center for
biomedical
technology

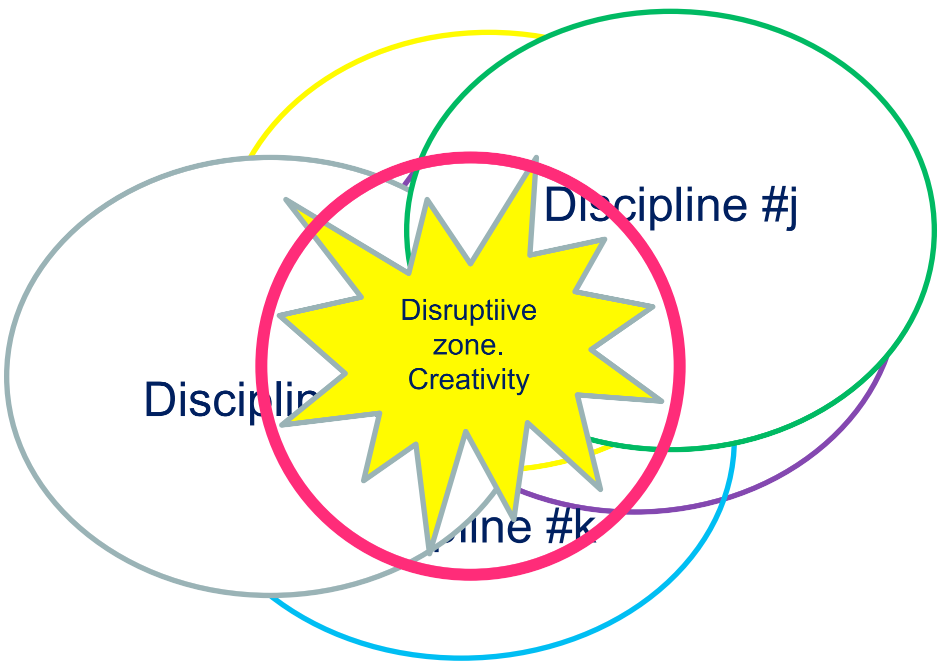
POLITÉCNICA
"Ingeniamos el futuro"

CAMPUS
DE EXCELENCIA
INTERNACIONAL

Disruptive healthcare technology: The case of Alzheimer Disease

Francisco del Pozo
Centro de Tecnología Biomédica CTB
Universidad Politécnica de Madrid UPM
Parque Científico y Tecnológico de Montegancedo
www.ctb.up.es

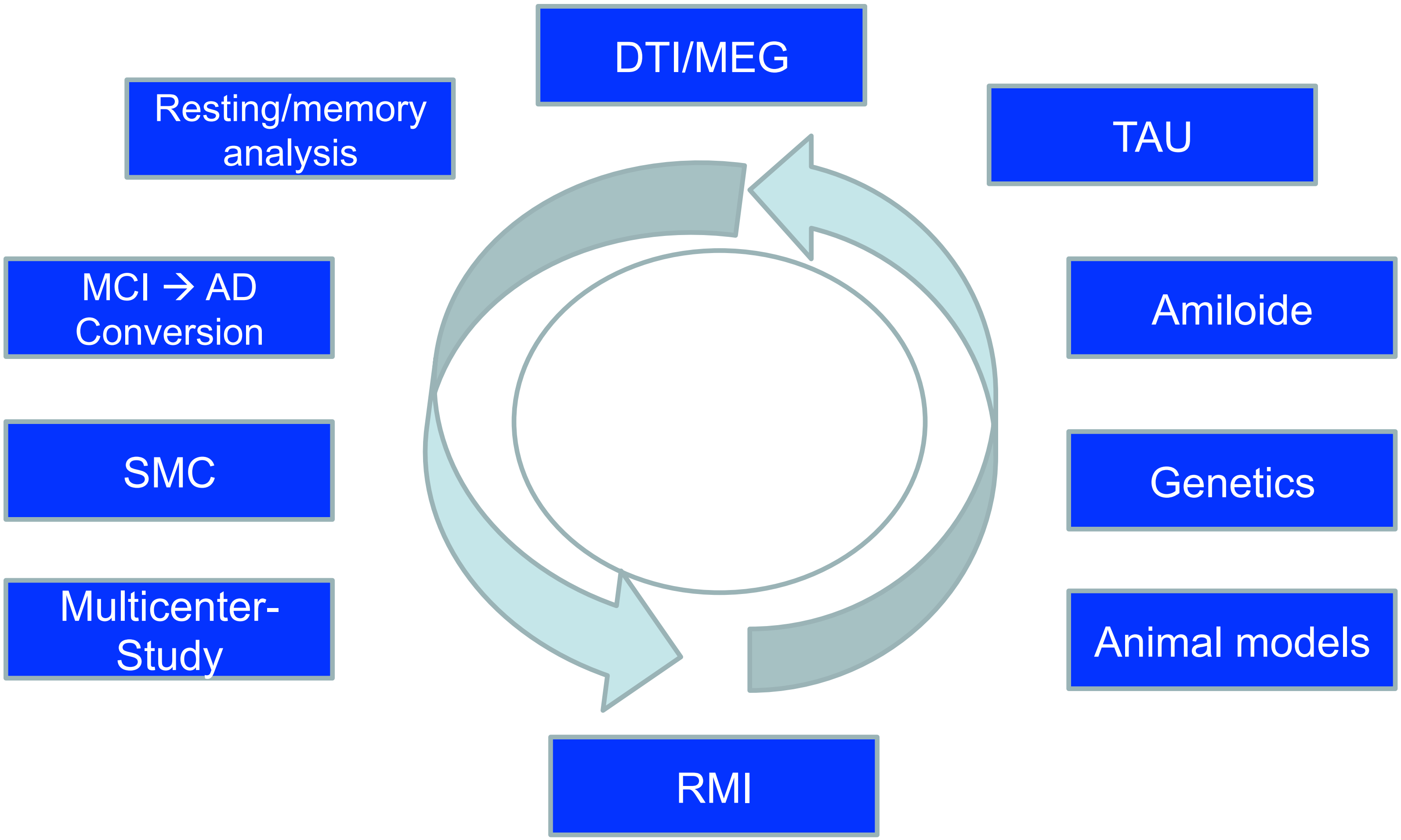
The disruptive condition of technology can arise from the aggregated application of several technologies, which normally act separately



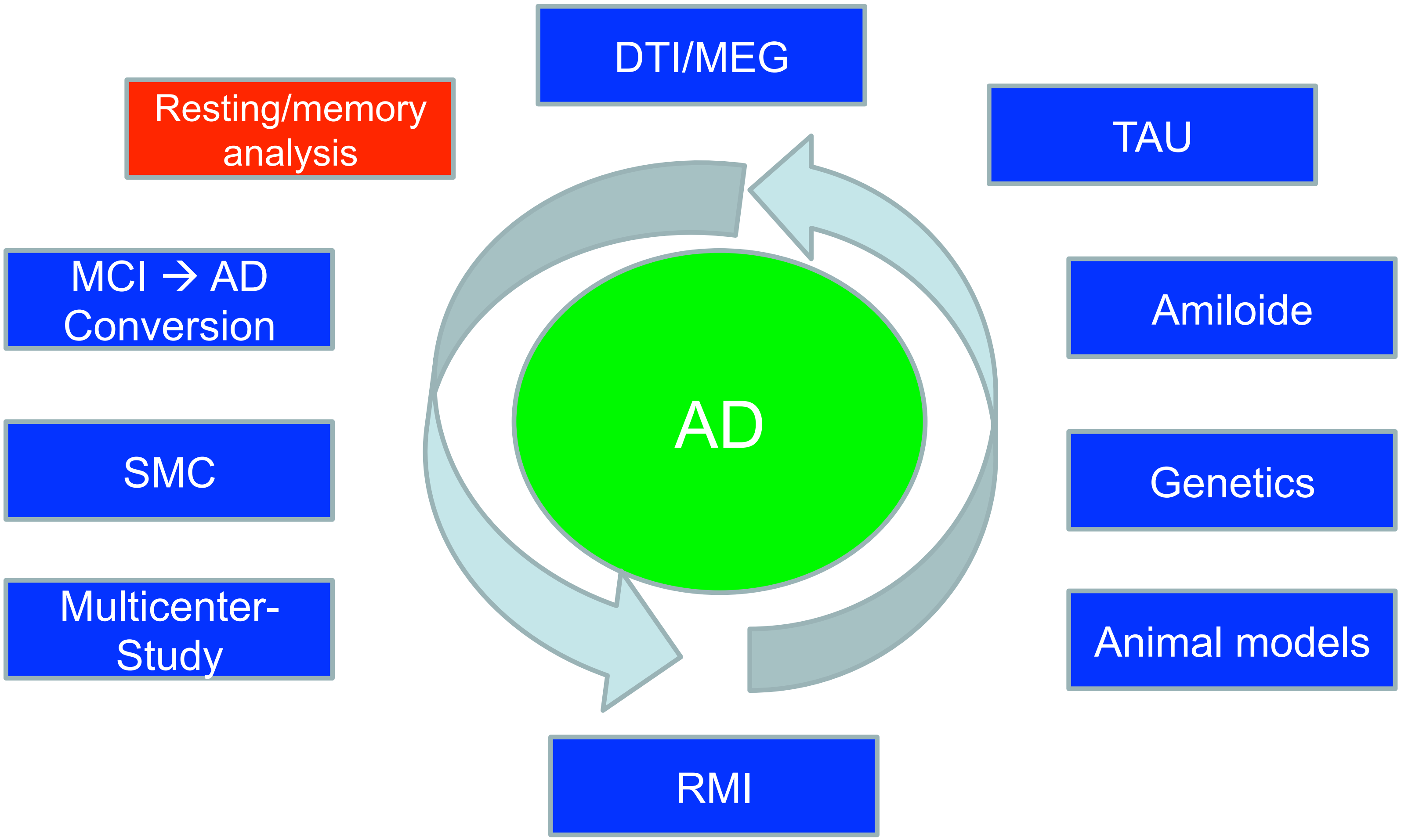
CTB center for biomedical technology

Technology for the early detection of AD: A multidimensional approach

POLITÉCNICA

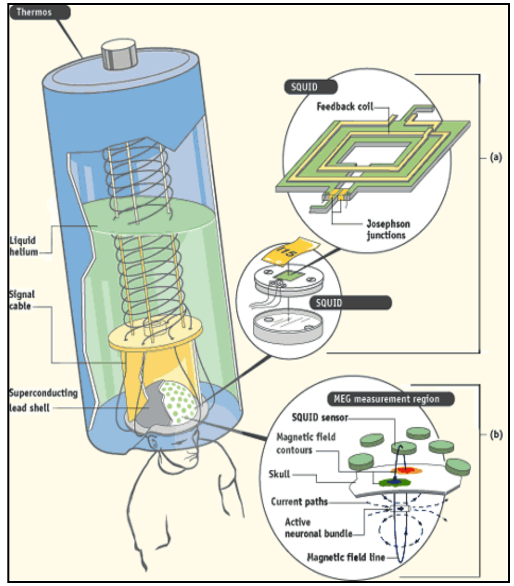


Technology for the early detection of AD: A multidimensional approach

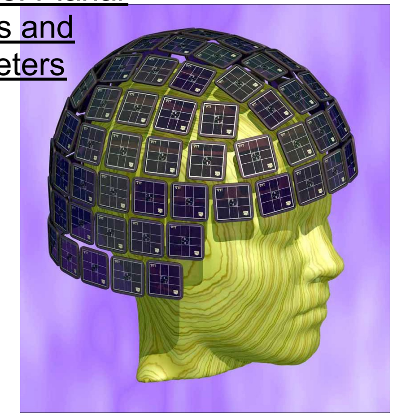


center for biomedical technology

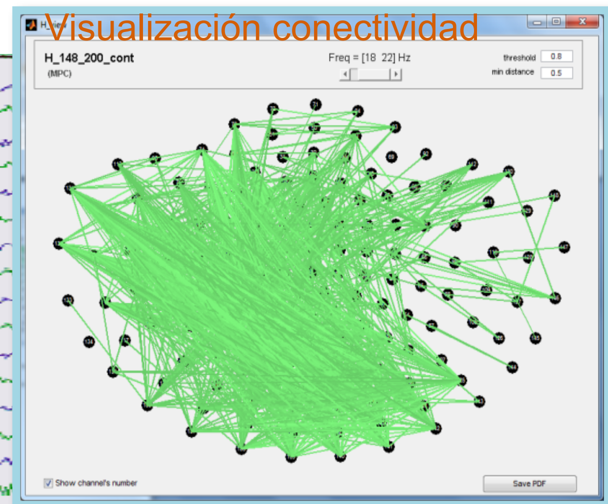
MEG recordings



306 sensors: Planar radiometers and magnetometers

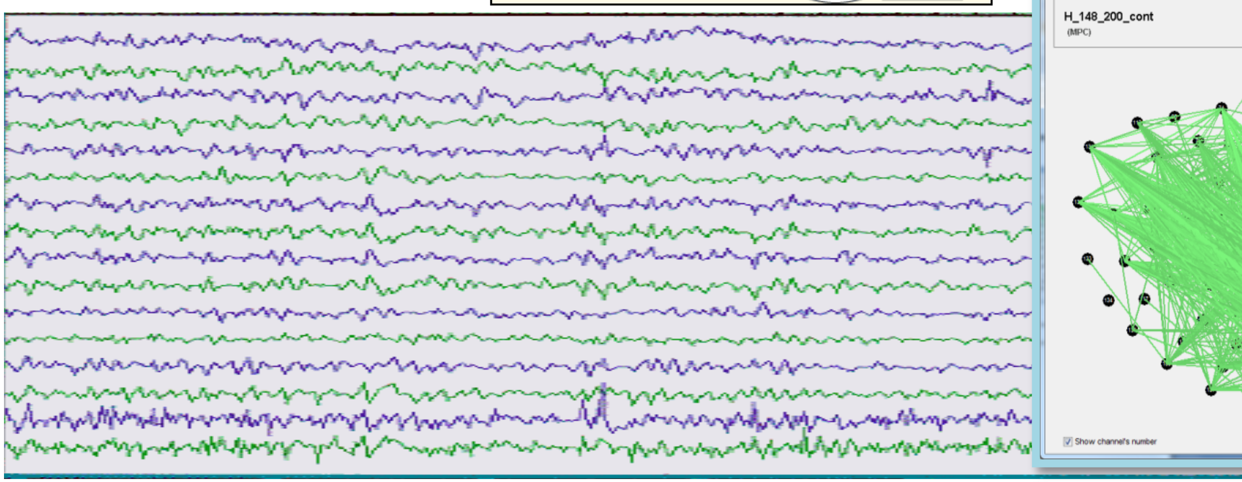


Visualización conectividad



Channel #1

MAGNETIC FIELD



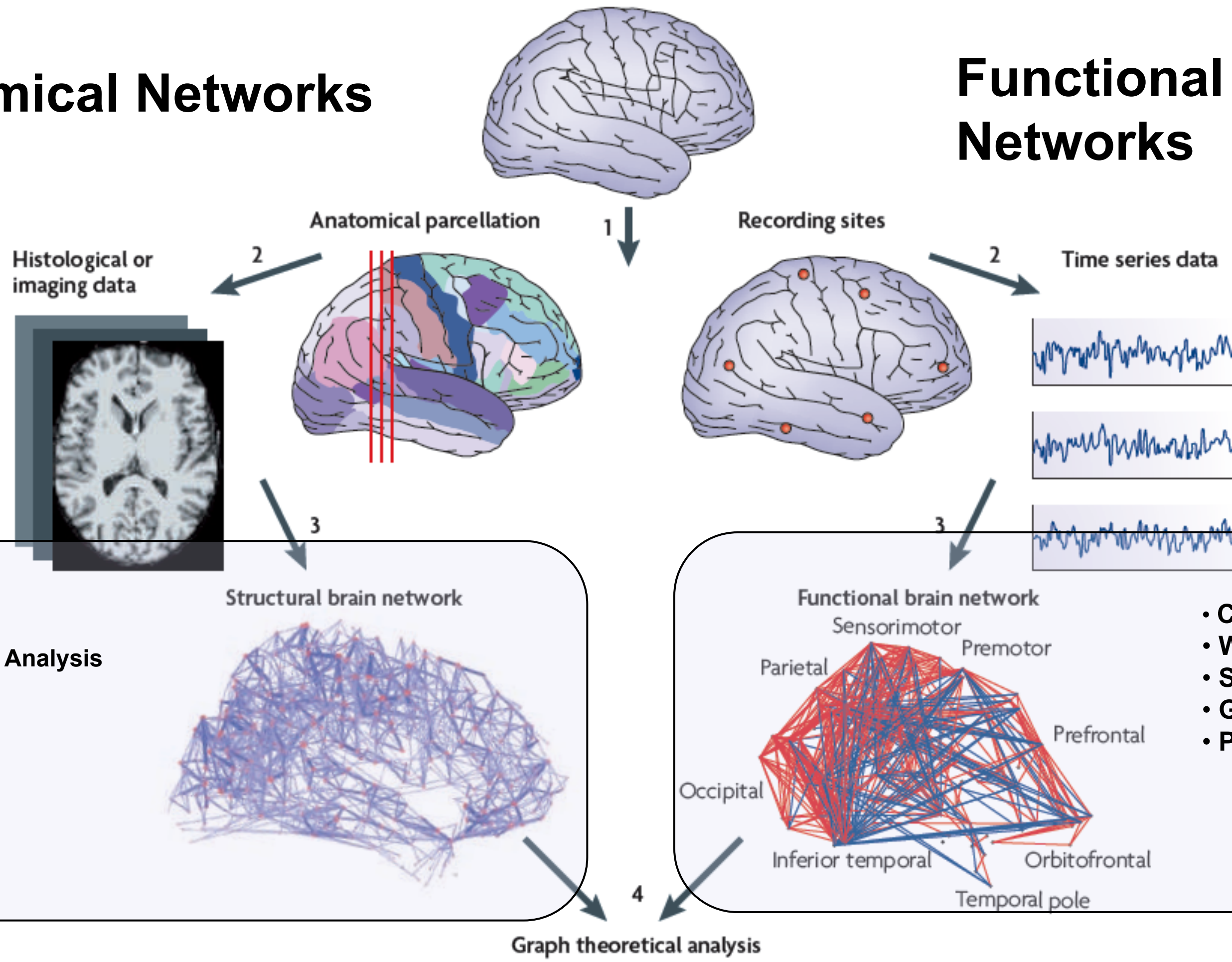
Channel #340

TIME

Describing brain connectivity

Anatomical Networks

Functional Networks



- EEG
- MEG
- fMRI

- **Histological Analysis**
- **DTI (MRI)**

- **Cross-correlation**
- **Wavelet coherence**
- **Sync. likelihood**
- **Generalized Sync.**
- **Phase Sync.**

From Bullmore & Sporns, Nature Rev. 10, 186 (2009)

center for biomedical technology

Functional networks: Time series technologies to describe connectivity

1. CLASSICAL MEASURES

- Cross-Correlation
- Correlation
- Coherence
- [C PARAMETERS]

2. PHASE SYNCRONIZATION MEASURES

- Phase Locking Value (PLV)
- Phase-Lag Index (PLI)
- Weighted Phase-Lag Index (WPLI)
- RHO
- [PS PARAMETERS]

3. GENERALIZED SYNCRONIZATION MEASURES

- S Index
- H Index
- N Index
- M Index
- L Index
- Synchronization Likelihood
- [GS PARAMETERS]

4. GRANGER CAUSALITY

- Clasical Linear Granger Causality
- Direct Transfer Function (DTF)
- Partial Directed Coherence (PDC)
- [GC PARAMETERS]

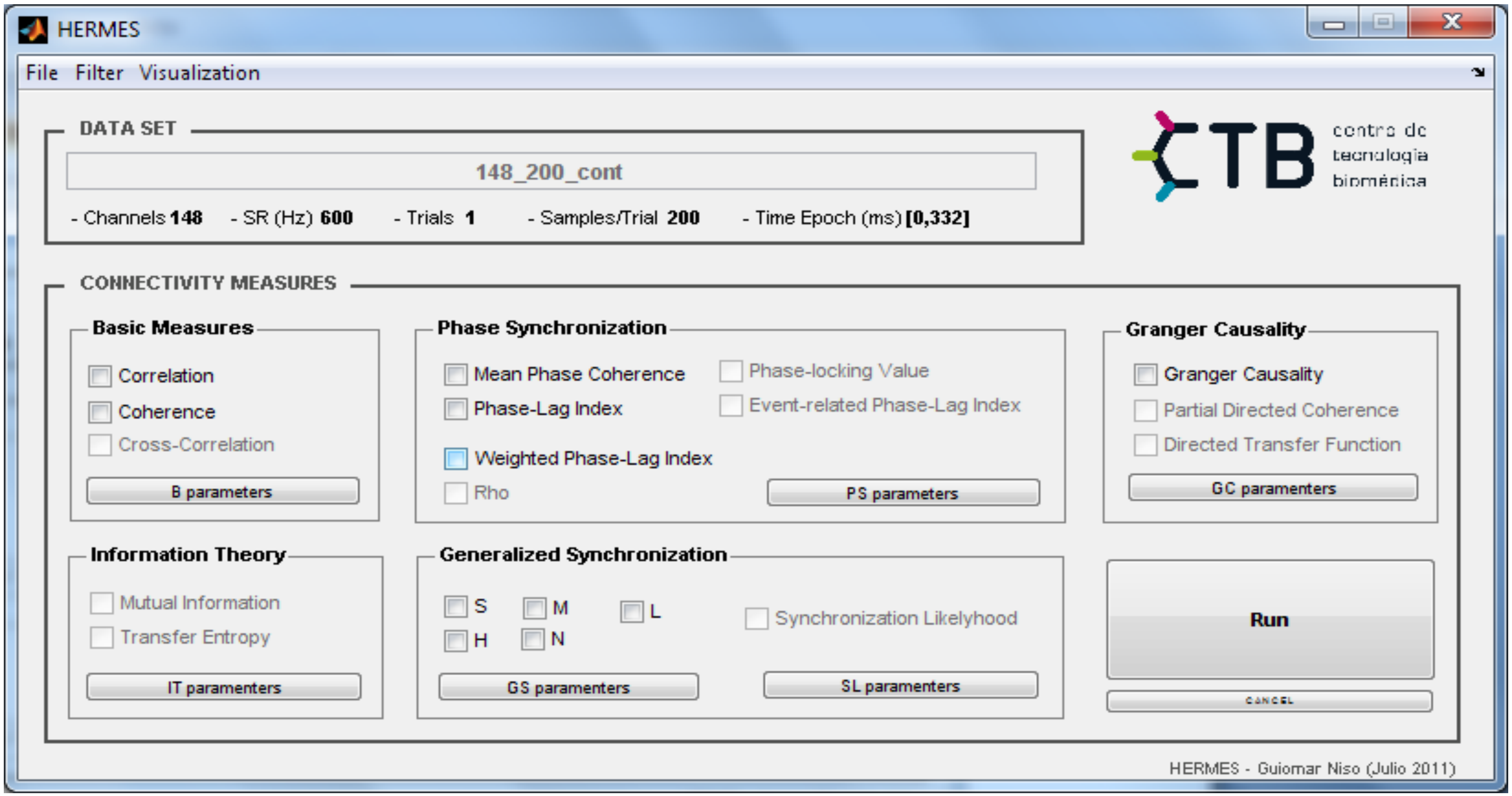
HERMES PLATFORM

http://hermes.ctb.upm.es/

Niso G, Bruña R, Pereda E, Gutiérrez R, Bajo R, Maestú F, del-Pozo F. “HERMES: towards an integrated toolbox to characterize functional and effective brain connectivity”. Neuroinformatics. 2013 (4): 405-34. F.I: 3,136

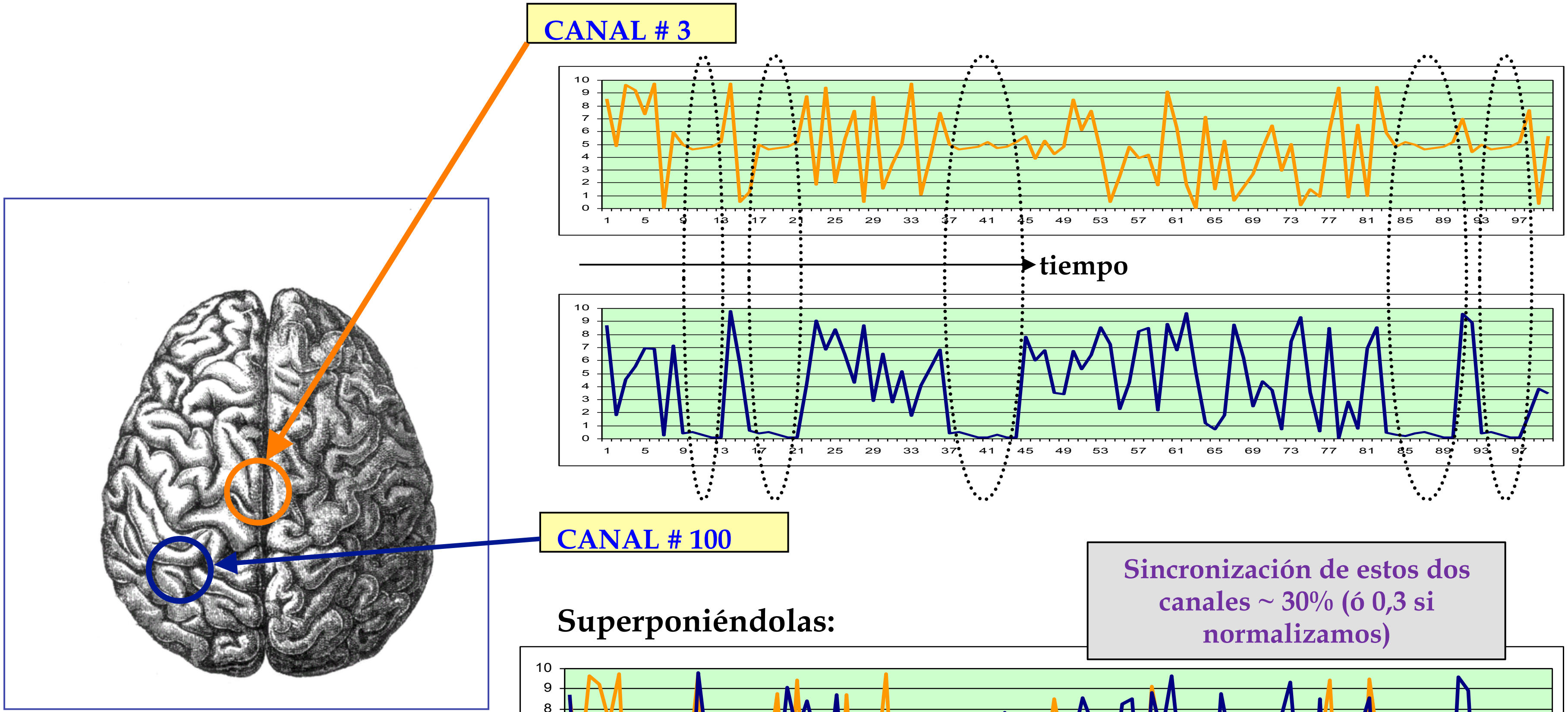
Hermes Workstation: UI

HERMES a friendly software for connectivity analysis



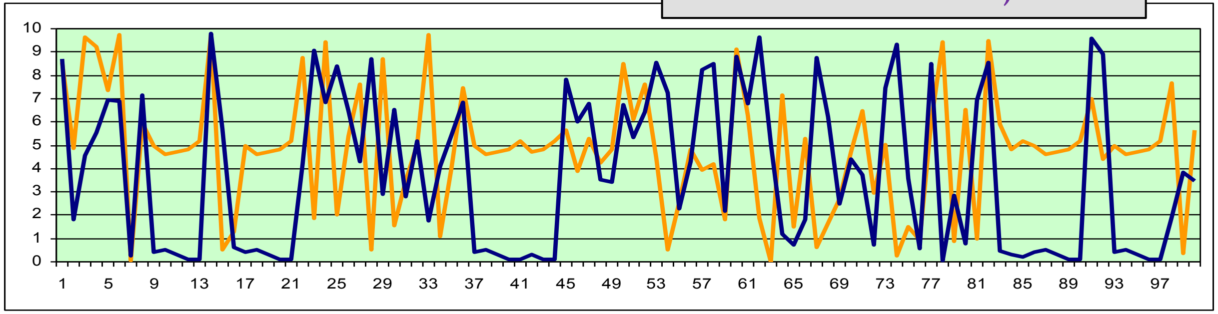
http://hermes.ctb.upm.es/

Synchronization Likelihood



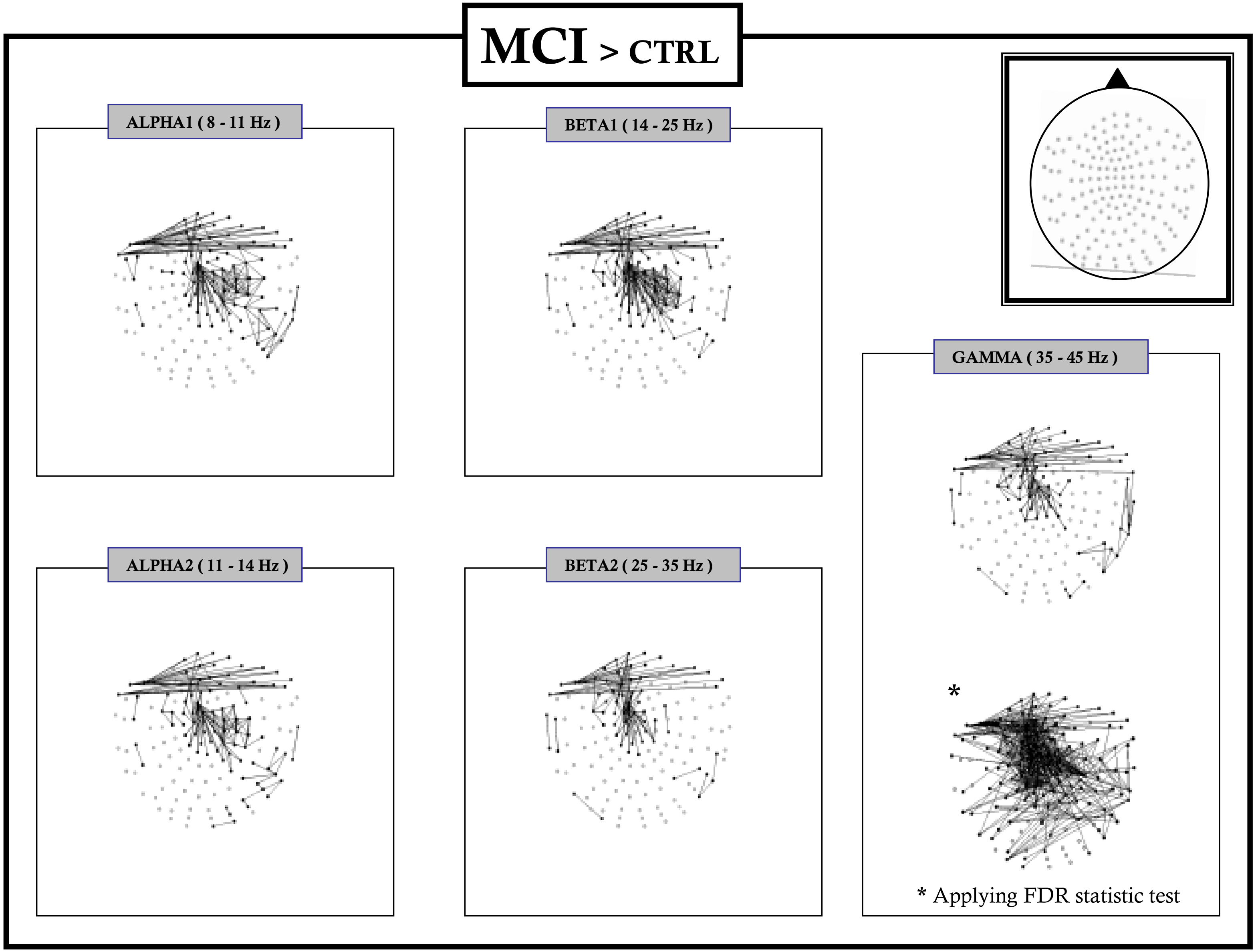
Sincronización de estos dos canales ~ 30% (ó 0,3 si normalizamos)

Superponiéndolas:



<u>Synchronization Likelihood</u> (Stam & van Dijk, 2002): Probability of coincidence in time of specific signal patterns in two time series X and Y

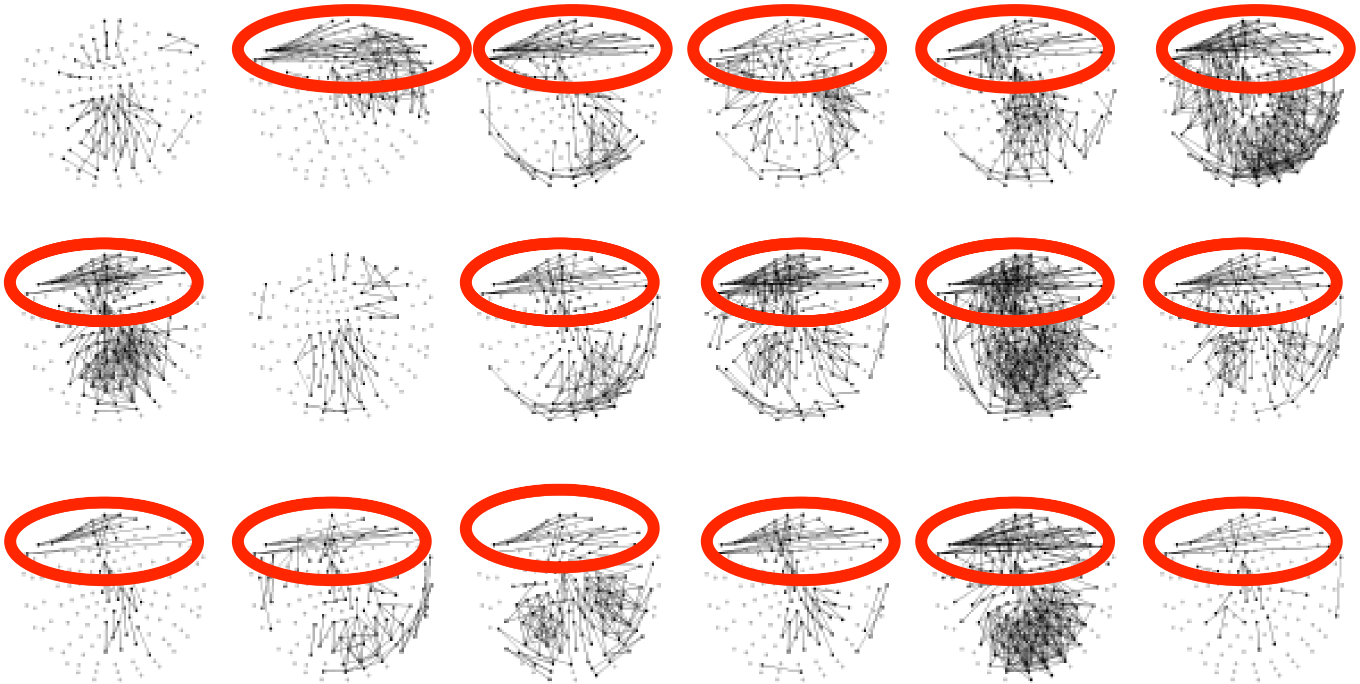
MCI vs Control differences



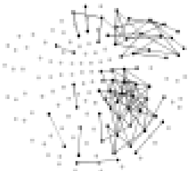
MCI vs Control differences

MCI patients (ALPHA1 band)

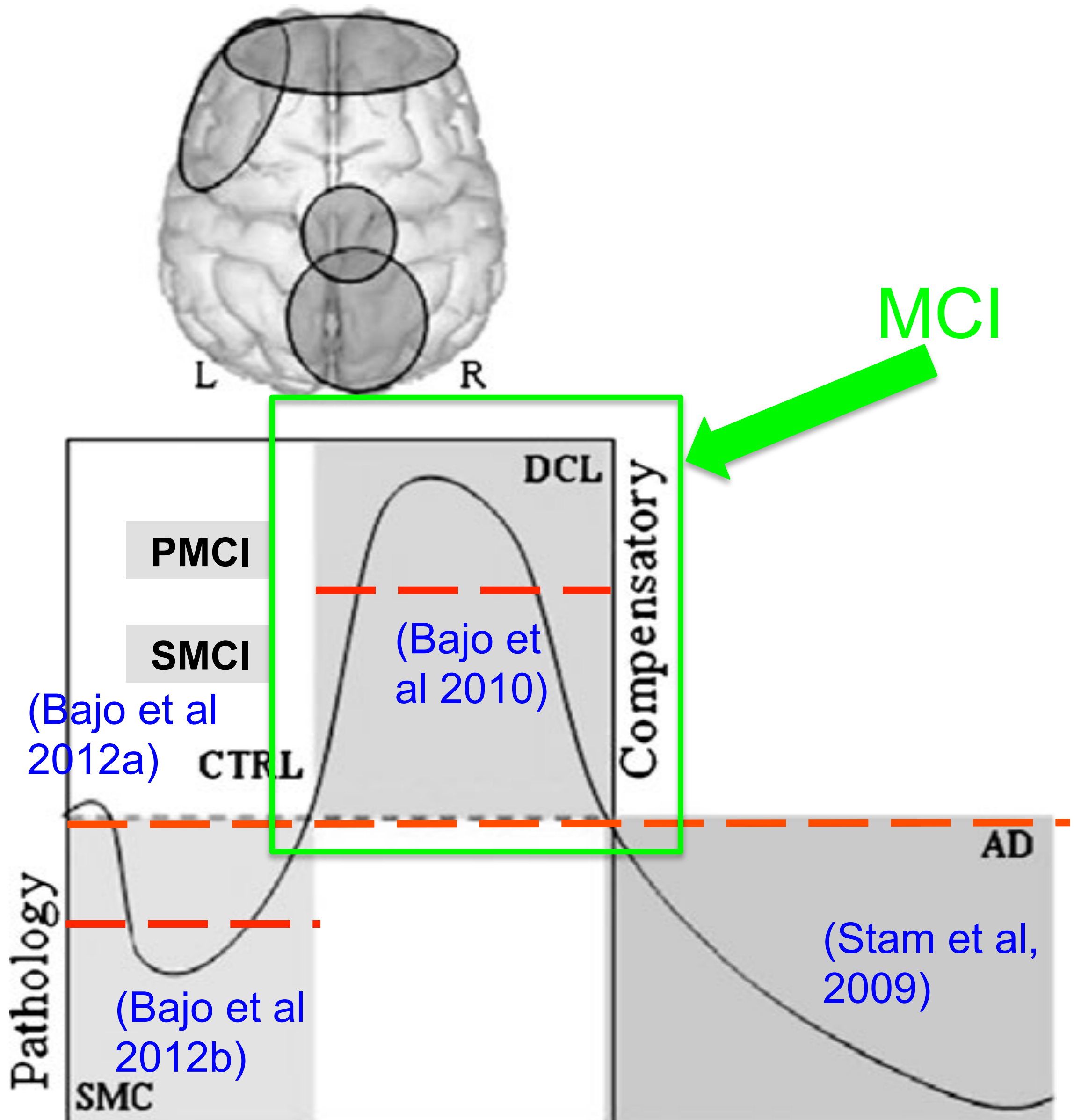
84% (16/19) show frontal inter-hemispheric high S.L. values



2 SD above the baseline



A MEG-Functional Connectivity model in pathological aging (MCI)



center for biomedical technology

Read more

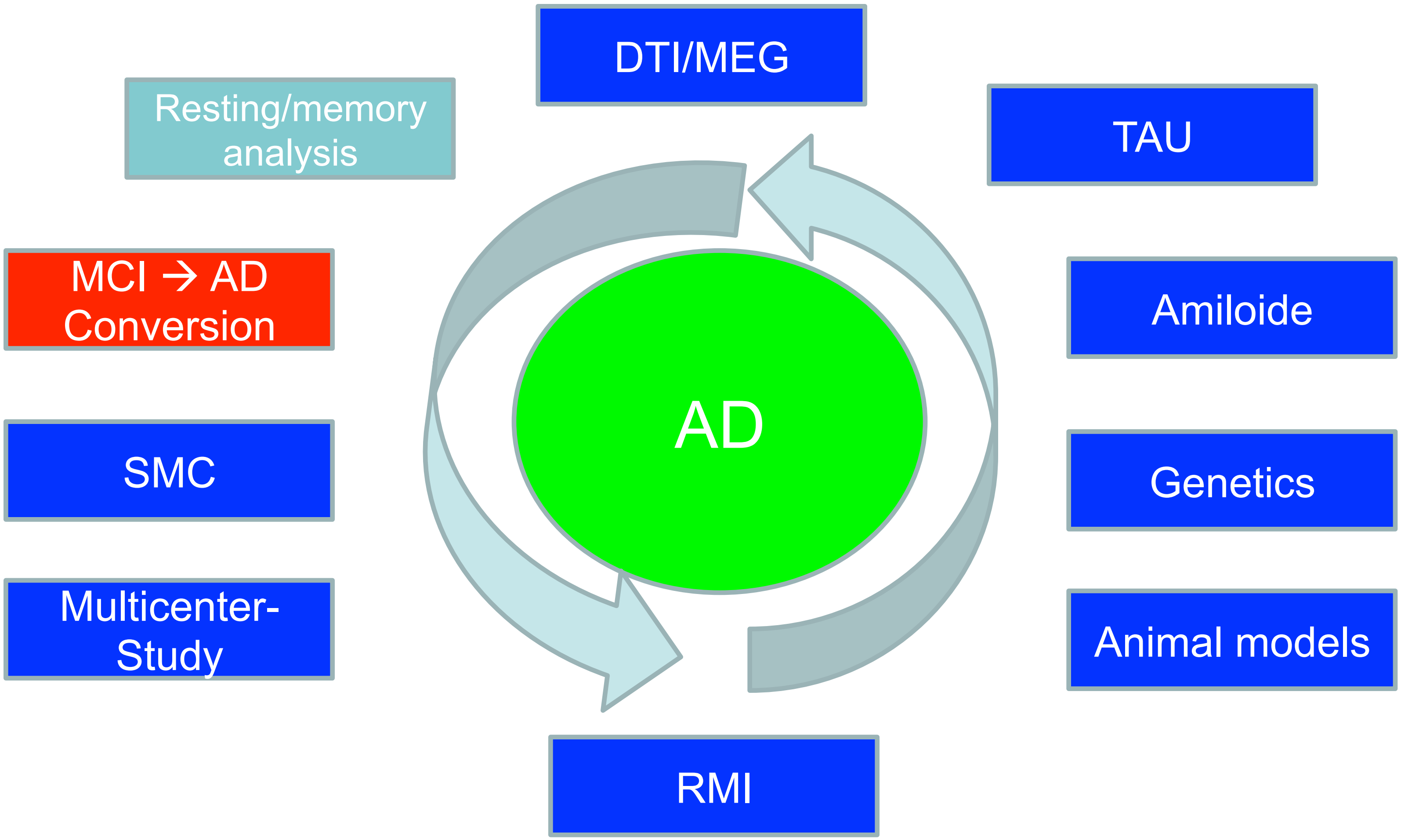
Journal of Alzheimer's Disease 22 (2010) 183–193
DOI 10.3233/JAD-2010-100177
IOS Press

Functional Connectivity in Mild Cognitive Impairment During a Memory Task: Implications for the Disconnection Hypothesis

Ricardo Bajo[a,1,*], Fernando Maestú[a,b,1], Angel Nevado[a,b], Miguel Sancho[c], Ricardo Gutiérrez[a], Pablo Campo[a], Nazareth P. Castellanos[a], Pedro Gil[d], Stephan Moratti[a,e], Ernesto Pereda[f] and Francisco del-Pozo[a]

Bajo R et al, Age, 2011
Buldu J, et al, PLOSone, 2011
Bajo R et al, Brain Connectivity, 2012

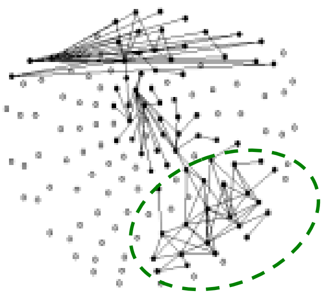
Technology for the early detection of AD: A multidimensional approach



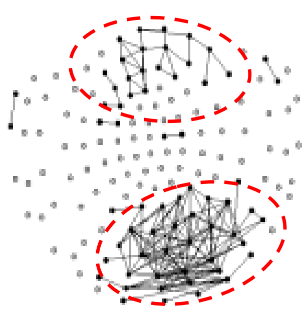
MCI that evolves to AD. Sources study

Alpha1 band

MCI develop AD > Control group

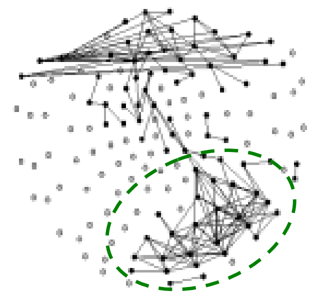


MCI develop AD > MCI no develop AD

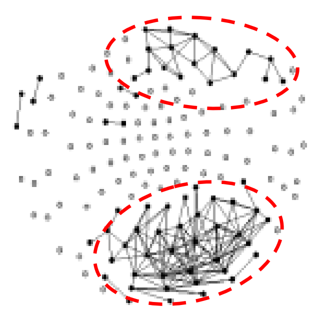


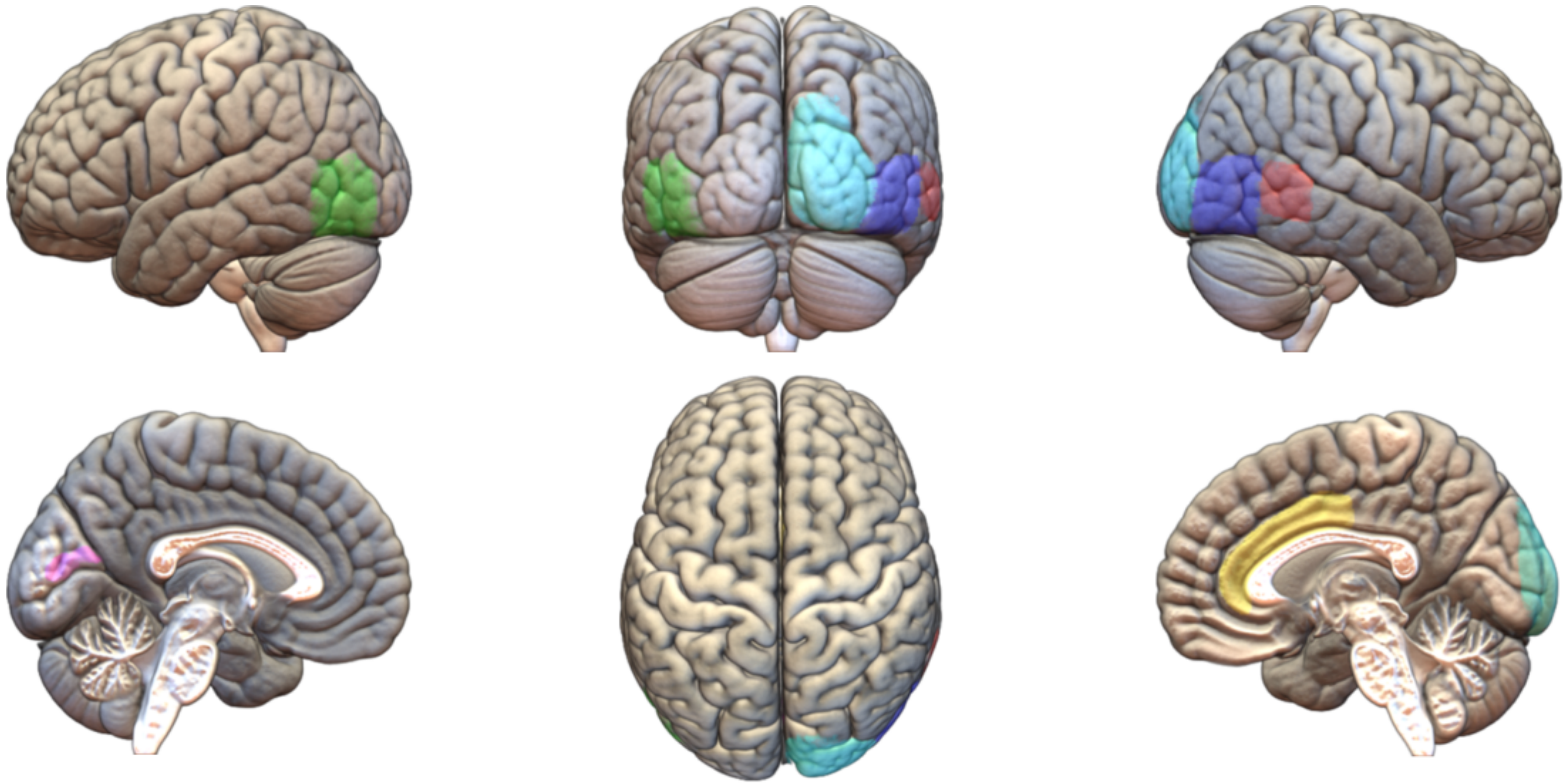
Alpha2 band

MCI develop AD > Control group



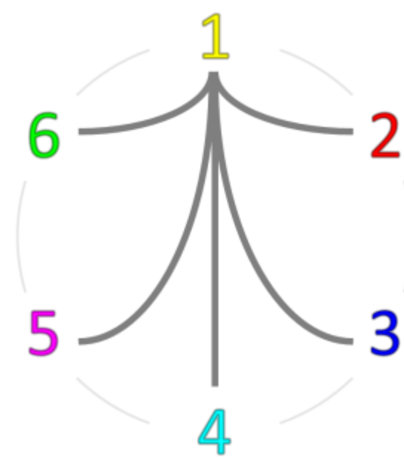
MCI develop AD > MCI no develop AD





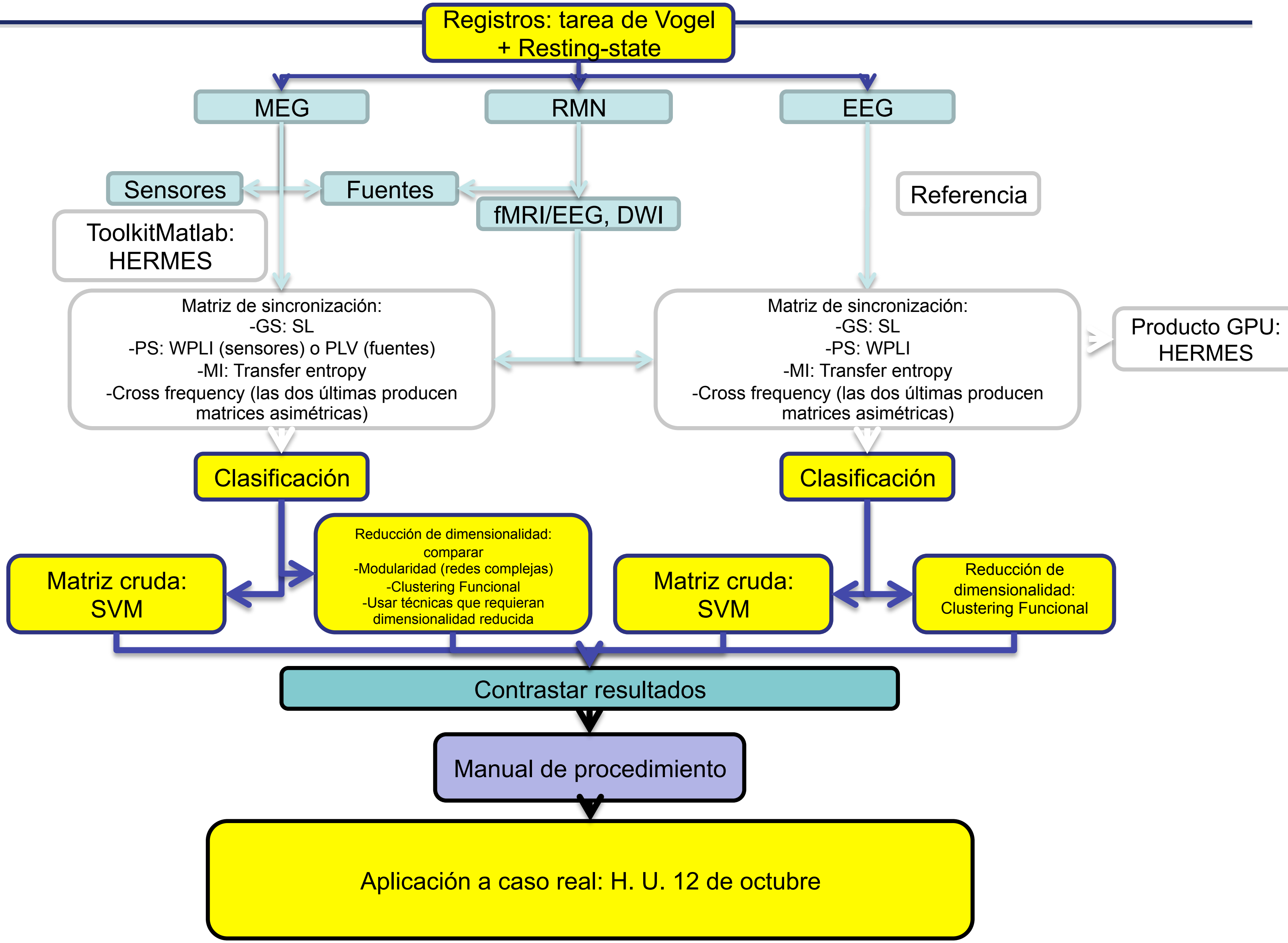
A

1. Right Cingulate Gyrus, anterior division
2. Right Middle Temporal Gyrus
3. Right Lateral Occipital Cortex, inferior division
4. Right Occipital Pole
5. Left Supracalcarine Cortex
6. Left Lateral Occipital Cortex, inferior division



B (López, Bruña et al, submitted) **C**

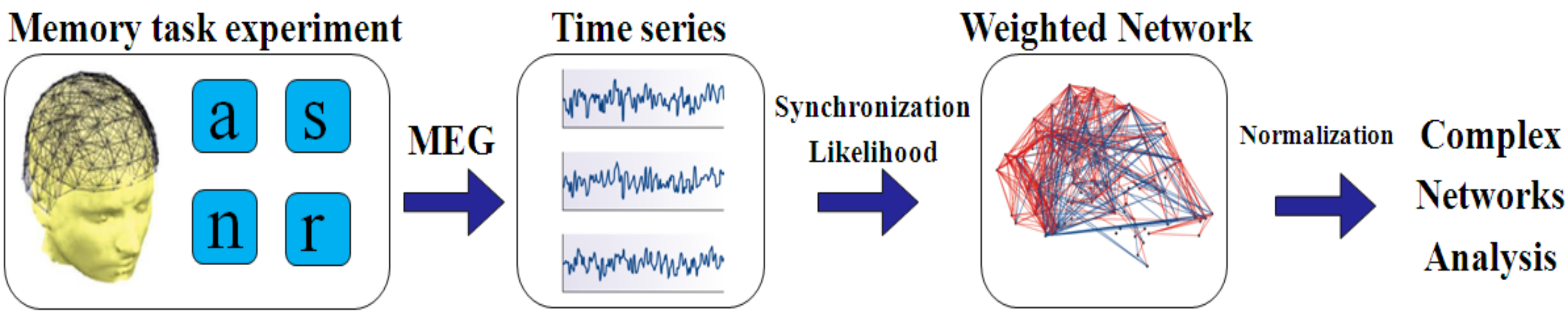
Hermes Project (P.Nacional 2011)



Laboratory of cognitive and computational neuroscience
Center for Biomedical Technology

center for
biomedical
technology

Modeling Brain Newtworks. Application to MCI/AD



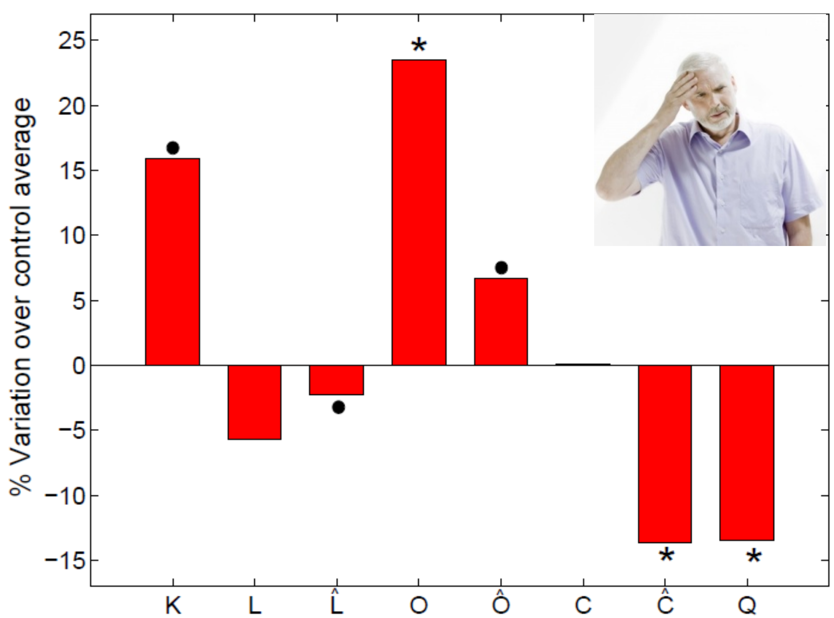
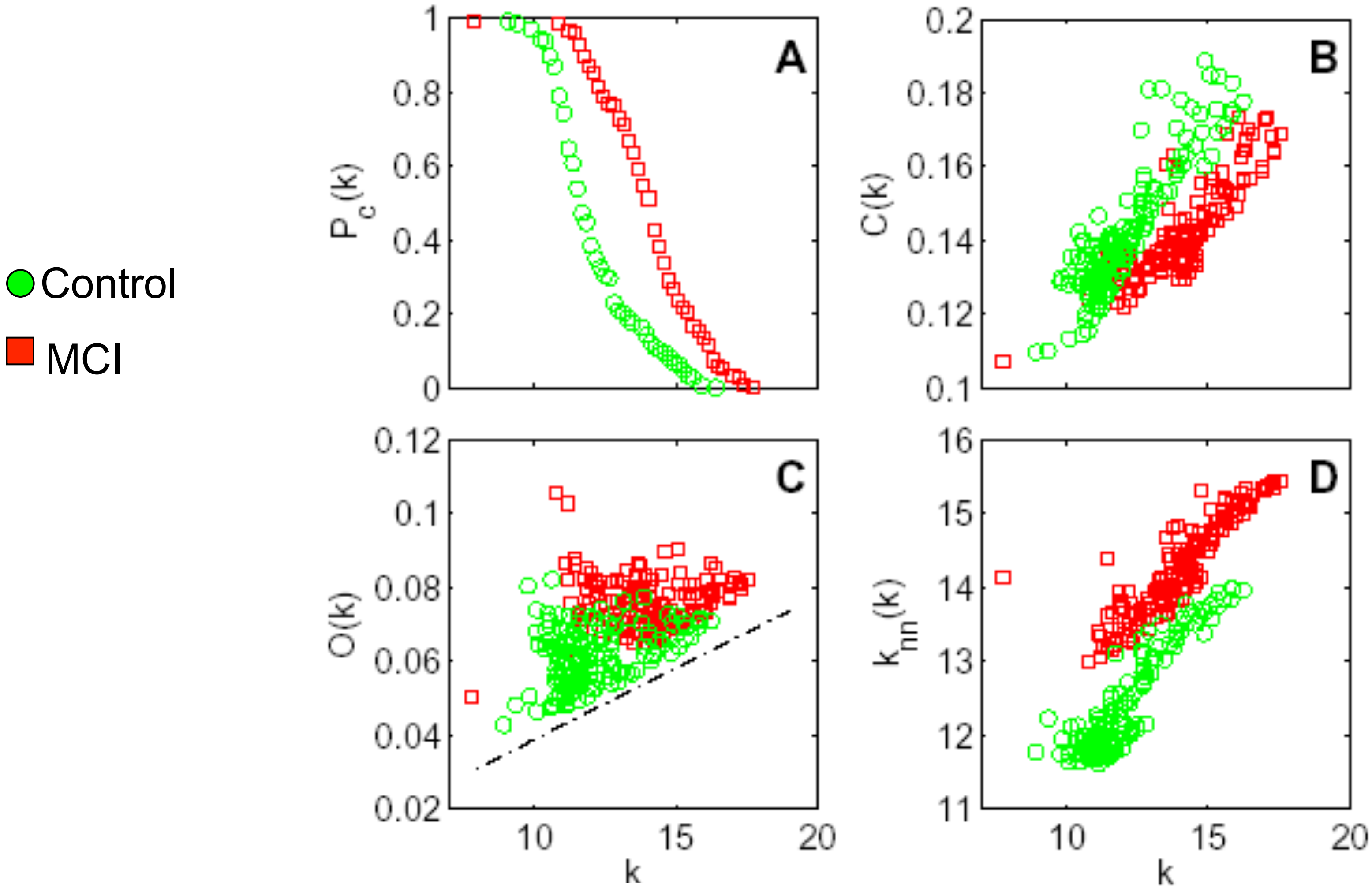


Fig. 4. Percentage of variation and statistical significance. Percentage of variation of the average degree K, average shortest path L and its normalized value $\hat{L} = \frac{L}{L_{ran}}$, network outreach O and normalized outreach $\hat{O} = \frac{O}{O_{ran}}$, clustering C and normalized clustering $\hat{C} = \frac{C}{C_{ran}}$ and network modularity. Circles correspond to $p < 0.03$ and stars to $p < 0.001$, specifically: O $(p = 0.007)$, $\hat{C}$ $(p = 0.002)$, Q (p = 0.0033), K,$(p = 0.018)$, L_z $(p = 0.025)$ and $\hat{O}$ $(p = 0.027)$.

- The network strength *K* increases (+15.9%)
- Network outreach increases (+23.4%)
- The network modularity decreases (-13.5%)
- Normalized clustering decreases (-13.6%)
- Normalized outreach increases (+6.7%):



OPEN ACCESS Freely available online
PLoS one

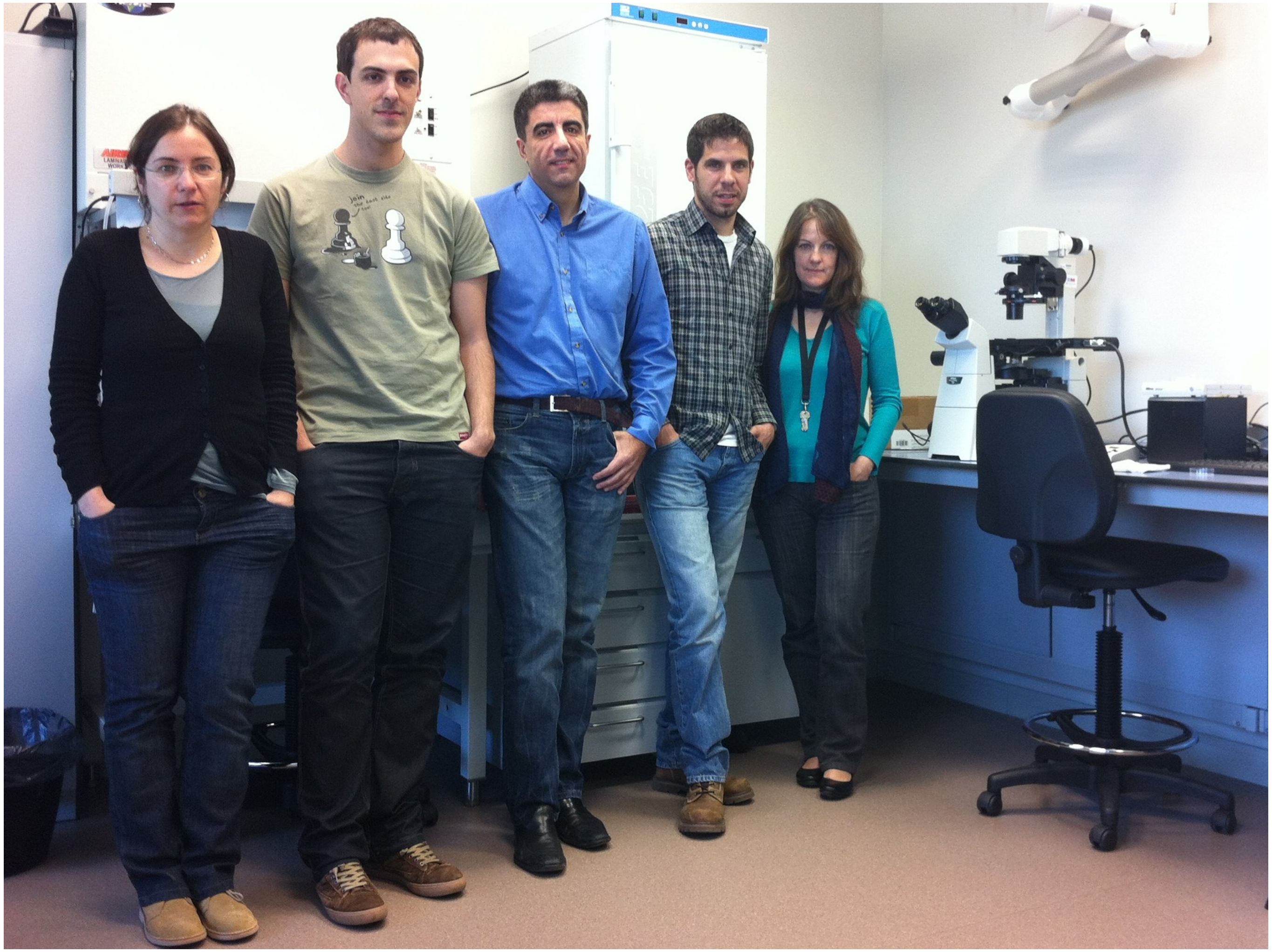
Reorganization of Functional Networks in Mild Cognitive Impairment

Javier M. Buldú[1,2*], Ricardo Bajo[3], Fernando Maestú[3], Nazareth Castellanos[3], Inmaculada Leyva[1,2], Pablo Gil[4], Irene Sendiña-Nadal[1,2], Juan A. Almendral[1,2], Angel Nevado[3], Francisco del-Pozo[3], Stefano Boccaletti[5,6]

CTB center for biomedical technology

Computational Systems Biology

POLITÉCNICA

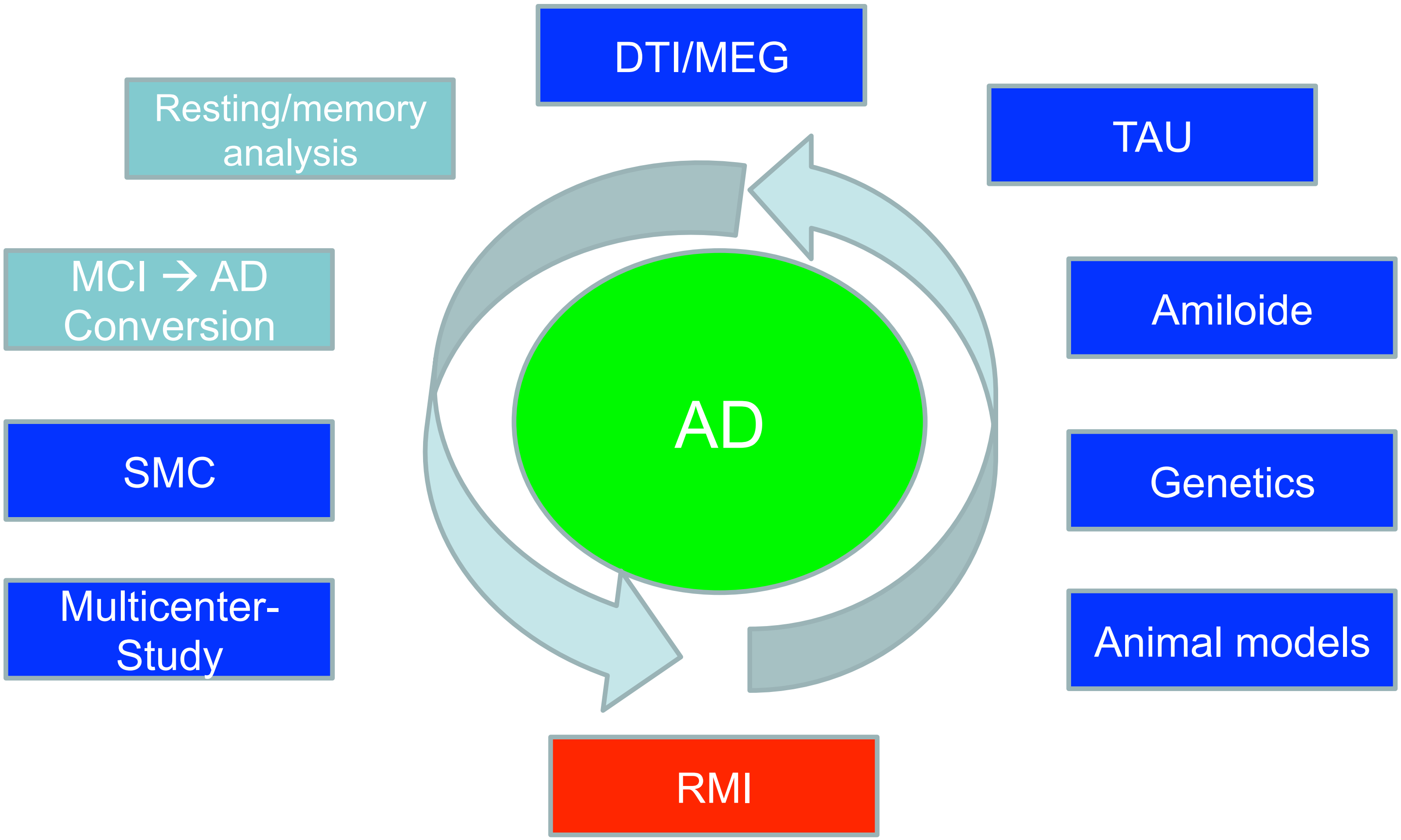


From Left to right: Irene Sendiña-Nadal, Daniel de Santos, Juan A. Almendral, Javier M. Buldú, Inmaculada Leyva.

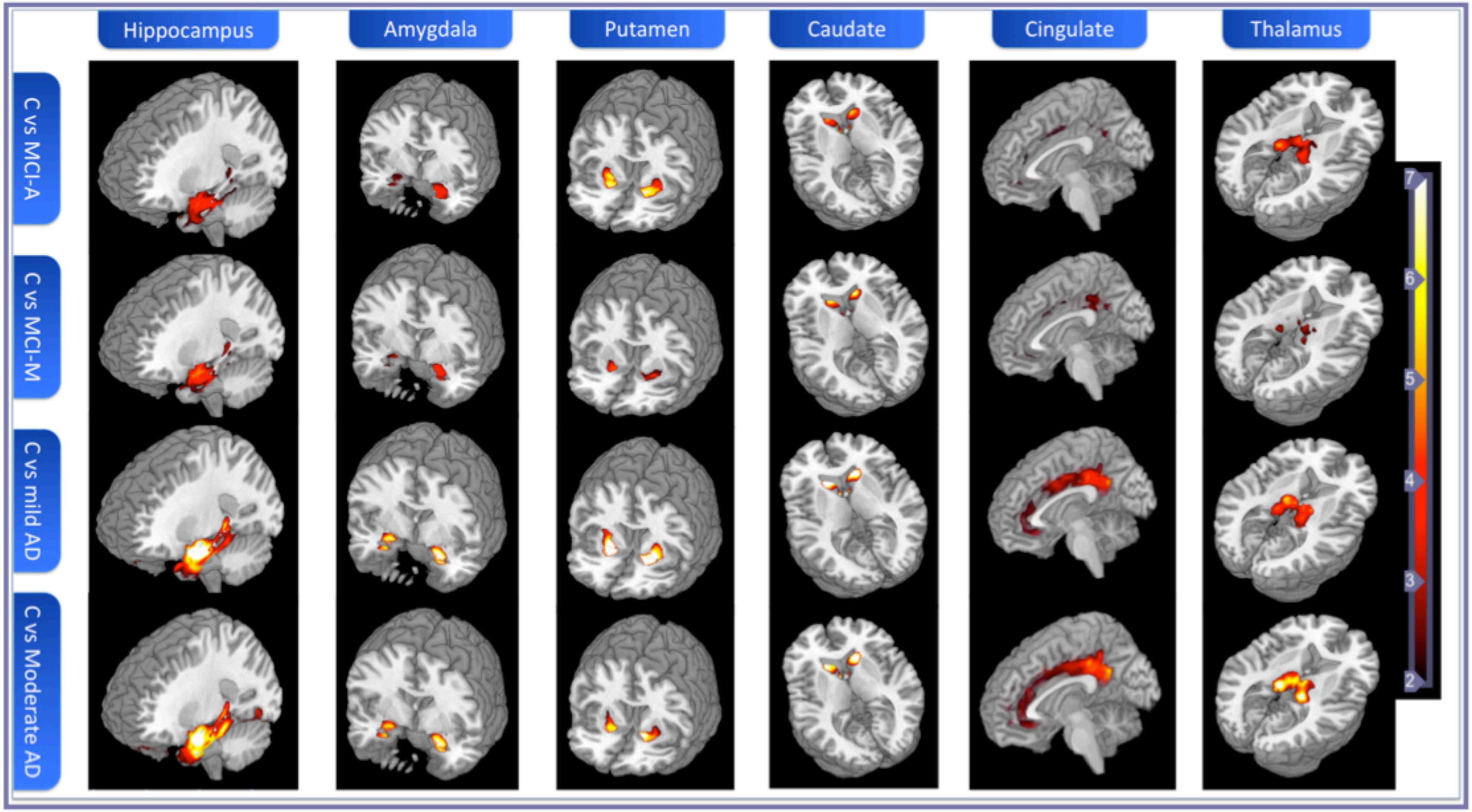
CTB center for biomedical technology

Technology for the early detection of AD: A multidimensional approach

POLITÉCNICA



Neuroimaging

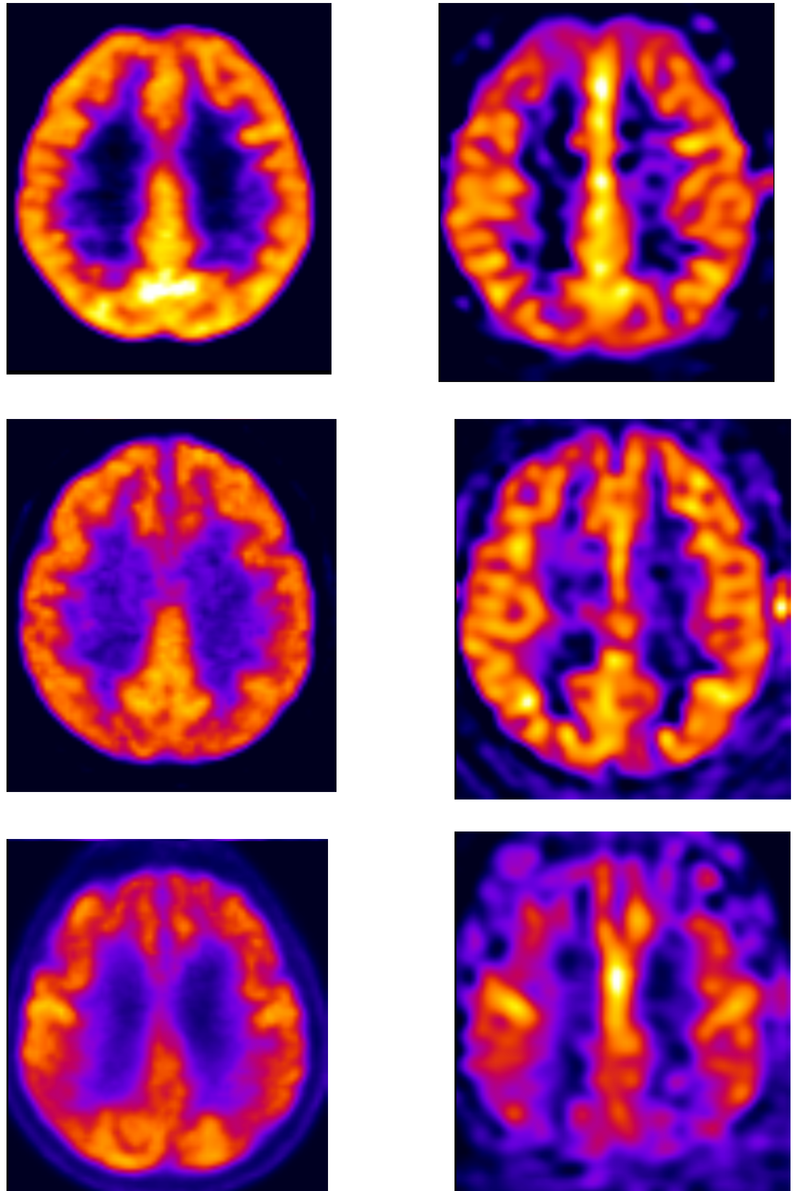


Neuroimaging Biomarkers in Aging and Dementia. Application of volumetric techniques (Voxel-Based Morphometry, VBM) at different stages of neurodegenerative diseases.

Metabolismo y Perfusión ASL

alidating new imaging methods

PET ASL



Joven. 29 años

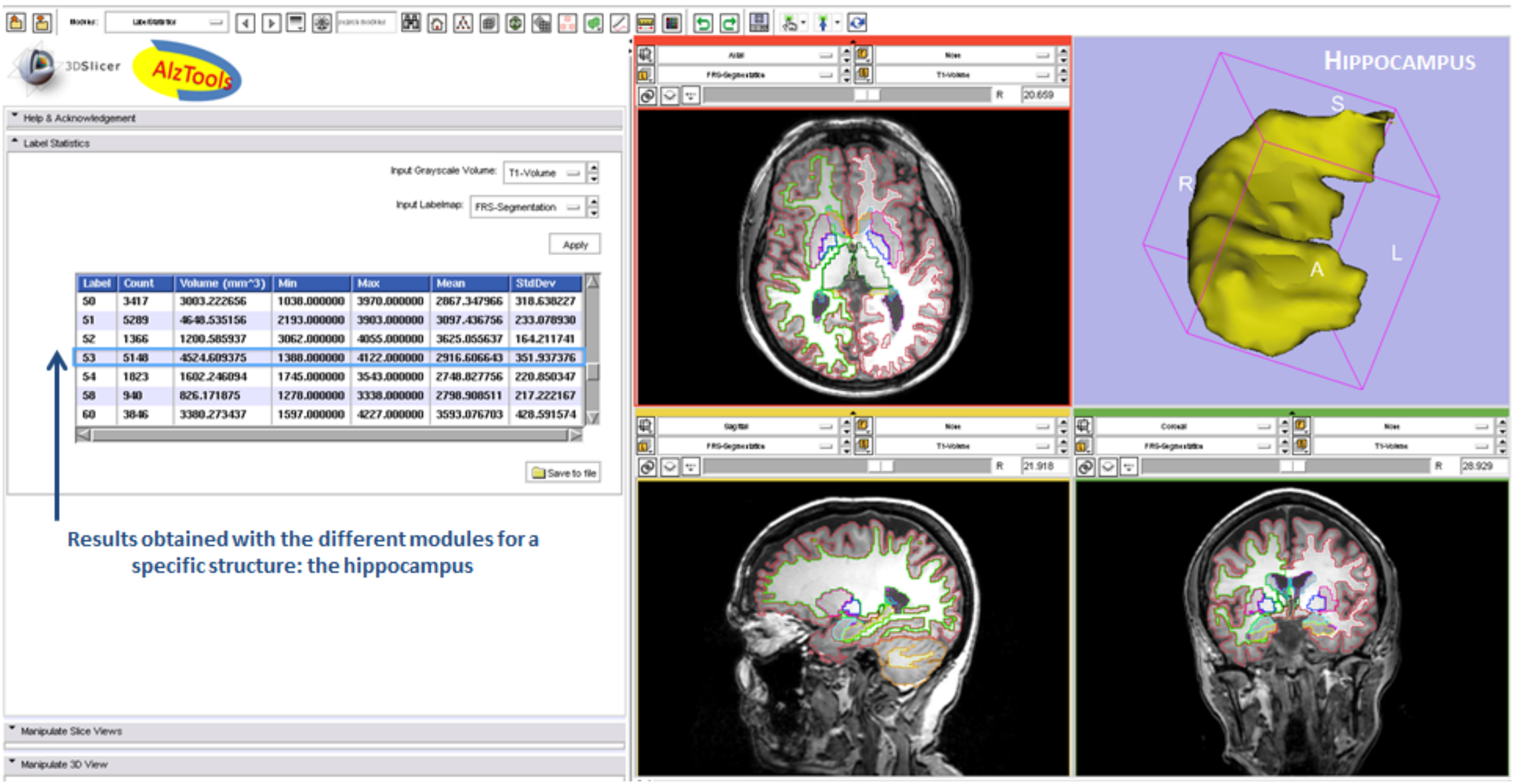
Anciano 85 años Sano

Anciano 84 años Alzheimer

Arterial Spin Labeling (ASL) using gold standards.

Second row: an 84-year old healthy male. Left: caption obtained with PET; right: equivalent image obtained with ASL. Third row: images an 85-year old male with Alzheimer’s disease.

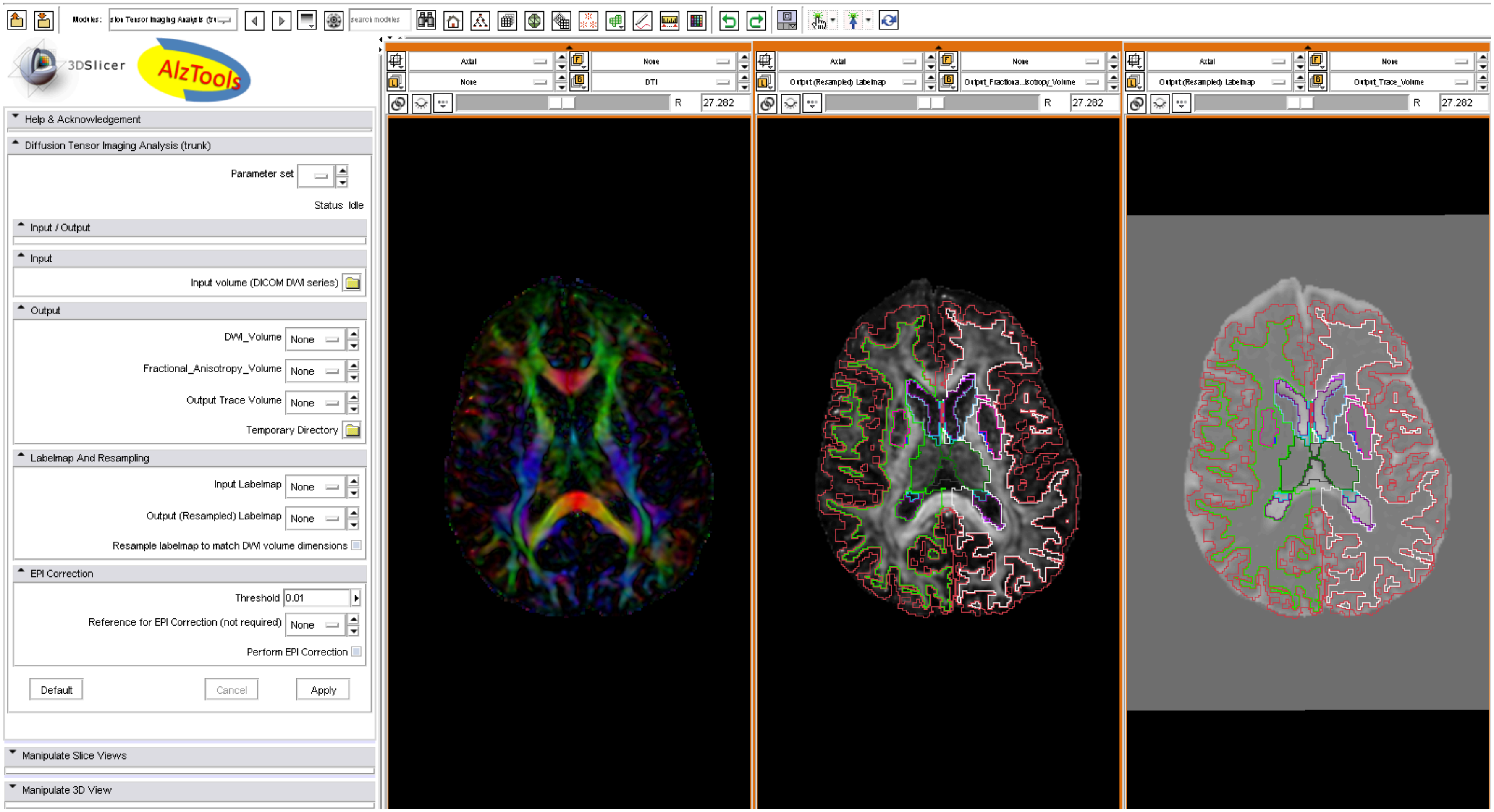
Hippocampus volumetry



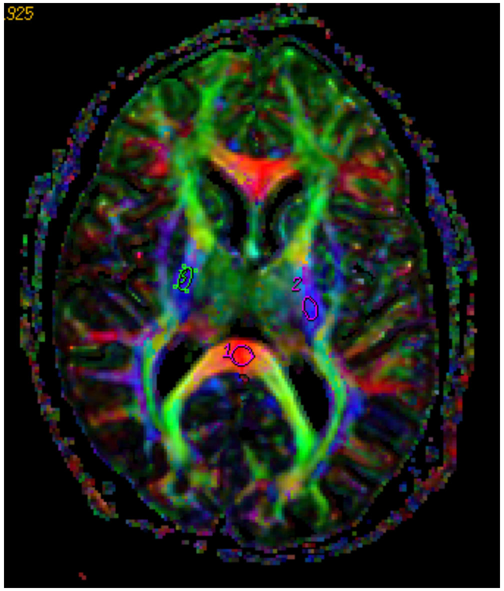
Label	Count	Volume (mm^3)	Min	Max	Mean	StdDev
50	3417	3003.222656	1038.000000	3970.000000	2867.347966	318.638227
51	5289	4648.535156	2193.000000	3903.000000	3097.436756	233.078930
52	1366	1200.585937	3062.000000	4055.000000	3625.055637	164.211741
53	5148	4524.609375	1388.000000	4122.000000	2916.606643	351.937376
54	1823	1602.246094	1745.000000	3543.000000	2748.827756	220.850347
58	940	826.171875	1278.000000	3338.000000	2798.908511	217.222167
60	3846	3380.273437	1597.000000	4227.000000	3593.076703	428.591574

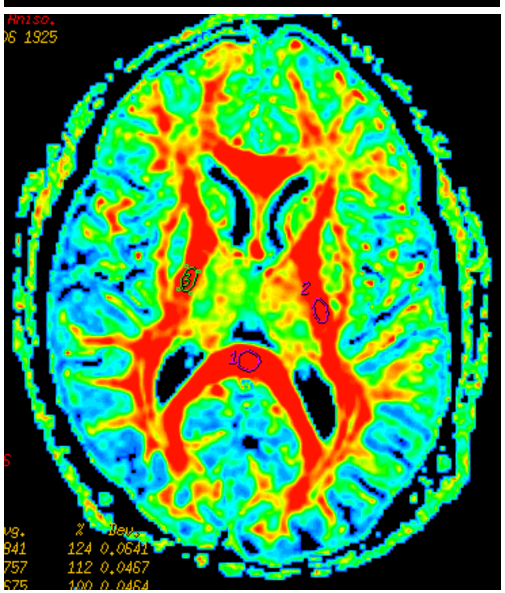
Results obtained with the different modules for a specific structure: the hippocampus

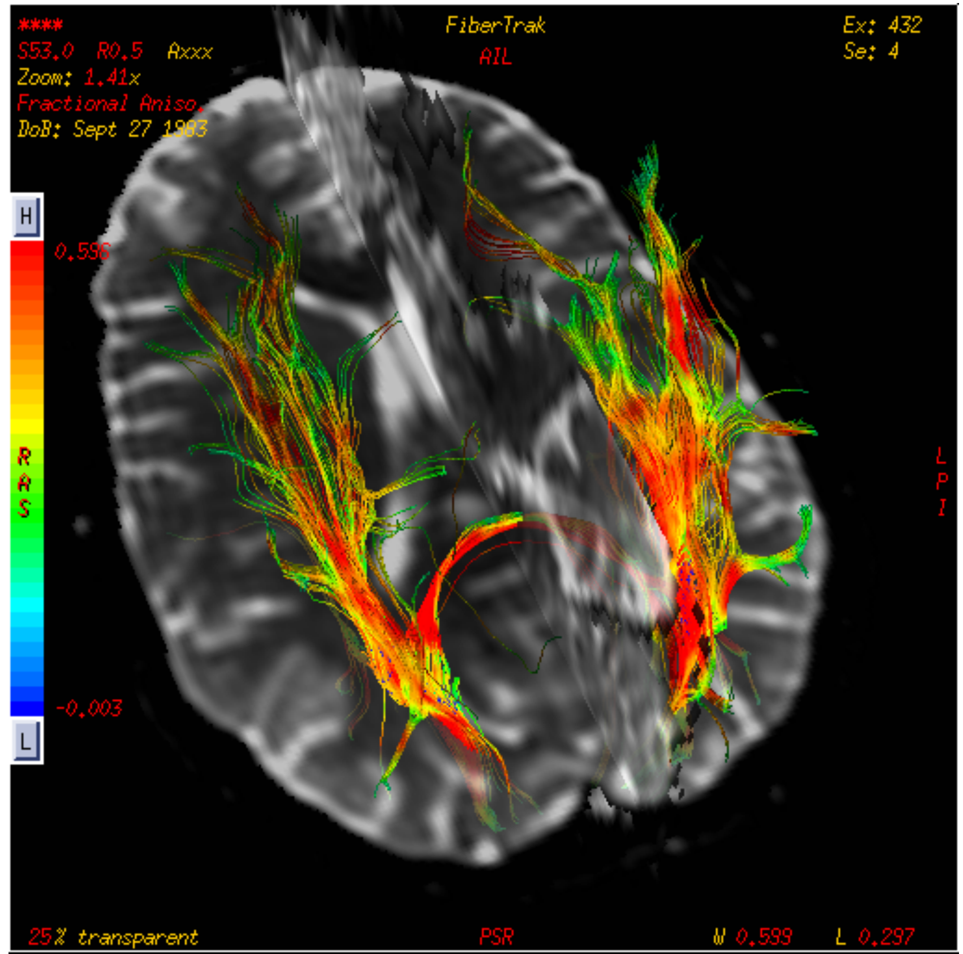
Difussion imaging



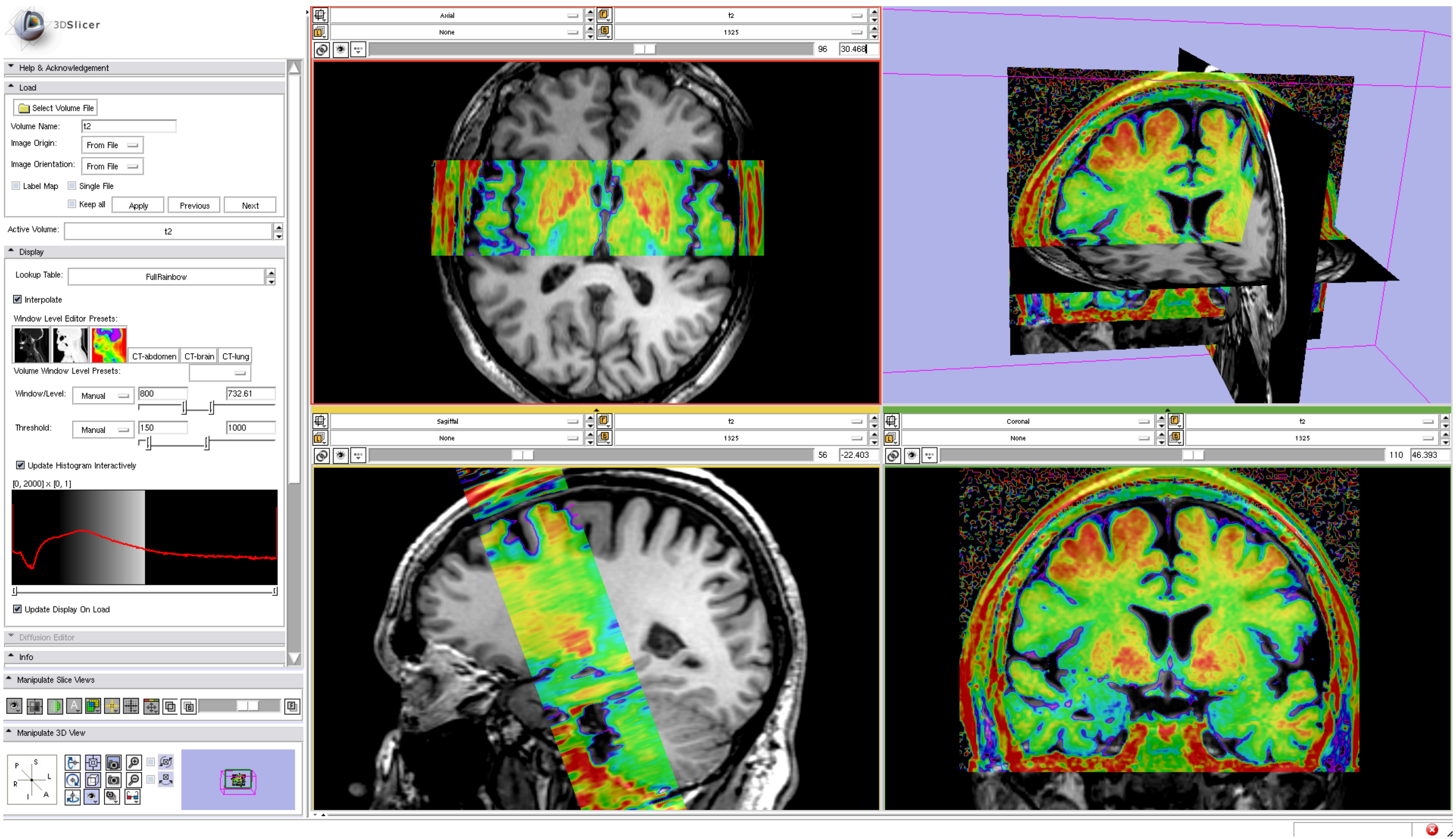
Difussion Tensor



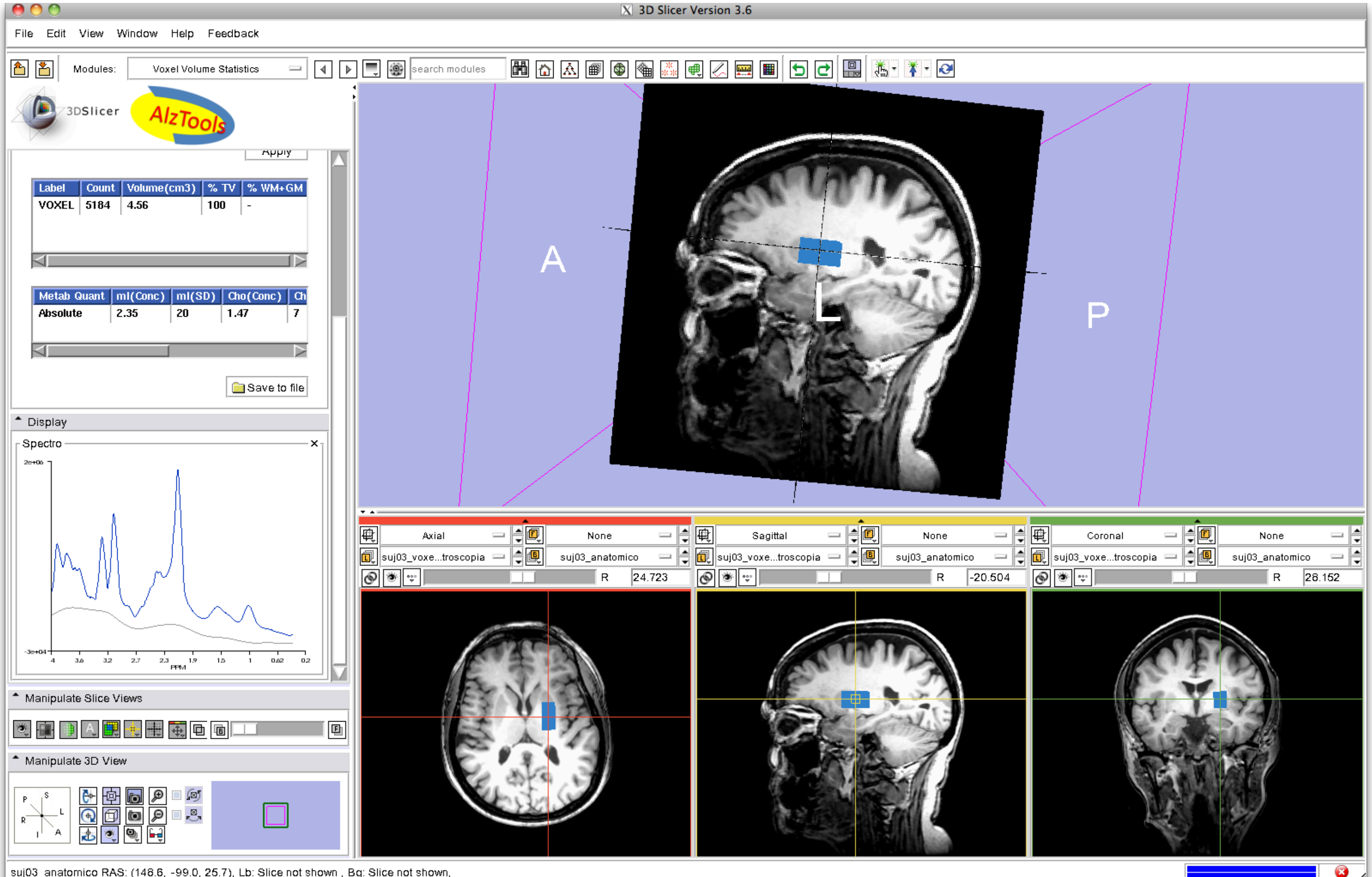




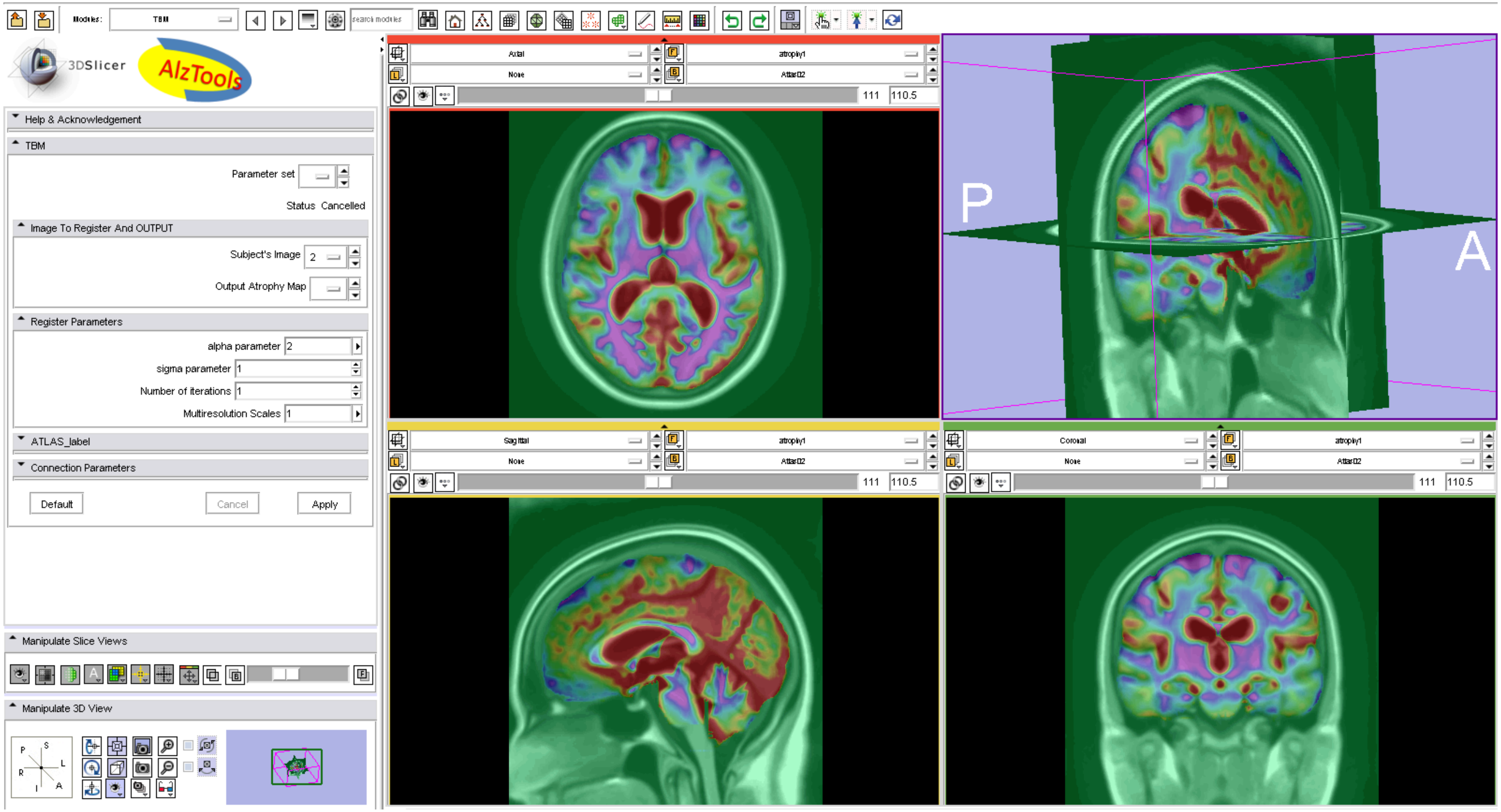
Iron deposit quantification



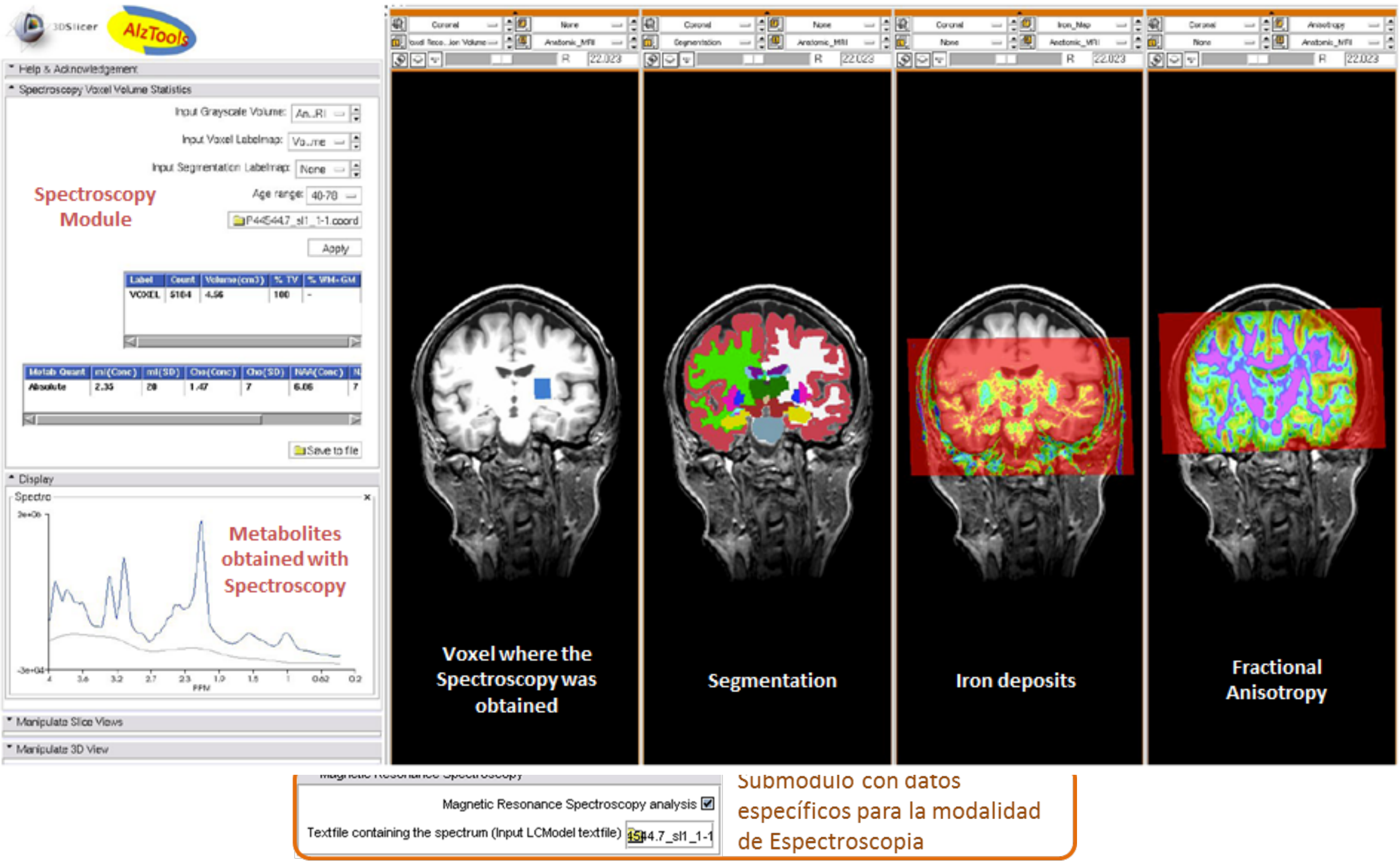
Spectroscopy. Molecular imaging



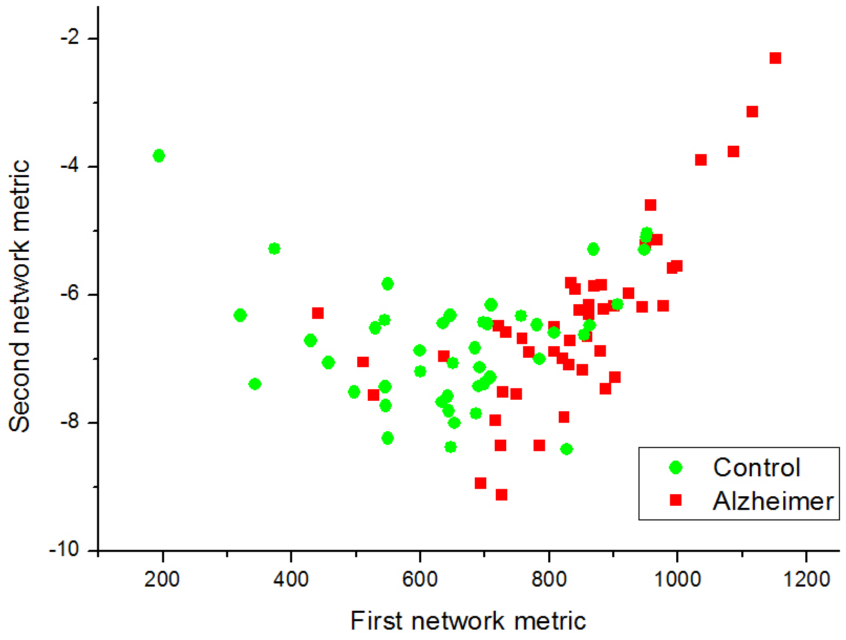
Tensor-based morfometry

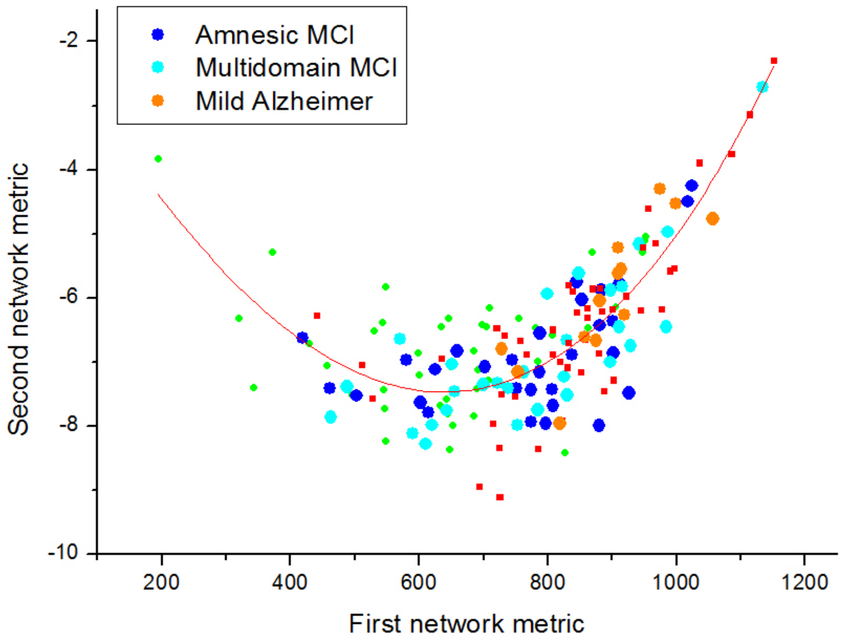


Looking for biomarkers: image multimodality



Multimodal imaging classifiers



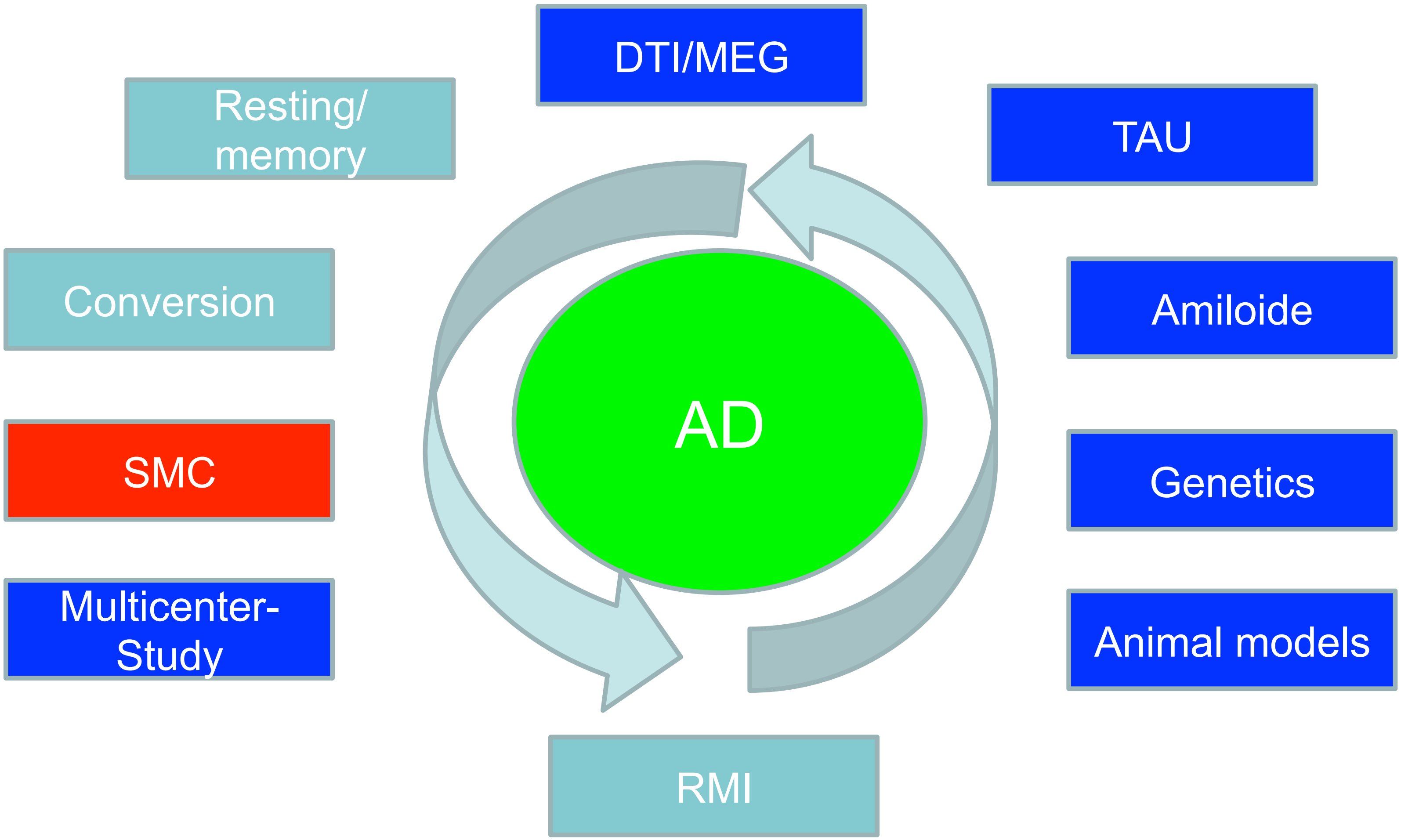


Neuroimaging Lab

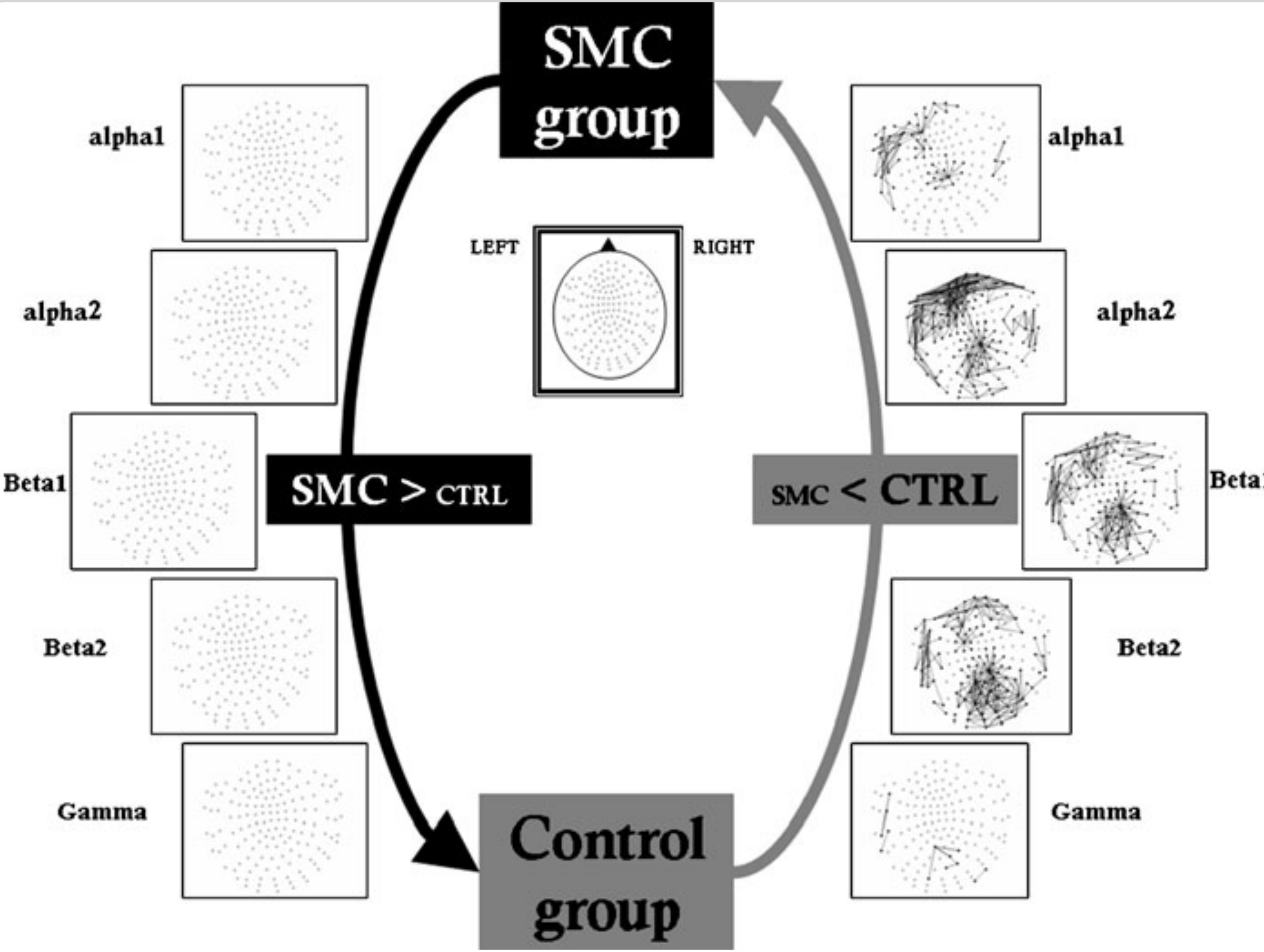
From left to right: Susana Borromeo, Pablo García-Polo, Elena Molina, Eva Alfayate, José Ángel Pineda, Aranzazu Narciso, Juan Antonio Hernández-Tamames, Juan Álvarez Linera, Gonzalo Pajares, Norberto Malpica, Javier González, Andrea Rueda, Juan Francisco Garamendi, Miguel Hernández, Virginia Mato, Roberto Colom, Daniel García

center for biomedical technology

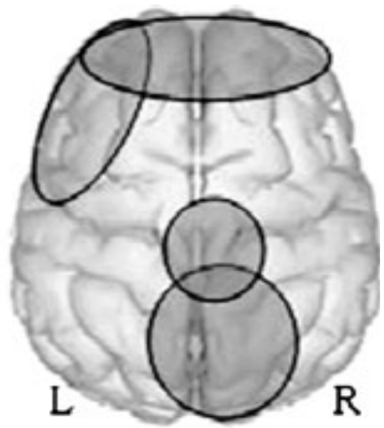
Technology for the early detection of AD: A multidimensional approach



Subjetive Memory Complaints (SMC)



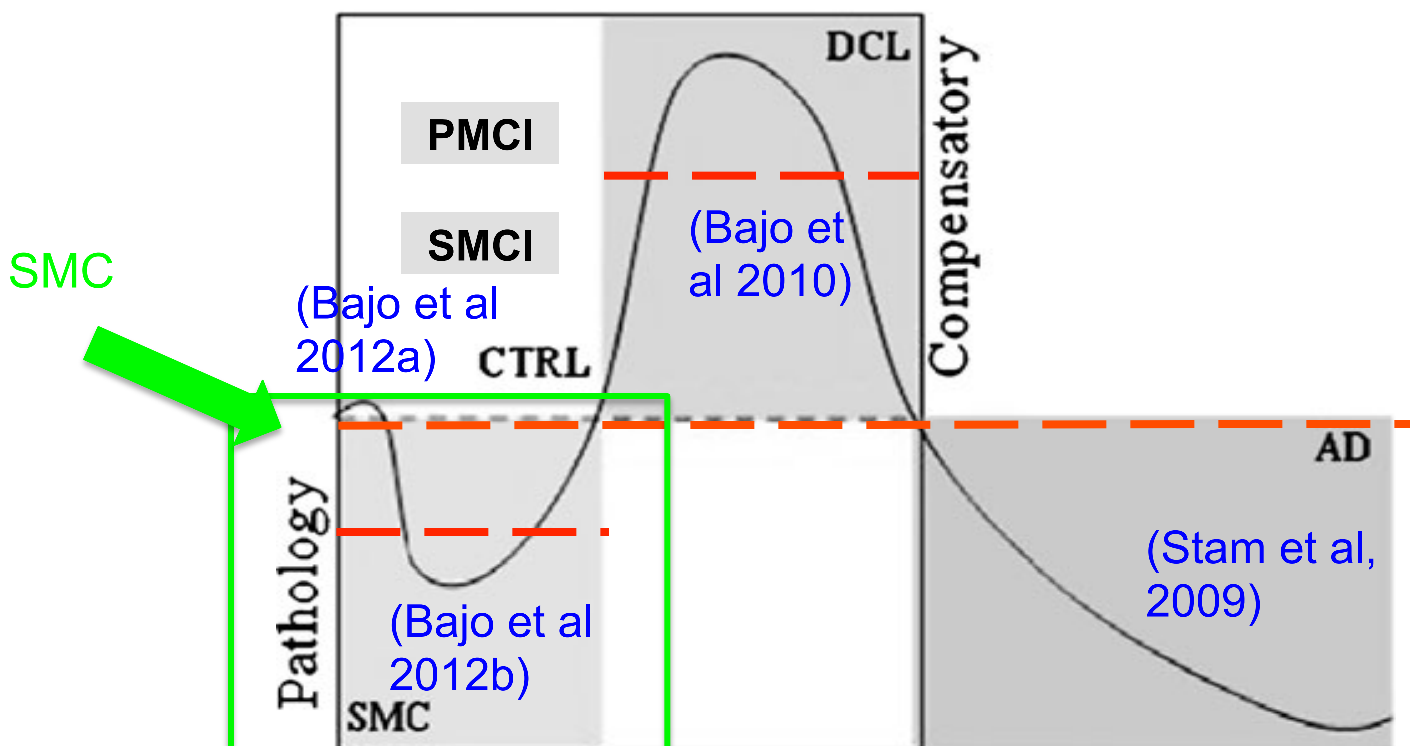
A MEG-Functional Connectivity model in pathological aging (SMC)



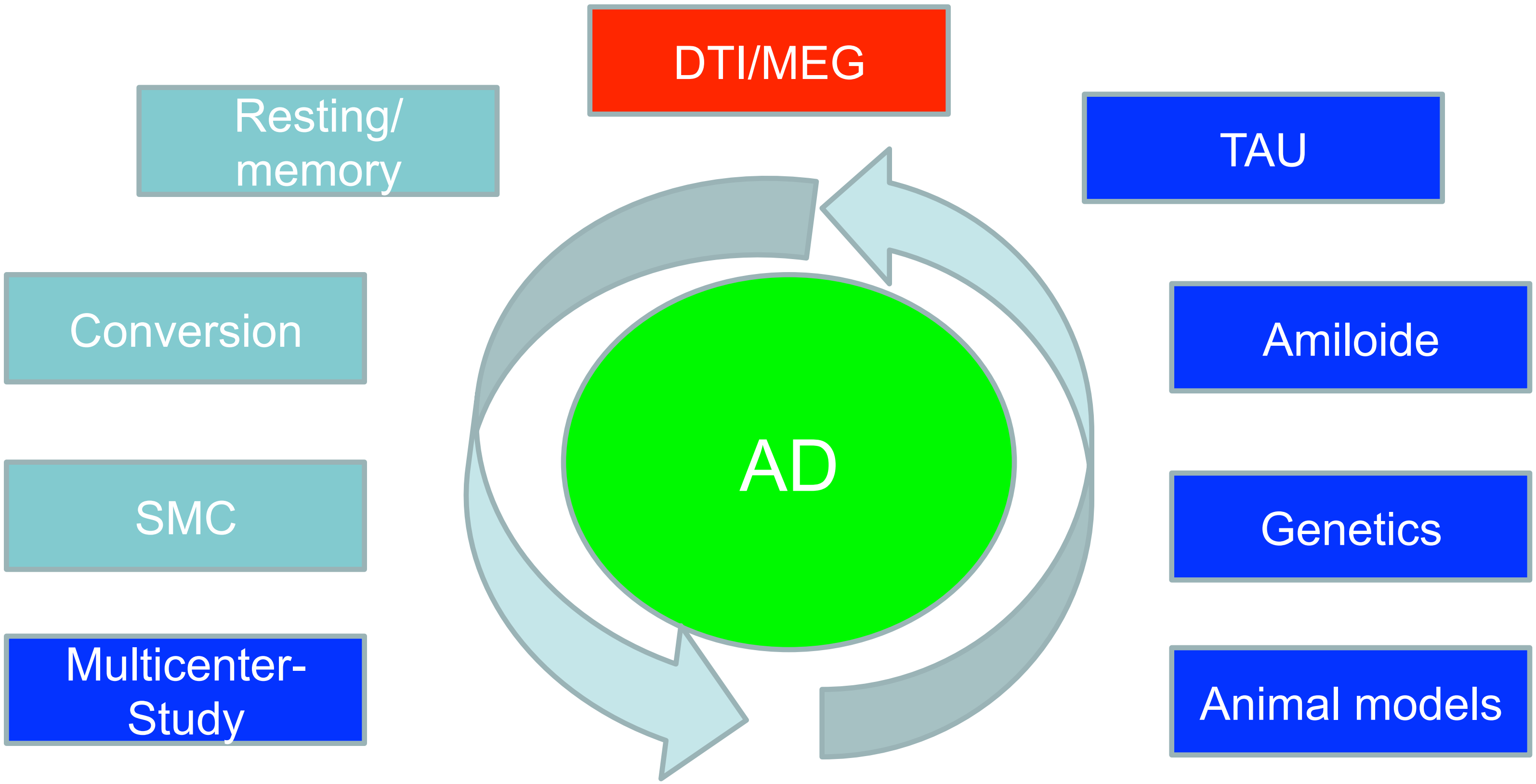
AGE (2012) 34:497–506
DOI 10.1007/s11357-011-9241-5

Early dysfunction of functional connectivity in healthy elderly with subjective memory complaints

Ricardo Bajo · Nazareth P. Castellanos · Maria Eugenia López · José María Ruiz · Pedro Montejo · Mercedes Montenegro · Marcos Llanero · Pedro Gil · Raquel Yubero · Evgenia Baykova · Nuria Paul · Sara Aurtenetxe · Francisco Del Pozo · Fernando Maestu

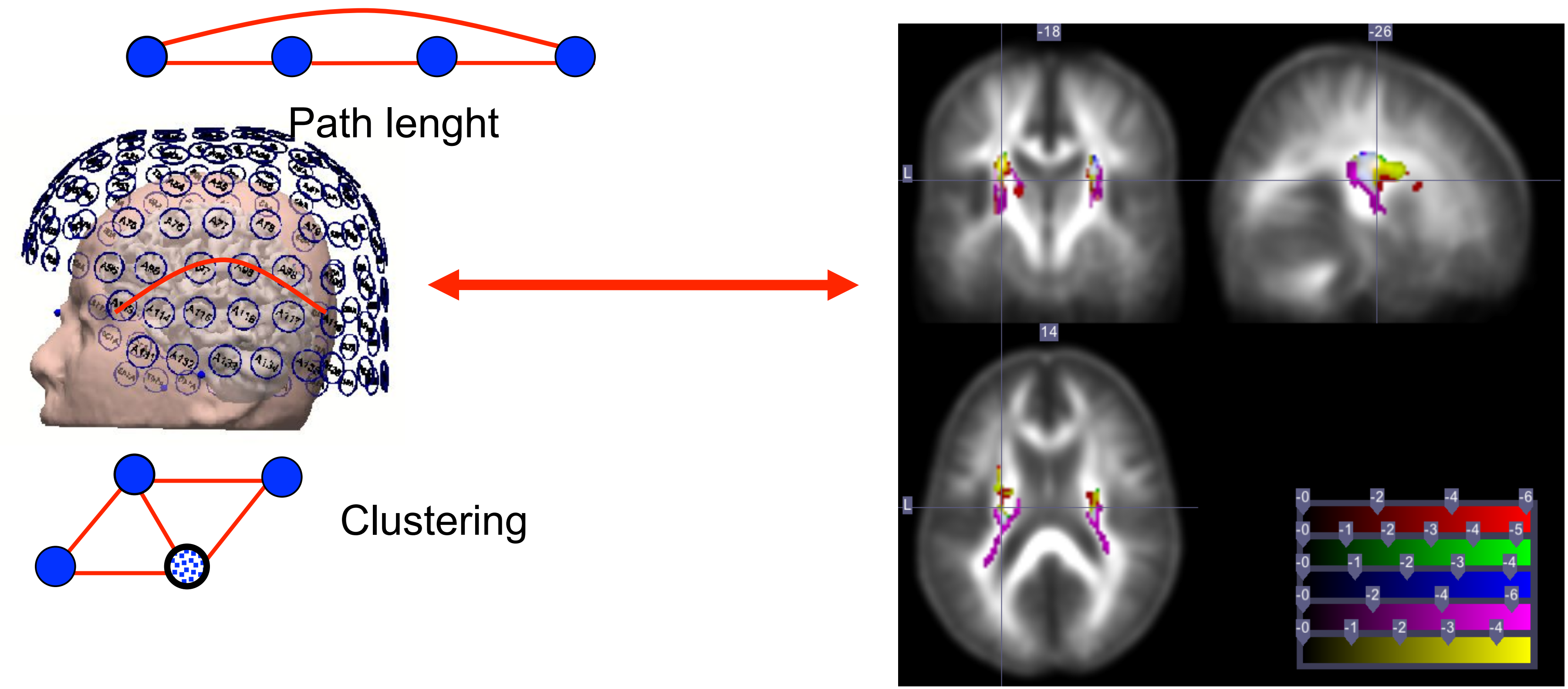


Technology for the early detection of AD: A multidimensional approach

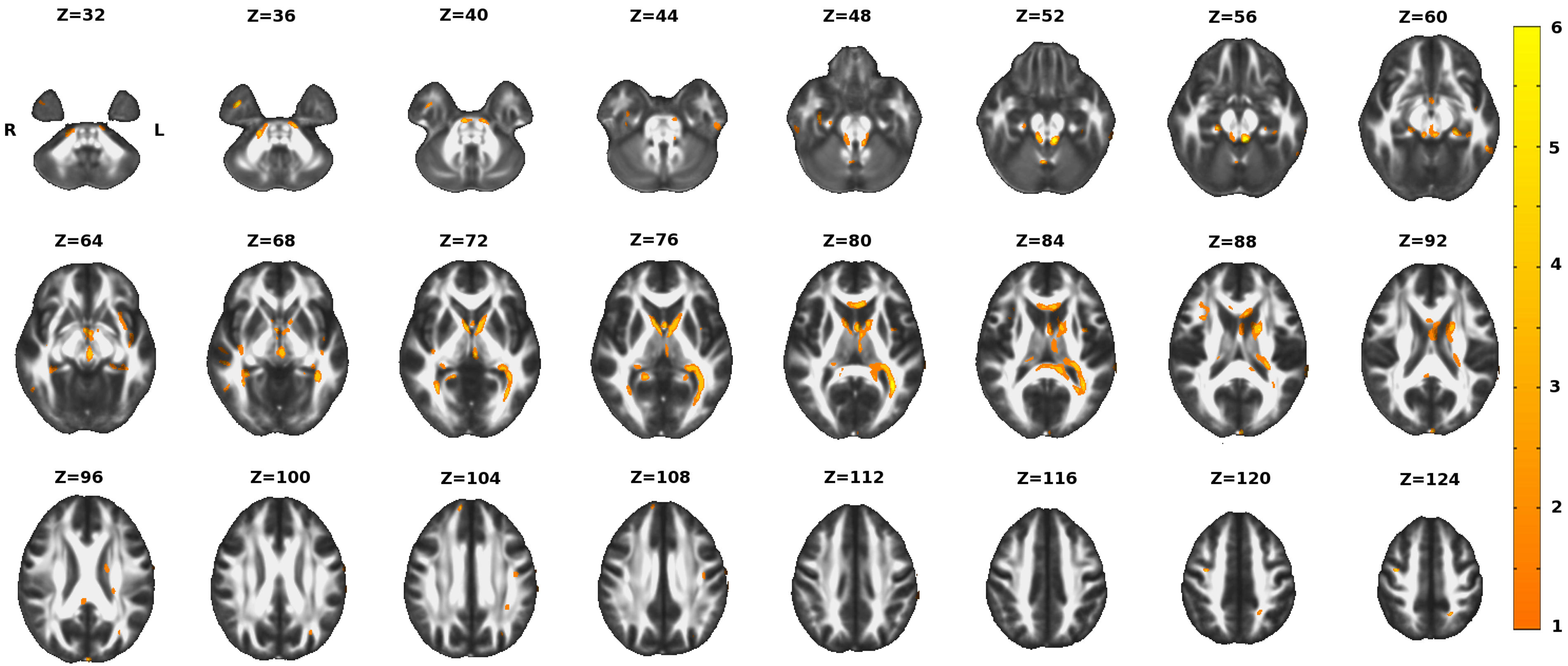


Graph theory: MEG/DTI

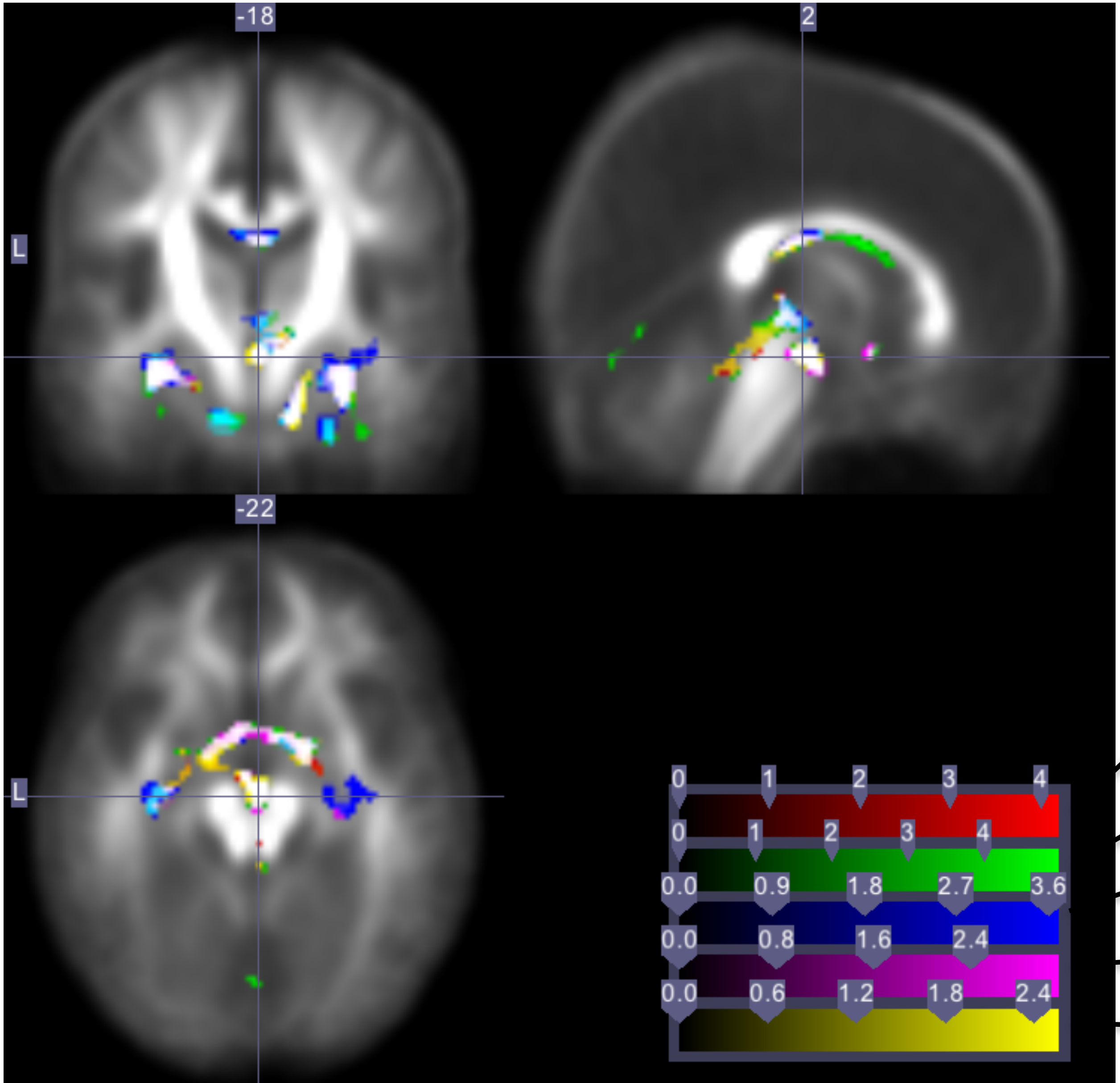
- Combination of anatomo functional connectivity
- Is the functional connectivity architecture depending on the integrity of the white matter?



White Matter Integrity HA > MCI



MCI_Cluster



Correlation

The lower the anisotropy value the lower the tendency to show a SW architecture in fc-MEG data

Delta

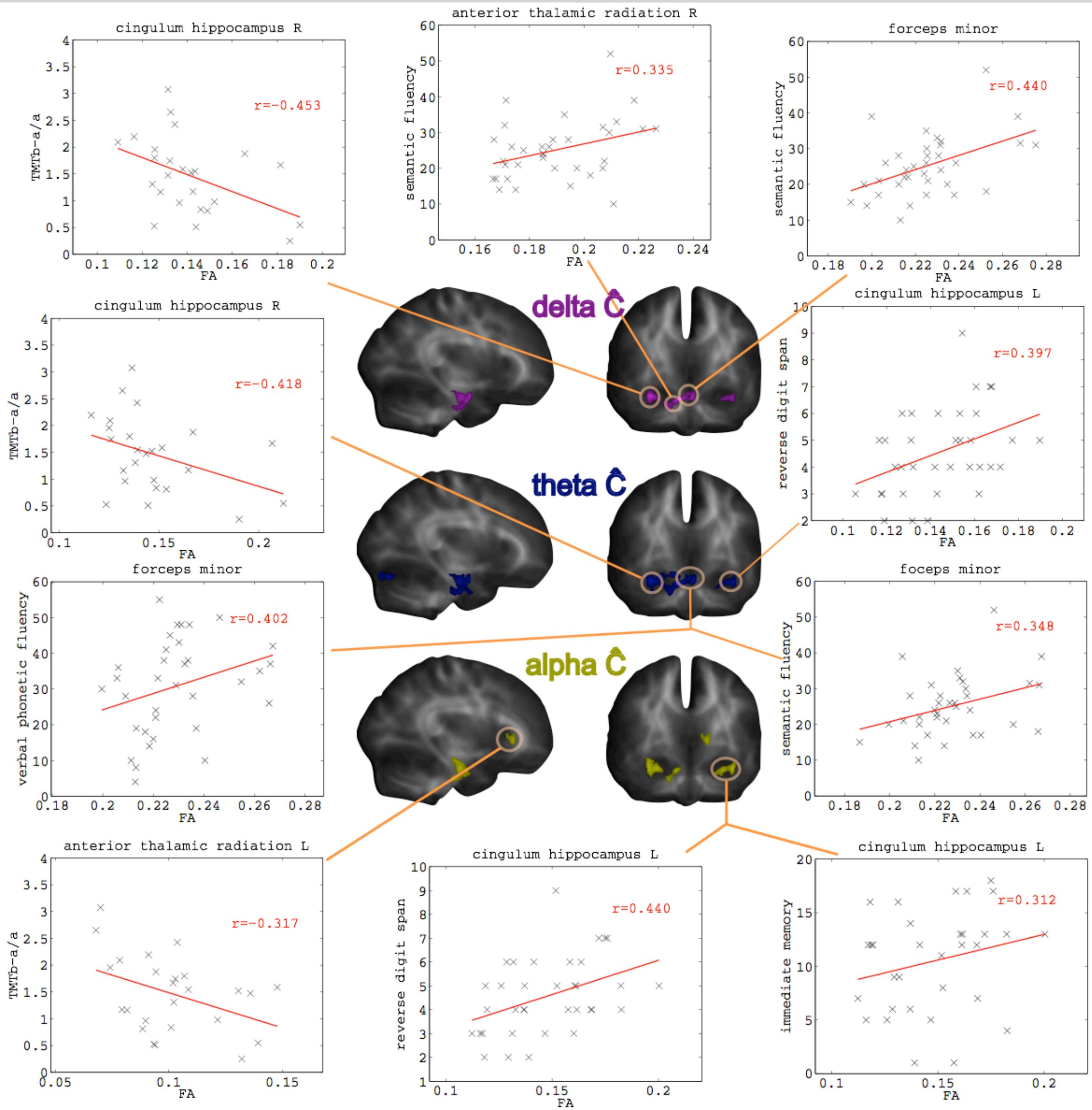
Theta

Alpha

Beta

Gamma

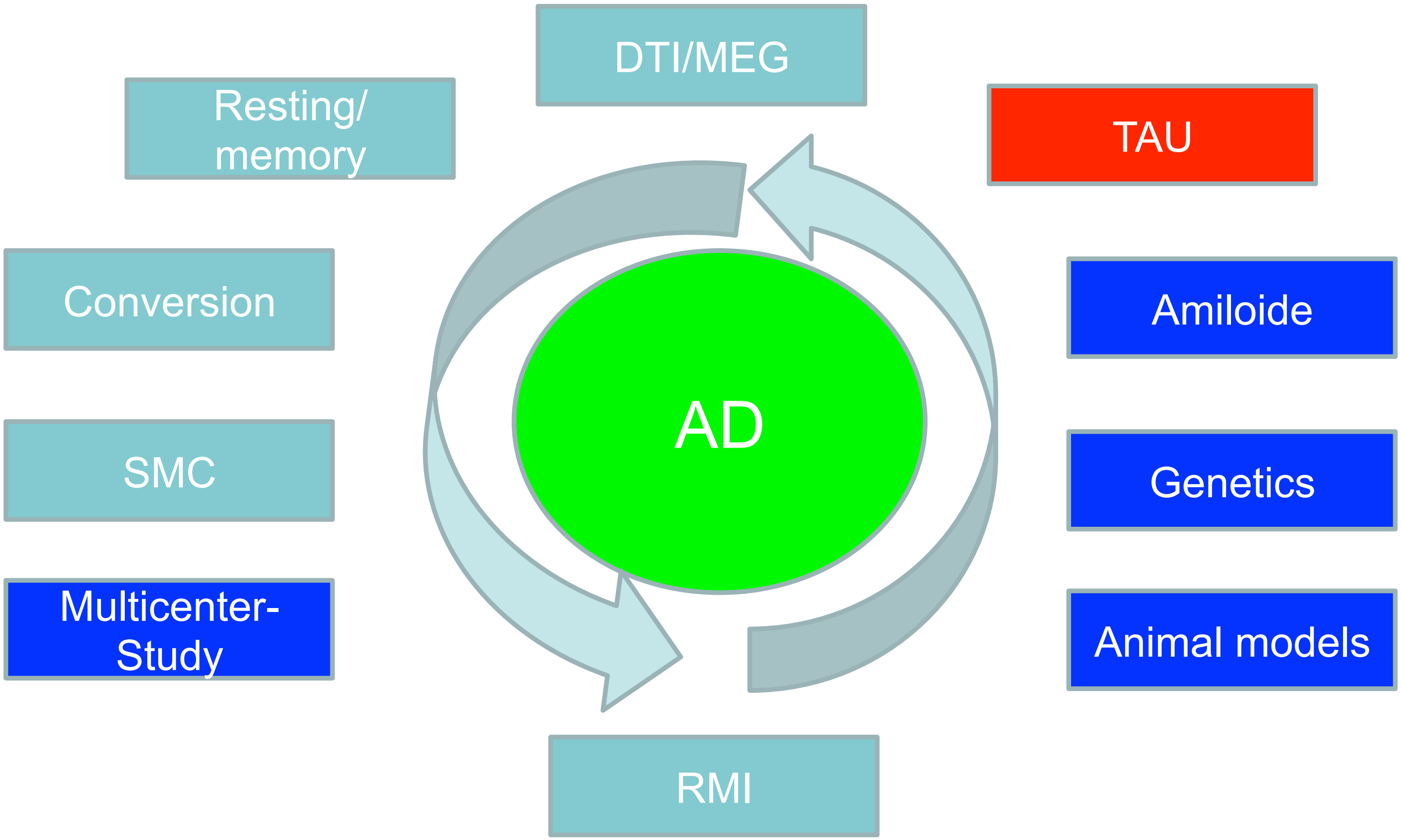
Relationship between neurophysiology and network scores



center for biomedical technology

Technology for the early detection of AD: A multidimensional approach

POLITÉCNICA



MEG-Functional connectivity as a potential marker of p-TAU in the CSF

center for biomedical technology

POLITÉCNICA

Position Paper

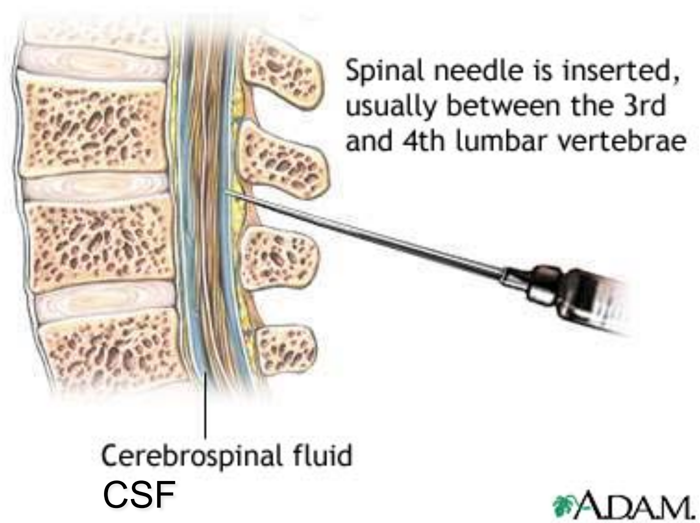
Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria

Bruno Dubois, Howard H Feldman*, Claudia Jacova, Steven T DeKosky, Pascale Barberger-Gateau, Jeffrey Cummings, André Delacourte, Douglas Galasko, Serge Gauthier, Gregory Jicha, Kenichi Meguro, John O'Brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Yaakov Stern, Pieter J Visser, Philip Scheltens*

Lancet Neurol 2007; 6:734-46

The NINCDS–ADRDA and the DSM-IV-TR criteria for Alzheimer's disease (AD) are the prevailing diagnostic

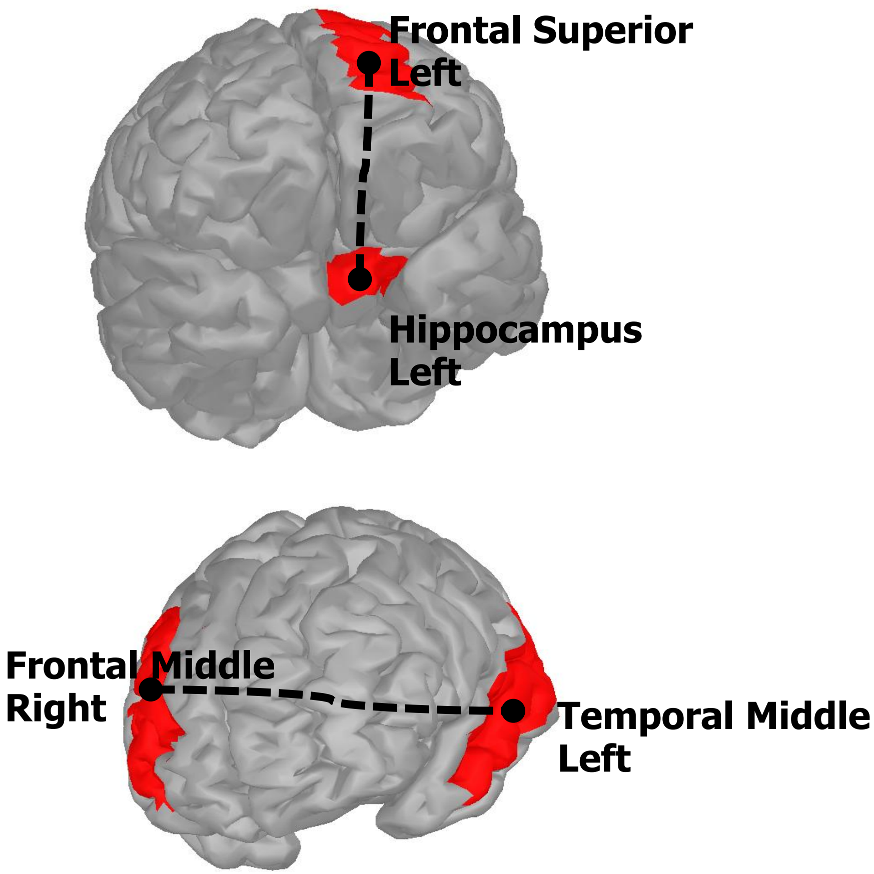
TAU concentration has been associated with neuronal damage and cognitive impairment



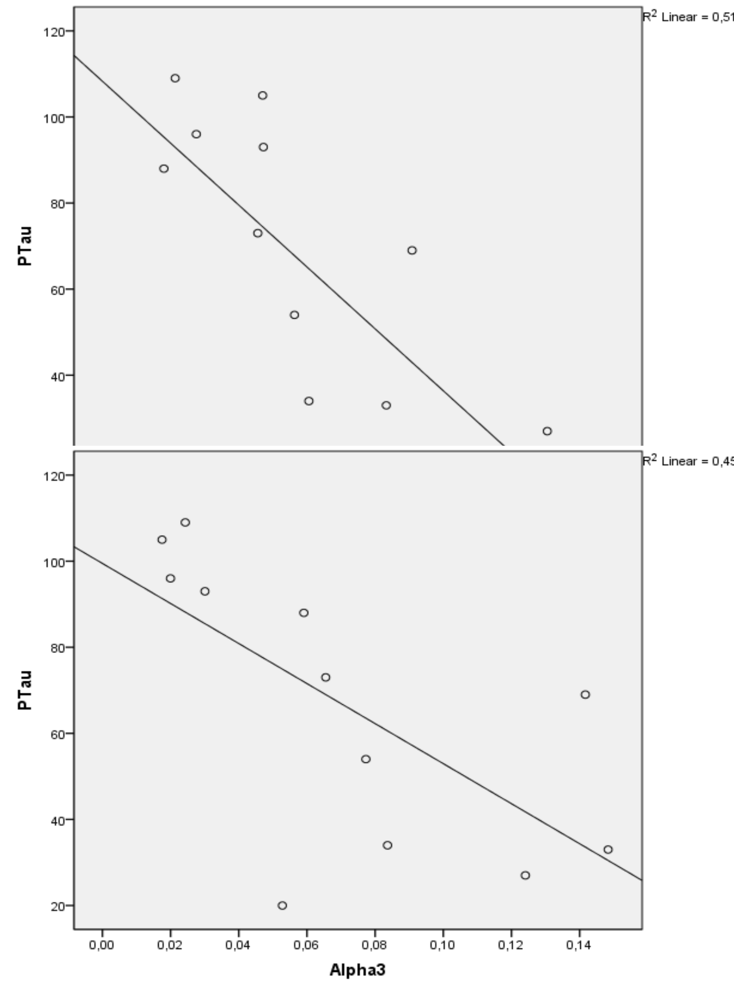
CSF

MEG-Functional connectivity as a potential marker of p-TAU in the CSF

Alpha pTau



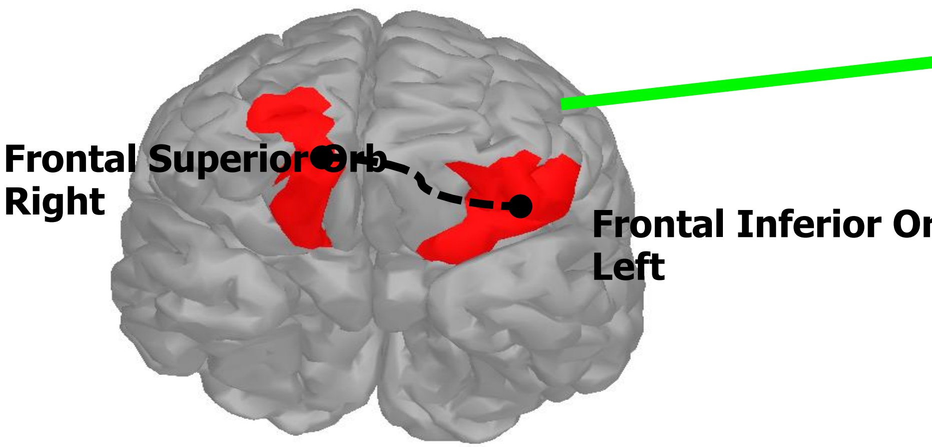
The higher the pTau levels the lower the FC values

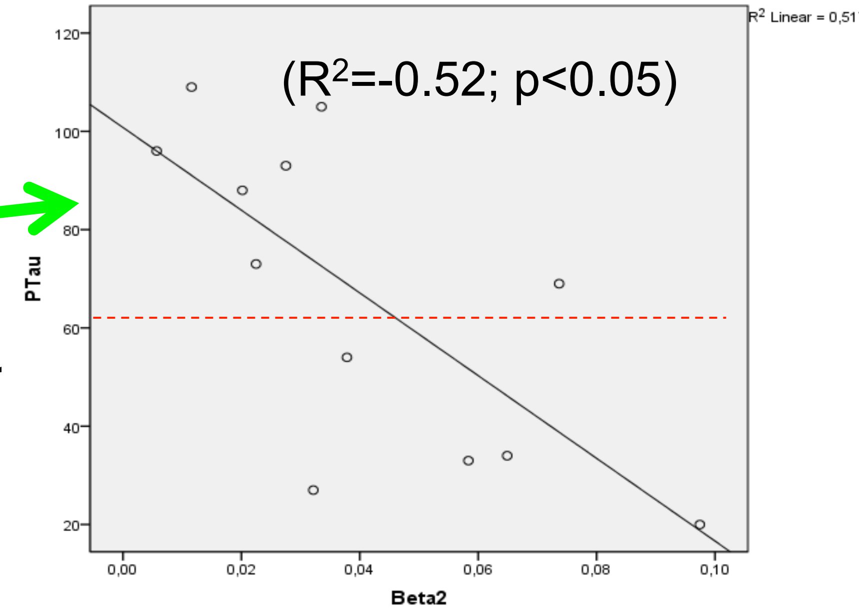


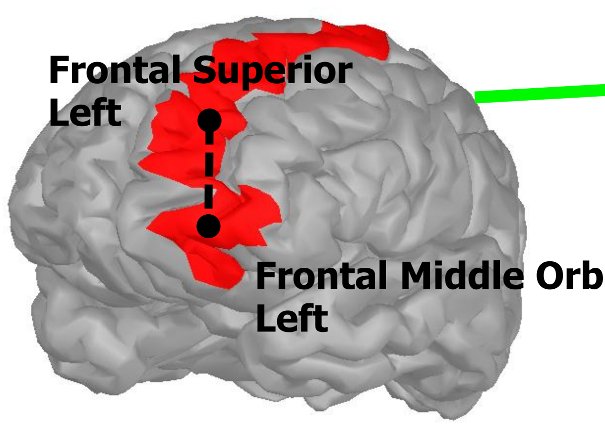
CTB center for biomedical technology

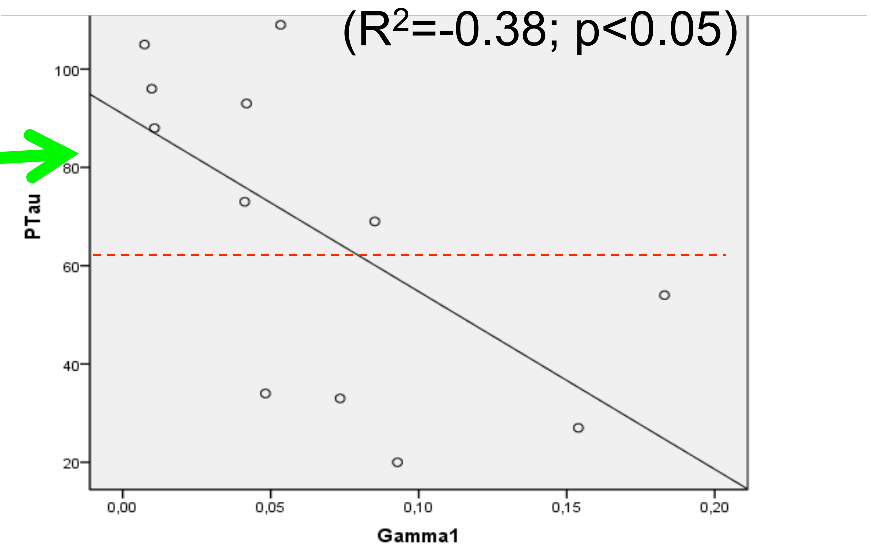
MEG-Functional connectivity as a potential marker of p-TAU in the CSF

POLITÉCNICA





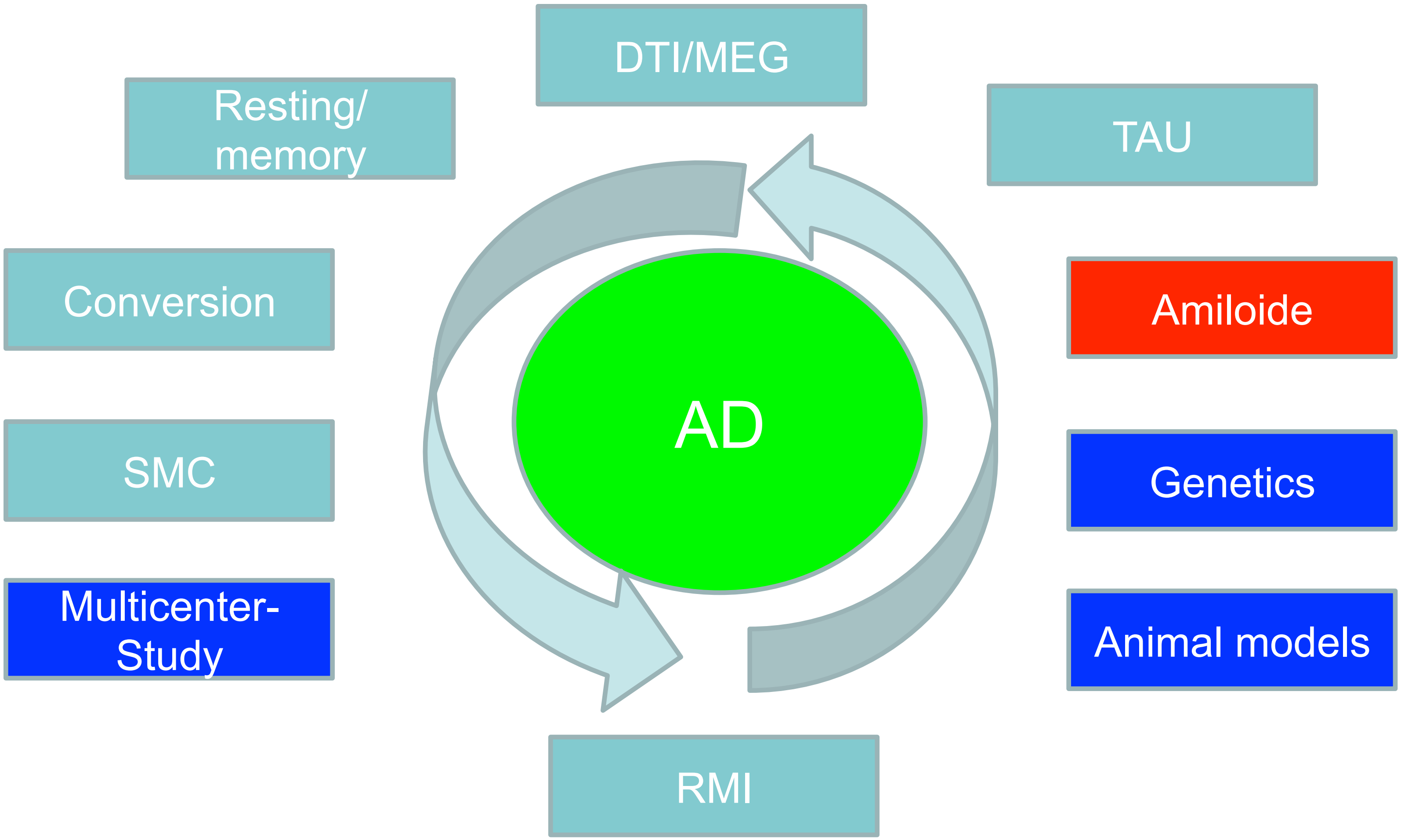




center for biomedical technology

Technology for the early detection of AD: A multidimensional approach

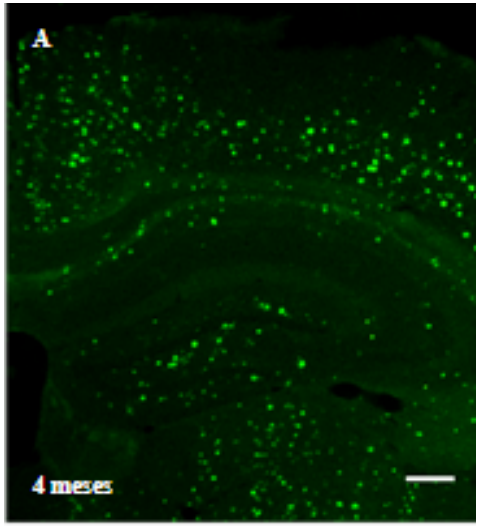
POLITÉCNICA



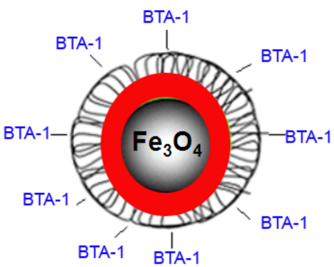
Biofuncionalization of magnetic nanoparticles as a MRI contrast agent of amyloid plaque in EA

injected NPMs

Brain amyloid plaque in transgenic mice

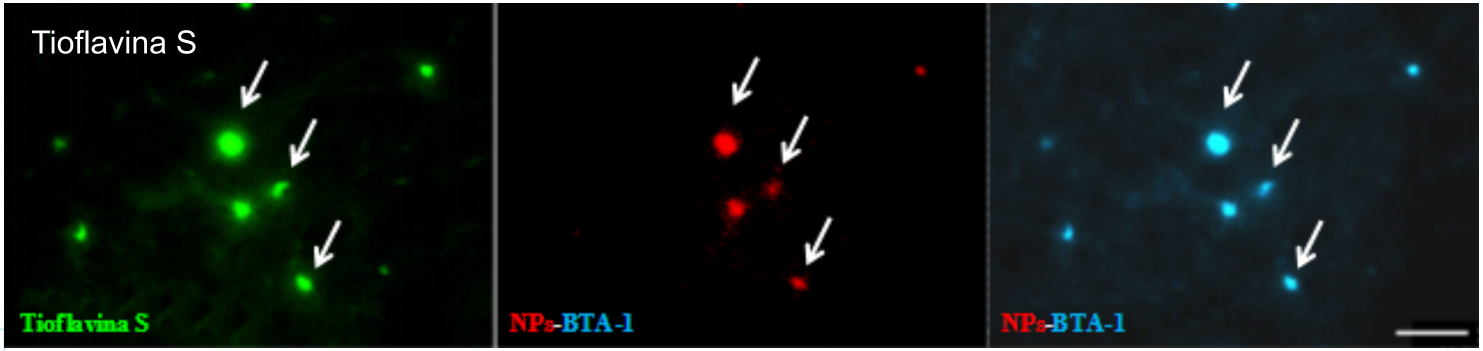


NPMs
fluoroforos
+BTA-1



BTA-1:high affinity to amyloid plaques

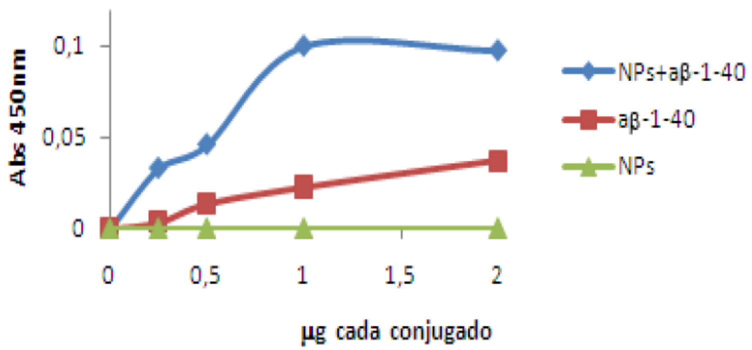
NPMs-BTA1 intravenous injection of Tg **EA**



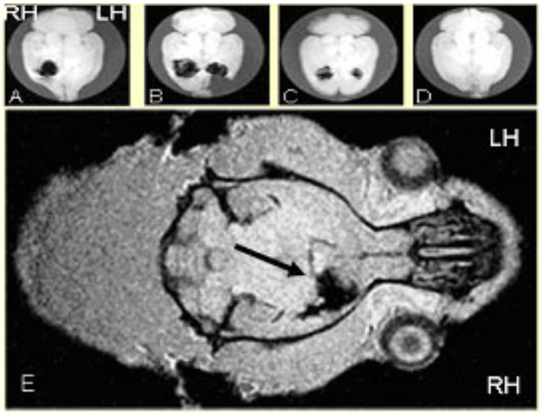
Florescent microscopy of brain coronal sections

Development of selective contrast agents (RMI) for Alzheimer Disease

Different peptides have been conjugated with the magnetic nanoparticles to achieve a specific marker of the amyloid plaque. *in vitro* tests to evaluate the specific binding, affinity and toxicity of the conjugates.



Results obtained by an ELISA test carried out in P96 wells that have been previously treated with 1 µg of aβ1-42 peptide. The nanoconjugate NP-aβ shows an even higher affinity to bind to aβ1-42 than the aβ peptide alone. Interestingly NPs alone do not show any affinity to binding to aβ1-42.



Dextran coated magnetic nanoparticles (MNPs) can be detected efficiently by MRI in *ex vivo* and *in vivo* brains.

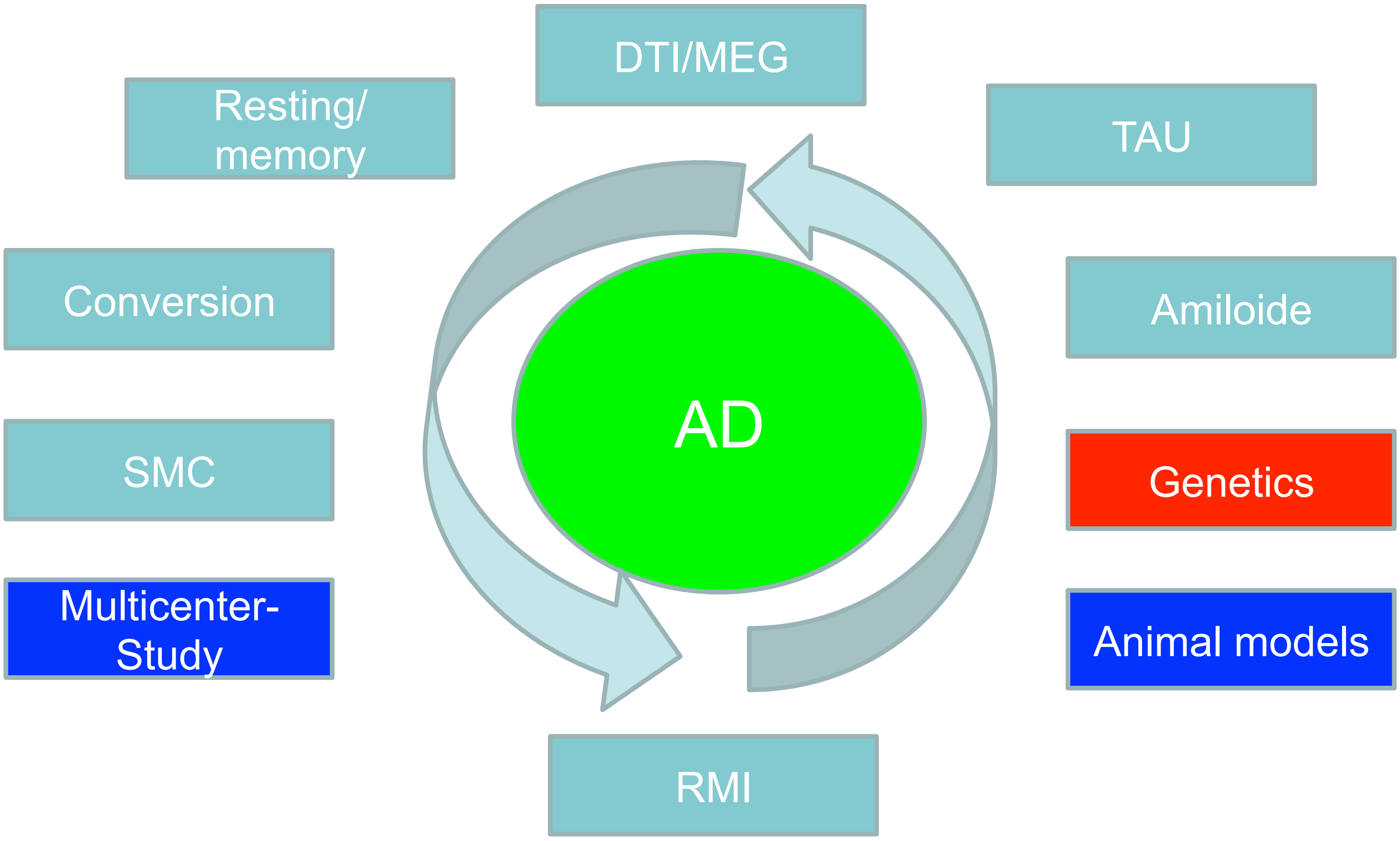
Challenges: highly stable in vivo; cross the Blood - Brain Barrier (BBB) non-destructively following intravenous injection; bind specifically to plaques with high affinity and produce local changes in tissue contrast detectable by MRI. Animal models: transgenic mice for AD (5xFAD)

Cellular & animal models:
Molecular Biology and Biochemistry

From left to right: Frank Mikuski, Daniel González-Nieto, Milagros Ramos, Laura Fernández, Norma Ramírez, Soledad Martínez, José Luis Gaztelú-Quijano, Juan Barios, Ceferino Maestú, José Mª Arguelles

From left to right: Nazaríao Féliz, Flavio Vinicio Changoluisa, Alfonso Muinelo, Ana Lorena Urbano, Rodolfo Maestre, Javier Serrano, Cristina Sánchez, Jorge Díaz Mateus.

Technology for the early detection of AD: A multidimensional approach

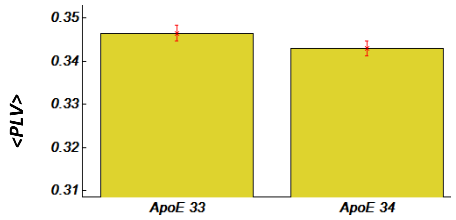


Functional connectivity and genetic profiles

Delta Band APOE effect

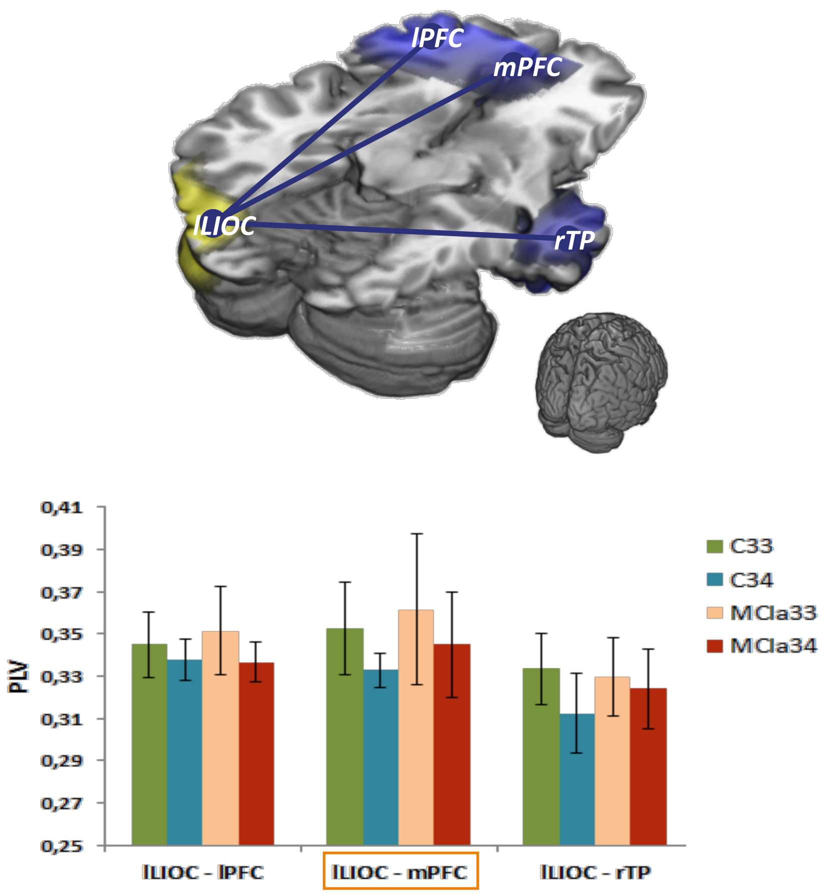
lLIOC <PLV>

ApoE Genotype Effect p = 0.049 (F = 4.03)

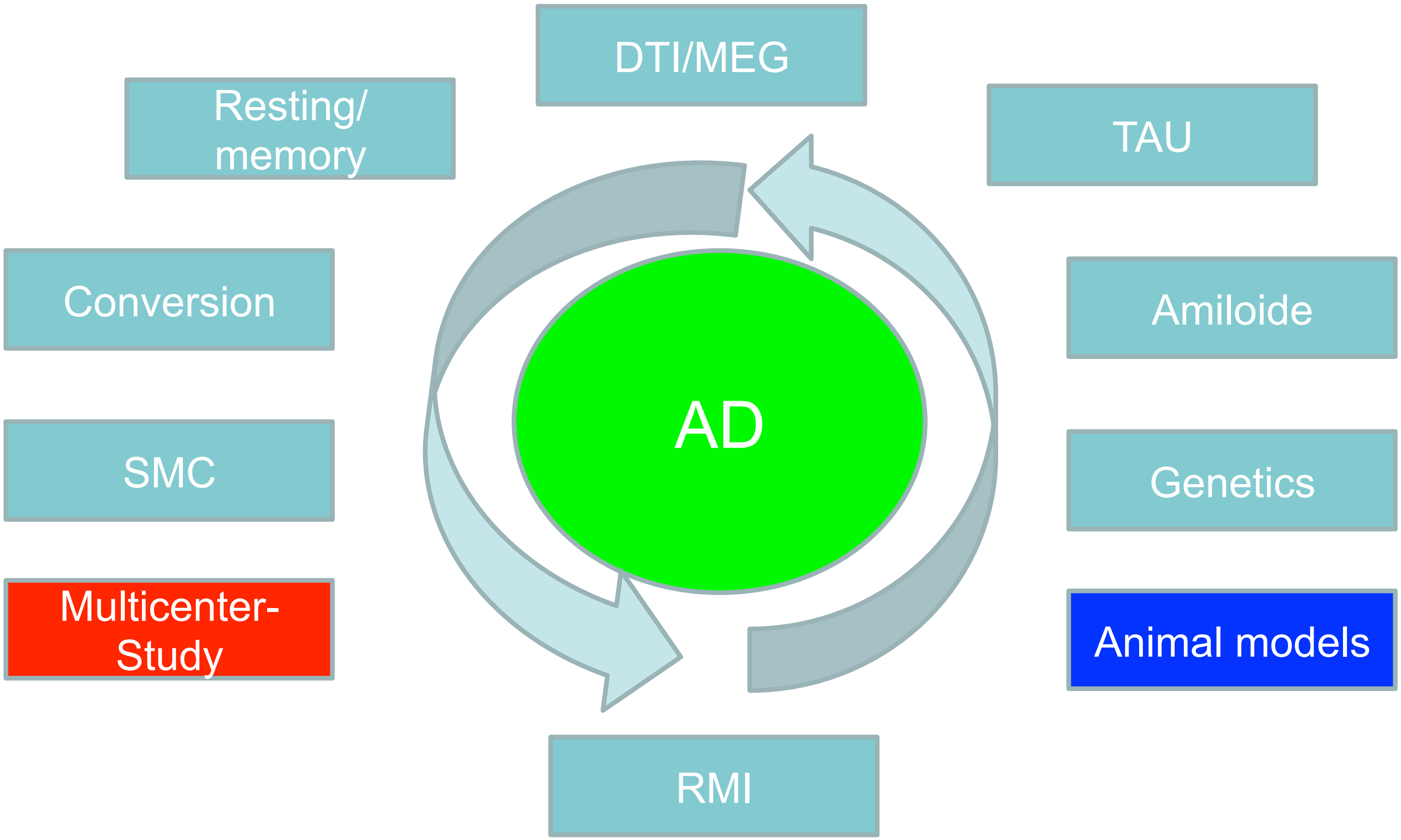


carriers versus non carriers of apoe 3/4

lLIOC Disrupted Links



Technology for the early detection of AD: A multidimensional approach



MAGIC-AD project: Objectives

It has been examined differences in functional connectivity between MCI and healthy controls with MEG **at the group level**.

- In order for MEG to be useful, it must be able to detect abnormal function at the **level of the individual patient.**

-There were **two goals** to the present study:

To develop a model, using data mining techniques, that reliably distinguishes between MCI patients and healthy controls.

Test this model using an unseen dataset of MCI and control subjects acquired by the MAGIC-AD consortium.

MAGIC-AD: MEG International Consortium for the study of Alzheimer's Disease

center for biomedical technology

POLITÉCNICA

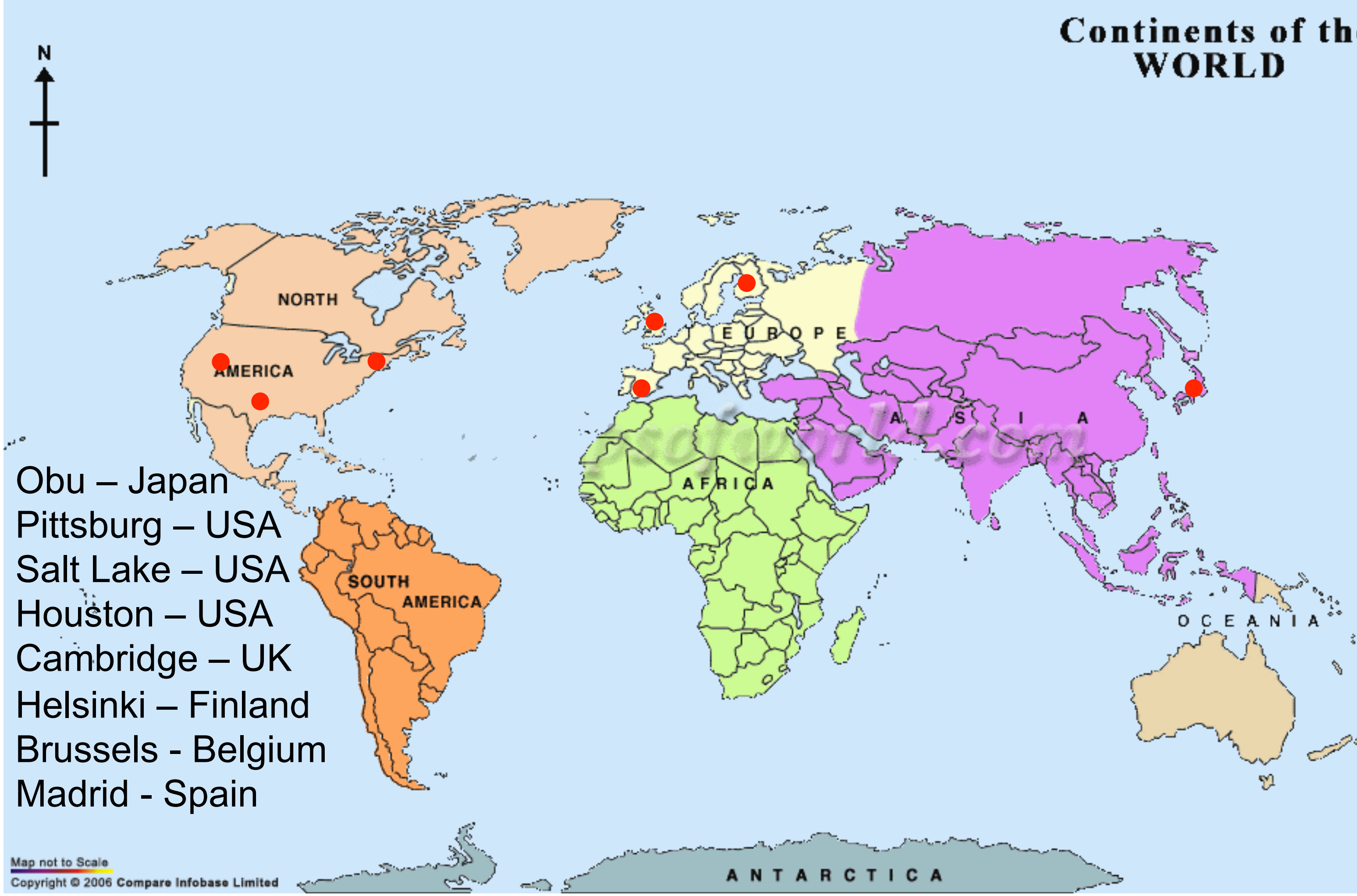
National Center for Geriatrics and Gerontology

UNIVERSITY OF HELSINKI

THE UNIVERSITY OF UTAH

centro de tecnología biomédica

POLITÉCNICA



Obu – Japan
Pittsburg – USA
Salt Lake – USA
Houston – USA
Cambridge – UK
Helsinki – Finland
Brussels - Belgium
Madrid - Spain

Elekta-Neuromag supported the annual meeting of the consortium

CTB center for biomedical technology

Health care business ecosystem

POLITÉCNICA

Rik Henson

Akinori Nakamura

Anto Bagic

James Becker

Gustavo Sudre

Ed Zamrini

Jyrki Mäkelä

Lauri Parkonen

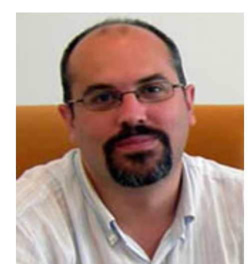
Eero Pekkonen

Michael Funke

Ricardo Bajo

Pilar Garcés

Pablo Cuesta



Jose M Peña

Stages of the study

1. Training datasets (known subjects)

- All data recorded (resting state) in Madrid
- MEG Datasets: 83 MCI and 54 controls

2. Validation datasets (Unseen/ blind study)

- Data recorded at five different MEG labs
- MEG data sets: 24 MCI and 28 controls

Results of the data mining classification. Madrid data

Internal validation

	Real class			
Predicted class	MCI	Control		
MCI	65	15	81,25%	PPV
Control	13	39	75,00%	NPV
	83,33%	72,22%	78,79%	Accuracy
	Sensitivity	Specificity		

Analysis of MAGIC-AD DATA

Recordings of MEG data

University of Pittsburgh (USA)

University of Utah (SLC, USA)

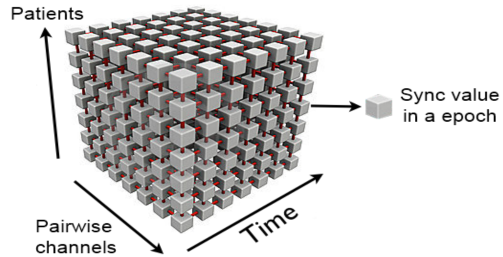
University of Cambridge (UK)

University of Helsinki (FN)

University of Houston (USA)

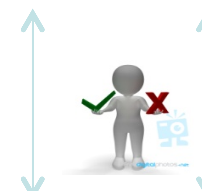
National Center for Gerontology and Geriatrics (Obu-Japan)

Blind Data Mining analysis



Center for Biomedical Technology (Madrid, Spain)

Meeting to assess results



center for biomedical technology

Results of the data mining blind classification. MAGIC-AD DATA

POLITÉCNICA

External validation

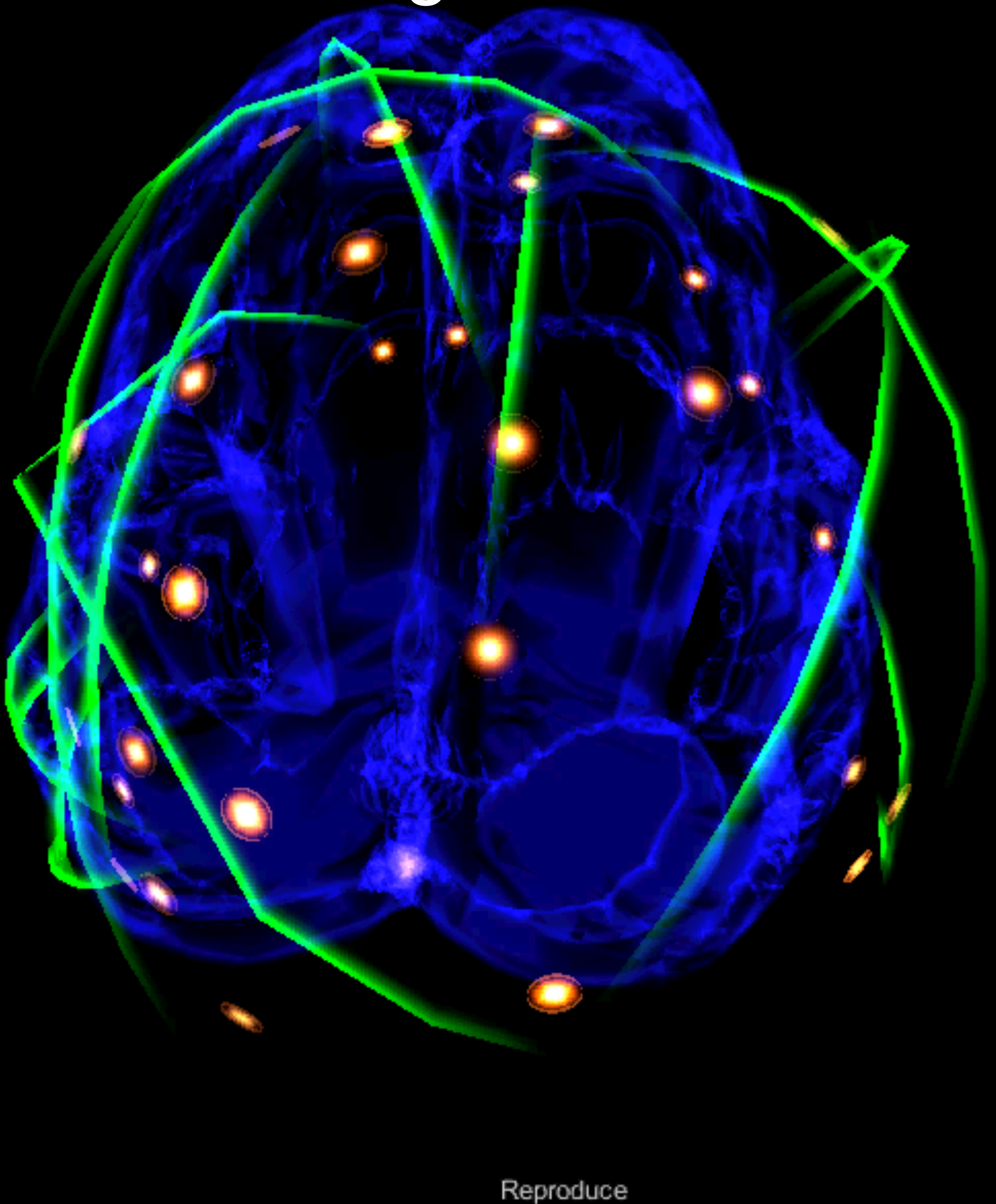
Predicted class	Real class: MCI	Real class: Control		
MCI	12	4	75,00%	PPV
Control	1	11	91,67%	NPV
	92,31%	73,33%	82,14%	Accuracy
	Sensitivity	Specificity		

Results of the data mining blind classification. MAGIC-AD DATA

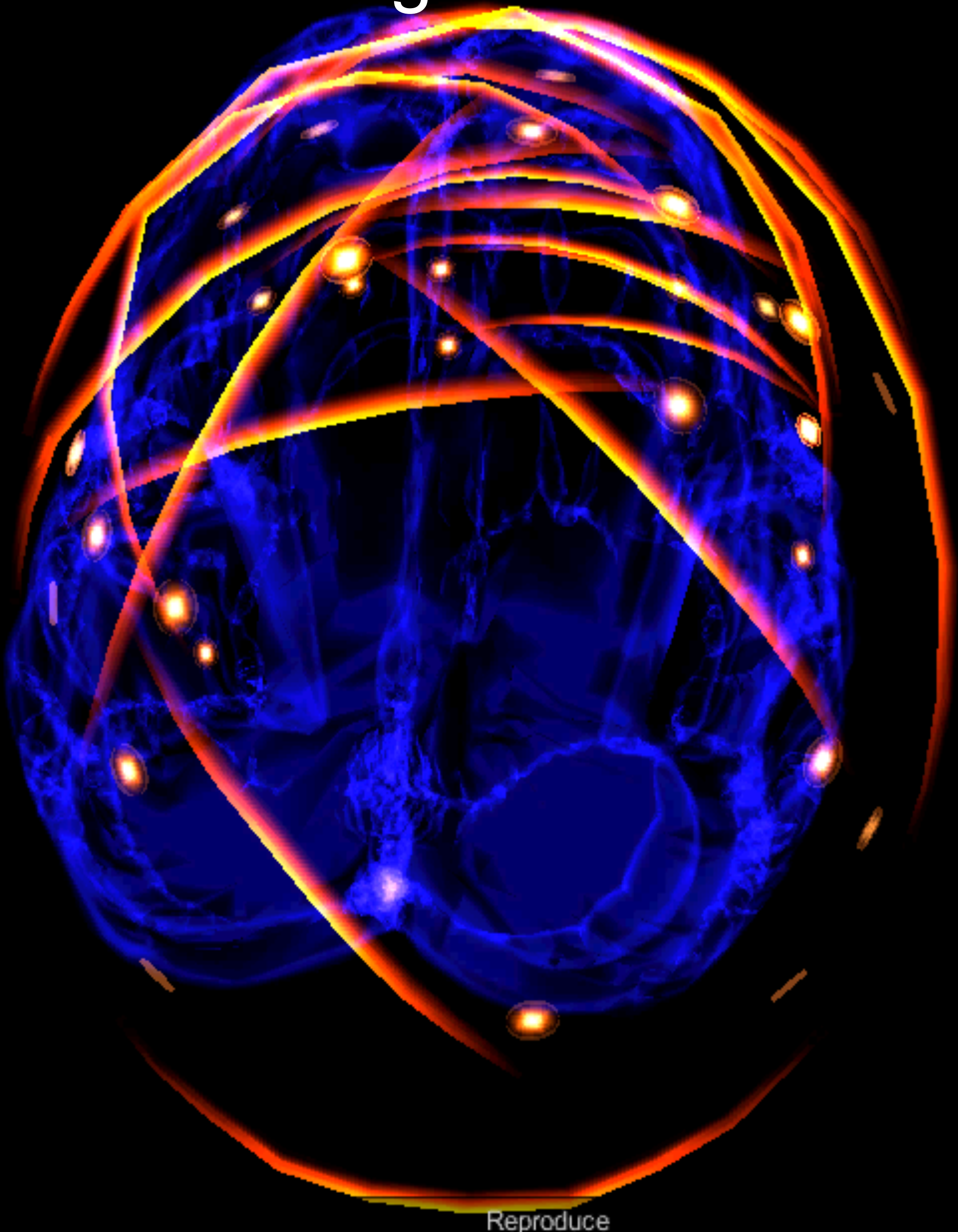
External validation (Second Round)

Predicted class	Real class: MCI	Real class: Control		
MCI	11	4	73,33%	PPV
Control	0	9	100,00%	NPV
	100,00%	69,23%	83,33%	Accuracy
	Sensitivity	Specificity		

Fronto-parietal links achieving classification values



Inter-hemisph links achieving classification values



Data Mining and Simulation LAB

From left to right: (back row) Santiago González, Jorge Peña, Felix de las Pozas, , Juan Morales, Carlos Garcia, Santiago Muelas, Angel Garcia, Jesus Sanchez, (front row) Chema Peña, Victor Robles, Consuelo Gonzalo, Ernestina Menasalvas, Sandra Saez, Antonio Latorre, Juan Hernando.

Read more

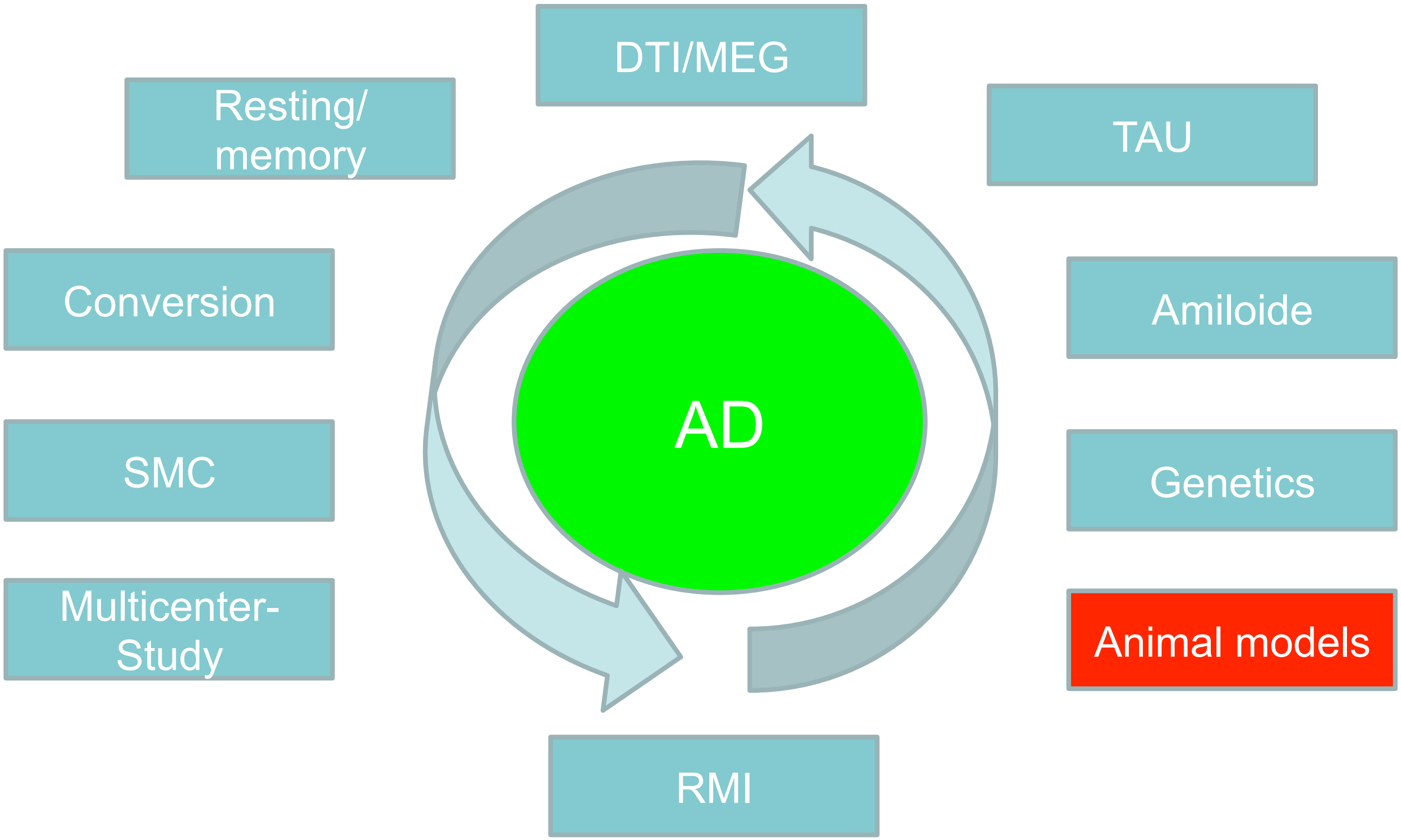
SAGE-Hindawi Access to Research
International Journal of Alzheimer's Disease
Volume 2011, Article ID 280289, 10 pages
doi:10.4061/2011/280289

Review Article

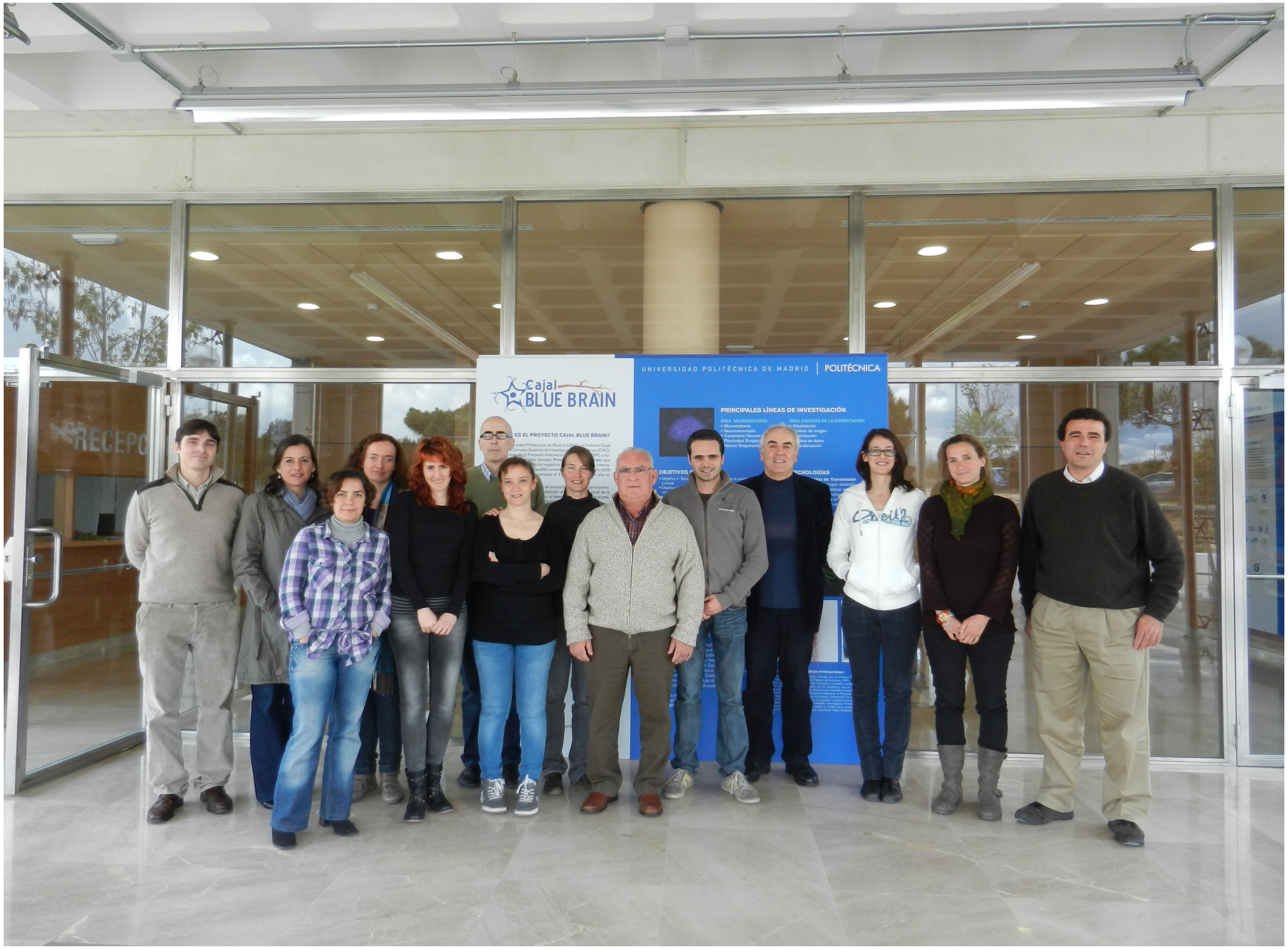
Magnetoencephalography as a Putative Biomarker for Alzheimer's Disease

Edward Zamrini,[1] Fernando Maestu,[2] Eero Pekkonen,[3] Michael Funke,[1] Jyrki Makela,[4] Myles Riley,[1] Ricardo Bajo,[2] Gustavo Sudre,[5] Alberto Fernandez,[2] Nazareth Castellanos,[2] Francisco del Pozo,[2] C. J. Stam,[6] Bob W. van Dijk,[7] Anto Bagic,[8] and James T. Becker[8,9,10,11]

Technology for the early detection of AD: A multidimensional approach



Cajal Blue Brain Project



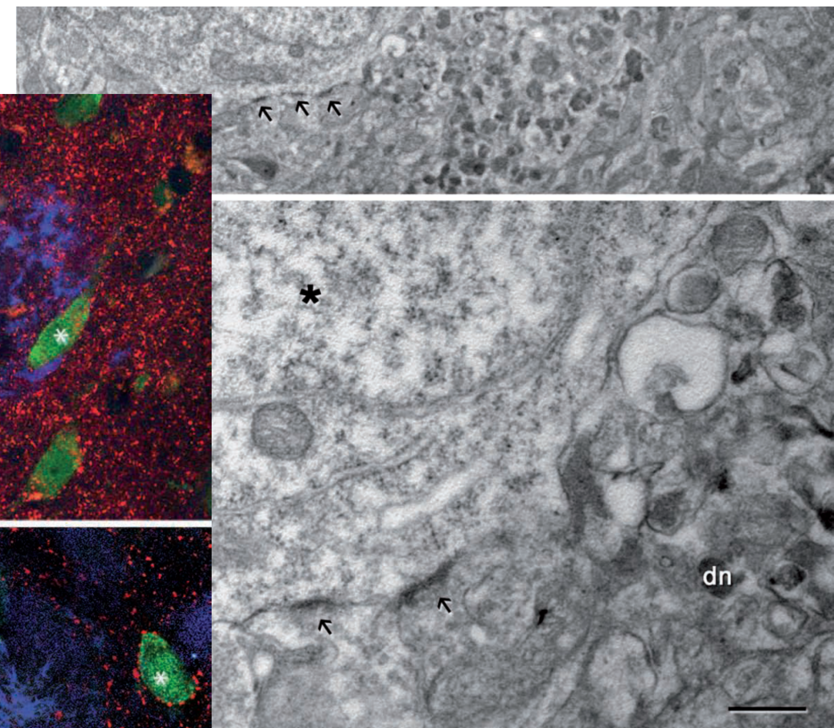
From left to right: Gonzalo León, Pilar Flores, Isabel Merchán, Diana Sánchez, Lorena valdés, Ángel Merchán, Ana Isabel García, Ruth Benavides, Rodrigo Pérez, Miguel Miguens, Javier DeFelipe, Lidia Alonso, Paula Merino, Alberto Muñoz.

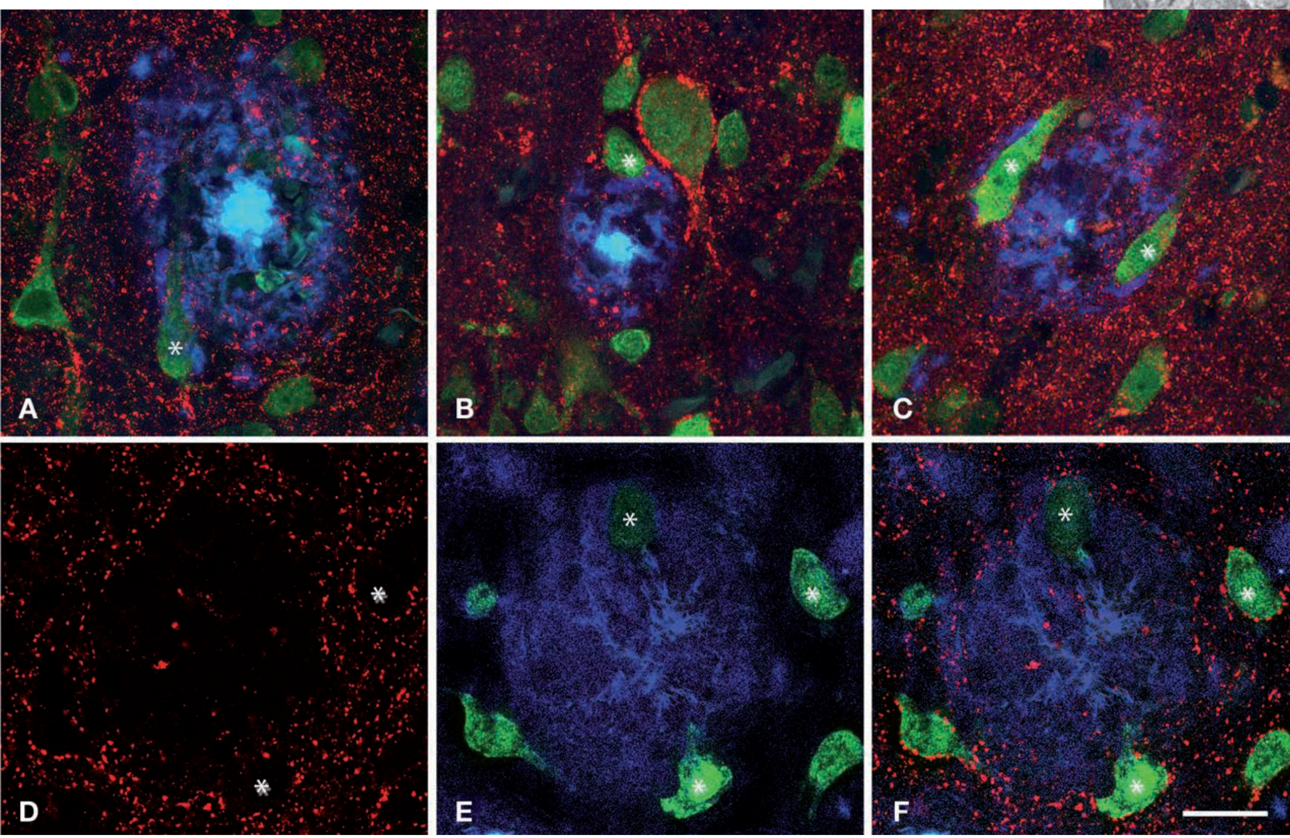
frontiers in
NEUROANATOMY

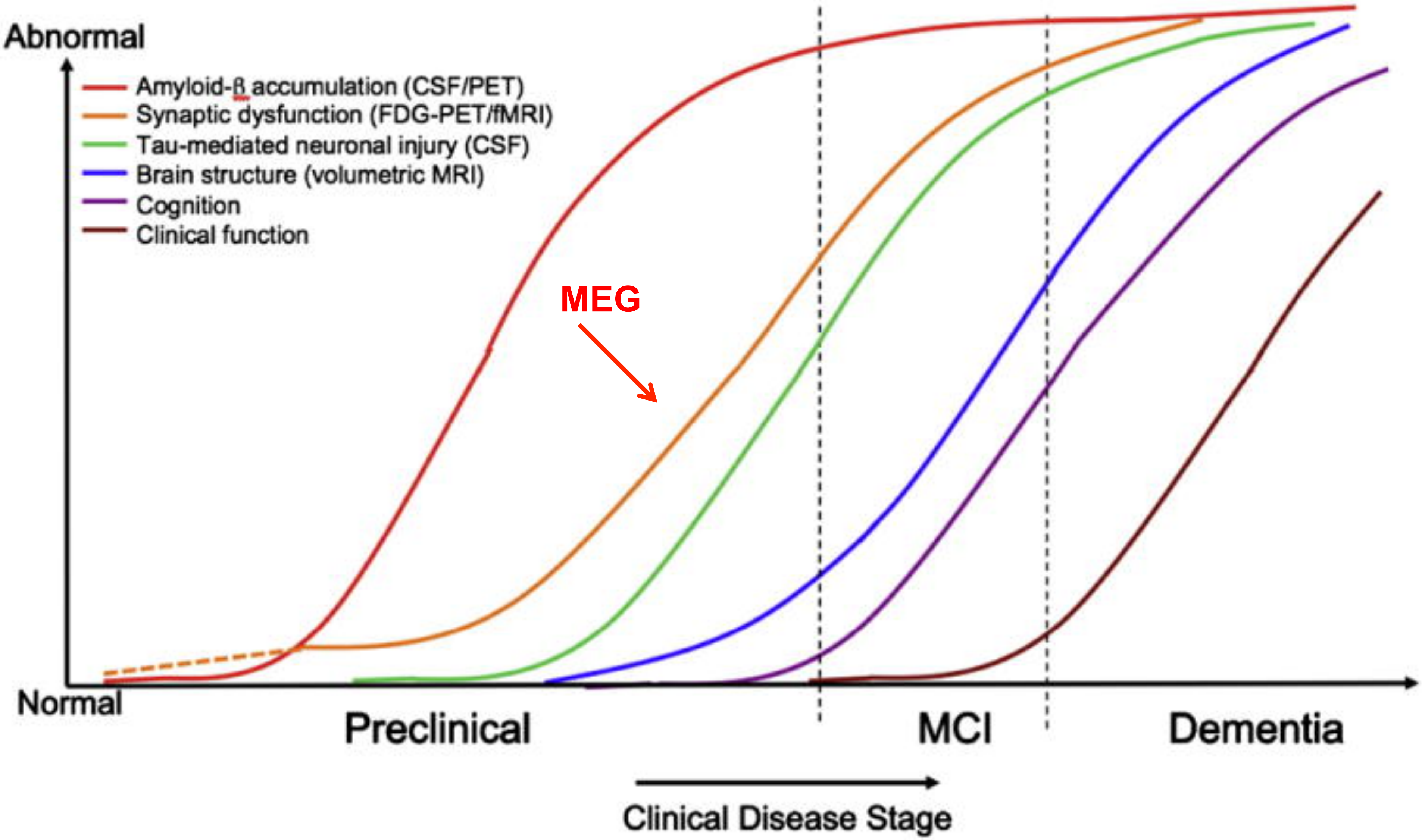
ORIGINAL RESEARCH ARTICLE
published: 20 November 2009
doi: 10.3389/neuro.05.028.2009

Diminished perisomatic GABAergic terminals on cortical neurons adjacent to amyloid plaques

*Virginia Garcia-Marin[1,2†], Lidia Blazquez-Llorca[1,2†], José-Rodrigo Rodriguez[1,2], Susana Boluda[3], Gerard Muntane[3], Isidro Ferrer[3] and Javier DeFelipe[1,2]**







(Jack et al, 2010; Sperling et al, 2011)