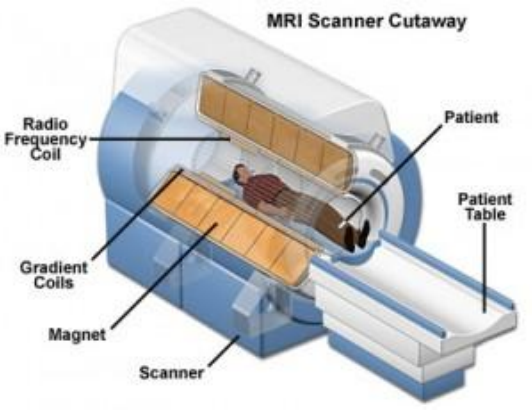
Neuroimage analysis

—

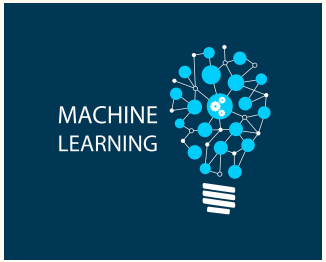
Application to dementia (and brain lesions)

Motivation



INPUT:

High dimensional data
Multi modal data
Huge amount of data



PROCESSING:

Machine learning
Statistics
Automation
Complex patterns

Outcome measure
Prediction
Inference
Diagnosis

OUTPUT:

Observational research
Interventional research
Clinical practice

Outline

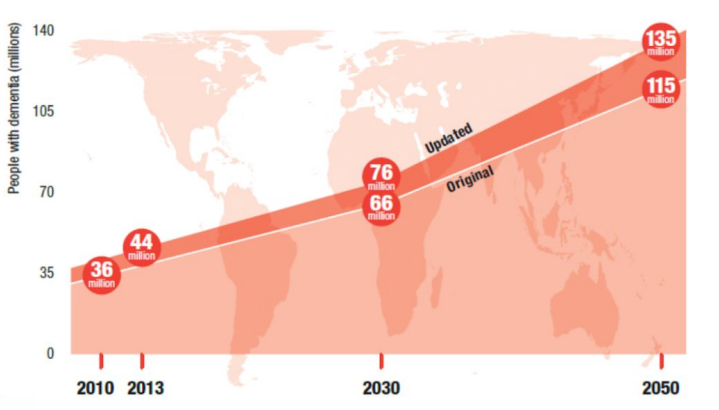
1. Alzheimer's disease

2. UPC - FPM research
    a. MRI-based screening: building datasets with subjects at risk.
    b. NeAT: Neuroimaging Analysis Toolbox.
    c. Latent processes governing brain morphology and brain biomarkers.
    d. Longitudinal studies. Relationship between jacobian and biomarkers

3. Conclusions & future work

Alzheimer's disease

A global epidemic



Clinical diagnosis (probable AD: acc.: 70%):

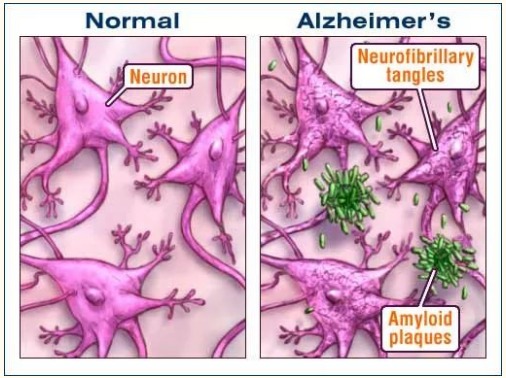
- Tests: memory, problem solving, etc.
- Questionnaire: daily activities, behavior, personality, etc.

True diagnosis: post-mortem.

Clinical practice: AD defined as a syndrome.

- It gives no clue about its etiology
- Disease modifying therapies must engage biological targets.

Need for a **AD continuum definition** based on **biomarkers** that could potentially lead to dementia [1]



[1] Jack, C. R. J., et al. "NIA-AA research framework: towards a biological definition of Alzheimer's disease." (2017).

Alzheimer's disease

Biological definition of AD

Using **biomarkers** for brain state inference. [2]

- **A:** amyloid biomarker (CSF, PET)
- **T:** tau pathology biomarker (CSF, PET)
- **N:** neurodegeneration or neuronal loss (CSF, MRI, FDG-PET)

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N>	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Cognitive staging:

1. Cognitively normal (CN)
2. Mild cognitive impariment (MCI)
3. Dementia

	Syndromal Cognitive Stage			
Biomarker Profile		**Cognitively unimpaired**	**MCI**	**dementia**
	$A^- T^- (N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	$A^+ T^- (N)^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	$A^+ T^- (N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
	$A^+ T^+ (N)^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI (Prodromal AD)	Alzheimer's disease with dementia
	$A^+ T^+ (N)^+$			

[2] Jack, Clifford R., et al. "A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers." Neurology 87.5 (2016): 539-547.

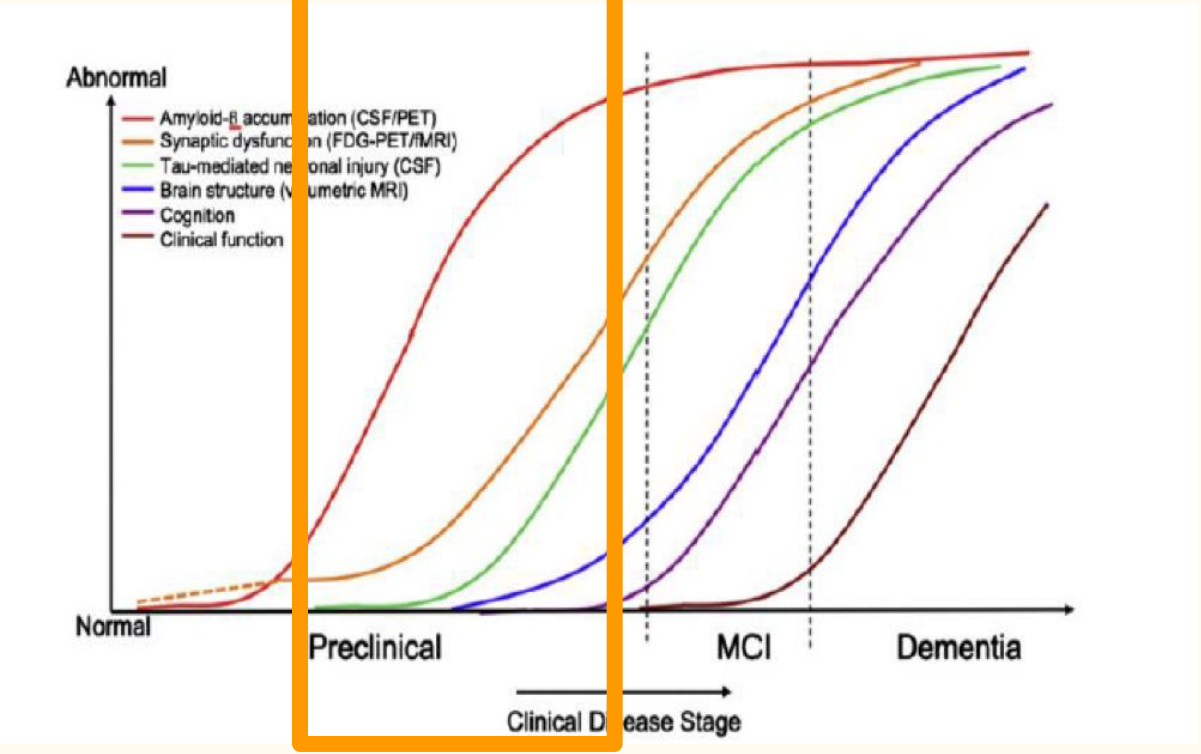
Alzheimer's disease

Preclinical stage of AD

Brain alterations appear ~20 years before clinical symptoms appear:

- Better understanding of AD
- Better disease-modifying therapies.

Alterations to the A/T/N profile might occur before clinical and/or cognitive impairment occur.



Outline

1. Alzheimer's disease

2. UPC - FPM research
   a. MRI-based screening: building datasets with subjects at risk.
   b. NeAT: Neuroimaging Analysis Toolbox.
   c. Latent processes governing brain morphology and brain biomarkers.
   d. Longitudinal studies. Relationship between jacobian and biomarkers

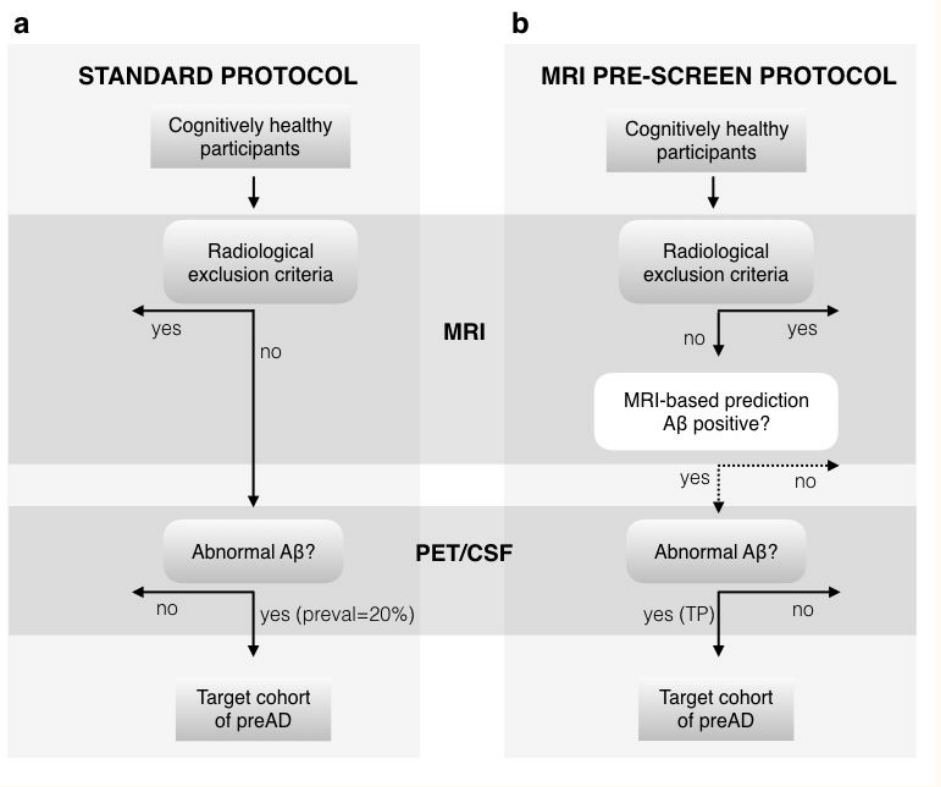
3. Conclusions & future work

Casamitjana et al. MRI-based screening of preclinical Alzheimer's disease for prevention clinical trials *Journal of Alzheimer's and Disease (2018)*

MRI-based screening

Goal of the study:

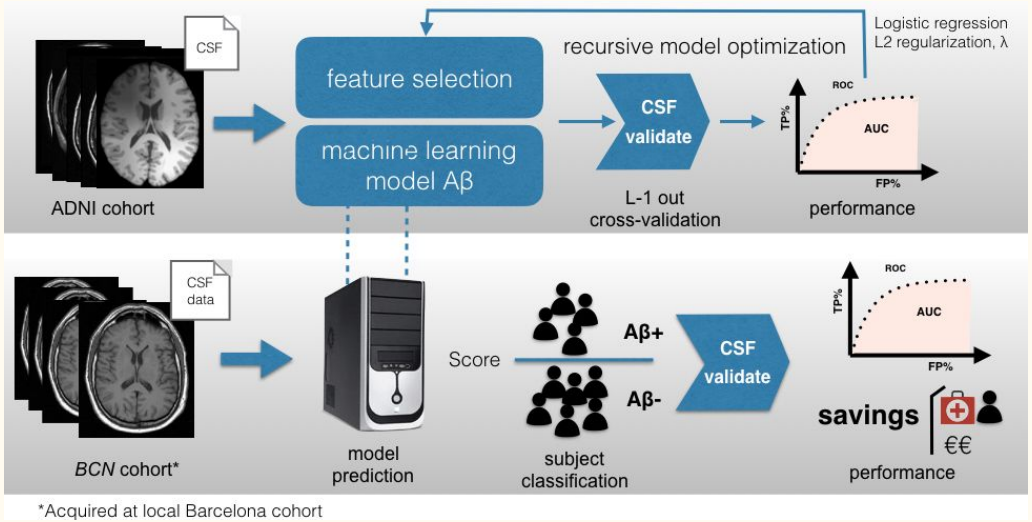
- Devise an MRI-based protocol for screening preclinical subjects:
  - Non-invasive
  - Cost-efficient
- Provide a proof-of-concept study:
  - Use a public dataset to infere the model (ADNI)
  - Apply to private cohorts (HCB)



MRI-based screening

Case study: a proof-of-concept

- Use the publicly available ADNI cohort to build the model
- Use a private cohort to evaluate the model.



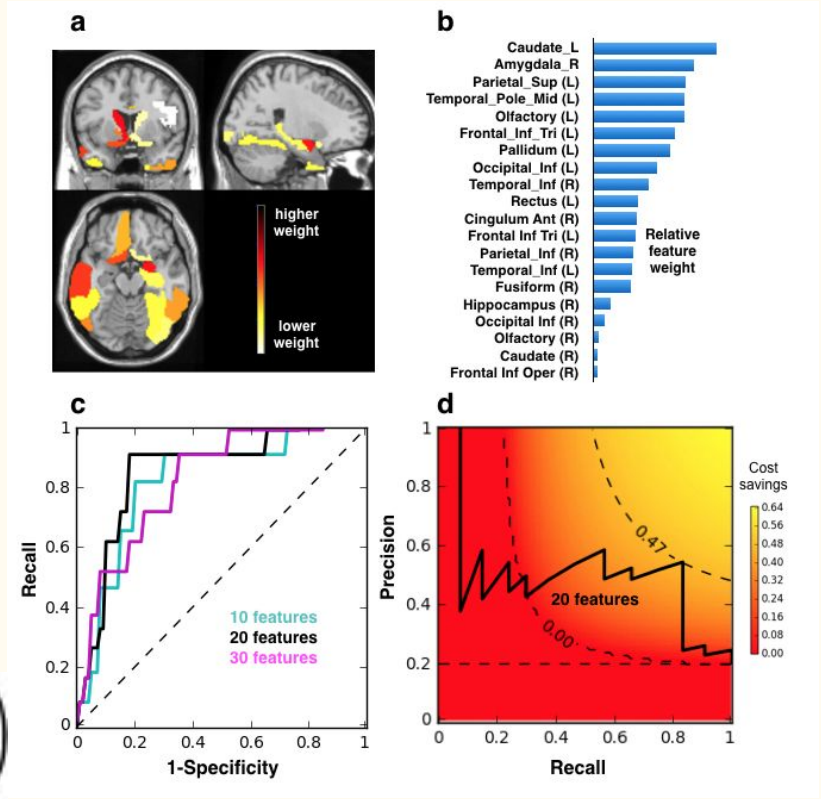
MRI-based screening

Results:

- **ρ** - prevalence of preclinical subjects among cognitively impaired subjects (~20%)
- **P** - precision
- **R** - recall/sensitivity
- $\mathbf{C_{PET}}$ - cost of a PET scan (~3000€)
- $\mathbf{C_{MRI}}$ - cost of a MRI scan (~700€)
- $\mathbf{C_{avg}}$ - average cost of standard screening (~3700€)

$$Savings_{CSF/PET} = 1 - \frac{\rho}{P}$$

$$Savings_{COST} = 1 - \frac{1}{2C_{avg}}\left(\rho\frac{C_{PET}}{P} + \frac{C_{MRI}}{R}\right)$$



Outline

1. Alzheimer's disease

2. UPC - FPM research
   a. MRI-based screening: building datasets with subjects at risk.
   b. NeAT: Neuroimaging Analysis Toolbox.
   c. Latent processes governing brain morphology and brain biomarkers.
   d. Longitudinal studies. Relationship between jacobian and biomarkers

3. Conclusions & future work

Puch et al. VNeAT: Voxelwise neuroimage analysis toolbox. *NIPS Workshop (2016).*

Casamitjana et al. NeAT: Neuroimaging Analysis Toolbox. Application to non-linear modelling of aging and atrophy in Alzheimer's Disease. *MLMI Workshop (Under review).*

NeAT: Neuroimaging Analysis Toolbox

Motivation:

- Standard image analysis softwares include only linear modeling of the brain

Goal:

- Provide the neuroimaging community with non-linear modelling techniques
- Include statistical inference and model comparison
- Work with data preprocessed using different software:
  - Voxel-based morphometry VBM (e.g: SPM)
  - Surface-based morphometry SBM (e.g: FreeSurfer)

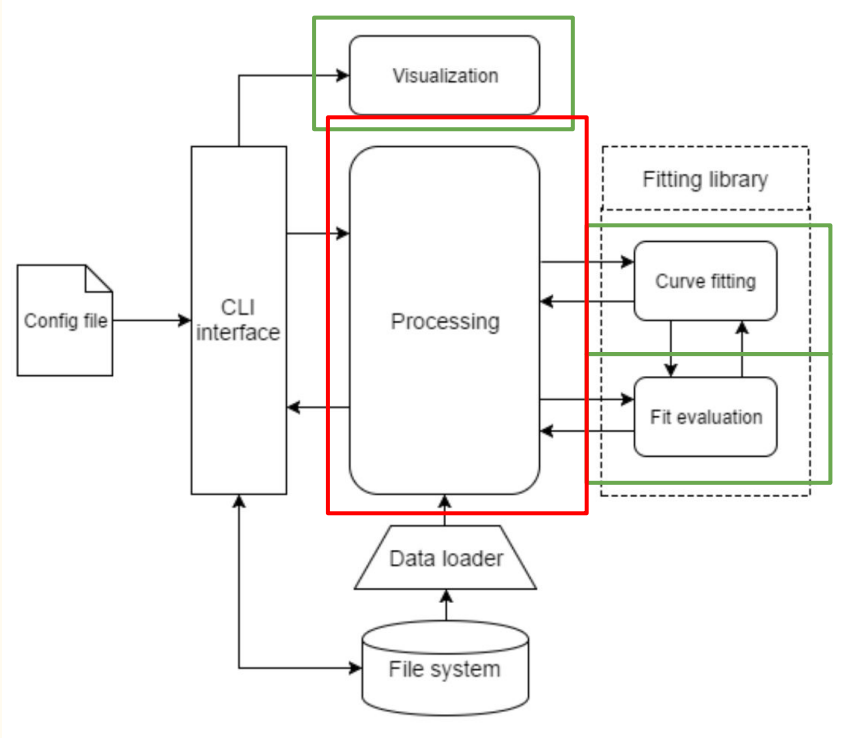
NeAT: Neuroimaging Analysis Toolbox

Toolbox:

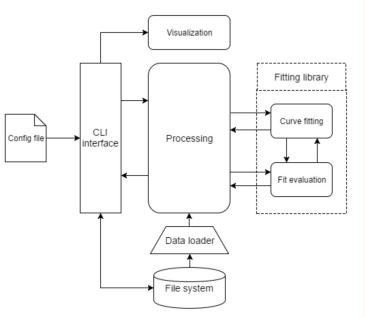
- **Modular**
- **Low-memory constraints:** batch processing
- **Cost-efficient:** parallelization of the most demanding tasks.

Usage:

- Command-line interface
- Config file (*.yaml)
- Data loader:
  - Images: *.nii, *.nii.gz, *.thickness
  - Variables: *.csv, *.xls



NeAT: Neuroimaging Analysis Toolbox



Modelling methods:

- **GLM:** General Linear Model
- **PolyGLM:** GLM with polynomial basis expansion.
- **GAM:** Generalized Additive Model
- **PolySVR:** SVR with polynomial kernel
- **Gaussian SVR:** SVR with Gaussian kernel.

Statistical inference:

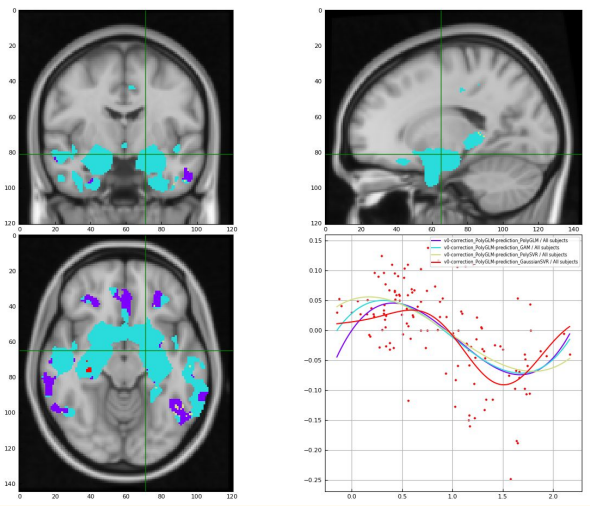
- **F-test**
- **MSE and R2 coefficient**
- **AIC:** Aikaike information criteria
- **PRSS and VNPRSS:** (Variance-normalized) Penalized Residual Sum of Squares.

Model comparison (L statistical maps):

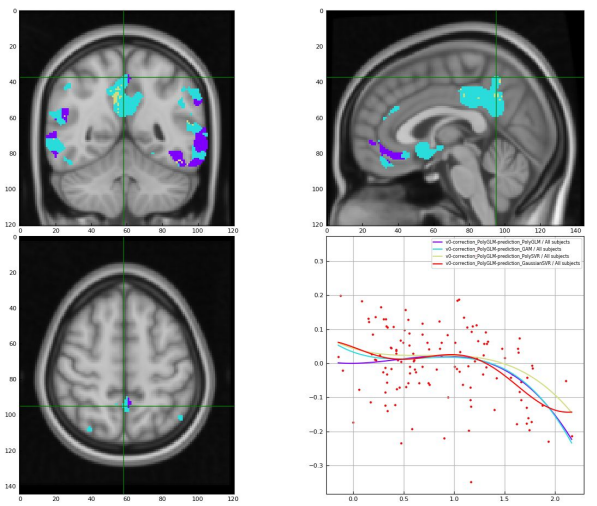
- **ABSdiff / SE maps** (L=2)
- **Best-fit map** (L>1)
- **RGB map** (L=3)

NeAT: Neuroimaging Analysis Toolbox

Validation results: **Atrophy patterns across AD continuum.**



Left Hippocampus

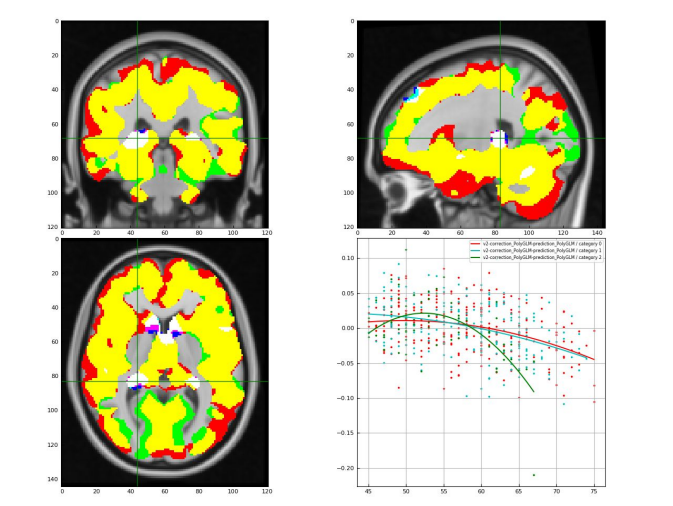


Right Precuneus

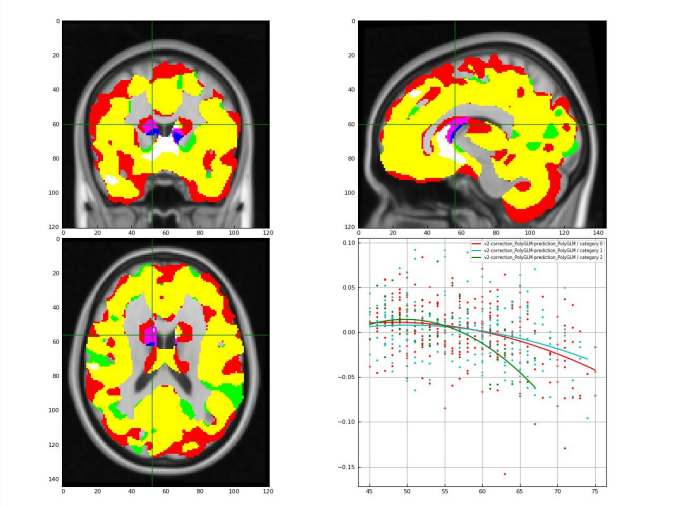
PolyGLM (**magenta**), GAM with B-splines (**cyan**), PolySVR (**yellow**), GaussianSVR (**red**) using the ‘Best-fit’ map

NeAT: Neuroimaging Analysis Toolbox

Validation results: **Effects of apoE4 in brain aging.**



Right Hippocampus



Right Caudate

Non-carriers NC (**red**), heterozygotes HE (**green**), homozygotes HO (**blue**)

HO - 2 copies of ε4 allele
HE - 1 copies of ε4 allele
NC - 0 copies of ε4 allele

Outline

1. Alzheimer's disease

2. UPC - FPM research
   a. MRI-based screening: building datasets with subjects at risk.
   b. NeAT: Neuroimaging Analysis Toolbox
   c. Latent processes governing brain morphology and brain biomarkers.
   d. Longitudinal studies. Relationship between jacobian and biomarkers

3. Conclusions & future work

Casamitjana et al. Projection to Latent Spaces Disentangles Specific Cerebral Morphometric Patterns Associated to Aging and Preclinical AD. *Abstract accepted in AAIC (2018)*

Casamitjana et al. Relationship between CSF biomarkers and structural brain information in the asymptomatic phase of AD. *To be submitted.*

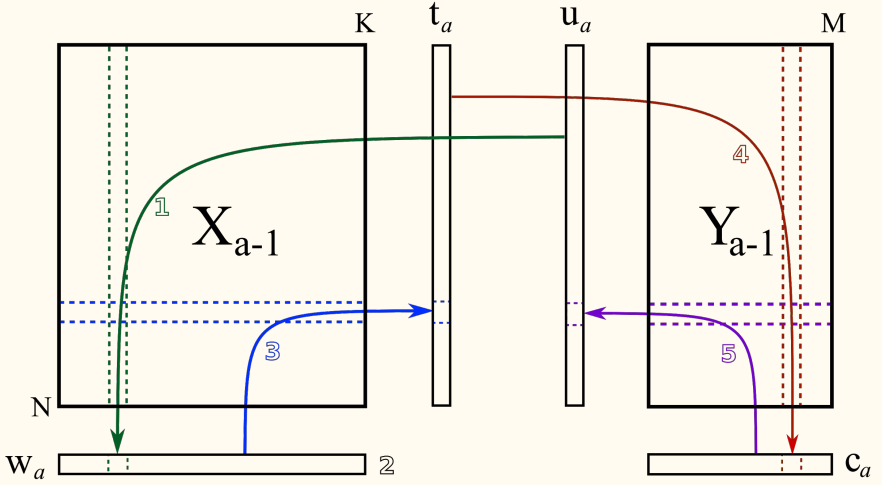
Latent processes for brain morphology

Goal:

- Disentangle brain aging and brain dementia pattern

Methodology:

- Projection to Latent Structures (PLS)
- Two orthogonal models:
  - Brain aging
  - Brain dementia



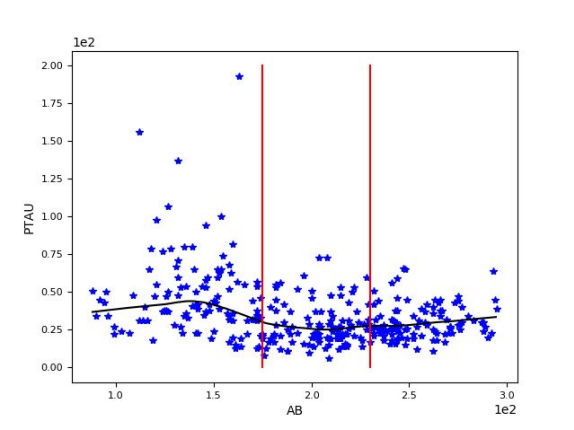
Latent processes for brain morphology

Dataset:

T0:= AB ∈ [230, 295]: N=104, Age=71.47 ± 6.07

T1:= AB ∈ [175, 230): N=109, Age=71.49 ± 5.52

T2:= AB ∈ [88,175): N=108, Age=75.03 ± 6.36



Model:

(A) ***PLS - aging***

X ~ age + gender → *w_1*
Y ~ imaging features (ALL).

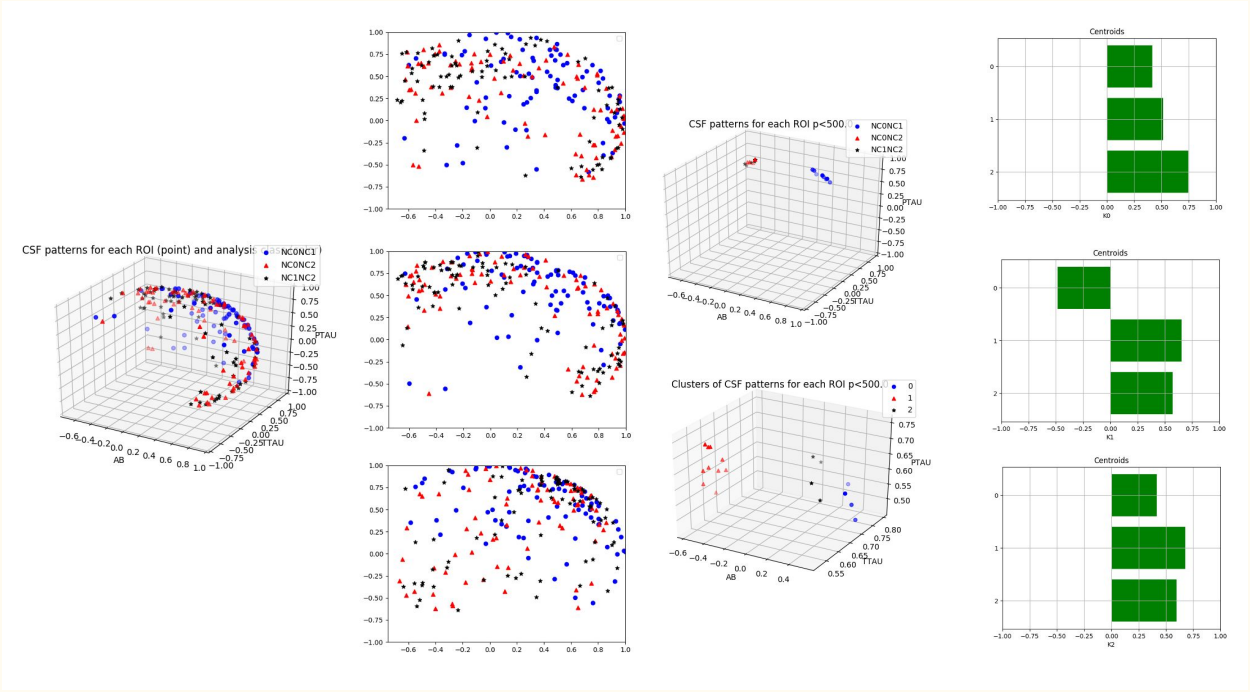
(B) ***PLS - dementia***

X ~ biomarkers: AB, PTAU, TTAU
Y_o ~ imaging features orthogonal to age, computed from ***PLS-aging***

$$\mathbf{Y\_o} = \mathbf{Y} - w\_1 \cdot w\_1^{\mathrm{T}} \cdot \mathbf{Y} = (\mathrm{I} - w\_1 \cdot w\_1^{\mathrm{T}}) \cdot \mathbf{Y}$$

A single PLS for each ROI (independent).

Latent processes for brain morphology



Relevant regions:

- **Temporal lobe: T0,1,2**
  - Amygdala
  - Inferior temporal
  - Enthorhinal cortex
- **Parietal lobe: T1,2**
  - Postcentral
  - Precentral
  - Paracentral
- **Frontal cortex: T0**

Outline

1. Alzheimer's disease

2. UPC - FPM research
   a. MRI-based screening: building datasets with subjects at risk.
   b. NeAT: Neuroimaging Analysis Toolbox.
   c. Latent processes governing brain morphology and brain biomarkers
   d. Longitudinal studies. Relationship between jacobian and biomarkers

3. Conclusions & future work

Petrone et al. Characteristic Brain Volumetric Changes in the AD Preclinical Signature. *Abstract accepted in AAIC Conference (2018)*

Petrone et al. Characteristic Brain Volumetric Changes in the AD Preclinical Signature. *To be submitted.*

Longitudinal studies

Definition:

- For each subject s_i under the study, several visits $\mathbf{L_i} \ni [l_{i1}, l_{i2}, ..., l_{iLi}]$ are collected. At each visit ***CSF***, ***MRI*** and ***cognitive profile (CP)*** are collected.

- For each l_{ij} with $j>1$ quantitative difference is computed for:
  - $dCSF_{i1} = CSF_{i2} - CSF_{i1}$ → called ***biomarkers***
  - $dMRI_{i1} = MRI_{i2} - MRI_{i1}$ → called ***Jacobian features***

Goal:

- Show that a preclinical signature is found in jacobian features and they can be used for image classification.

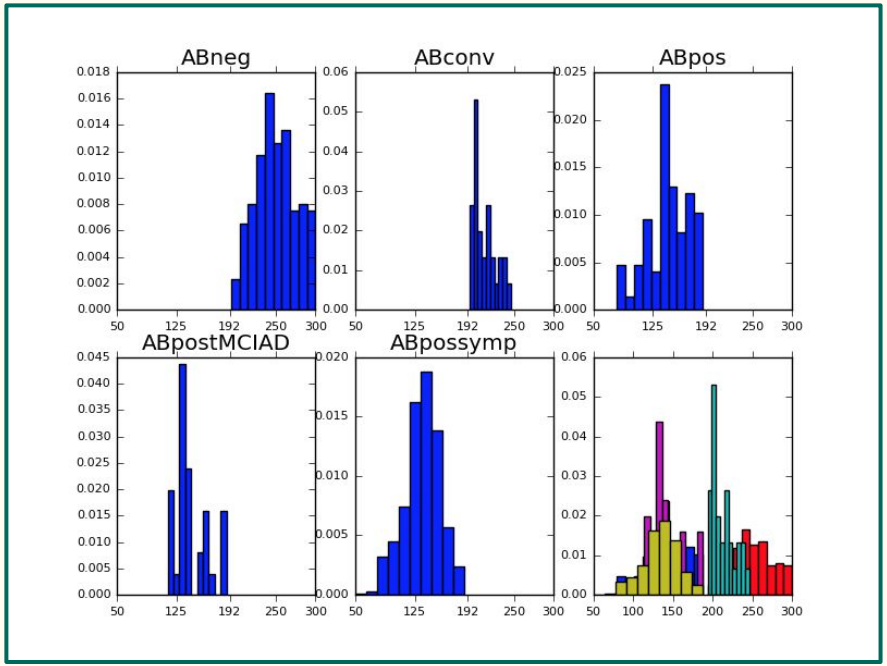
Longitudinal studies

Labels are defined using reference/target Aβ. Analysis is performed at the image level, not in the subject level.

1. **A-/A-** *(Neg)*
2. **A-/A+** (Conv)
3. **A+/A+ without symptoms** *(Pos)*
4. **A+**(NC)/**A+**(MCI,AD) *(PostMCIAD)*
5. **A+/A+ with symptoms** *(Possymp)*

Method:

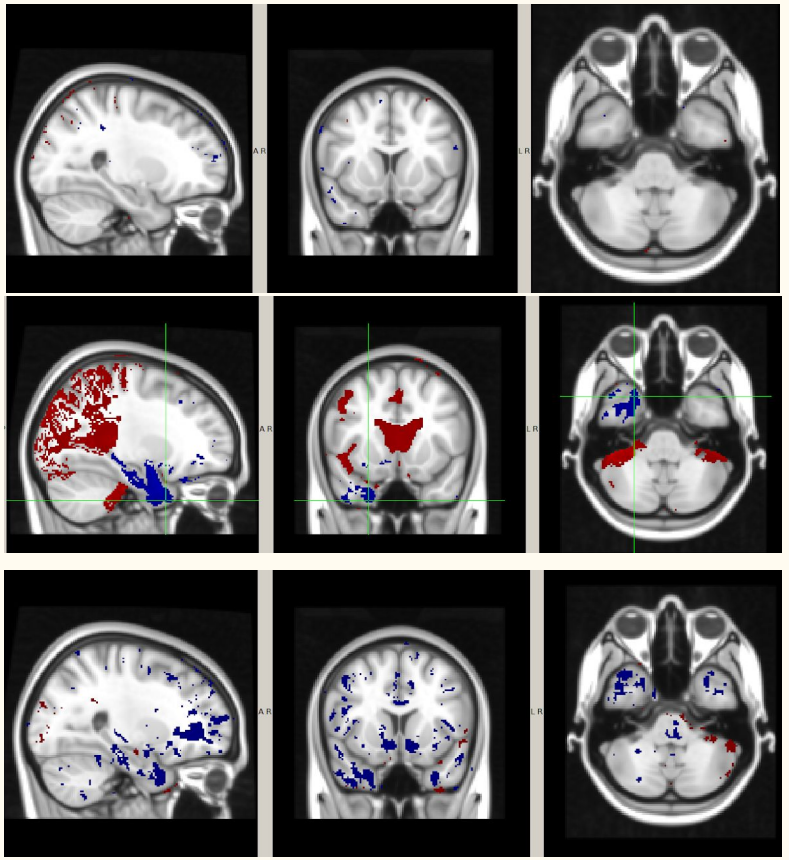
- Correlation between dCSF-A and dMRI
- Statistical maps with relevant correlations through hypotesis testing.



Longitudinal studies

Result 1. Relationship between CSF-MRI.

- Changes in CSF might describe changes in brain morphology in **preclinical** stages but not in **dementia** stages



Neg

Pos

PostMCIAD

Longitudinal studies

Result 2. Relationship between CSF-MRI.

- There are some regions that experience **atrophy** but others experience **neuro-compensation.**

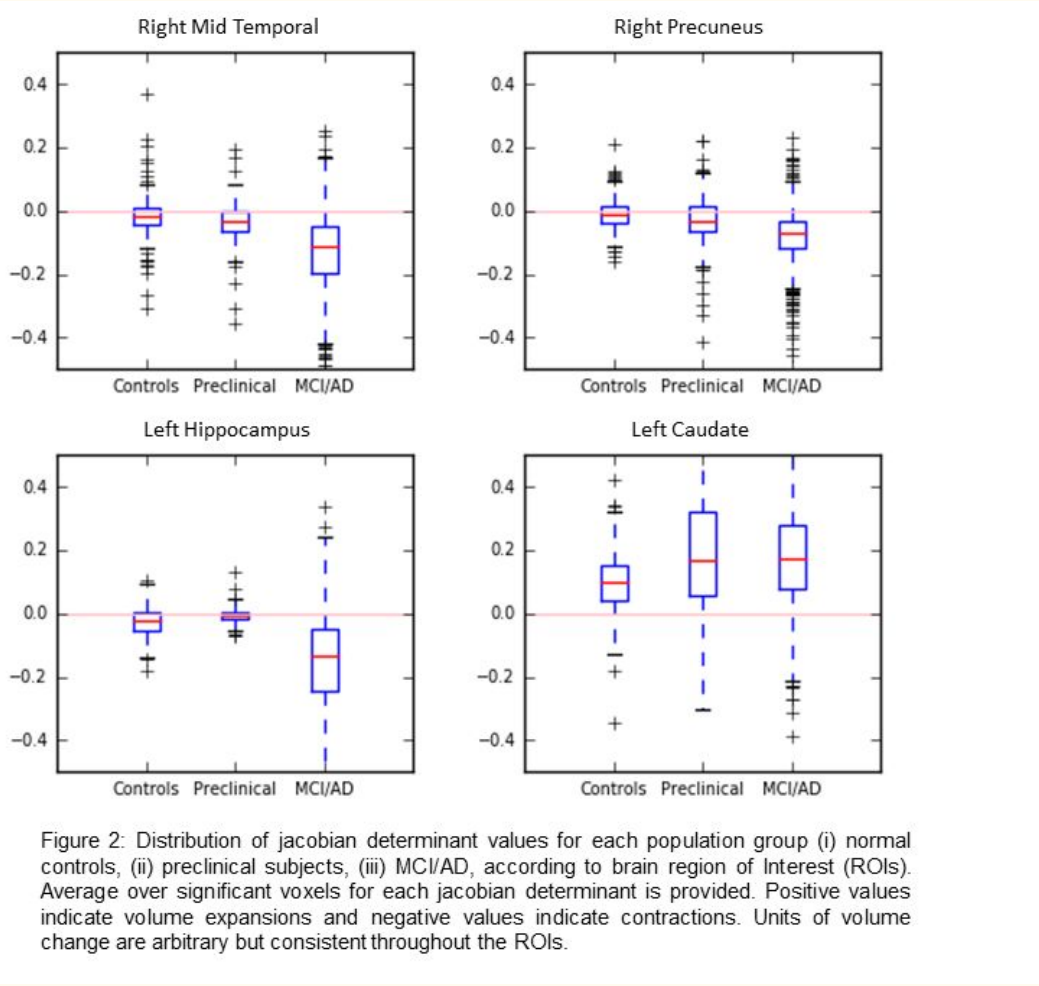
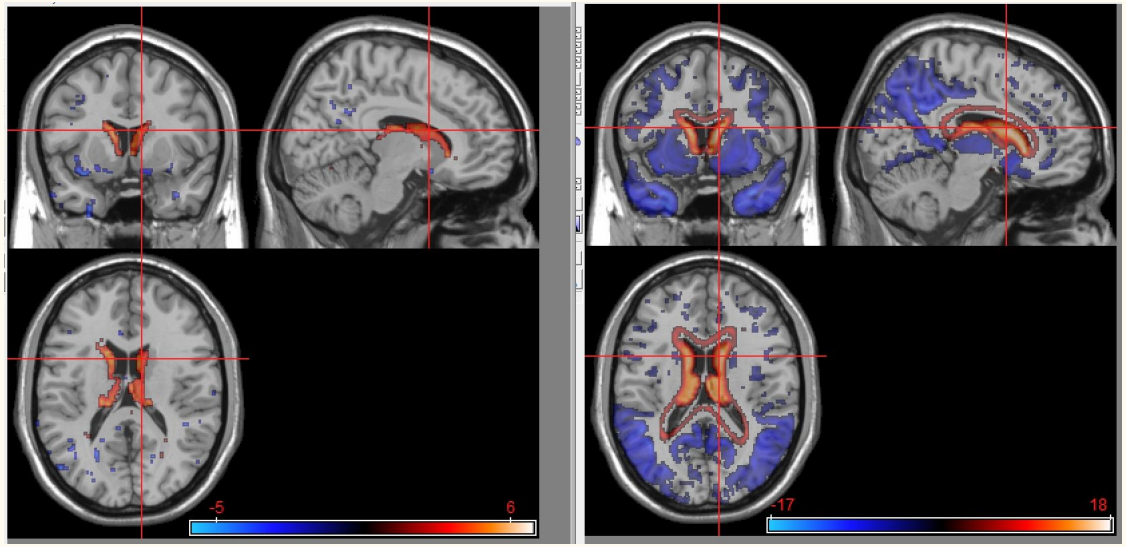


Figure 2: Distribution of jacobian determinant values for each population group (i) normal controls, (ii) preclinical subjects, (iii) MCI/AD, according to brain region of Interest (ROIs). Average over significant voxels for each jacobian determinant is provided. Positive values indicate volume expansions and negative values indicate contractions. Units of volume change are arbitrary but consistent throughout the ROIs.

Longitudinal studies

Result 3. Group comparison with controls.

- There are some regions that experience **atrophy** but others experience **neuro-compensation.**



Preclinical signature

Dementia signature

Outline

1. Alzheimer's disease

2. UPC - FPM research
   a. MRI-based screening: building datasets with subjects at risk.
   b. NeAT: Neuroimaging Analysis Toolbox.
   c. Latent processes governing brain morphology and brain biomarkers.
   d. Longitudinal studies. Relationship between jacobian and biomarkers

3. Conclusions & future directions.

Conclusions

- Dementia = syndrome; **disease = biological continuum.**

- Preclinical stage of AD is key to:
  - Better understanding of the etiology of the disease
  - Design better interventional/therapeutic plan.

- Large scale studies involving Pre-AD subjects might create huge impact on research:
  - Need for cost-effective clinical screening protocols (MRI-based, blood-based).

- Brain morphology follow non-linear patterns along the AD continuum.

- apoE4 is a risk factor for developing AD.

Future directions

- Observational research:
  - **Develop and apply multimodal modelling strategies:** design multimodal algorithms that help understanding AD biology and describe brain changes. MRI + fMRI + DWI
  - **Disease progression modelling:** use longitudinal data to model the progression along the AD continuum
  - **Differential diagnosis:** specific patterns for different type of dementia: AD, LBD, FTD

- Translational research: from the lab to clinic.
  - **Personalized medicine:** outlier detection for subject specific diagnosis of AD

Contact

Adrià Casamitjana

Image Processing Group (GPI)
ETSETB - TelecomBCN
D5 - 120

adria.casamitjana@upc.edu

@adri_casa (no profesional use, YET)

Outline

- Motivació: neuroimatge, tipus d'imatge, machine learning, predictive vs inference.
- Esquema de la xerrada
- Alzheimer: què és? Definició biològica. Menció a altres demències que poden compartir característiques. Tipus d'estudis: observational and interventional research.
- Objectiu: detectar els canvis biològics abans que els clínics
- App 1: necessitem construir bases de dades tant per estudi com per prevenció. Les millors tècniques són cares i invasives. Solucions: machine learning MRI (esmentar blood)
- App 2: nonlinear patterns of atrophy + apoe4 gene.
- App 3: latent processes governing brain morphology related to CSF biomarkers. Volume compensation in the preclinical stages of AD.
- App 4: Longitudinal jacobian features: improve classification performance + indicate structural changes.
- Future work:
    - Need for large study cohorts (efforts put in UK biobank, ADNI or Alpha).
    - Translational research.
    -