
Innovative Medicines Initiative

WP1: Challenge Models of Transient Cognitive Impairment in Healthy Volunteers

Lead: D Bartrès-Faz (Barcelona) & L Lanteaume (Marseille)

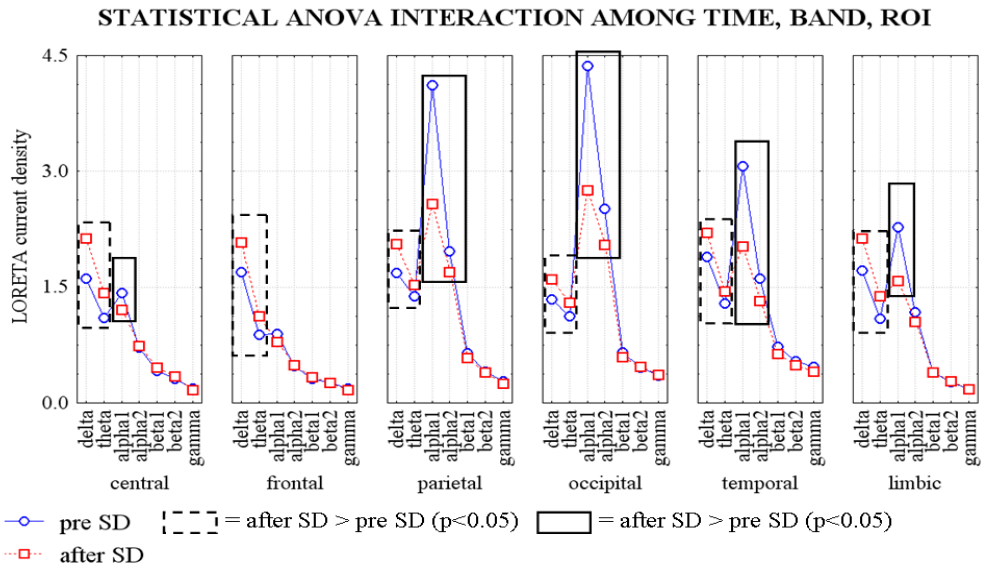


Effects of sleep deprivation on cortical sources of resting state eyes closed EEG rhythms in healthy volunteers are reminiscent of that in AD patients



Mean across individual EEG datasets (grand average, N=75) of the LORETA source solutions (EEG markers) before (pre SD) and after (post SD) SD.

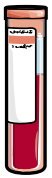
SD induced: (1) an increase of current density values in widespread delta and theta sources and (2) a decrease of current density values posterior alpha 1 and alpha 2 sources.



Grand average of the regional normalized LORETA solutions relative to a statistically significant ANOVA interaction effect (F=14.4; p<0.0001) among the factors Time (pre SD, post SD), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic).

WP5 : Development of Disease Markers in Humans

Lead: G Frisoni (Brescia to Genova) & O Blin (Aix Marseille Univ)

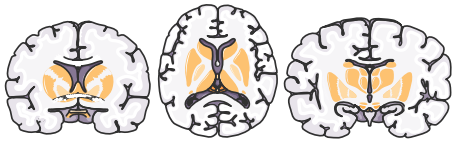


Blood analysis

Brain talk (EEG)

Cognitive testing

2 year follow up of
150 MCI patients
Italy, France, Germany, Spain



Brain scans

Harmonize collection of a new biomarker matrix and qualify multiple centres across Europe

Biomarker matrix in which change over time in MCI patients is most closely related to atrophy development and clinical deterioration/conversion to AD

Biomarker matrix at baseline in MCI patients that is most closely related to atrophy development and/or clinical deterioration/conversion to AD

Novel Disease Markers in Development by SMEs

AlzProtect :

- Platelets: quantification of APP metabolites, namely 55 kD and 25 kD fragments, determined by immunoblotting

Exonhit (now Diaxonhit):

- Lymphocytes: about 150 RNA transcripts including transcripts related to Abeta pathway, to inflammatory pathway and to immune mechanism determined by microarray

Innovative Health Diagnostics (IHD):

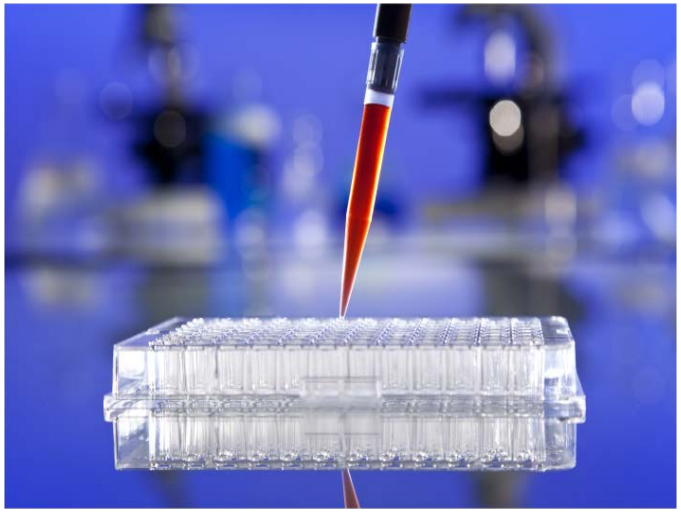
- Red blood cells: binding of Abeta1-42 on cellular membrane and change in PKC conformation, determined by specific fluorescent probes

Innovative Concept in Drug Development (ICDD):

- PBMCs and plasma: mutliplexed panel of 13 inflammatory protein markers – AD Flag

Update on ADFlag Results: A Game Changer for stratification of early presymptomatic AD groups

- 213 SCI, MCI and AD patients collected in 2 longitudinal trials in 14 CIC – end of baseline recruitment in 2014 (The Pharmacog & Alzpredict cohorts).The ADFlag, an **inflammatory** panel of 22 candidates, was measured in 195 patients from the two cohorts
- **6 markers** classify 4 presymptomatic groups with **91% accuracy**, consistently with neuropsychological assessments
- Of these, 65 patients were from the PharmaCog WP5 study and 55% of these were classified according to levels of Abeta42 in the CSF
- The inability to properly stratify AD patients in PoC trials could be a major reason the 99.6% failure rate in AD trials between 2002-2012*



iDD
Innovative Concepts in Drug Development

Assistance Publique
Hôpitaux de Marseille

* http://www.fiercebiotech.com/press-releases/cleveland-clinic-researchers-identify-urgent-need-alzheimers-disease-drug-d?utm_medium=nl&utm_source=internal

Clinical characteristics of 145 MCI by Abeta42 status CSF-pos Abeta42 <550 pg/mL

	All	CSF-positive (n=55)	CSF-negative (n=90)	p
Sociodemographics				
Age	69.2±7.3	69.8±6.7	68.8±6.7	.40
Education	10.6±4.4	11.3±4.5	10.1±4.3	.11
Sex (F)	83 (57%)	31 (56%)	52 (58%)	.87
Cognitive history				
Onset of cognitive symptoms (years)	3.0±2.6	2.6±1.7	3.3±3.0	.12
Family history of dementia	57 (39%)	16 (29%)	41 (46%)	.05
Cognition, function, mood, and behaviour				
Mini Mental State Examination	26.6±1.8	26.1±1.7	27.0±1.8	.005
ADAS-cog				
Functional Assessment Questionnaire	2.6±2.5	2.6±2.5	2.6±2.6	.82
Geriatric Depression scale	2.4±1.8	2.4±1.8	2.5±1.9	.72
Neuropsychiatric Inventory	8.6±10.5	9.6±11.0	8.1±10.2	.43

Neuropsychological characteristics of 145 MCI by Abeta42 status (1/2)

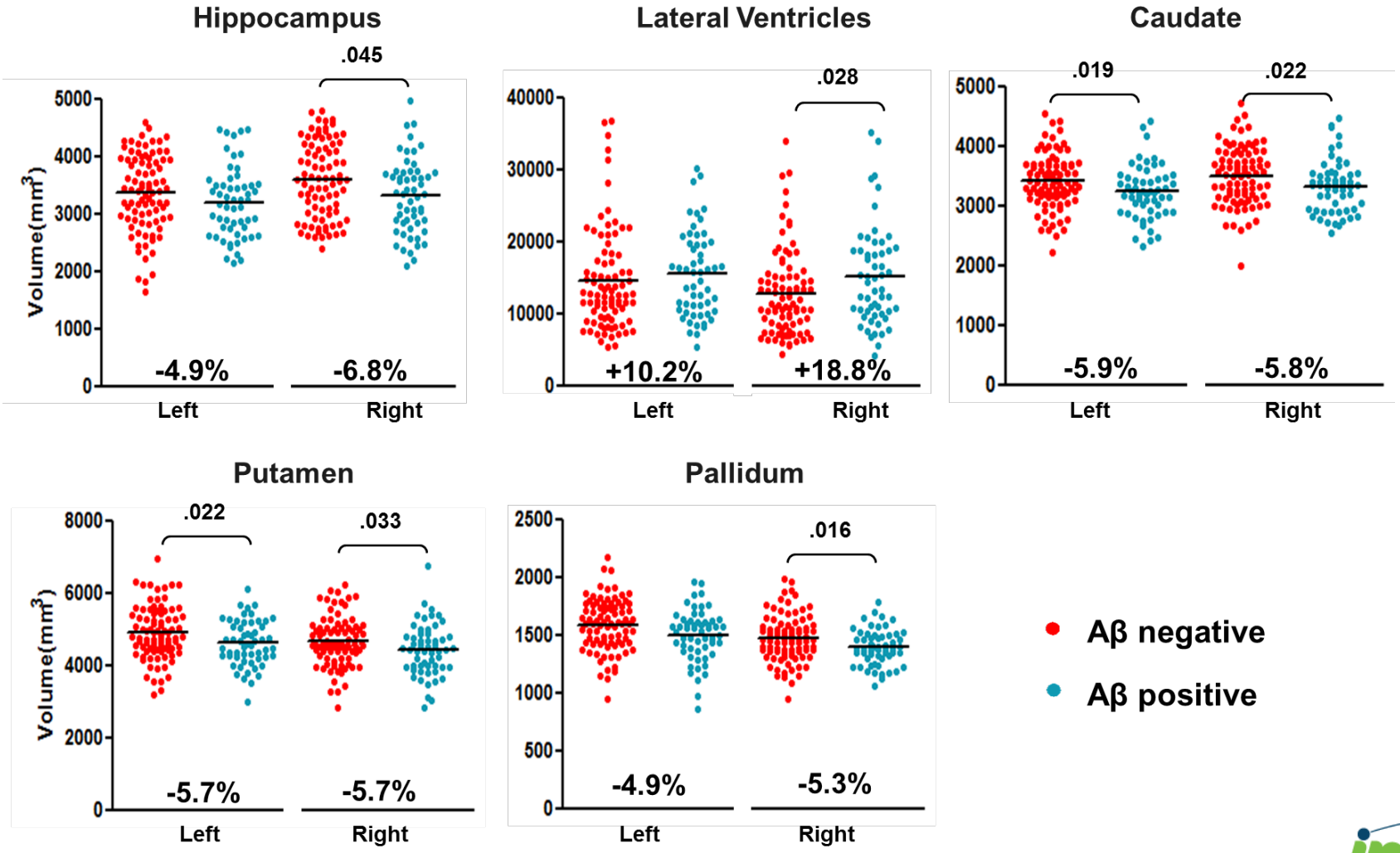
	All	CSF-positive (n=55)	CSF-negative (n=90)	p
Verbal memory				
AVLT, immediate recall	31.2±9.7	29.2±8.4	32.4±10.3	.05
AVLT, delayed recall	4.3±3.2	3.7±3.1	4.6±3.3	.11
Visual memory				
Paired associates learning test (n. of errors)*	19.2±11.6	19.8±11.9	18.7±11.4	.63
Delayed matching to sample (% correct all delays) *	68.0±16.5	62.7±16.9	72.0±15.1	.002
Pattern recognition memory test (% correct) *				
immediate	77.4±15.4	75.5±14.7	79.0±15.9	.23
delayed	65.0±18.0	63.5±17.6	66.1±18.3	.44
Spatial recognition memory test (% correct) *	63.8±13.3	58.8±12.9	67.5±12.5	<.0005
Working memory				
Digit Span forward	5.4±1.1	5.4±1.1	5.3±1.2	.78
Digit Span backward	3.8±1.1	3.8±1.0	3.8±1.1	1.00
Spatial working memory test (n. of errors) *	43.2±21.4	48.3±21.3	39.4±20.8	.02

Genetic and CSF features of MCI by Abeta42 status

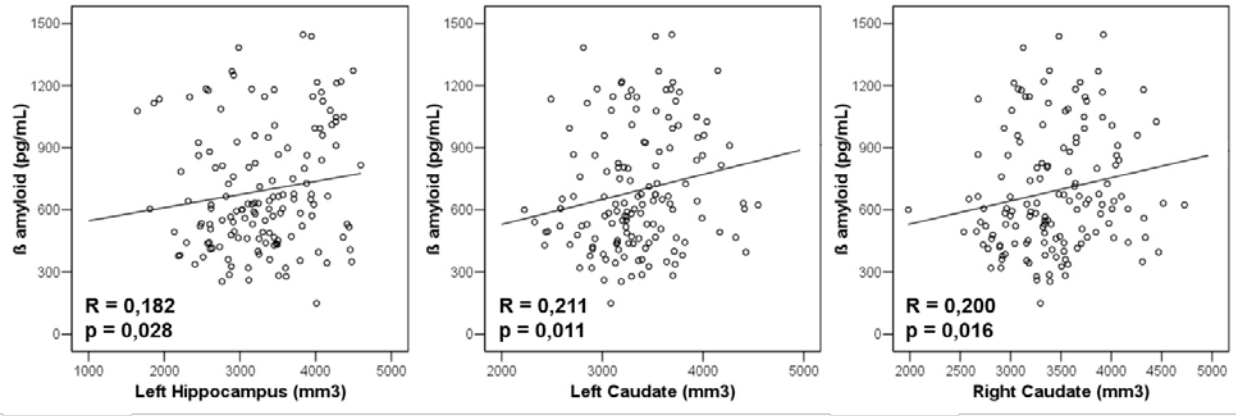
	CSF-positive (n=55)	CSF-negative (n=90)	p
ApolipoproteinE alleles, 1 or more			
E2	3 (8%)	5 (9%)	.88
E3	27 (75%)	54 (100%)	<.0005
E4	29 (81%)	17 (32%)	<.0005
CSF			
Tau (pg/ml)	556±335	426±346	.03
p-tau (pg/ml)	79±38	61±31	.002

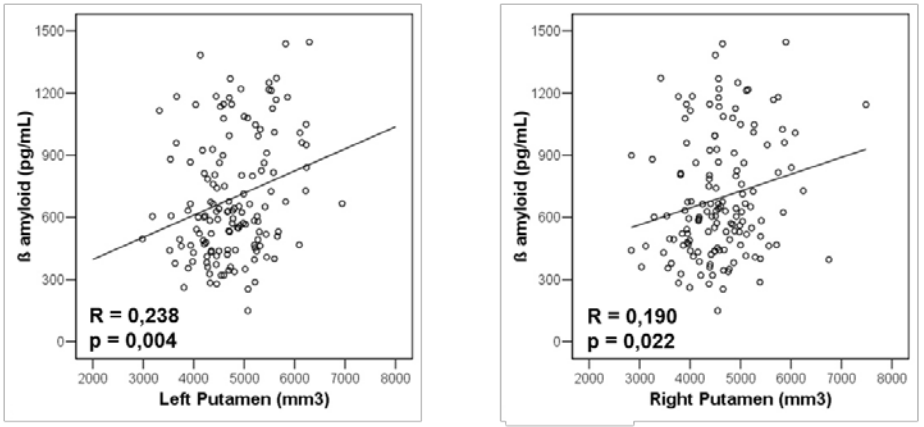
MRI – Brain volume estimates in 145 MCI by Abeta42 status

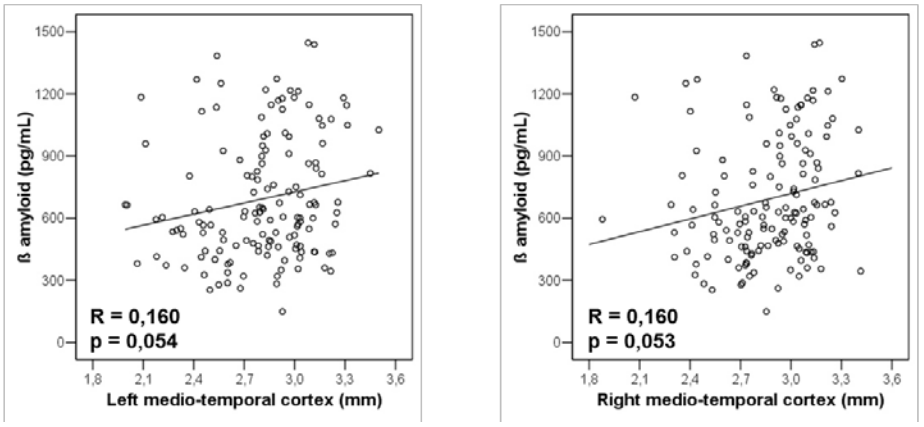
Task force leaders: Jorge Jovicich and Moira Marizzoni



Advancing science and treatment of Alzheimer's Disease





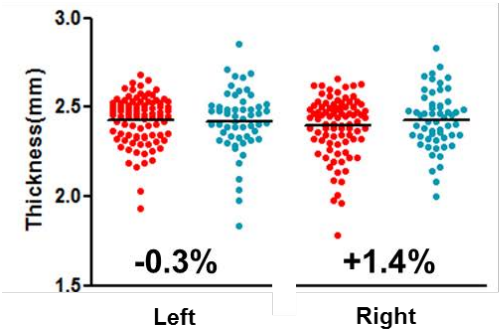


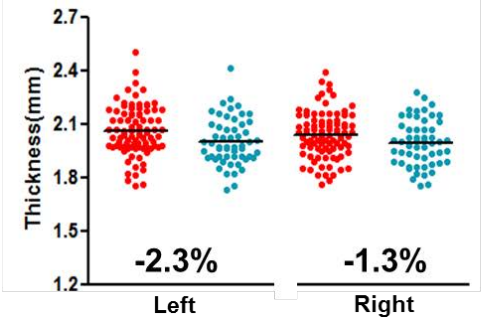
MRI – Morphometric correlations with Aβ CSF levels

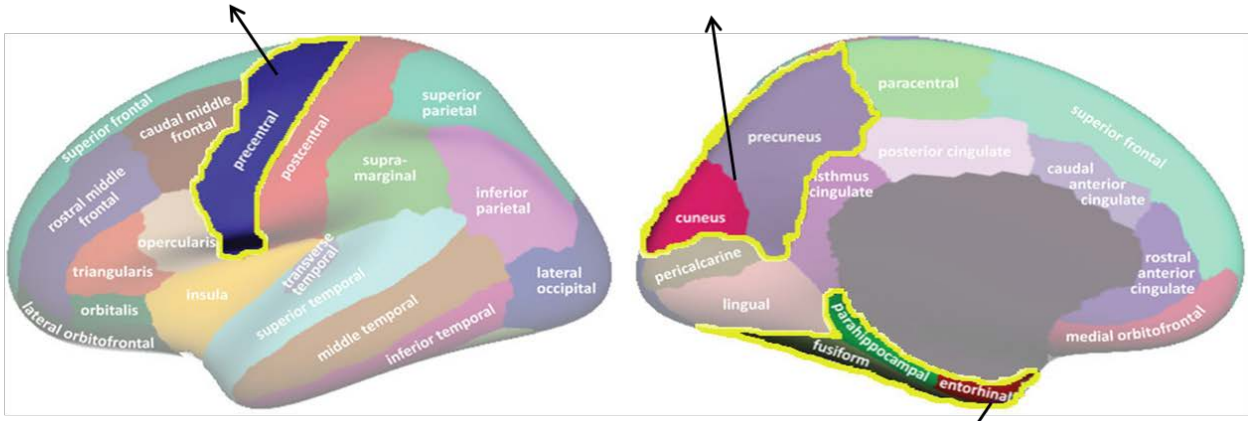
Task force leaders: Jorge Jovicich and Moira Marizzoni

MRI – Cortical thickness estimates in 145 MCI by Abeta42 status

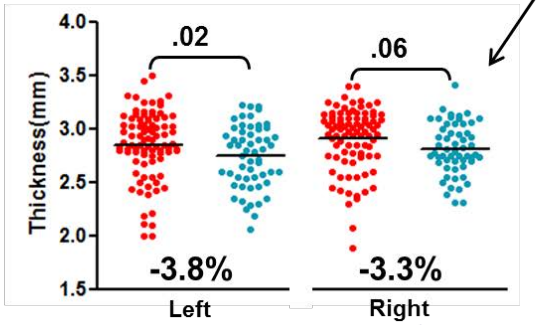
Task force leaders: Jorge Jovicich and Moira Marizzoni







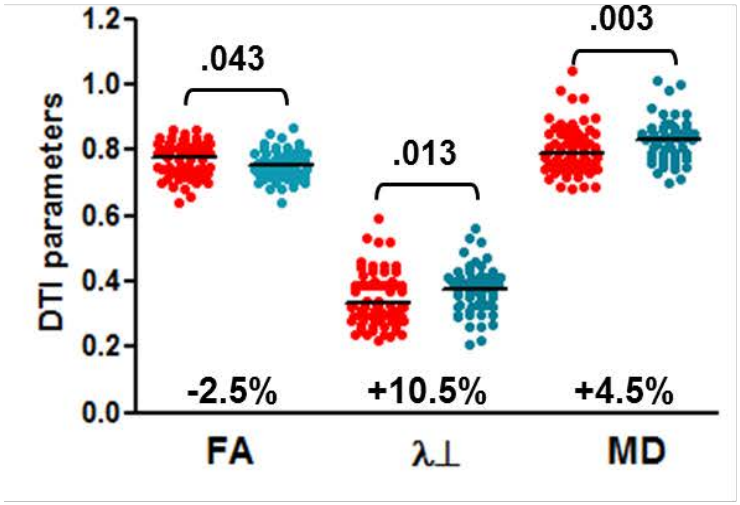
- Aβ negative
- Aβ positive

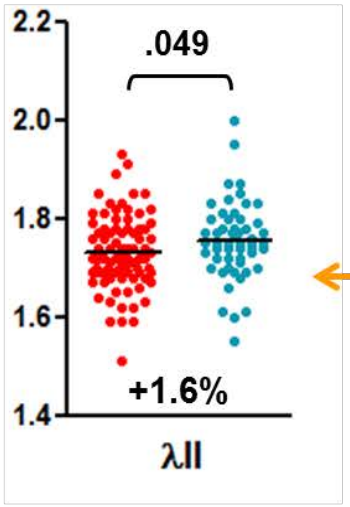


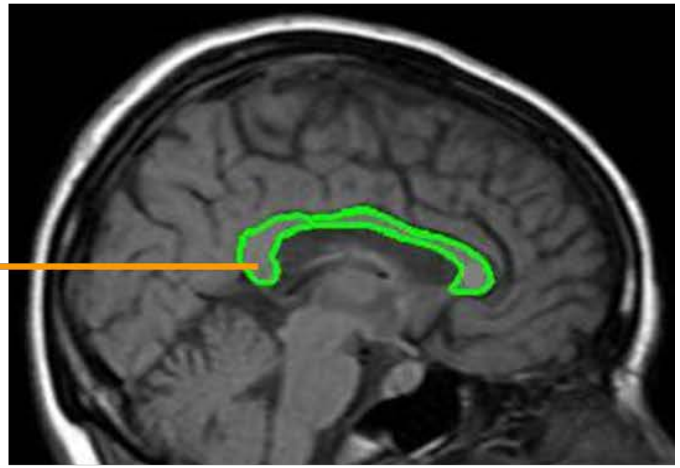
Advancing science and treatment of Alzheimer's Disease

MRI – Brain diffusion estimates in 145 MCI by Abeta42 status

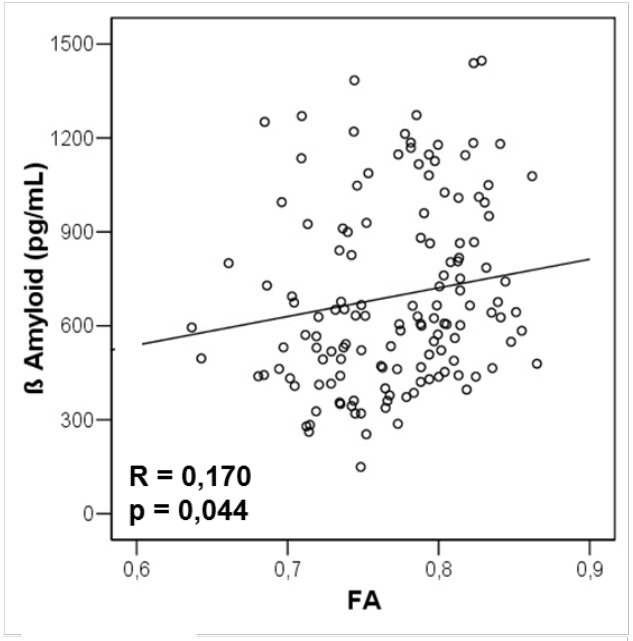
Task force leaders: Jorge Jovicich and Moira Marizzoni

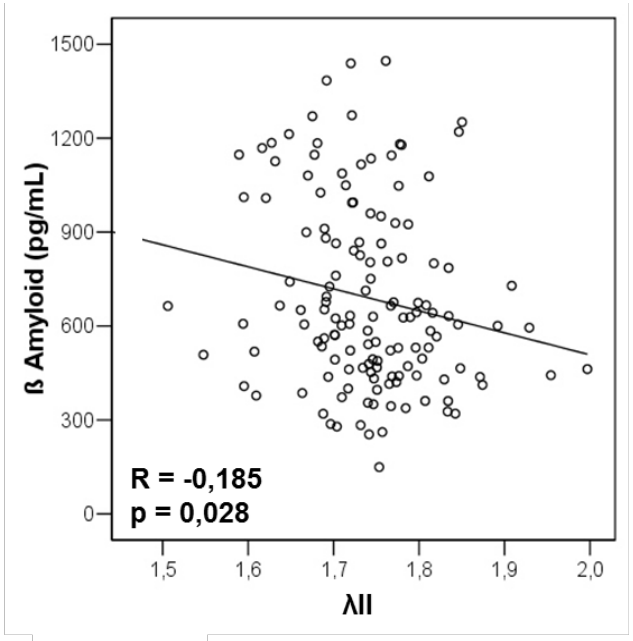


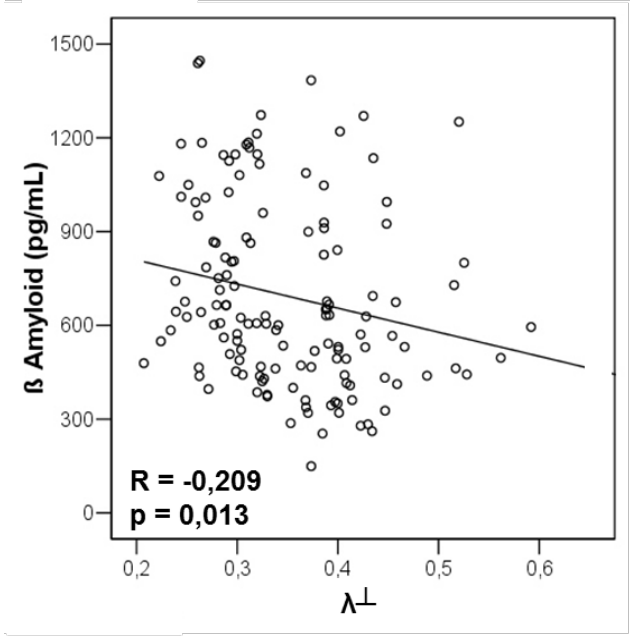


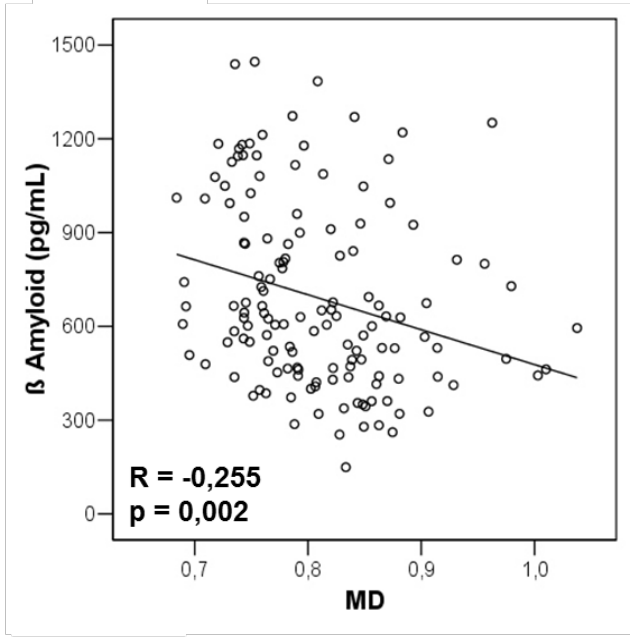


Aβ negative Aβ positive







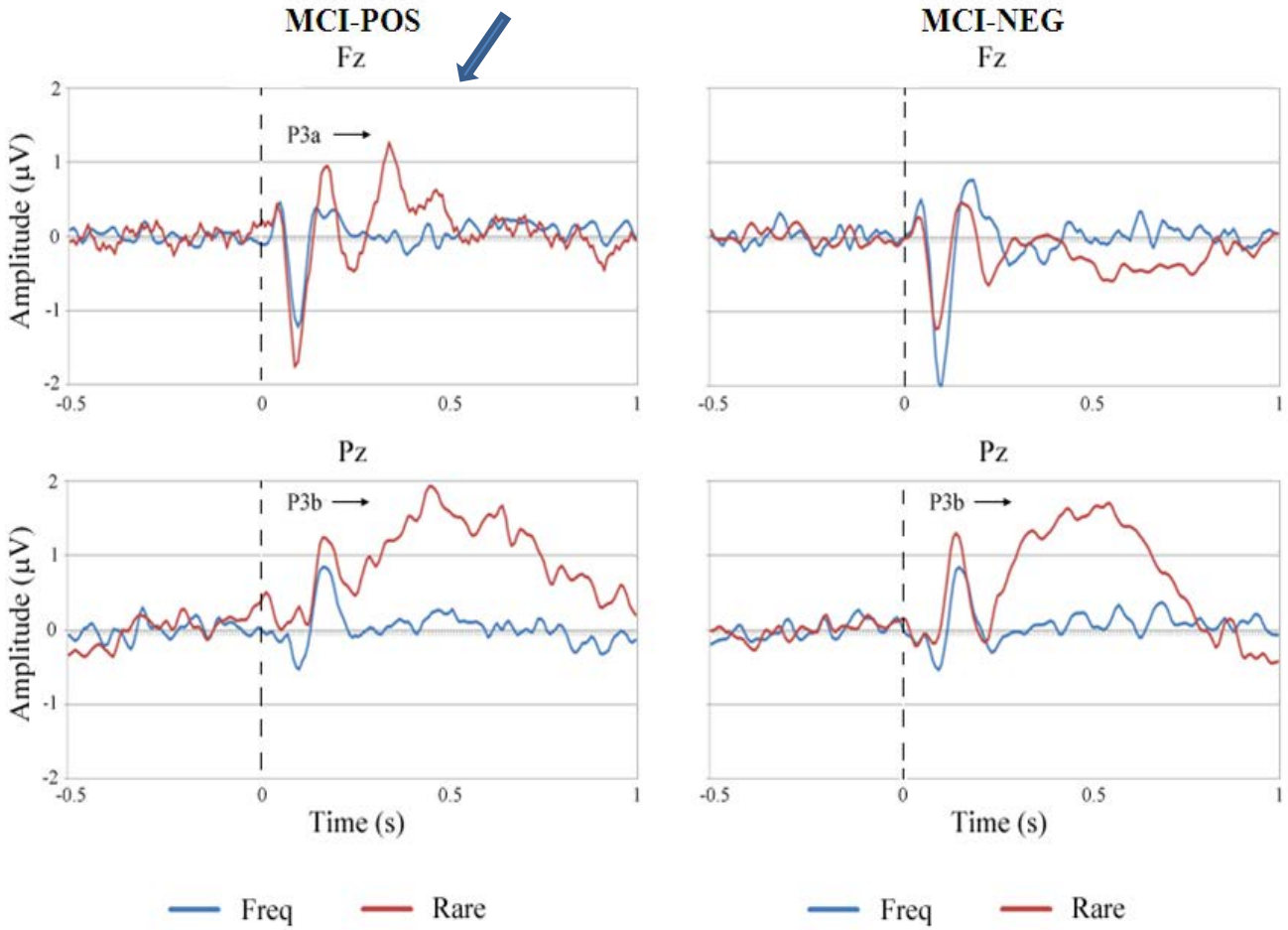


MRI – Splenium of the corpus callosum diffusion indices correlations with Aβ CSF levels

Task force leaders: Jorge Jovicich and Moira Marizzoni

Relationship between EEG auditory oddball event-related potentials (P3 component) and CSF Aβ level in amnesic MCI subjects: analysis at scalp electrodes

Recording units: Brescia, Perugia, Genoa, Naples , Rome, Barcelona, Marseille, Toulouse, Lille, Leipzig Duisburg-Essen, Thessaloniki **Data analysis unit:** University of Foggia (UNIFG)
Subjects: 107 amnesic MCI subjects subdivided into those with high CSF Aβ level (MCI-NEG, N=58, CSF Aβ>550 pg/ml) and those with low CSF Aβ level (MCI-POS, N=34, CSF Aβ<550 pg/ml),



Grand average waveforms of event related potentials (P3) for the MCI-POS and MCI-NEG subjects. The ERPs refer to rare and frequent stimuli at midline frontal (Fz) and parietal (Pz) electrodes.

We observed :

(1) a frontal positive peak at around 200–400 ms post-stimulus (P3a). The P3a peak was higher in the rare compared to the frequent stimuli only in MCI-POS subjects

(2) a parietal positive peak at around 400-600 ms post stimulus (P3b). The P3b peak was higher in the rare compared to the frequent stimuli in both MCI-POS and MCI-NEG subjects

From PharmaCog to H2020

NEXT STEPS

IMI 2 OPPORTUNITIES

RADAR PROGRAMME OFFICE COORDINATION
AND DATA SHARING
"Improve patient outcomes through remote assessment"

RADAR TOPIC 1: CNS

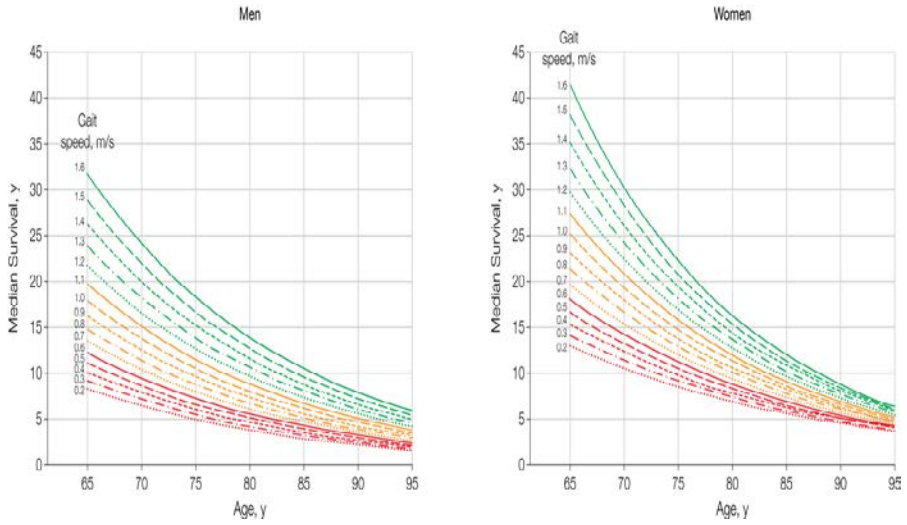
Initial Focus
Unipolar
Depression,
Multiple Sclerosis
and Epilepsy

Long-term goal
includes
Bipolar Disease,
Alzheimer's,
Schizophrenia and
Pain.

Remote Mobility Assessment as an outcome for neurodegeneration Application 28 aug 2014

Project acronym: MOBILe
Project full title: Maintaining mobility in older people; development and impact of personalised interventions
Topic: MG.3.4-2014 “Traffic safety analysis and integrated approach towards the safety of vulnerable road users”
Funding scheme: Research and Innovation Action
Name of coordinating person: Prof. Olivier BLIN
Coordinator organisation name: Aix-Marseille University

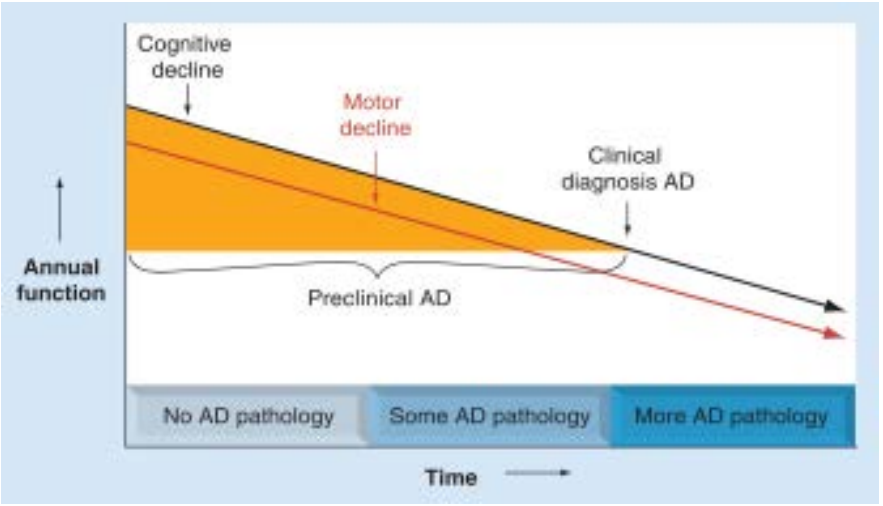
Motor function as early biomarker for Alzheimer's disease



Predicted Median Life Expectancy by Age and Gait Speed

Studenski, S. et al. JAMA 2011;305:50-58

Loss of motor function in preclinical Alzheimer's disease



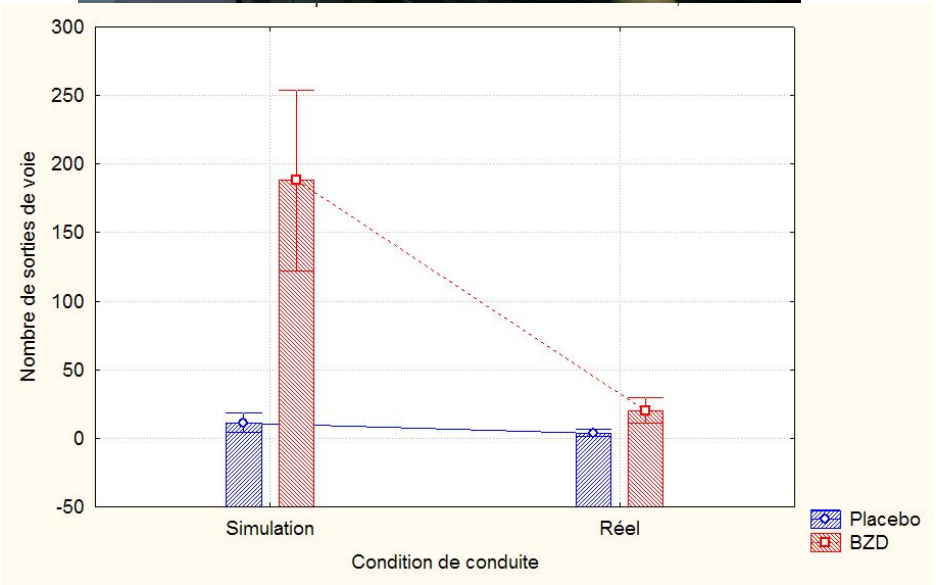
Buchman & Bennett, 2011

An illustration of previous Development of experimental paradigm using Virtual reality

-Comparison of driving performances on Simulator and Real Highway

-A single dose placebo double blind controlled trial of lorazepam 2mg

-Same paradigm used with cannabis

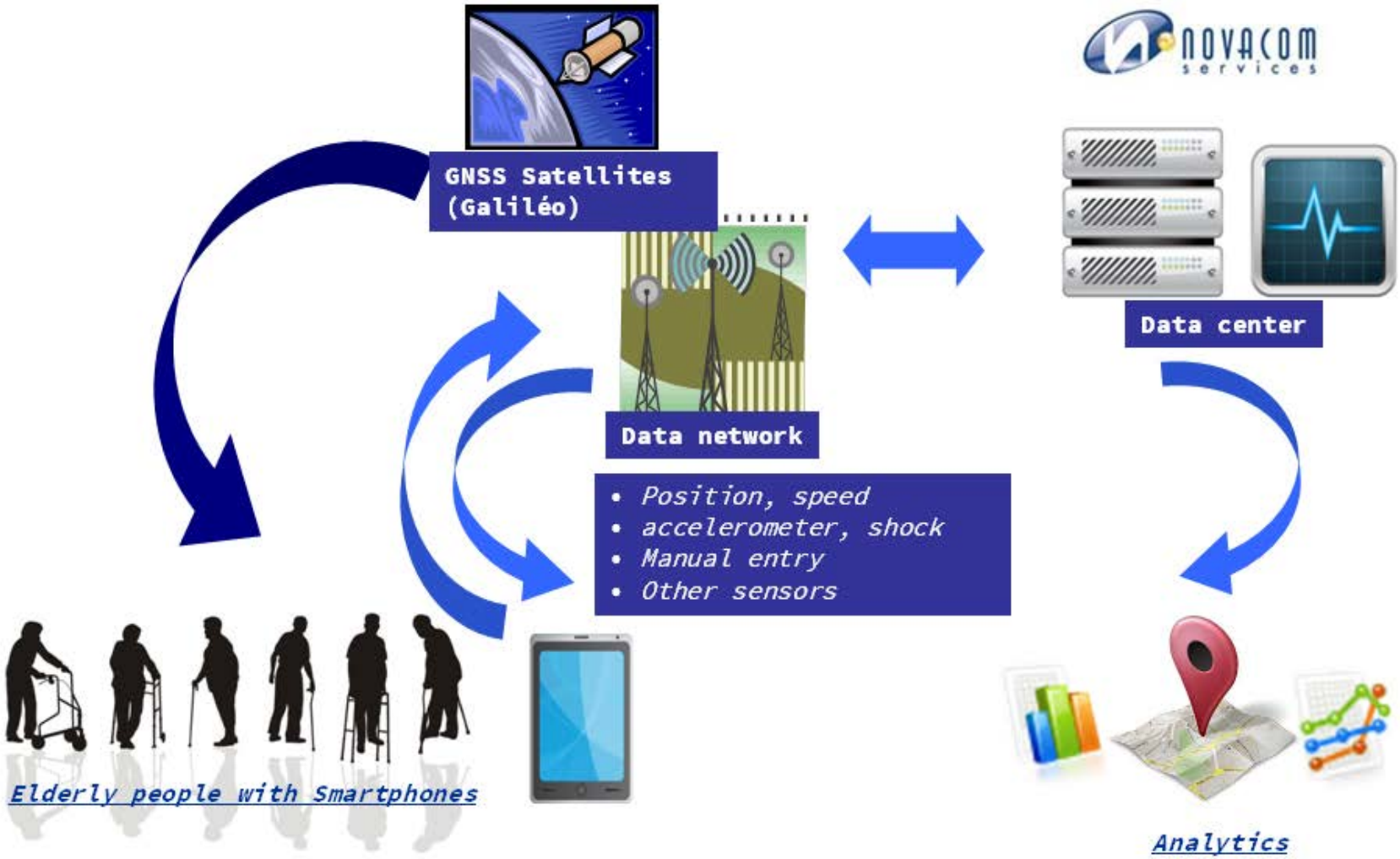


Collaboration Clinical Pharmacology &Center Reality Virtual; Marseille, O Blin & D Mestre

Medico ANR Grant, 2009

Patient shaped biomarkers

MOBILE SYSTEM FOR FIELD DATA COLLECTION



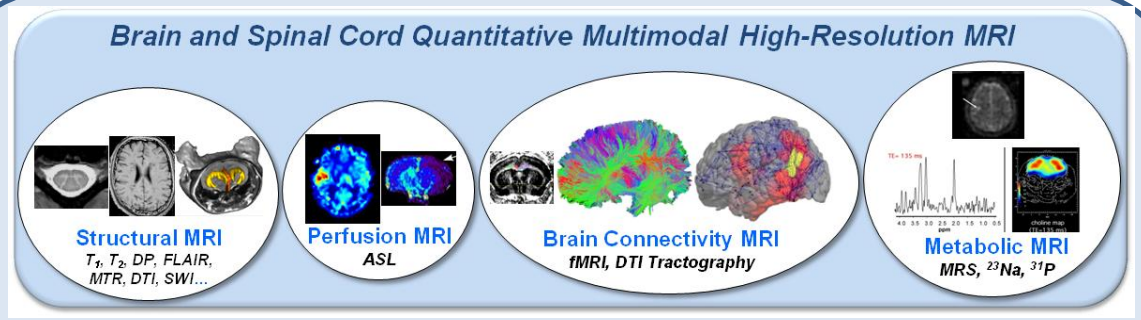
IMI 2 OPPORTUNITIES

LINKING CLINICAL NEUROPSYCHIATRY AND QUANTITATIVE NEUROBIOLOGY

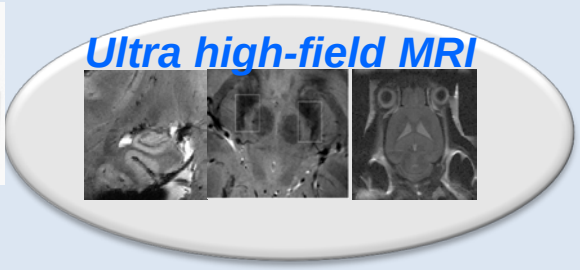
- Biological substrates of neuropsychiatric symptom constellations through the use of quantitative technologies.
- New classification (symptom constellations and biological correlates)
- Predictive systems for the exploration of the underlying biological process toward novel therapies or targets.
- Beneficial effect on healthcare costs (identification of the right patient for a given treatment of a specific symptom constellation)
- Proof-of-principle evidence to begin engagement with the regulatory authorities

IMI2: New Engine / CNS factory

Linking
Pre-existing consortia (EU and USA)
European networks
Research Infrastructures
Bio-informatic tools & Big Data



7T



11.5T

Cognition
Subtle changes
Dimensional approach
Relation with biomarkers

Mechanistic biomarkers
(Inflammatory, Neuroimmunology, UPR)
Neuronal Injury
VILIP1, sAPPß

PETscan

18F-TSPO PET imaging of microglial activation
68Ga-RGD nanoparticle for angiogenesis imaging
99mTc-Annexin 128 for apoptosis imaging
99mTc-DTPA for BBB disrupture imaging

Key points

Biomarkers will help to deliver (IMI2 SRA)
'the right prevention and treatment for the right patient at the right time'
They are of use for enrichment of the population
They will give additional/individual data as regards to the continuum of AD
They can avoid masking a drug effect depending of the MoA
They can increase population homogeneity (and results extrapolation)

Difficulties
Change over time might not be linear
Qualification of biomarkers : costly and time consuming
Homogeneity (preanalytics, methods…) is a critical aspect

Limitations
Correlation with function and cognitive decline/recovery
With the lack of positive control drug, the PPV is impossible to establish (yet)
Biomarkers are not surrogate endpoints (yet)

Consequence
Rapid concerted efforts are needed to sustain research in the field

Acknowledgements: The Pharmacog Team

- **David Bartres-Faz**, University of Barcelona
- **Laura Lanteaume, Isabelle Evrard-Amabile,** University of Marseille
- **Fabien Pifferi**, CNRS
- **Regis Bordet**, University of Lille
- **Xavier Langlois**, Janssen
- **Giovanni Frisoni, Cristina Bagnoli,** IRCCS Fatebenefratelli
- **Sophie Dix**, Eli Lilly & Co. Ltd
- **Gianluigi Forloni**, Mario Negri Istituto di Ricerche Farmacologiche
- **Claudio Bablioni**, University of the Studies of Foggia
- **Alex Teligadas,** Alzheimer Europe
- **Peter Schoenknecht**, Universitätklinikum Leipzig
- **Maria-Trinidad Herrero Ezquerro**, Universidad de Murcia
- **Philipp Spitzer**, Universität Duisburg-Essen
- **Severine Pitel**, Qualissima
- **Maria Isaac,** EMA
- **Pascal Beurdeley**, Exonhit
- **Jean de Barry**, Innovative Health Diagnostics
- **Nathalie Compagnone**, Innovative Concept in Drug Development
- **Bernd Sommer**, Boehringer Ingelheim Pharma GmbH & Co KG
- **Cristina Lopez Lopez**, Novartis Pharma AG,
- **Esther Schenker**, Institut de Recherche Servier
- **Heike Hering**, Merck Serono S.A.
- **Emilio Merlo-Pich**, F. Hoffmann-La Roche
- **Jan Egebjerg**, H. Lundbeck A/S
- **Yves Lamberty**, UCB
- **Jill Richardson, Oscar della-Pasqua, Lesley Stubbins, David Wille**, **Graham Somers** GlaxoSmithKline R&D Ltd
- **Pierre Payoux**, Institut National de la Santé et de la Recherche Médicale
- **Marina Bentivoglio**, University of Verona
- **Philippe Verwaerde**, Alzprotect
- **Lee Dawson**, Eisai