An heuristic approach to signal and noises on medical data

Andrea Chincarini
MIND project

XI Seminar on Software for Nuclear, Subnuclear and Applied Physics
25-30 May 2014
Porto Conte, Alghero

PHYSICS VS MEDICINE
SIGNAL & NOISES
CONSEQUENCES
CASE STUDY
BIOMARKERS FROM NEUROIMAGES
ADVANCED TECHNIQUES
BEYOND DATA ANALYSIS

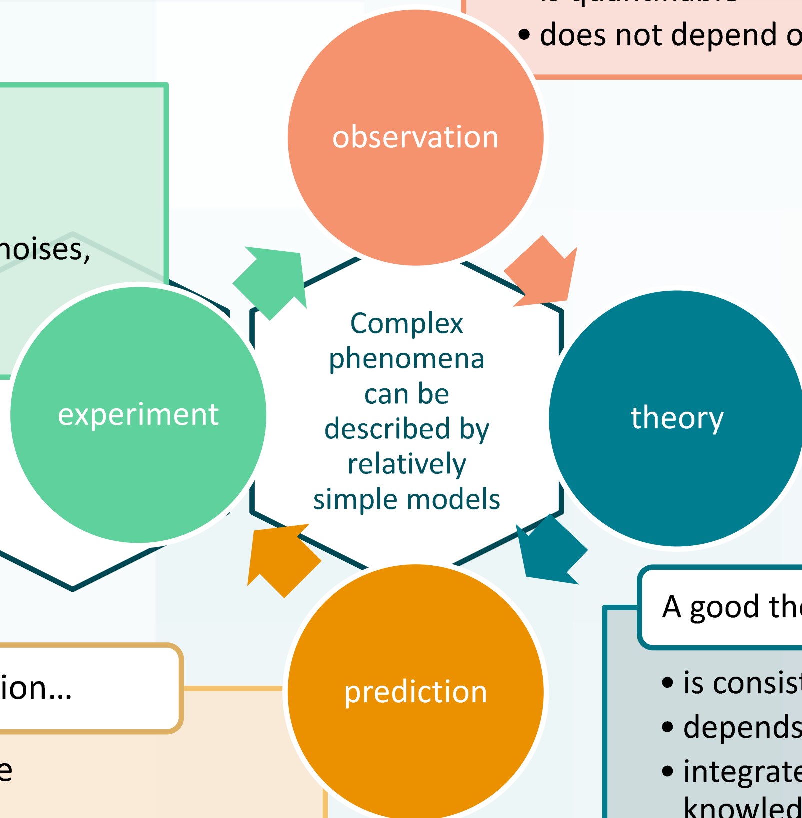
Measuring in physics

A good experiment…

- is simple
- is a measure [direct/indirect]
- can be fully characterized (signal, noises, …)
- is reproducible

A good observation…

- is reproducible
- is quantifiable
- does not depend on the observer



A good theory…

- is consistent
- depends on few [none] free parameters
- integrates with / extends existing knowledge

A good prediction…

- is quantitative
- is verifiable
- …

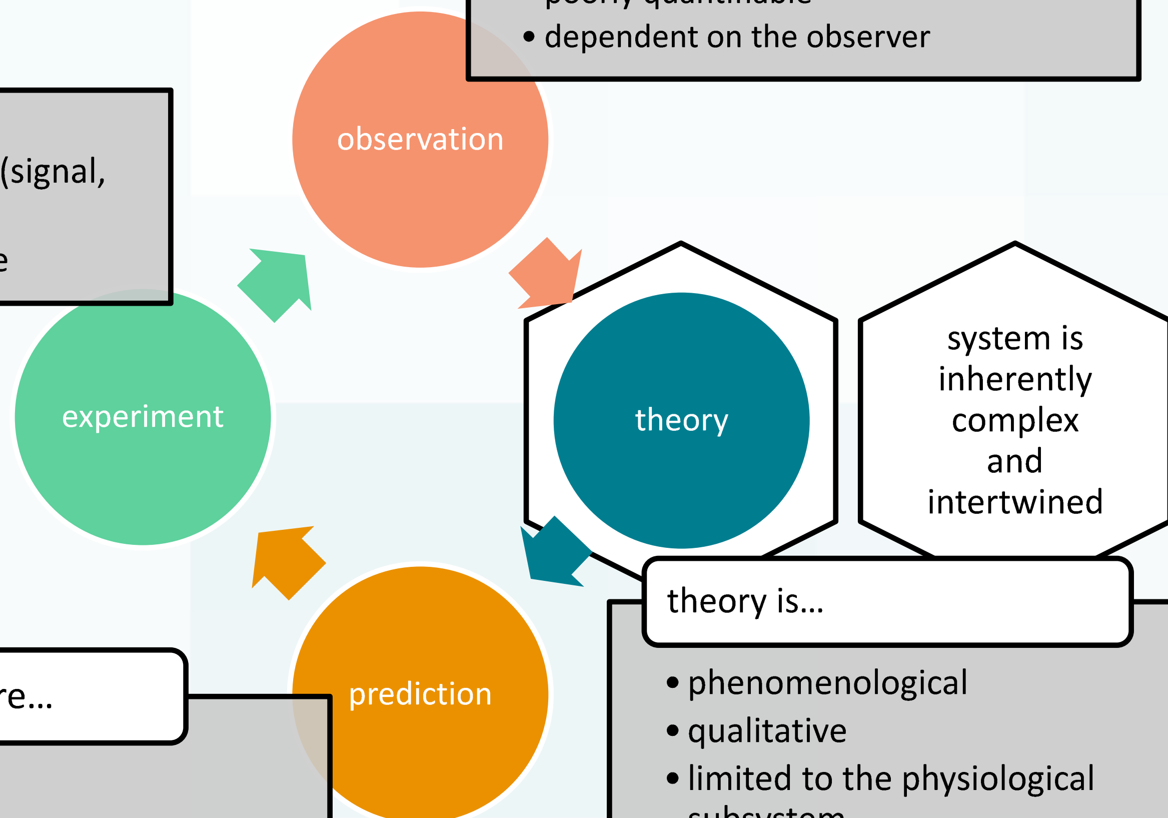
When things start going south…

experiments…

- cannot be fully characterized (signal, noises, …)
- are almost never reproducible

observation are…

- limited
- poorly quantifiable
- dependent on the observer

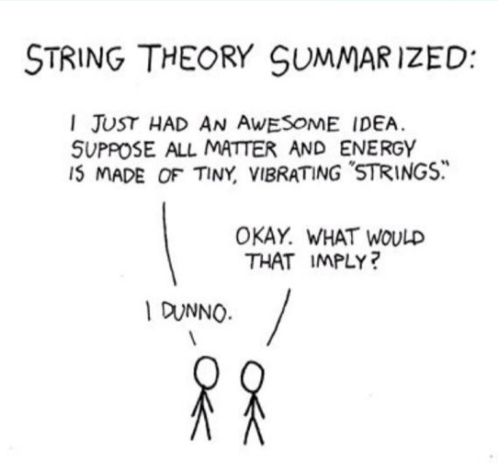


theory is…

- phenomenological
- qualitative
- limited to the physiological subsystem

predictions are…

- qualitative
- not easily verifiable



Physics

- Observations
  - Direct / indirect
  - Derived from previous experiments / better estimates of current theories
- Theory
  - One or more models, depend on free parameters
  - Few parameters = happy physicist
- Experiment
  - Designed to verify key aspects of theory, prove/disprove models
  - Typical paradigm: Out = signal + noise
  - Reproducibility is a key factor
- Data analysis
  - Designed to extract "signal" from "noise" [filters]
  - Experiment characterization [noise]
  - Estimate model parameters [from signal]
  - Error estimation relatively simple

Medicine

- Observations
  - Direct: Clinical practice
- Theory
  - No comprehensive models
  - Highly complex system
  - Subsystem interactions and history not negligible
- Experiment
  - Clinical trials (in vitro, in vivo, ….)
  - Typical paradigm: improvement / no-improvement
  - Reproducibility is rarely achieved
- Data analysis
  - Designed to extract "improvement probability"
  - Strong a-priori assumptions
  - What is "noise"?
  - Error estimation generally difficult

SIGNAL & NOISES

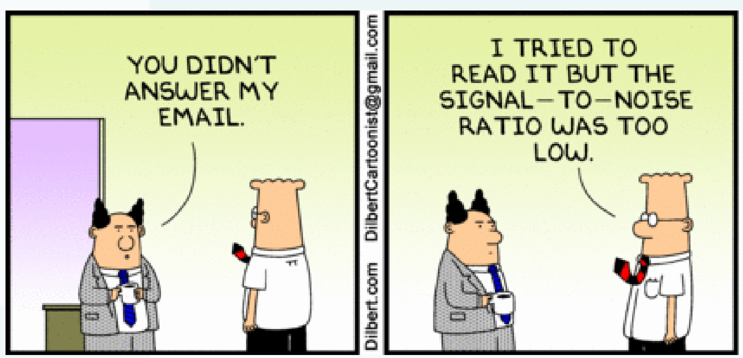
It all depends on the question

Noise

Random fluctuations that obscure or do not contain meaningful data or other information

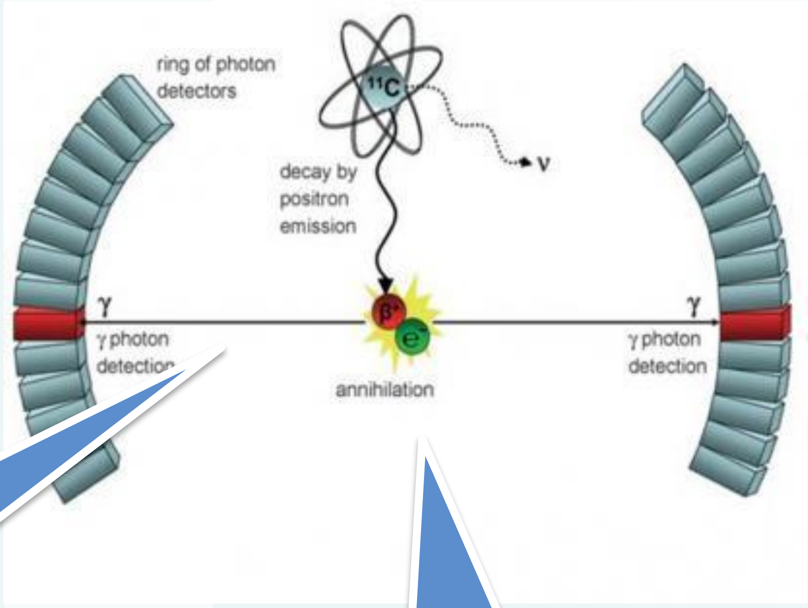
Signal

Those meaningful data or other information, which are interesting to us



For instance…

Positron emission tomography (PET)

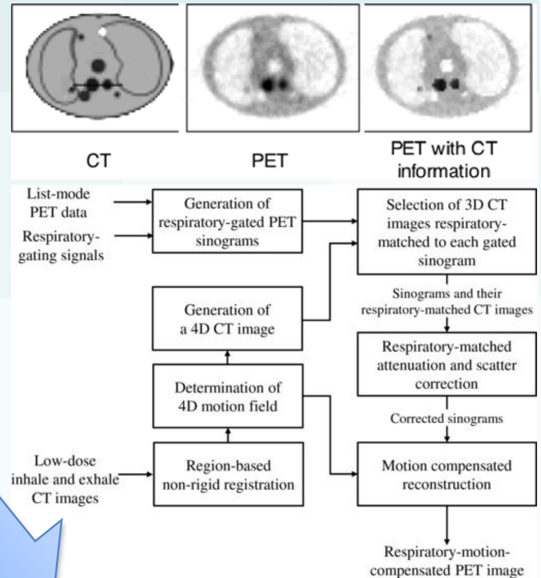


line of response (LOR) for unscattered photons

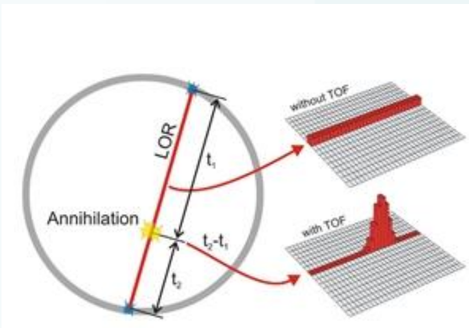
Physical process
511 keV γ photons

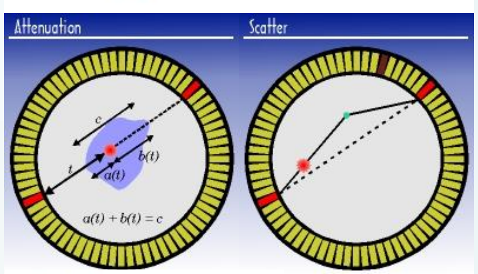
Signal = num. of counts in coincidence received on the detector

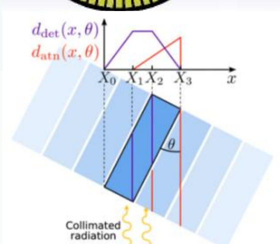
Add
ToF, attenuation, scatter correction, spatially variant PSF compensation



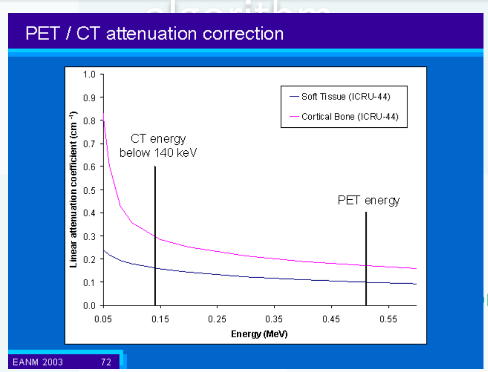
Signal = 3D image
… but which one?
Application specific parameter optimization!



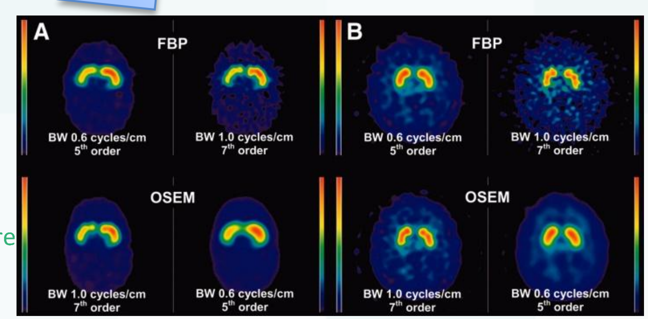




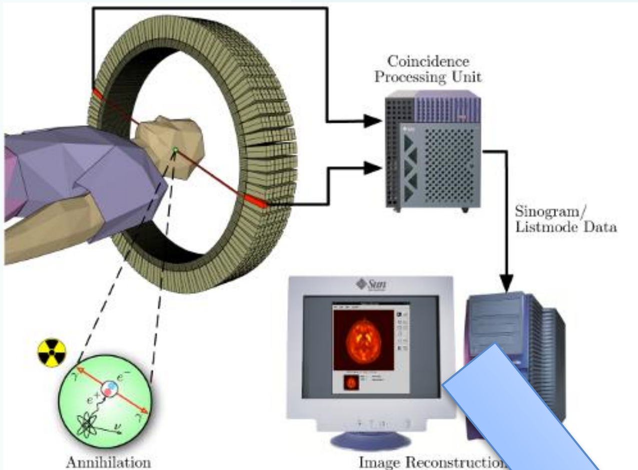
Add
CT (X-ray) tissue dependent 3D attenuation, motion compensation, reconstructing



n Software

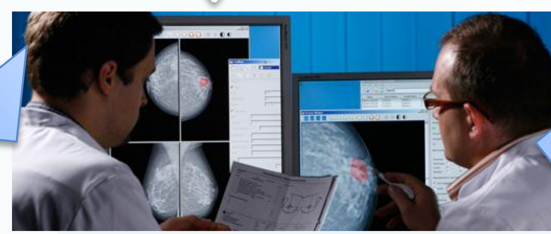


A few more steps



Complete acquisition, attenuation, image reconstruction, motion compensation, etc …

Image analysis + Clinical evaluation (metadata)



Signal [finally!] = How likely is the subject to be affected by pathology “X” ?

Pathological

Healthy

What about noises?

Acquisition

- Protocol (resolution, calibration, ...)
- Scanner/site quality issues (B-field inhomogeneities, electronic noise…)
- Chemical reagent batch, lab temperature, …
- Image artifacts (subject movements during acquisition, object driven B-field distortion, calibration, …)

Data processing

- Image reconstruction algorithm
- Signal is *deduced* by comparison among cohorts → method selection is important
- Information degradation due to sub-optimal processing
- Depends on assumptions on "signal"

Physiological

- Confounding variables (age, sex, education, general anamnesis,…) countless variables we do not control or even know about.
- Inter-individual variability can be more significant than normalcy vs. pathology difference
- Cohort size (representativity)
- Age range (general accuracy degrades with increasing average age)

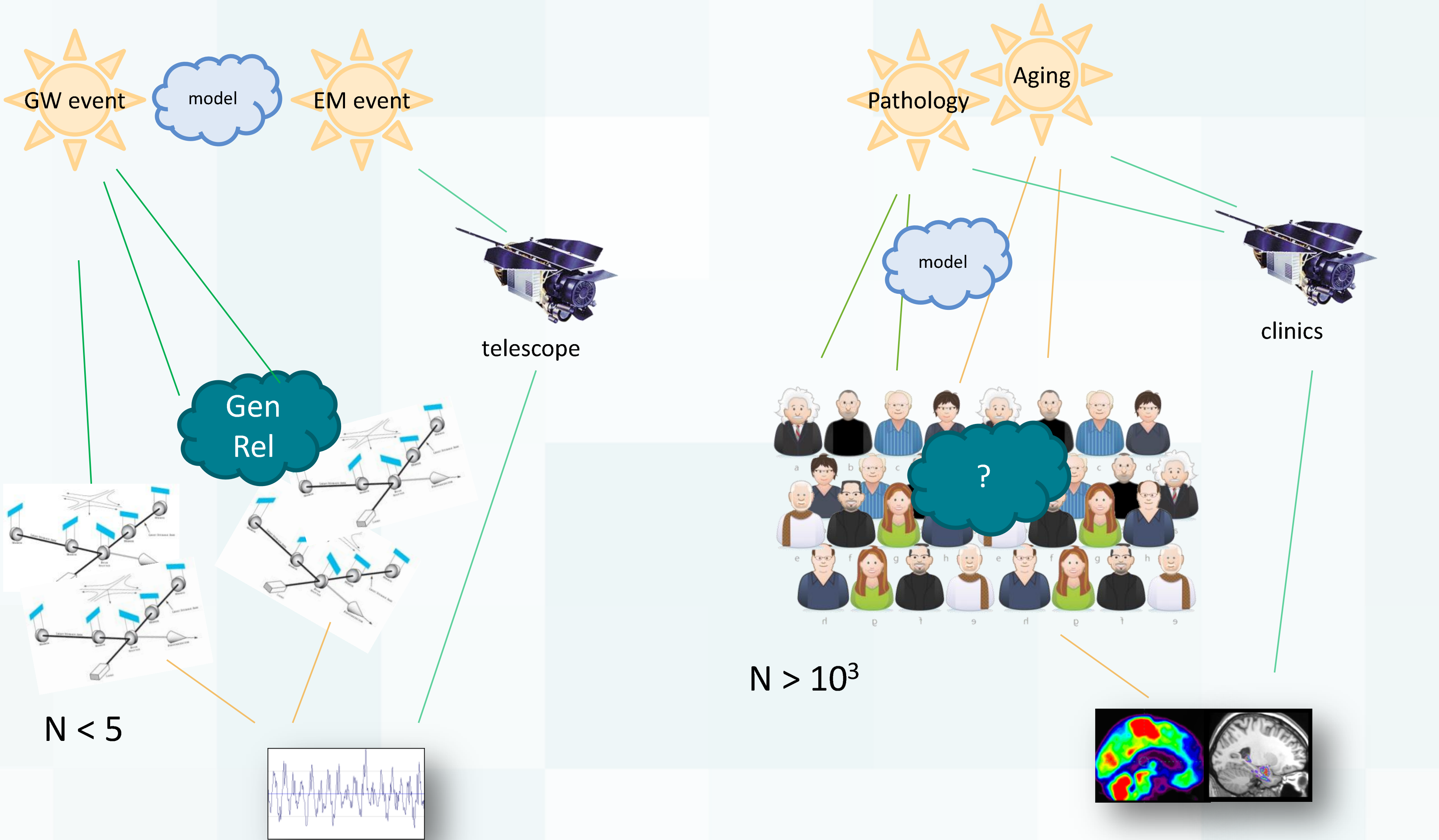
Gold standard

- What is our standard? Clinical evaluation? Autoptic studies?
- Group mixing (clinical assessment is not 100% accurate)
- Group purity (comorbidity, who is a "Normal/healthy control")

Pathology models

- Data interpretation depends on pathology model
- Critical decision about the prognosis
- Analysis validation, inclusion/exclusion criteria

A bold comparison



Link with GW?

- Similarities
  - Data Quality issues
  - Template matching techniques (atlases)
  - Multimodal approach
  - Non gaussian noises (physiology)
  - Event reproducibility (subject is unique)
  - Need for complex IT infrastructure / distributed computing
  - "Detection" is confirmed by 3rd party input (e.g. clinics, neuropsychology, …) & depends strongly on data processing

- Differences

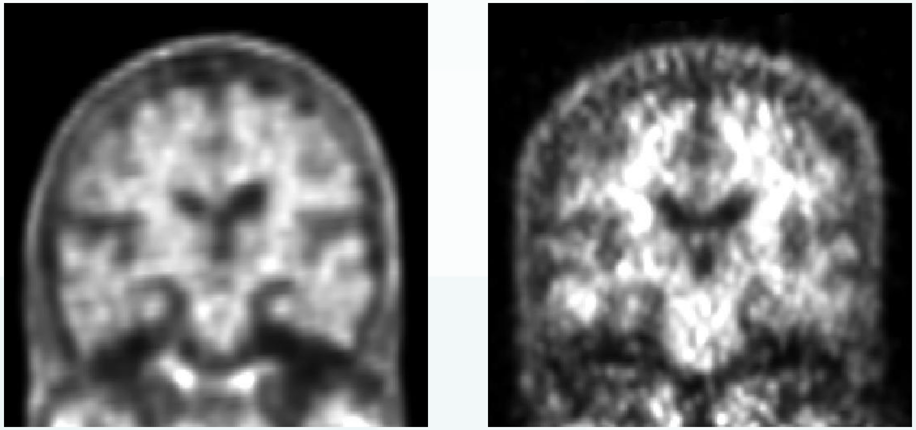
  PRO:
  - There really is a "signal" (clinical assessment)
    - We only want to measure it well before it becomes detectable by behavioural symptoms
  - Signal sources can be [in principle] absolutely verified (autoptic studies)
  - CTRL group (i.e. a detector not sensitive to GW)
  - Cohort studies (maybe this is coming in the near future when several GW detectors will be in operation…)

  CONS:
  - Pathological process modeling is only qualitative (vs. Gen.Rel. theory)
  - Individual anamnesis/physiology cannot be easily described by a [small] n. of parameters (BH/NS still simpler objects than the average Joe…)

CONSEQUENCES

Common strategies

- Acquisition
  - Standardized Operational Procedures (protocols)
  - Test/retest paradigm
    - E.g. 2 consecutive scans with subject repositioning
  - Frequent calibration
    - ADNI protocol require calibration with phantom before each subject scan
  - Quality control



Amyloid-PET (florbetapir) images.
Same injection protocol, same acquisition
Different PET scanner & reconstruction algorithm

Physiological

- Sample size
  - At least ~ 10^3
- Inclusion/exclusion criteria
  - Accurate anamnesis, need help from other branches of medicine
  - Reduce comorbidity
- Multi-center studies
  - Reduce bias

Gold standard

- Follow-up studies
  - Can change results in retrospective analysis
- Multiple, independent evaluators
  - Reduce group mixing
- Autoptic examination
  - Rarely available and useful for only a handful of pathologies
- Provide more than one independent validation set
  - Optimize validation and robustness

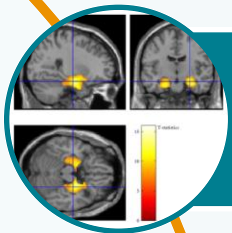
Data processing

- Keep it simple, test each step!
  - Use known textbook cases as well as random data
- Pipelined analysis
  - Can evaluate effect of the single step on the final result
- Take the necessary train/test steps
  - Avoid bias pitfalls and overtraining effects

Pathology models

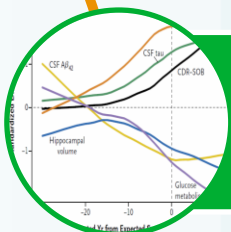
- Large multi-centric studies
  - Robust results
- Longitudinal and multi-domain
  - Pathology model discrimination

Assumptions



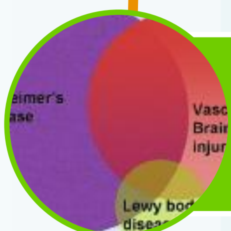
Space-like

- Pathology manifestation is characterized by a “common signature” in the data and throughout the subjects



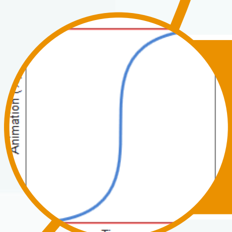
Time-like

- Pathology development is slow [quick] with respect to other physiological variabilities



Linearity

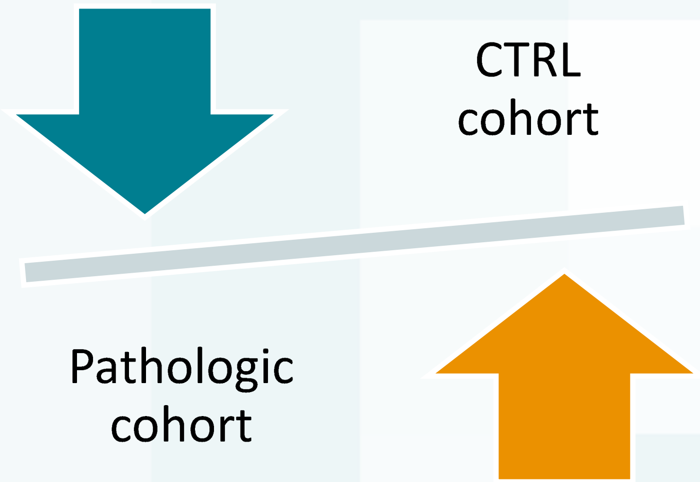
- Comorbidity is [is-not] an issue



Derivative

- The path from normalcy to pathological state can be modeled as a “smooth, continuous” transition so that we can use the two extremes as reference

The basic paradigm

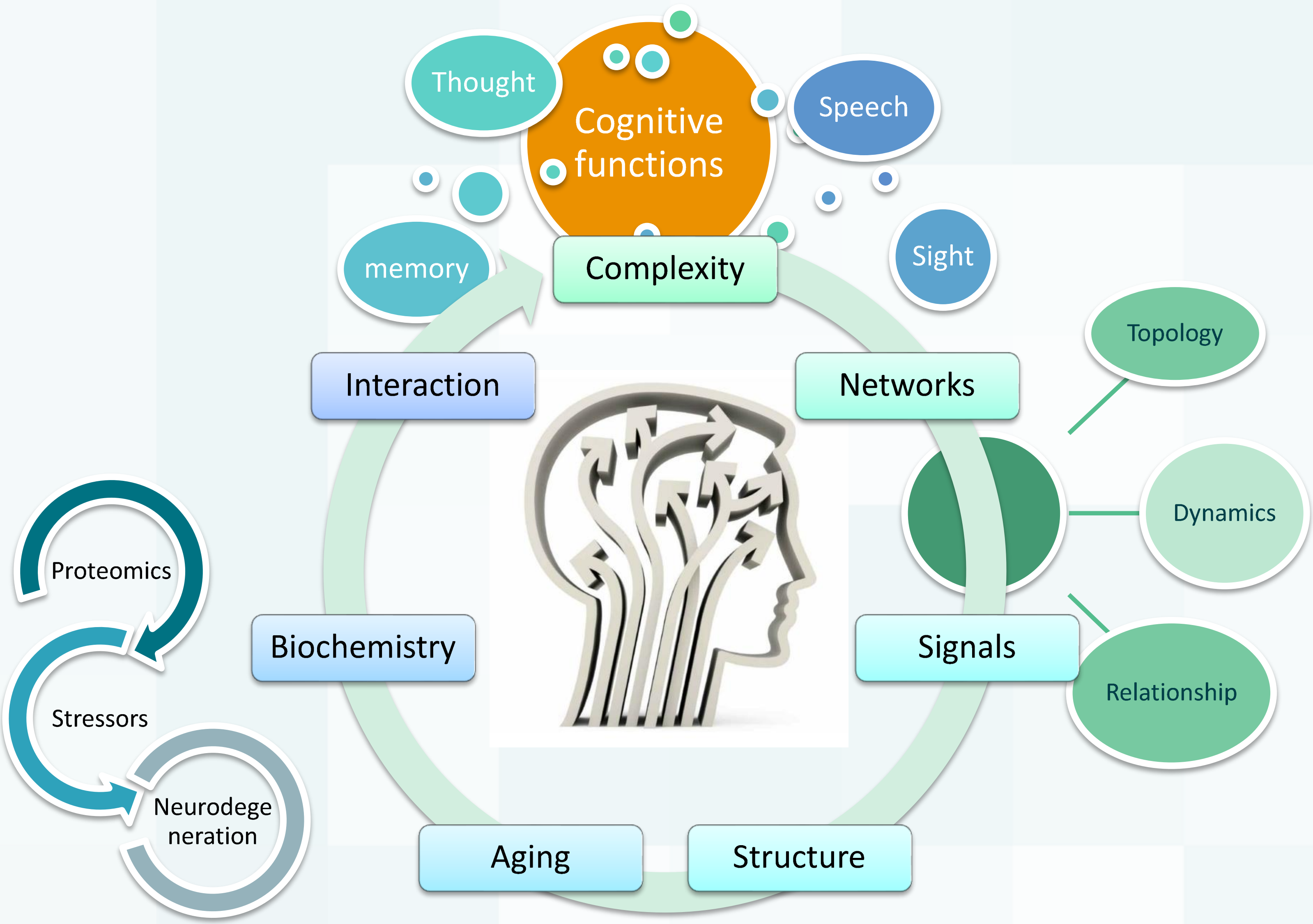


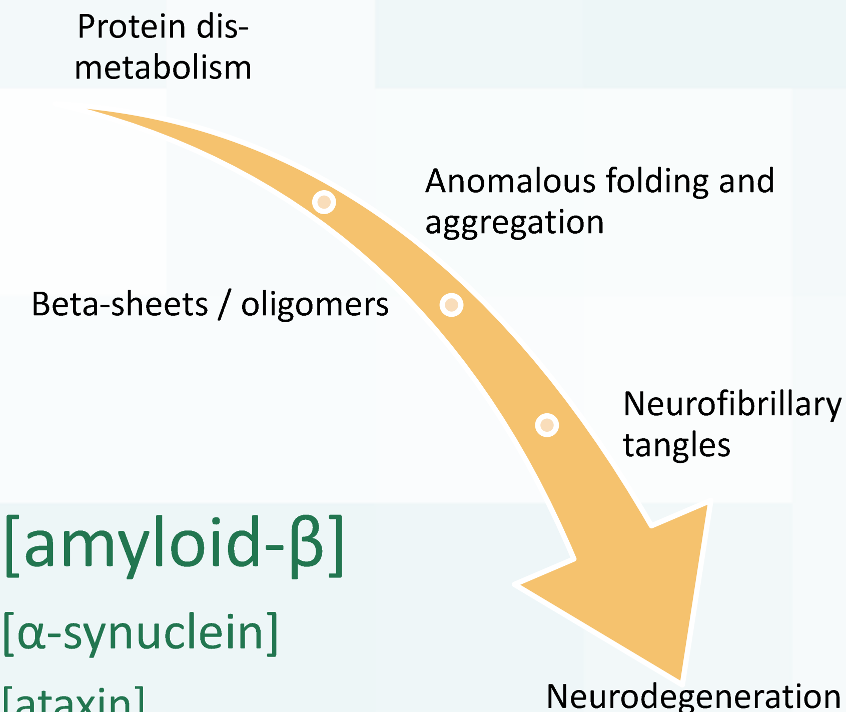
1. Make data commensurable
2. Find common traits within cohorts
3. Find differences between them

1. Depends on the “pathology fingerprint” assumption
2. Needs 3rd party input on the feature set
3. Good for group analysis but single subject is not straightforward

CASE STUDY

The ever-changing brain





- Patologies
  - Alzheimer’s disease [amyloid-β]
  - Parkinson’s disease [α-synuclein]
  - Huntington’s disease [ataxin]
  - Amyotrophic lateral sclerosis [TDP-43 SOD1]
  - Frontotemporal dementia [Tau]
  - Progressive sopranuclear palsy
  - Progressive nonfluent afasia
  - Cortico-basal degeneration
  - …

“… progressive functional and structural decline up to the cellular death of neurons and glia …”

Alzheimer's disease in a nutshell

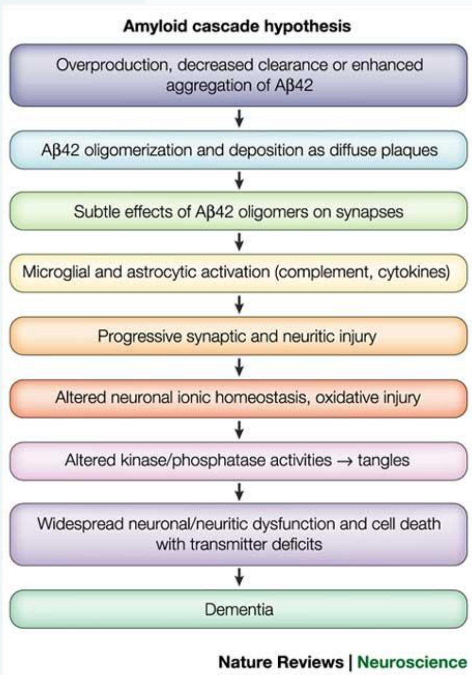
1906
- First description of progressive cognitive decline (Alois Alzheimer)

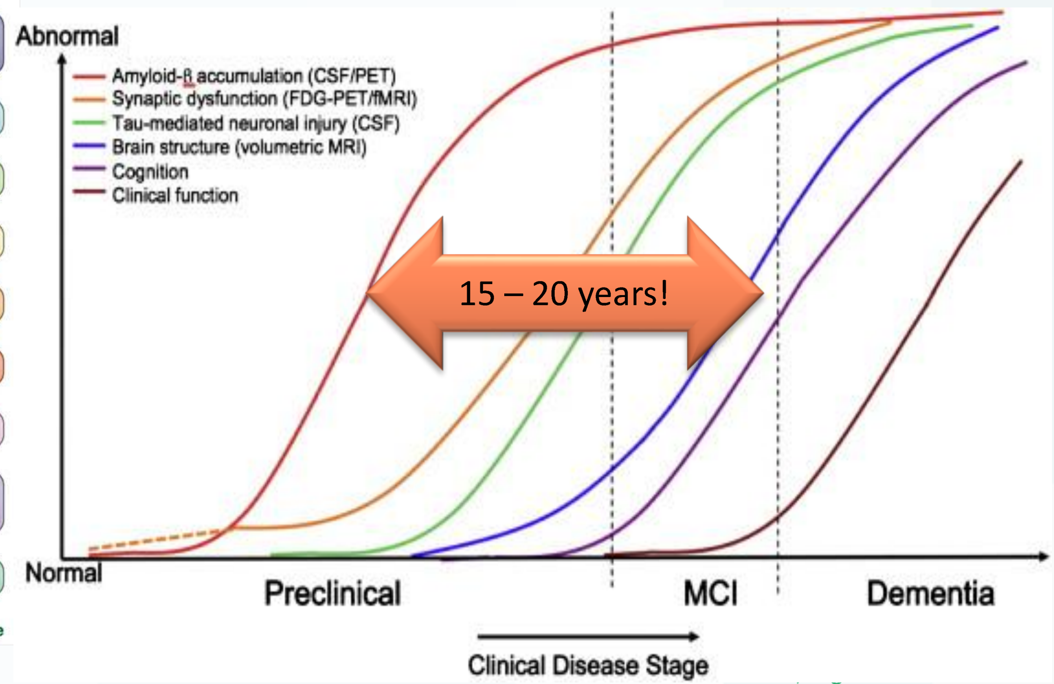
1960
- Link with neuritic plaques

1984
- Diagnostic criteria: disease=dementia

2007
- Disease stages: MCI preclinical condition

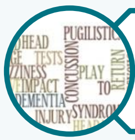
2011
- New diagnostic criteria: neurodegenerati on markers needed!



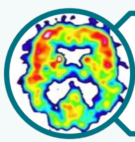


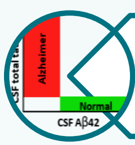
Investigating the disease progression


Clinical assessment

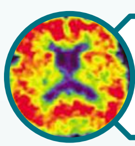

Neuropsychology

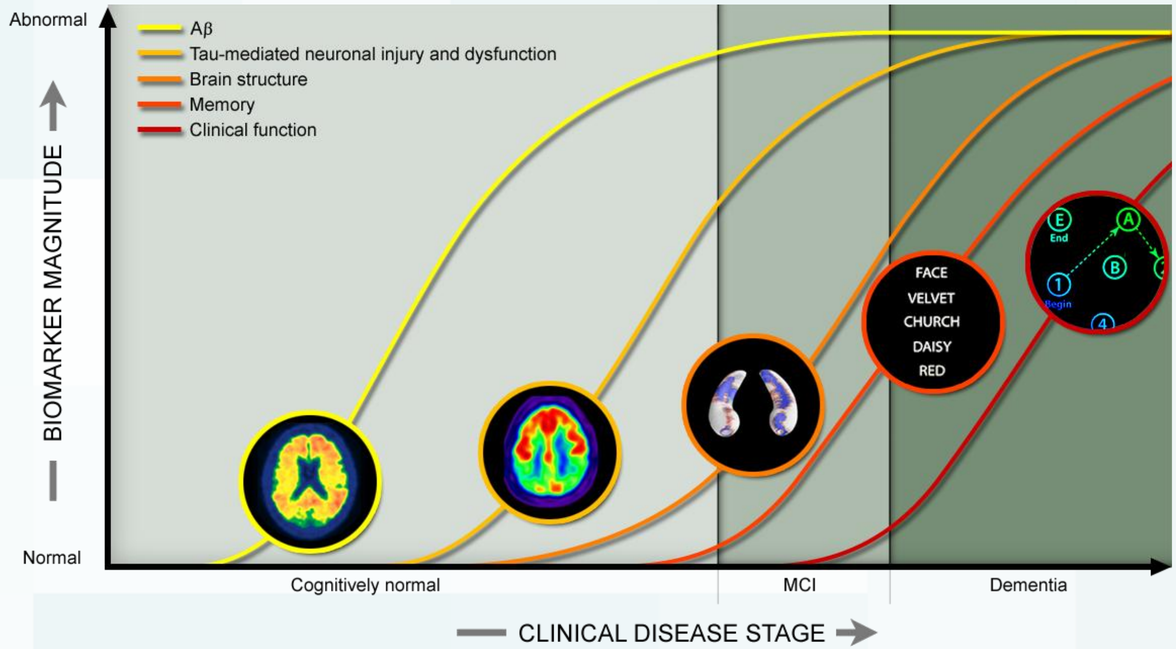

MRI / fMRI / DTI


FDG-PET



CSF


Amyloid-PET

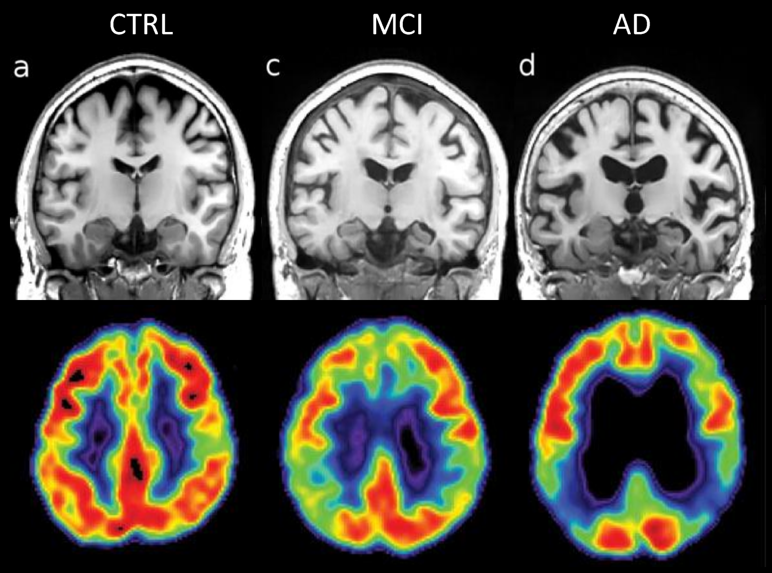


- Neuroimages are by far the most promising and informative techniques available today
- Disease model influences both data interpretation and analysis technique.

Measuring neurodegeneration

- Signal
  - Atrophy [structural MRI]
  - Hypometabolism [FDG-PET]

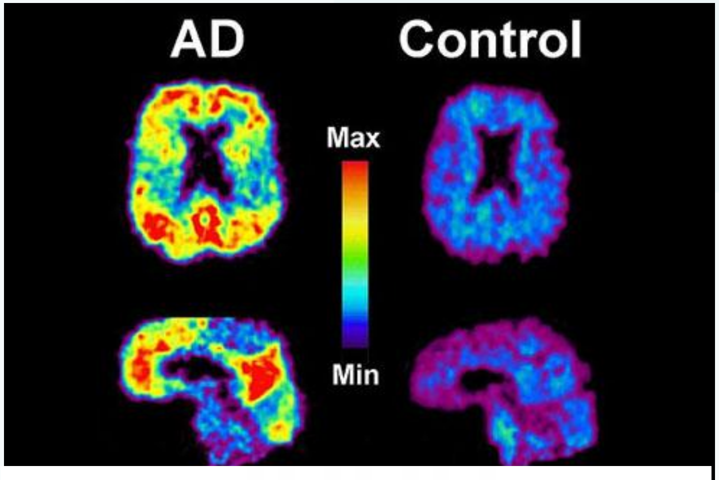
Textbook images are nice and clear but real life is different . . .

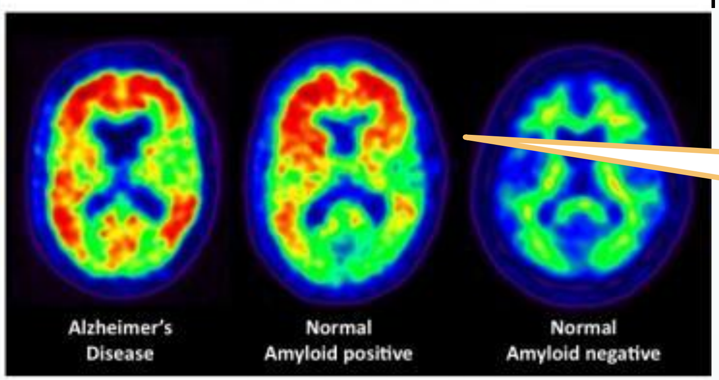


- Noises
  - Acquisition
    - Image artifacts, electronics, misalignments, scanner, protocols, …
  - Physiological (intrinsic)
    - Age, sex, education, clinical history, genetics, …
  - “Gold standard”
    - Validation, follow- up, comorbidity, control selection, …
  - Data processing
    - Results are method dependent, without a quantitative model cohort comparison is the only guide
  - Disease model
    - Technique appropriateness
    - Result interpretation and context

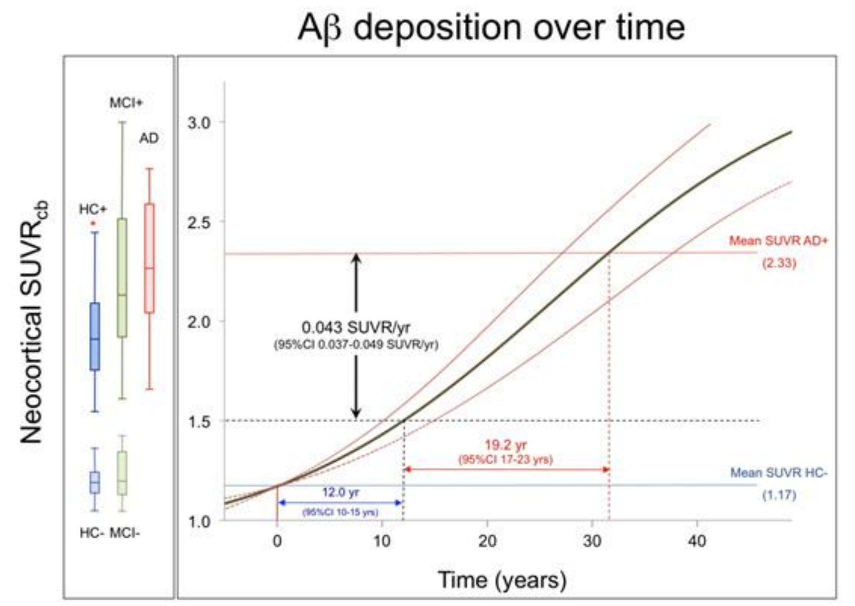
- How do we extract the clinically relevant information?
- How do we develop a neurodegeneration-sensitive analysis with robustness against all other confounding factors?
- How do we validate the results?

Amyloid imaging





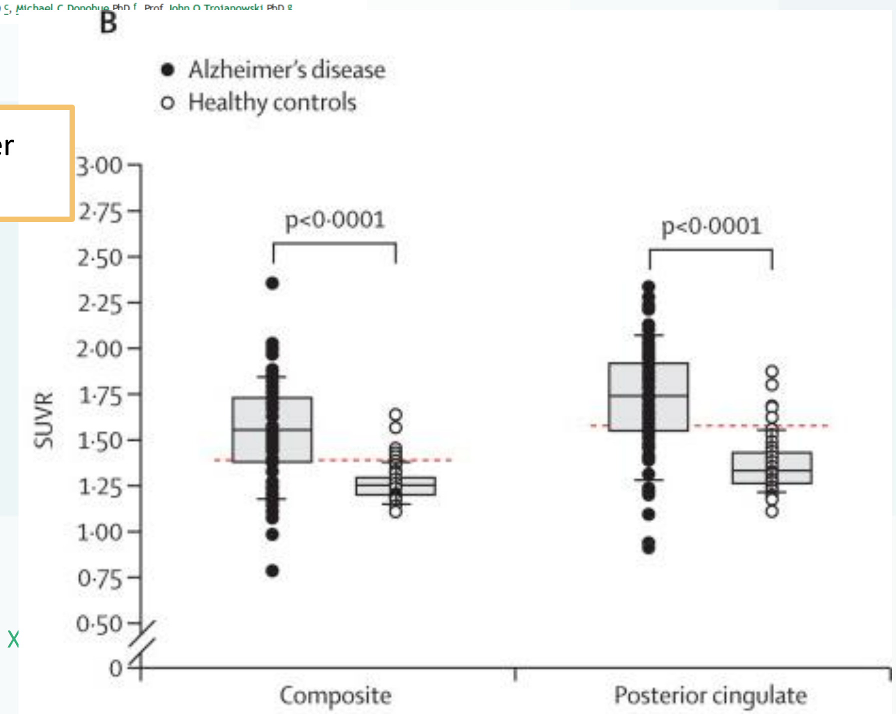
Will this subject ever develop AD?



The Lancet Neurology, Volume 12, Issue 2, Pages 207 - 216, Febr
doi:10.1016/S1474-4422(12)70291-0 Cite or Link Usin

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Prof Dr Clifford R Jack MD [a], Prof David S Knopman MD [b], Prof William J Jagust MD [d], Prof Ronald C Petersen MD [b], Prof Michael W Weiner MD [e], Prof Paul S Aisen MD [f], Prof Leslie M Shaw PhD [g], Prashanthi Vemuri PhD [a], Heather J Wiste [c], Stephen D Weigand [c], Timothy G Lesnick [c], Vernon S Pankratz PhD [c], Michael C Donohue PhD [f], Prof John Q Trojanowski PhD [g]



THE LANCET Neurology
Volume 10, Issue 5, May 2011, Pages 424–435
Fast track — Articles

Cerebral amyloid-β PET with florbetaben ([18]F) in patients with Alzheimer's disease and healthy controls: a multicentre phase 2 diagnostic study

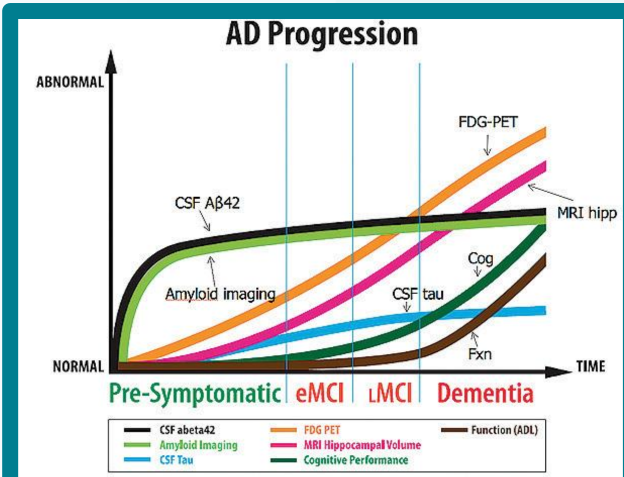
Dr Henryk Barthel, MD[a], Hermann-Josef Gertz, MD[b], Stefan Dresel, MD[c], Oliver Peters, MD[d], Peter Bartenstein, MD[e], Katharina Buerger, MD[f], Florian Hiemeyer, PhD[g], Sabine M Wittemer-Rump, PhD[g], John Seibyl, MD[h], Cornelia Reininger, MD[g], Osama Sabri, MD[a], for the Florbetaben Study Group[‡]

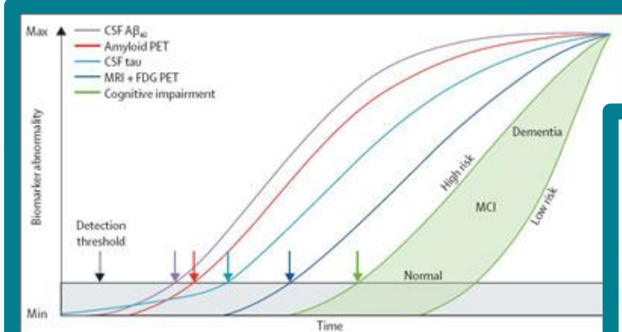
Standardized Uptake Value Ratio (SUVR) for amyloid-PET on 81 AD and 69 CTRL subjects

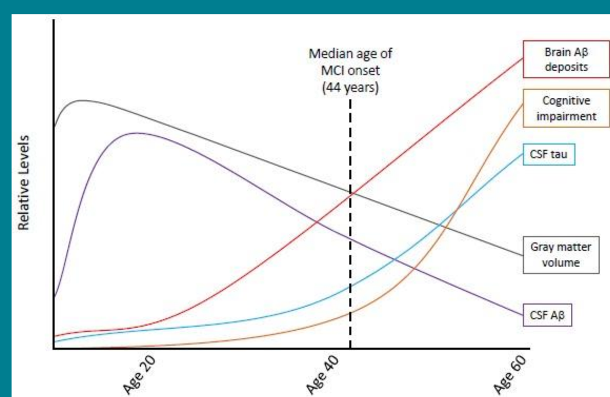
X

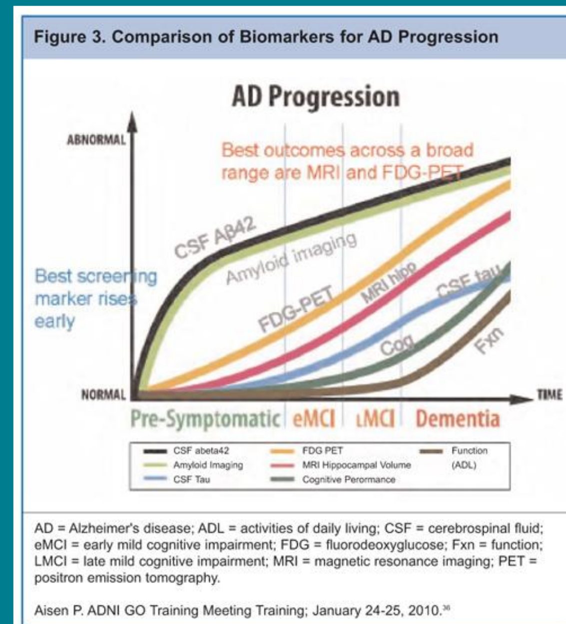
What disease model?

Amyloid cascade	•amyloid plaques
Tau hypothesis	•Tangles
Oxidative stress	•High ROS concentration
Inflammatory	•pro-inflammatory products
Cell cycle	•cell transition from G0 to G1
Vascular	•cerebral hypoperfusion
Cholesterol hypothesis	•γ-secretase activity and amyloidogenic pathway









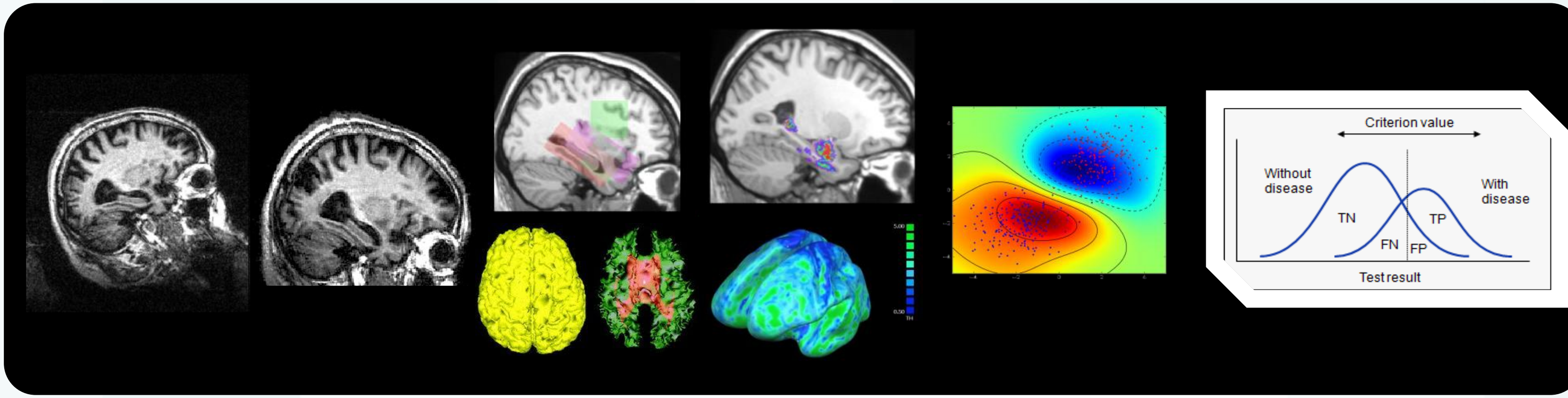
BIOMARKERS FROM NEUROIMAGES

What are biomarkers?

- Def #1:
  - a characteristic by which a particular pathological or physiological process, disease, etc. can be identified.
- Def #2:
  - objective indications of medical state which can be measured accurately and reproducibly

- Requirements
  - Relevance
    - the ability to appropriately provide clinically relevant information
  - Validity
    - the ability to consistently and accurately predict a clinical outcome

Squeezing out the biomarker



Signal contribution	Physics, scanner, protocols	Image modality	Clinical input	Information theory	Data set
Processing	Quality assessment	Normalization	Characterization	Feature extraction	Classifier
Noises	Acquisition noises	Physiological	Processing, Gold standard	Data processing	Gold standard

Raw data
10^7 DoF / image

Abstraction layer
$10^2 – 10^3$ DoF

Marker
1-2
DoF

Raw data

Synthesis

Abstraction layer

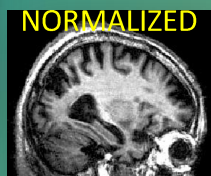
MARKER

Standard processing

Acquisition noises, Image reconstruction algorithm

Quality assessment

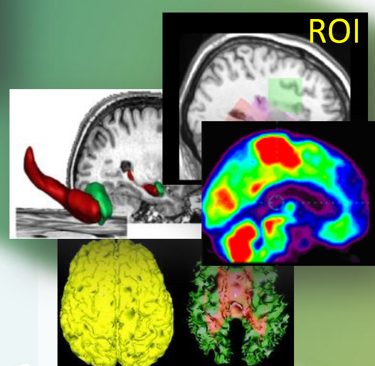
Physiological Data Processing



Spatial and intensity normalization

__A-priori:__
Neurodegeneration model
Clinical evidence,
Post-mortem studies

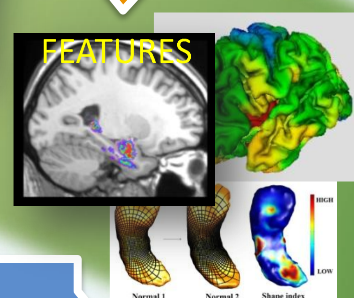
__Data driven:__
Gold standard, cohort selection



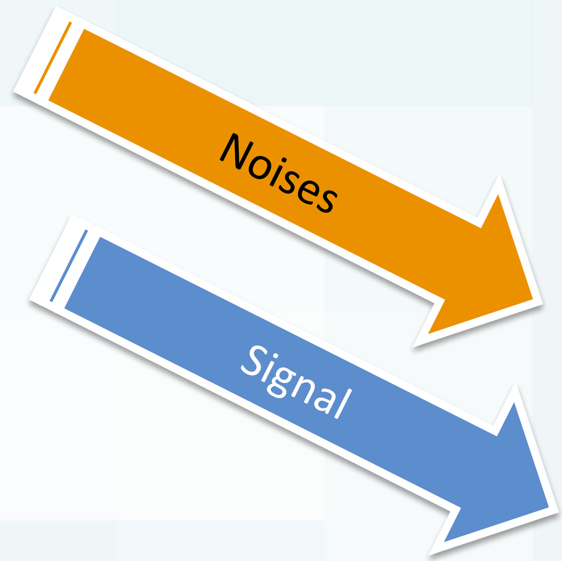
__VBM__:
Direct voxel comparison
Disease-specific volumes
Atlases

__Segmentation:__
cortex, hippocampus …

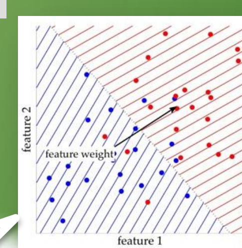
Data Processing
Feature selection



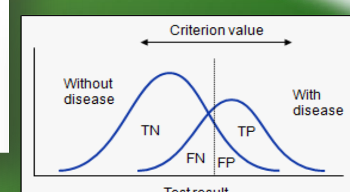
Features: intensity, texture, geometrical properties, shape analysis, cortical thickness



Cohort selection
Gold standard

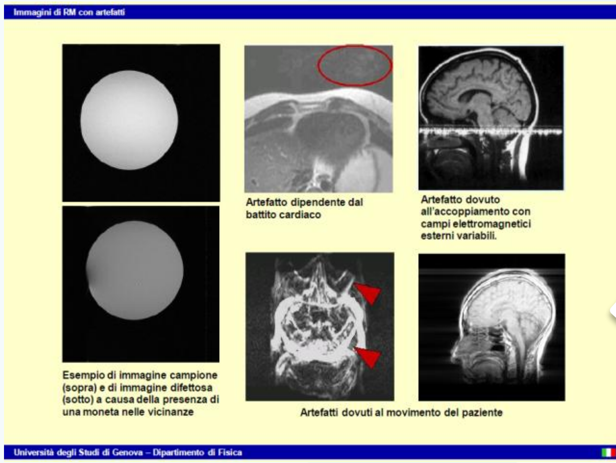


Classification
Statistical Tests

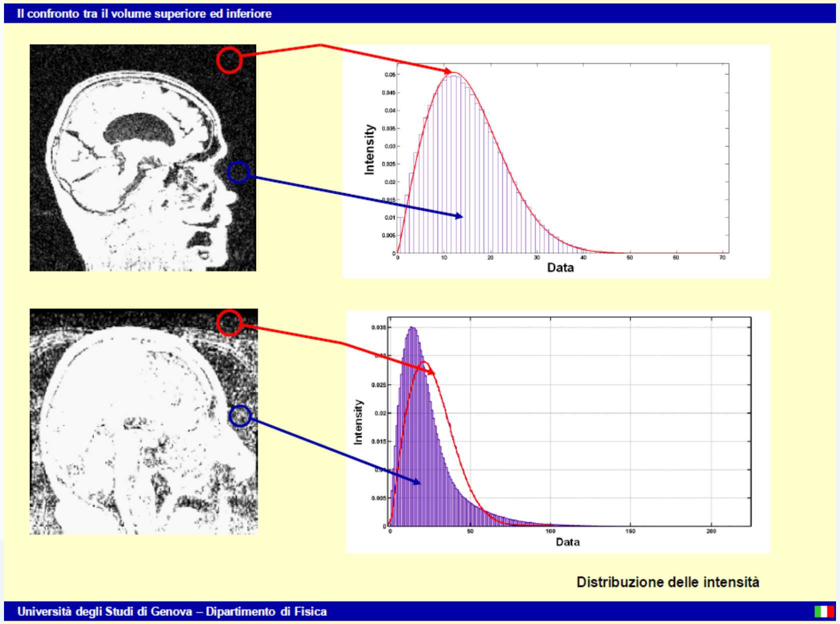


MARKER

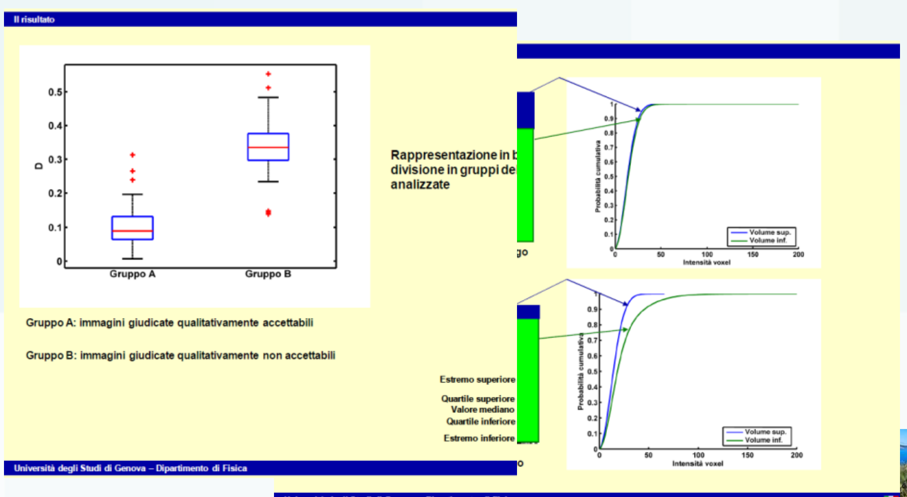
Quality filters



Many artifact types, it's hard to filter them based on signal characteristics



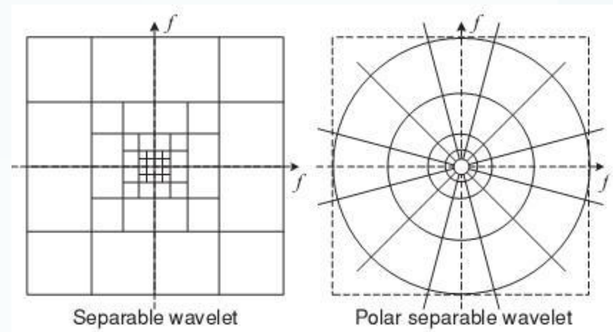
Noise statistics sampled on several disjoint regions outside the brain

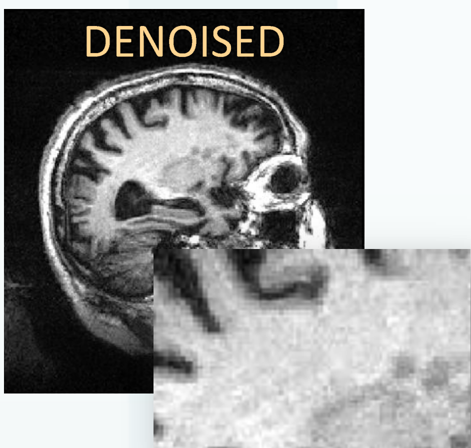


Non parametric tests on distribution delivers quality index

Acquisition noise reduction

- The steerable pyramid filter performs a polar-separable decomposition in the frequency domain, thus allowing independent representation of scale and orientation





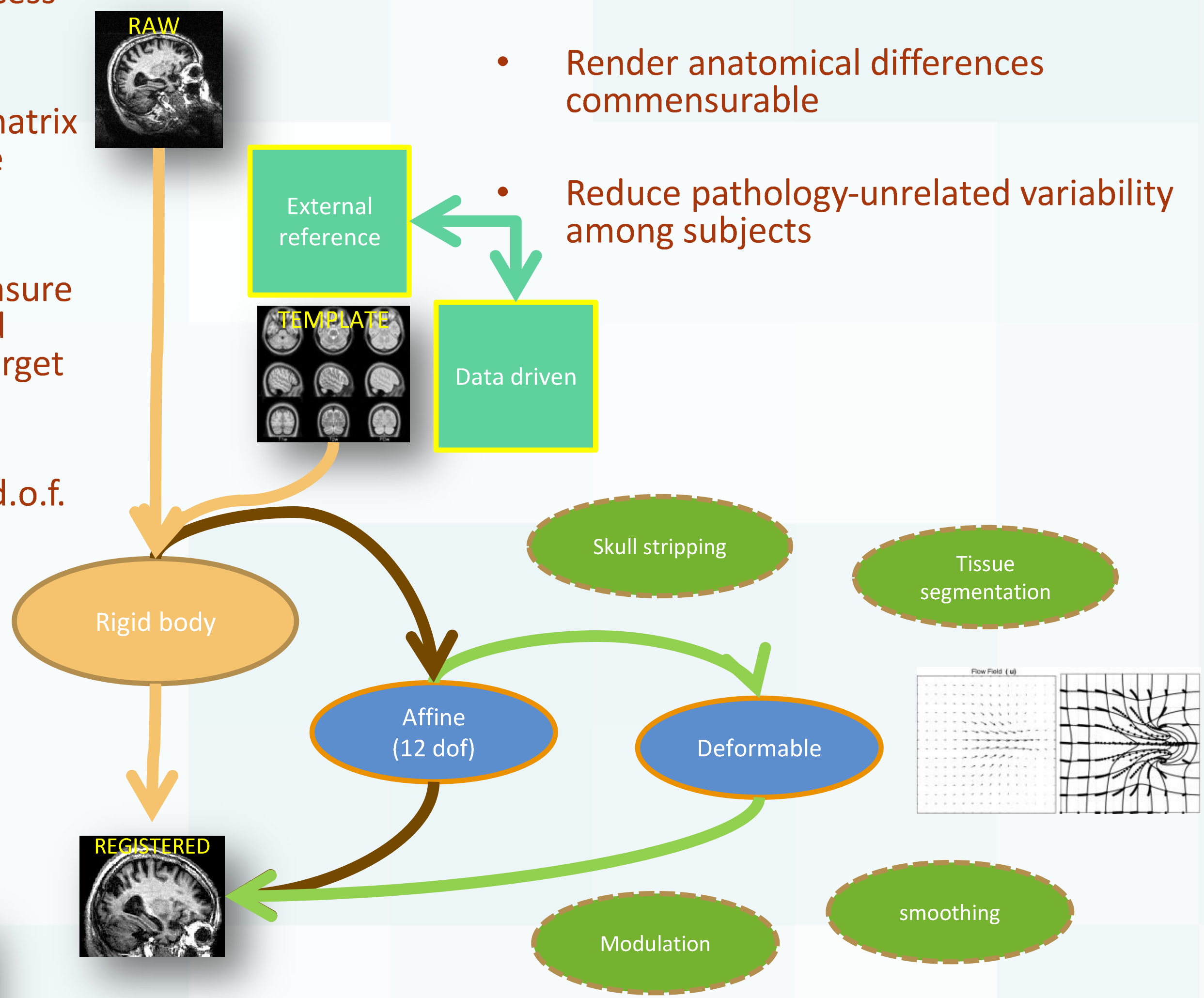
- Noise threshold is automatically computed as a dependent on the inflection point in the SSI function

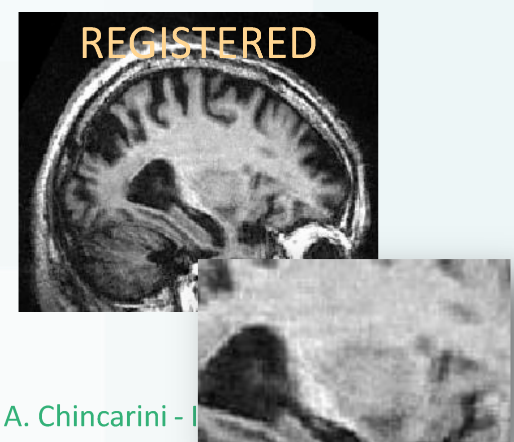
$$SSIM(x,y) = \frac{(2\mu_x\mu_y + c_1)(2\sigma_{xy} + c_2)}{(\mu_x^2 + \mu_y^2 + c_1)(\sigma_x^2 + \sigma_y^2 + c_2)}$$

Spatial registration

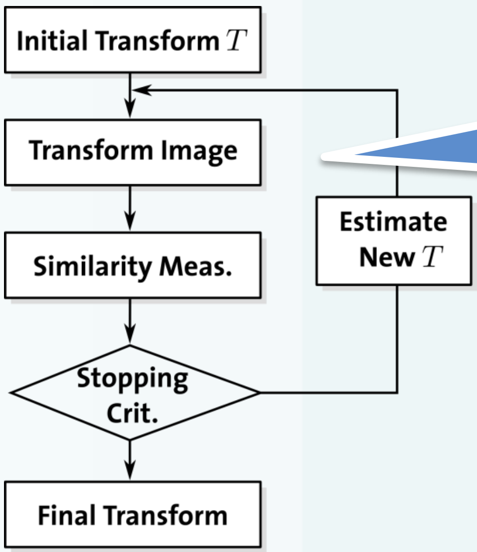
- Registration: iterative process mapping two domains
- Map is a transformation matrix depending on a set of free parameters (d.o.f.)
- A metric is defined to measure how similar is the mapped domain (moving) to the target domain (fixed)
- Metric is minimized over d.o.f.

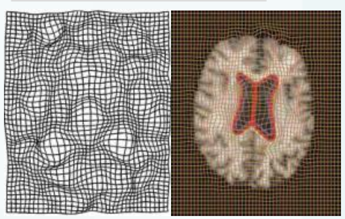
- Use the same coordinates and spatial discretization
- Render anatomical differences commensurable
- Reduce pathology-unrelated variability among subjects





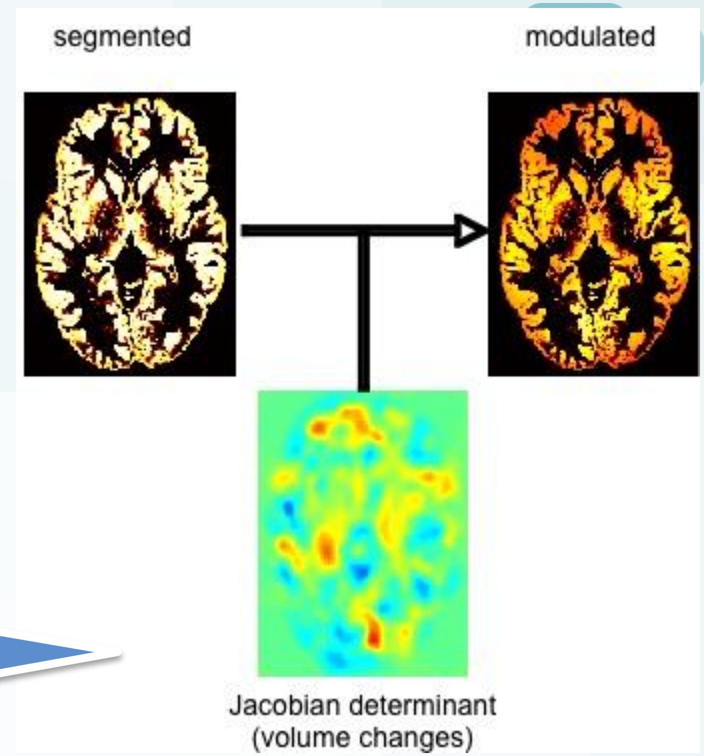
Remarks on nonlinear registration



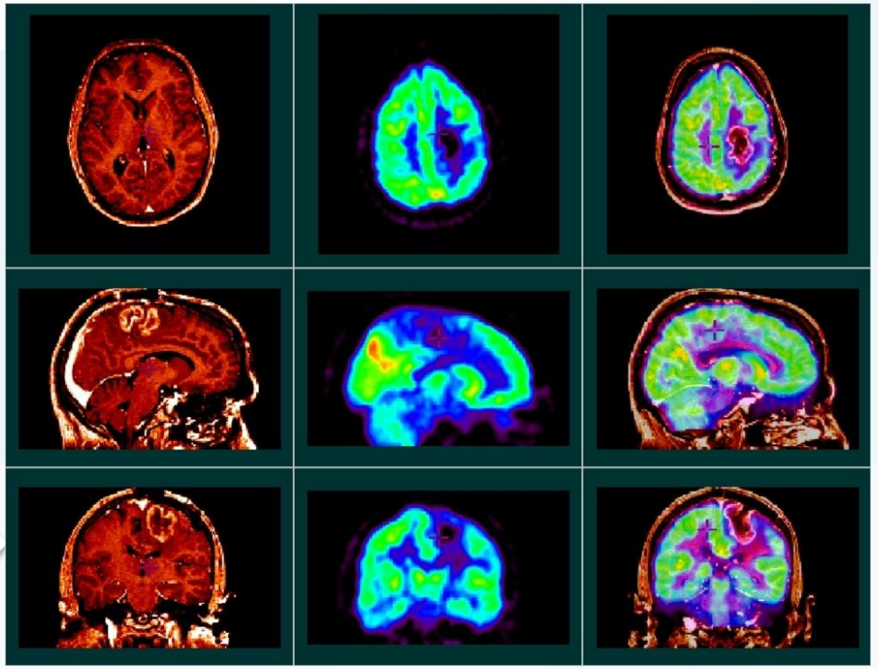


[Too] many choices of nonlinear deformation and metric

Jacobian modulation needed to restore volume information



Preconditioning, regularization techniques, multi-modality metrics (i.e. mutual information) are needed.
Problem is generally ill-posed



Intensity normalization

Original intensities

Easiest BUT:

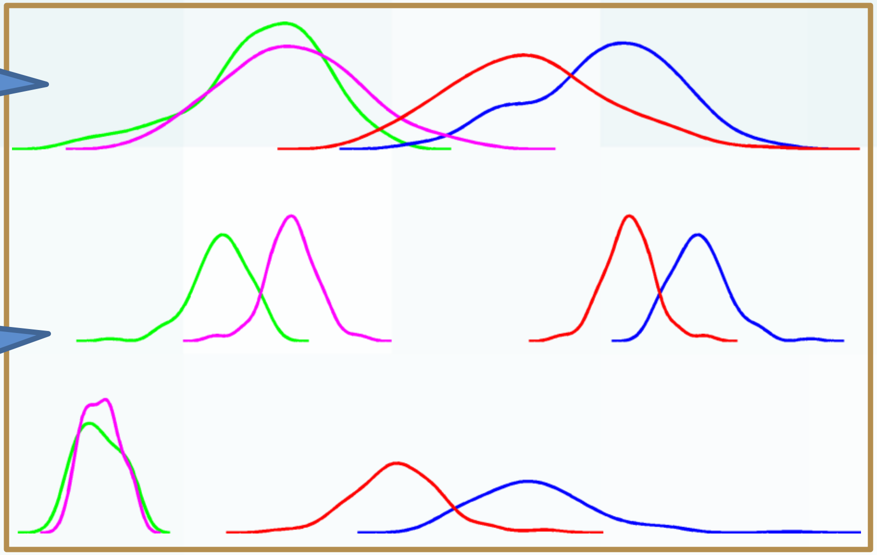
•Not applicable to multi-center studies
•Prone to sample size effect

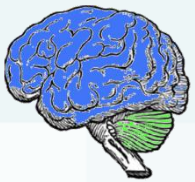
Normalized to total counts

Smaller variance
Good for relative measures, pca, …

BUT:

•VBM studies may come out with unexpected ROIs





Cohort 1

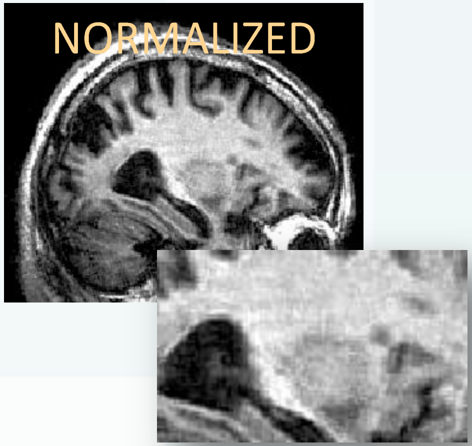
Cohort 2

Normalized to ROI

Even smaller variance
Accurate ROI in VBM
Good for longitudinal studies, small differences evaluation

BUT:

•More complex
•Need knowledge of reference region
•Rely on segmentation



<u>*Intensity normalization important when*</u>

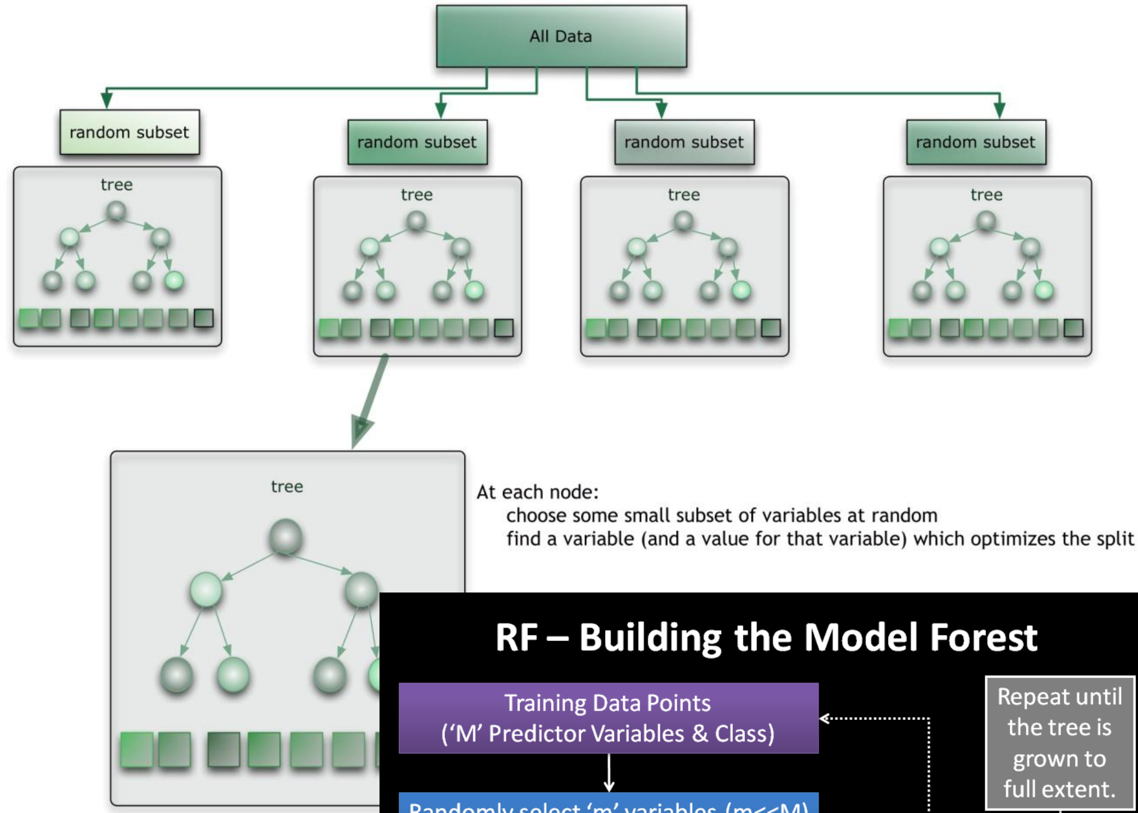
•Images come from multi-center studies
•Accurate variance is necessary for group comparison
•Looking for discriminating ROIs (if reference region is known)
•Longitudinal studies
•Network studies

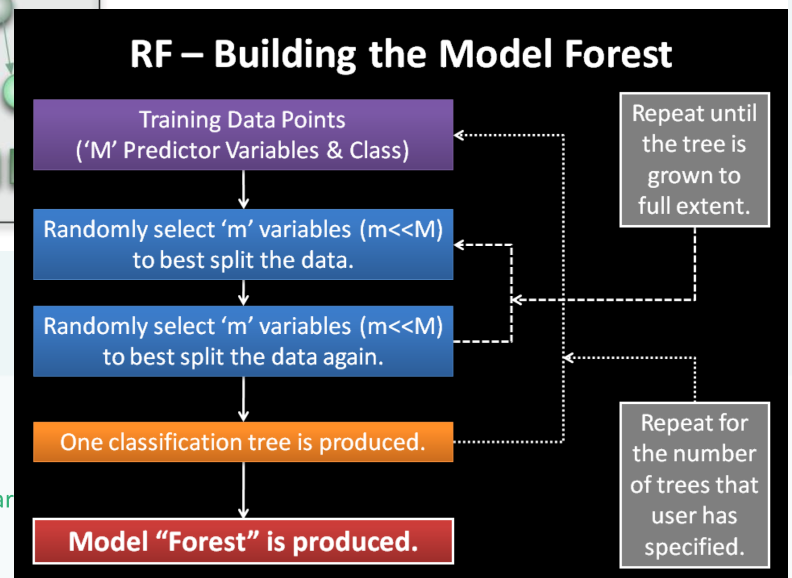
Machine learning

"…concerns the construction and study of systems that can learn from data. "

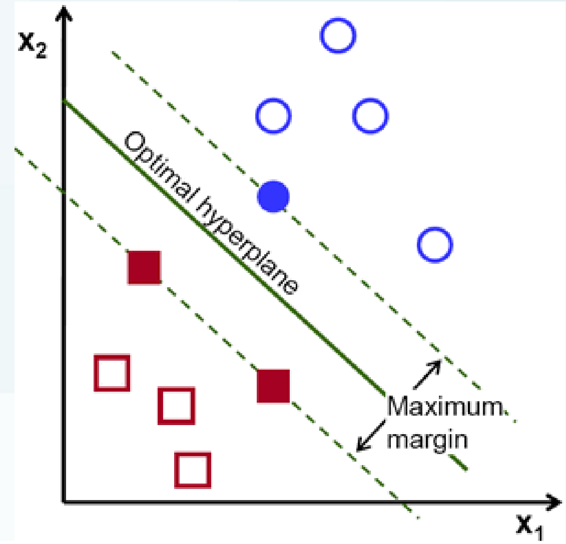
RANDOM FOREST

- It has excellent accuracy
- It runs efficiently on large data bases.
- It can handle thousands of input variables without variable deletion.
- It gives estimates of what variables are important in the classification.
- It has an effective method for estimating missing data and maintains accuracy when a large proportion of the data are missing.
- It offers an experimental method for detecting variable interactions.





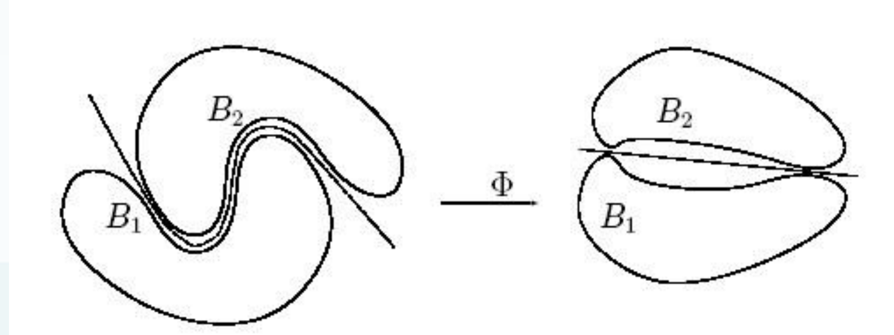
Machine learning

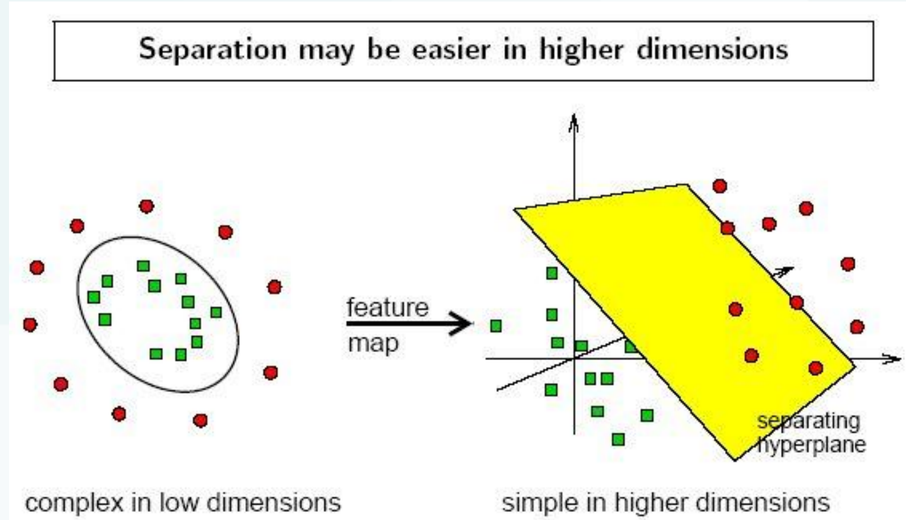


SUPPORT VECTOR MACHINE

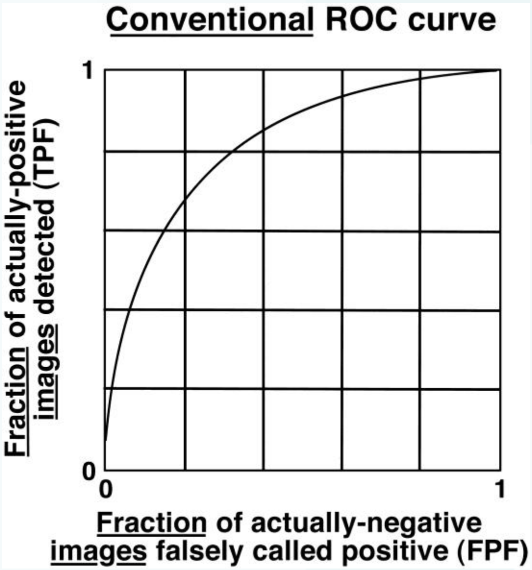
" … is a discriminative classifier formally defined by a separating hyperplane. In other words, given labeled training data (supervised learning), the algorithm outputs an optimal hyperplane which categorizes new examples."

- Can outperform RF
- It runs ok on large data bases.
- It uses the "kernel trick" to map data onto new dimensions
- It can handle thousands of input variables without variable deletion.
- It gives estimates of what variables and elements are important in the classification.





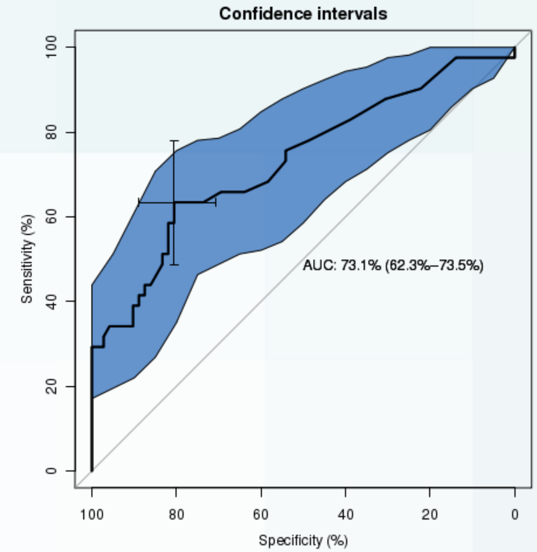
Receiver Operating Characteristic (ROC) curves

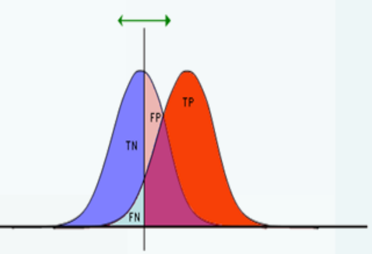


Sensitivity vs (1-specificity)

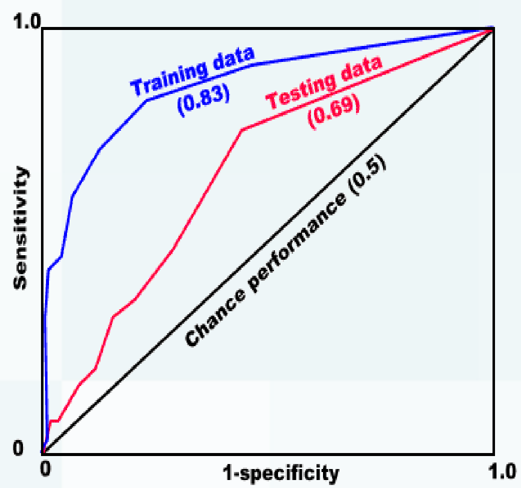
Used for:

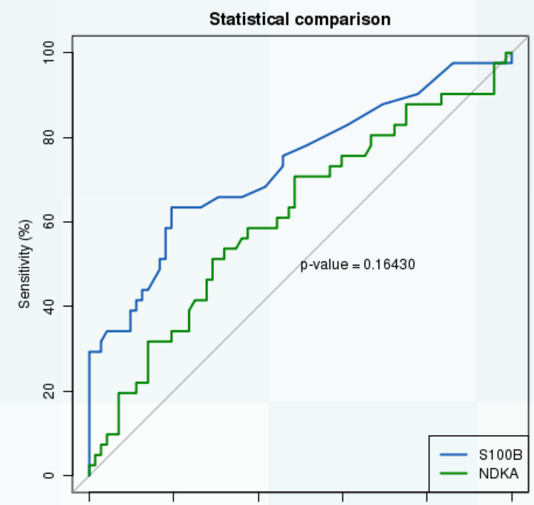
test reliability,
analysis comparison,
optimal working point

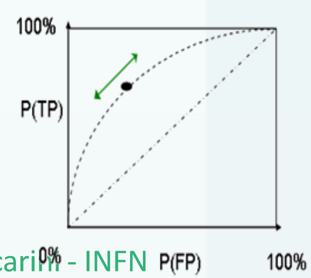




TP	FP
FN	TN
1	1



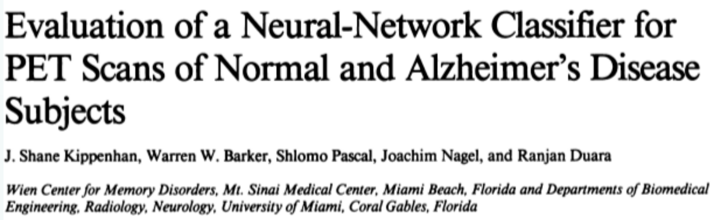




Classifiers vs. tests

Classifiers

- Pro
  - Capture links among variables
  - Multidomain approach
  - ROC curves
  - Group & single subject discr.
  - Discr. error estimation
  - Performance
- Cons
  - Complex implementation
  - Require train/test set
  - Require high number of subjects (≈ 100/cohort, overtr. / gener.)
  - Less straightforward interpretation

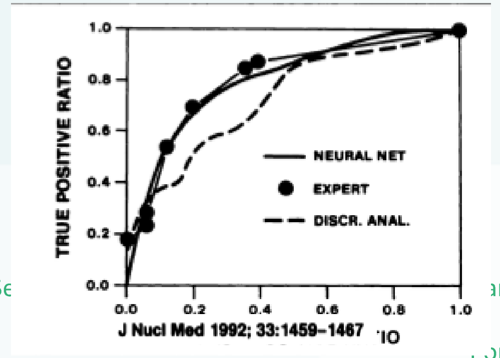

Evaluation of a Neural-Network Classifier for PET Scans of Normal and Alzheimer's Disease Subjects

J. Shane Kippenhan, Warren W. Barker, Shlomo Pascal, Joachim Nagel, and Ranjan Duara

Wien Center for Memory Disorders, Mt. Sinai Medical Center, Miami Beach, Florida and Departments of Biomedical Engineering, Radiology, Neurology, University of Miami, Coral Gables, Florida

t-test statistics

- Pro
  - Easy implementation
  - Require smaller number of subjects (≥ 30)
  - Immediate evaluation (variable significance)
- Cons
  - No link among variables
  - Single domain approach (commensurable variables)
  - p-value only
  - Group discr ok but single subject is questionable
  - Gaussian distribution only

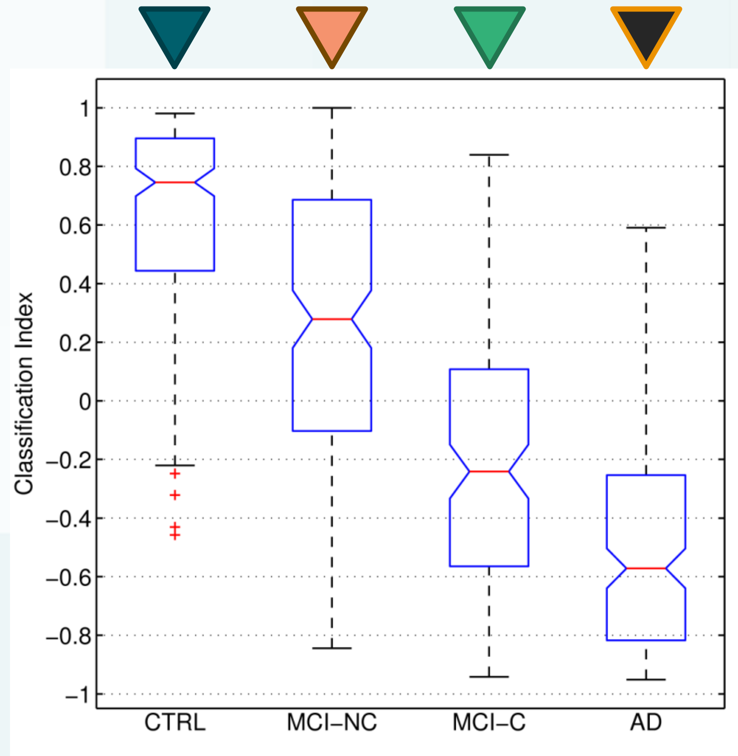


Example: MRI marker in AD

- ADNI data
  - 191 CTRL subjects (76.6 ± 5.1) y
  - 302 aMCI (75.0 ± 7.0) y
  - 145 AD (75.5 ± 7.5) y MMSE score (22.3 ± 3.2)

	ROC auc
CTRL / AD	0.97
CTRL / MCI-conv	0.92
MCI-nc / MCI-conv	0.74

- All MRI @ baseline
- 136 MCI converted to AD in t ≈ 2 years



Age matched controls

Non-converters [yet ?]

Converted in t ≈ 3 years

Alzheimer's

NeuroImage 58 (2011) 469–480

Contents lists available at ScienceDirect

NeuroImage

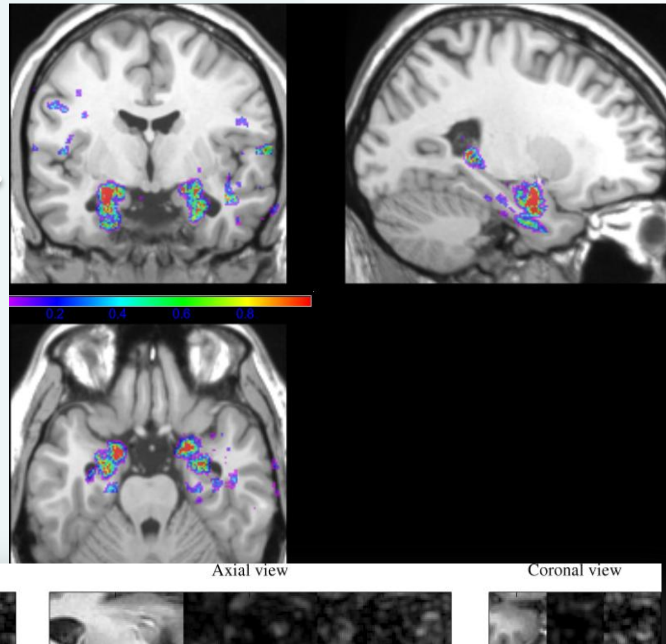
journal homepage: www.elsevier.com/locate/ynimg

ELSEVIER

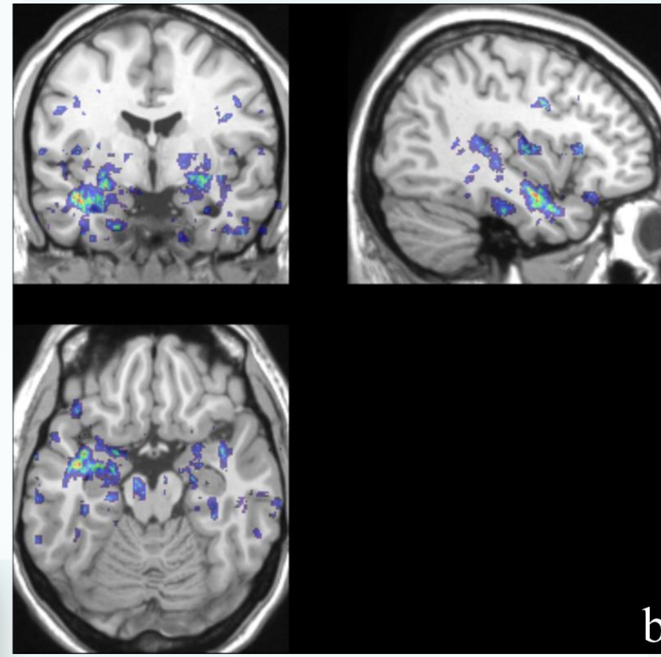
Local MRI analysis approach in the diagnosis of early and prodromal Alzheimer's disease☆

Andrea Chincarini [a,*], Paolo Bosco [a,b], Piero Calvini [a,b], Gianluca Gemme [a], Mario Esposito [a,b], Chiara Olivieri [c], Luca Rei [a,b], Sandro Squarcia [a,b], Guido Rodriguez [d], Roberto Bellotti [e,f], Piergiorgio Cerello [g], Ivan De Mitri [i,h], Alessandra Retico [j], Flavio Nobili [d] and The Alzheimer's Disease Neuroimaging Initiative

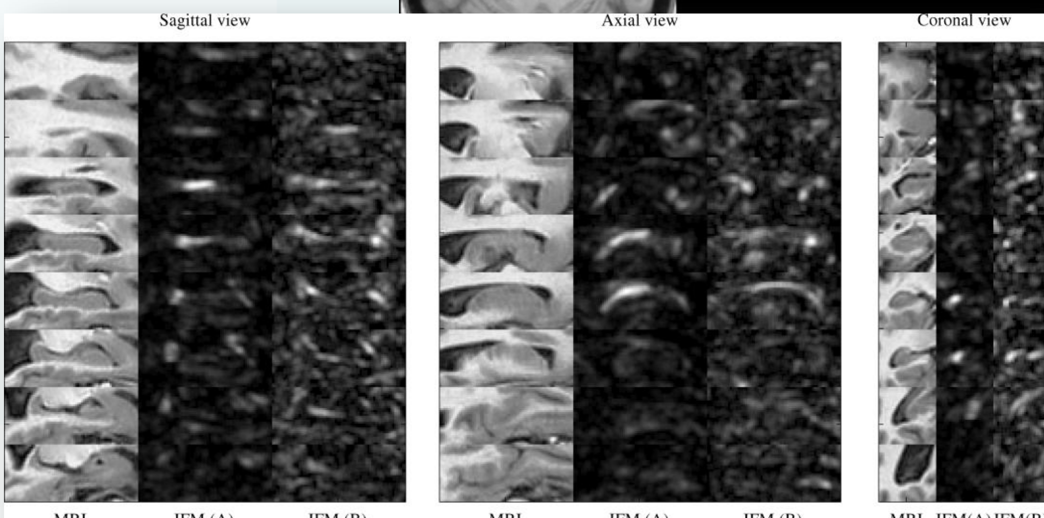
Relevant features



Relevant features when training on ADNI CTRL/AD



Relevant features when training on ADNI MCI-nc/MCI-co



Detailed relevant features on the hippocampal region

ADVANCED TECHNIQUES

Better markers are likely coming from...

- More complex/specialized imaging techniques
  - fMRI / DTI / High field MRI / new PET tracers / ...
- Combined techniques
  - MRI + PET + CSF + Neuropsychology + ...
- Longitudinal studies (differential measures)
  - Quantitative marker trend / aging models / ...
- Networks / pattern
  - Structural-functional connectivity / coherence analysis / ...

Combined techniques

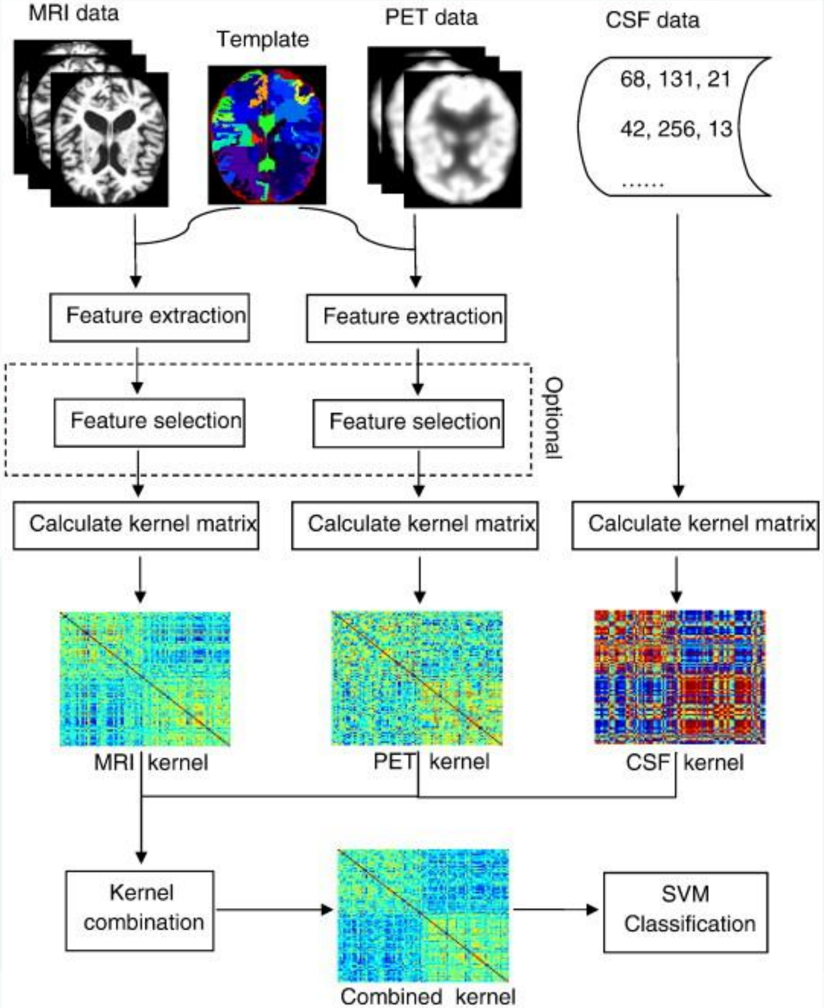
NeuroImage
Volume 55, Issue 3, 1 April 2011, Pages 856–867

Multimodal classification of Alzheimer's disease and mild cognitive impairment

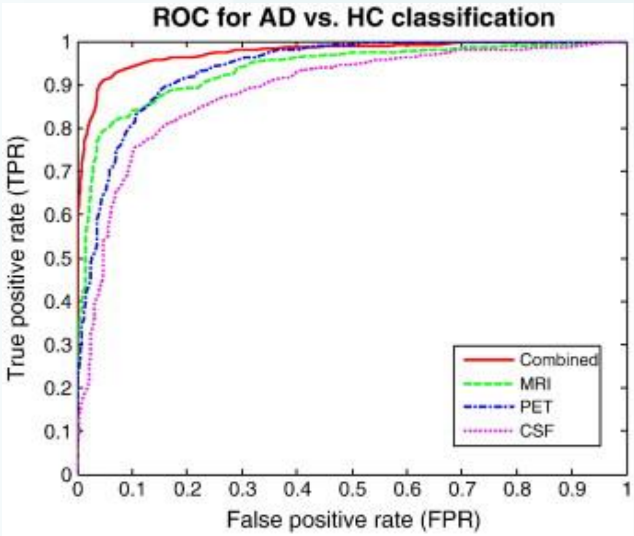
Daoqiang Zhang[a], Yaping Wang[a, b], Luping Zhou[a], Hong Yuan[a], Dinggang Shen[a], the Alzheimer's Disease Neuroimaging Initiative[1]

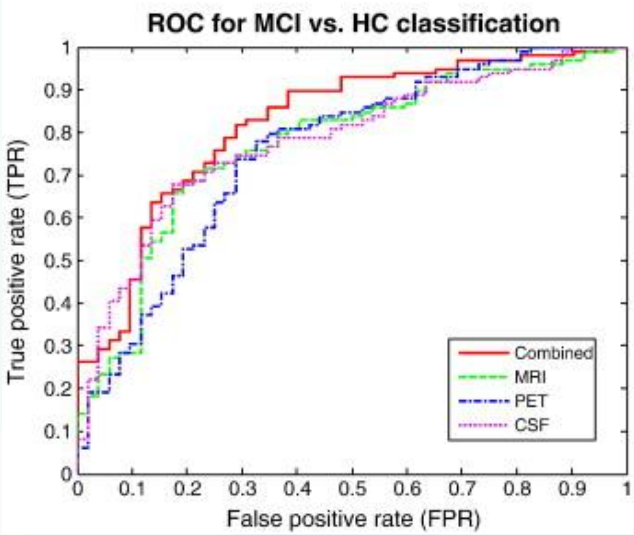
Research Highlights

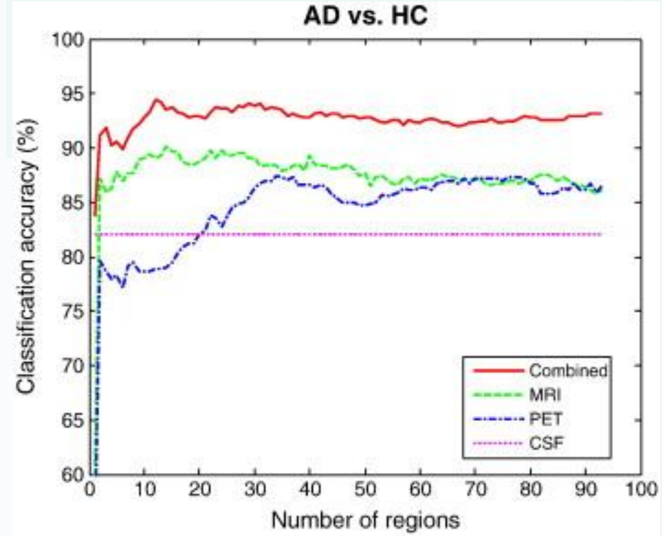
► We propose to combine MRI, FDG-PET, and CSF biomarkers, to discriminate between AD (or MCI) and healthy controls, using a kernel combination method. ► A high accuracy of 93.2% for AD classification and a high sensitivity of 91.5% (for MCI converters) for MCI classification. ► Each modality is indispensable for achieving good classification. ► CSF and PET have the highest complementary information and MRI and PET have the highest similar information for classification.

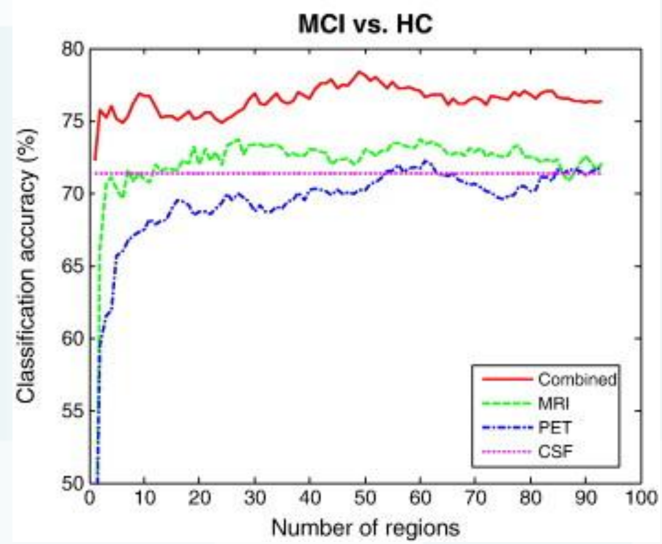


Local vs. multiple regions analysis









Longitudinal studies

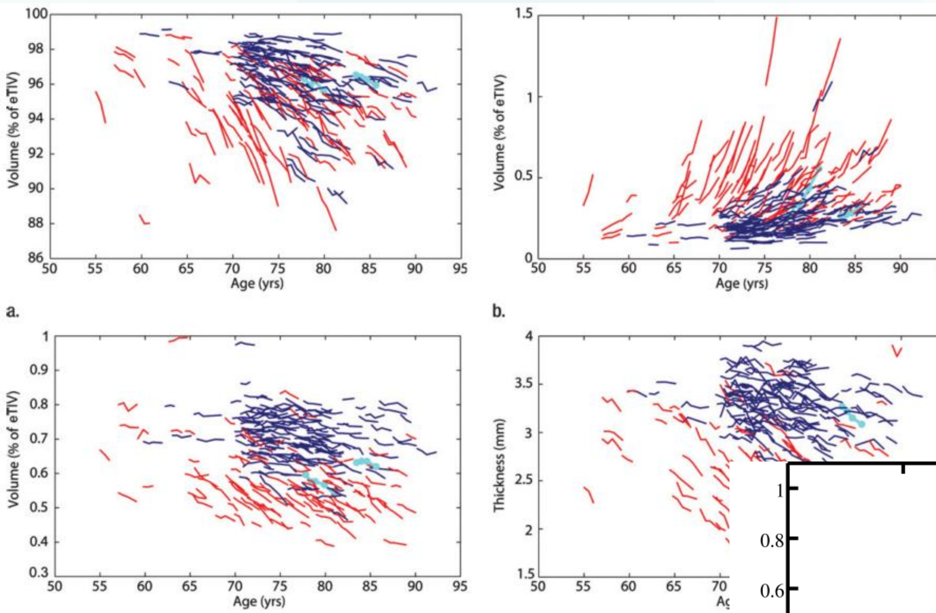


Figure 2: Spaghetti plots illustrate volumes (as percentages of estimated total intracranial volume [eTIV]) an… evaluatable follow-up visits as functions of age for (a) whole brain, (b) inferior lateral ventricle, and (c) hippoca… thicknesses and changes in thickness are shown. Healthy control subject data are in dark blue; AD data are in… control subjects whose cognitive status chan… from the healthy control subject group before… measures to AD atrophy in individuals in a cli…

Radiology: Volume 259: Number 3—June 2011

ORIGINAL RESEARCH ■ NEURORADIOLOGY

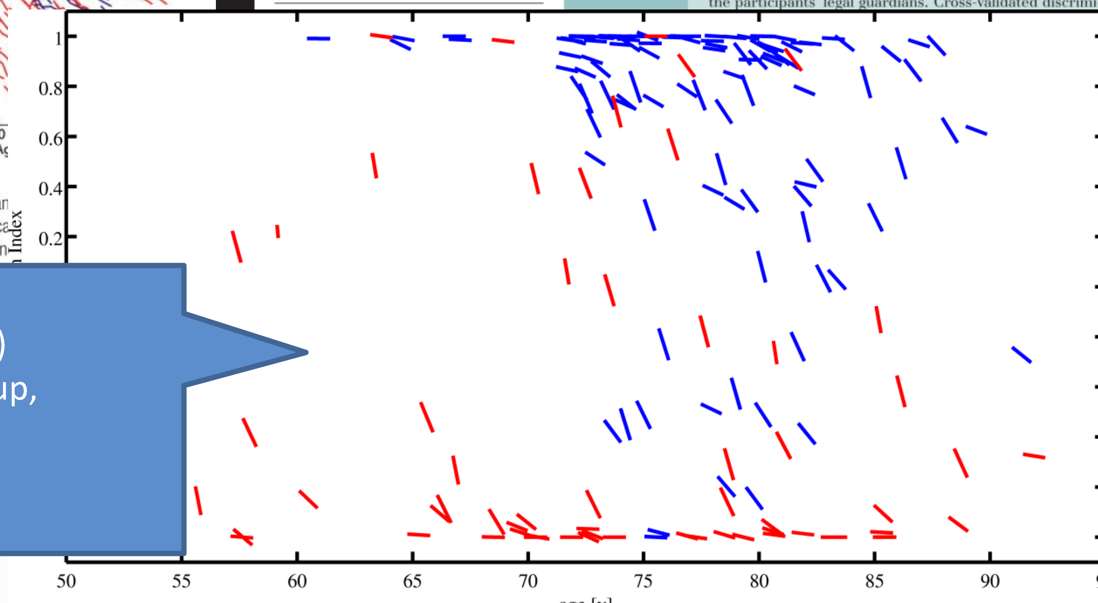
Mild Cognitive Impairment:

Baseline and Longitudinal Structural MR Imaging Measures Improve Predictive Prognosis[1]

Linda K. McEvoy, PhD
Dominic Holland, PhD
Donald J. Hagler, Jr, PhD
Christine Fennema-Notestine, PhD
James B. Brewer, MD, PhD
Anders M. Dale, PhD
For the Alzheimer's Disease Neuroimaging Initiative

Purpose: To assess whether single-time-point and longitudinal volumetric magnetic resonance (MR) imaging measures provide predictive prognostic information in patients with amnestic mild cognitive impairment (MCI).

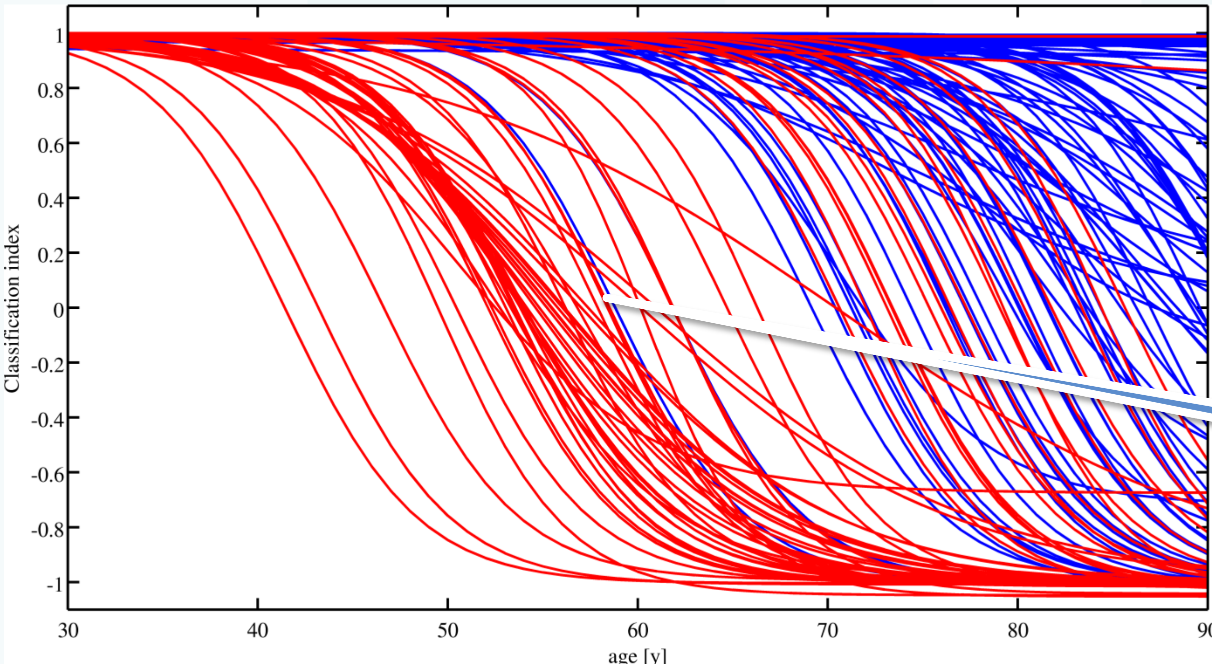
Materials and Methods: This study was conducted with institutional review board approval and in compliance with HIPAA regulations. Written informed consent was obtained from all participants or the participants' legal guardians. Cross-validated discrimi-

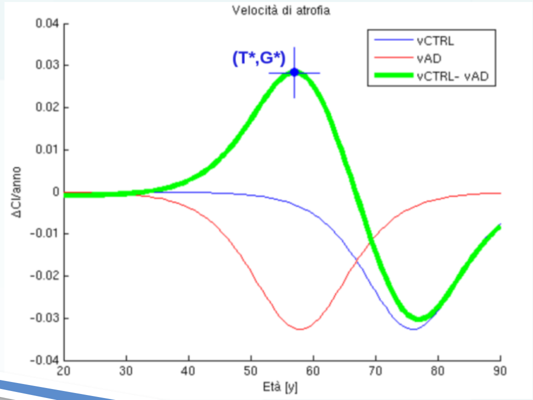


528 subjects (ADNI data)
(≈ 300 training, ≈ 200 test)
Age 55 – 93; >2 y follow-up,

CTRL → CTRL
AD → AD

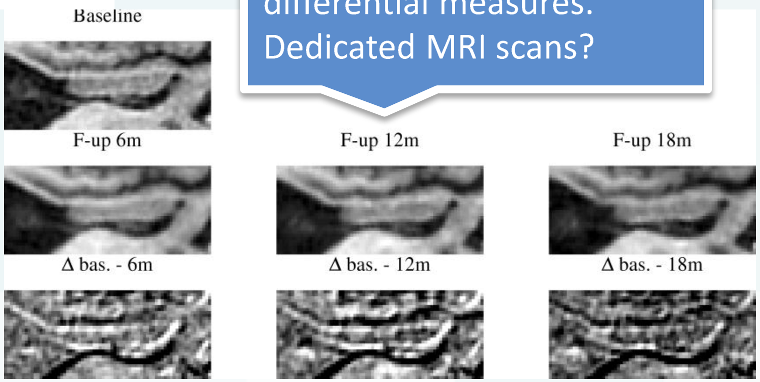
Aging models





Best sensitivity @ T*

Accurate image analysis for differential measures. Dedicated MRI scans?



- Aging model to be checked against other biomarker such as CSF tau fraction, …
- Early detection via differential MRI measures?
- Developing dedicated protocols for 1.5/3T scanners with local high resolution & intensity calibration
- Paper in preparation

Relaxing some assumptions

Bypass intrinsic (physiological) noises

- Can it be used instead of suppressed?

Relax pathology fingerprint as cohort characteristic

- Perhaps it holds true only for smaller groups

Avoid machine learning techniques

- They are powerful but generalization and validation are still a nuisance

Include multidomain data: imaging, npsy, biochemistry, genetic, …

- Not by juxtaposition but with true intermodality relationship

Easily accommodate multiple diseases

- Kinda of a "holy grail"

… and many more… but at what cost?

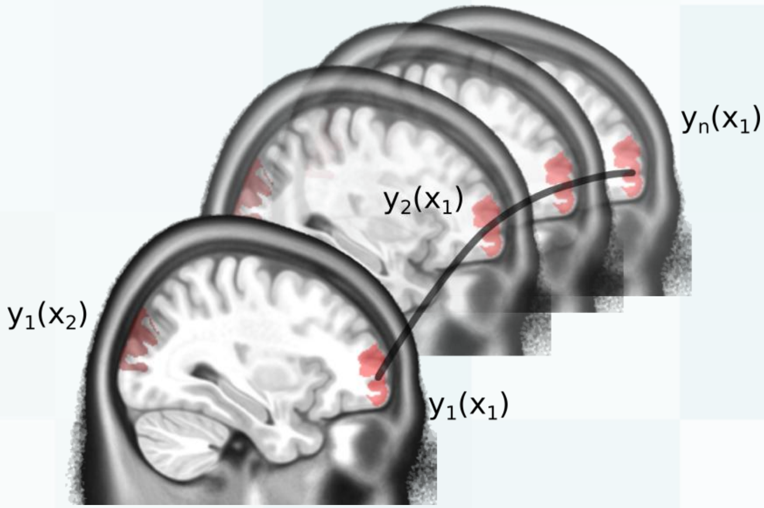
Neurodegeneration as brain pattern

Does the neurodegeneration process leave a signature other than a volume (methabolism) loss?

Is there a common trait to normal/pathological aging?

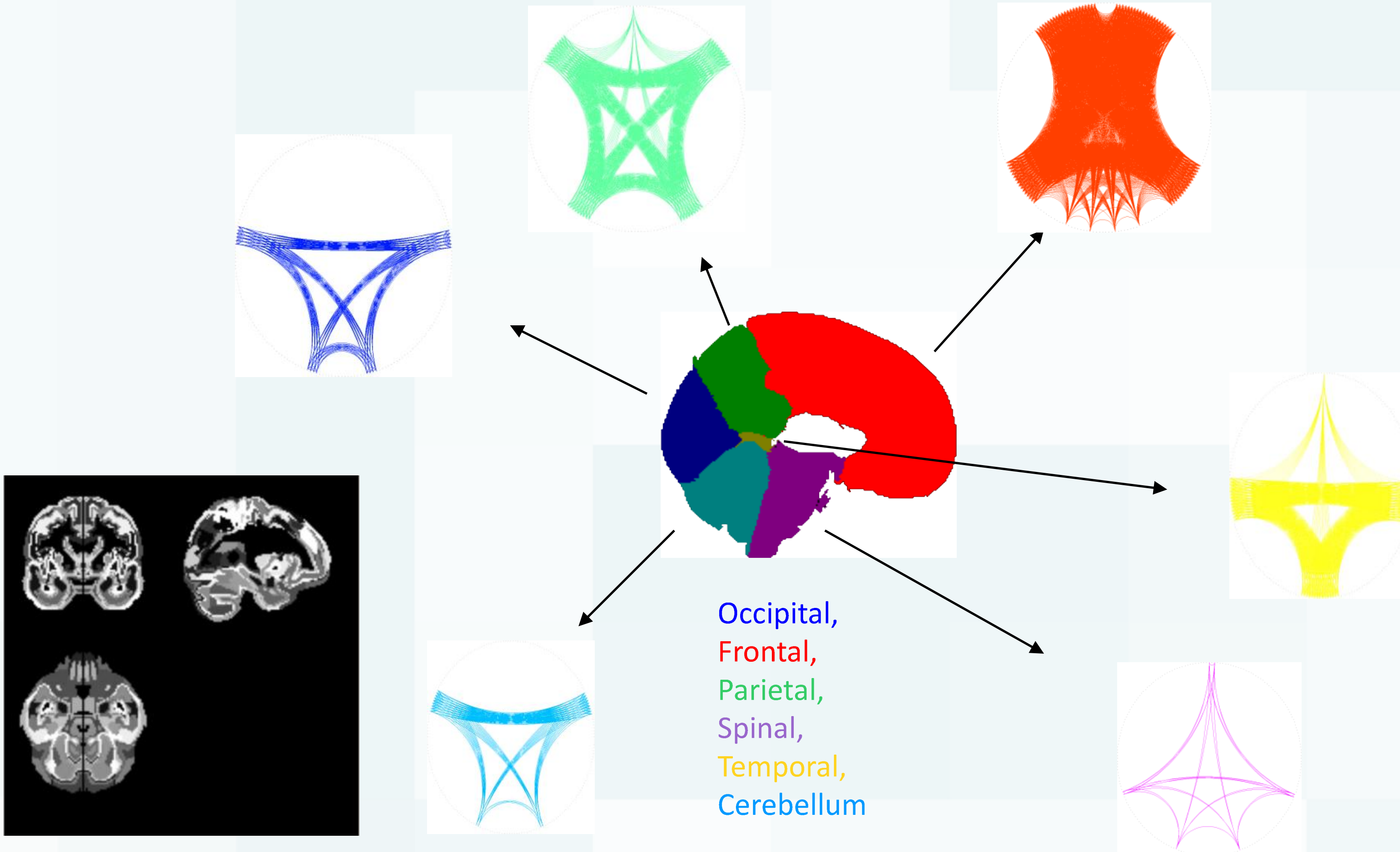
x_1 , x_2, … Voxel positional index
y_1 , y_2, … Subject index

I_{xy} Gray intensity on voxel x from image y

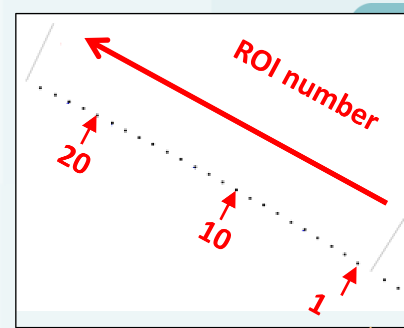


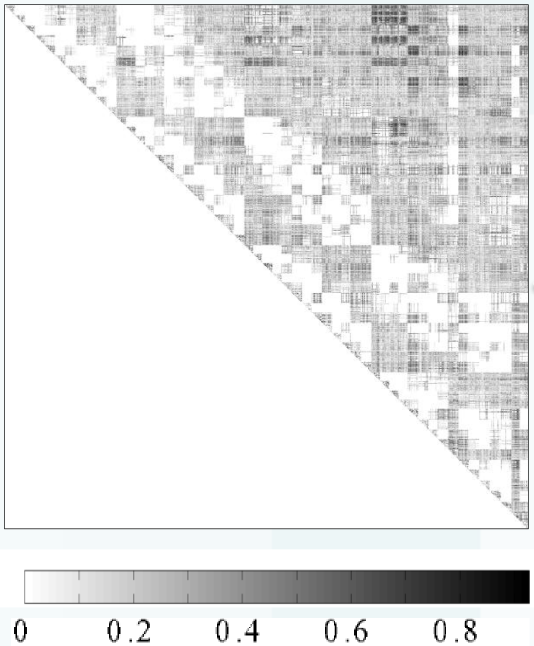
1. Homogeneous group (clinical parameter)
2. Aligned images (same anatomical structure in the same position)
3. Correlation coefficient between any two disjoint positions
4. Correlation is just one of the possible metrics

The connected brain



Representation

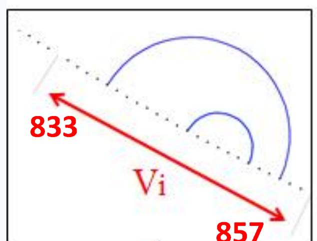


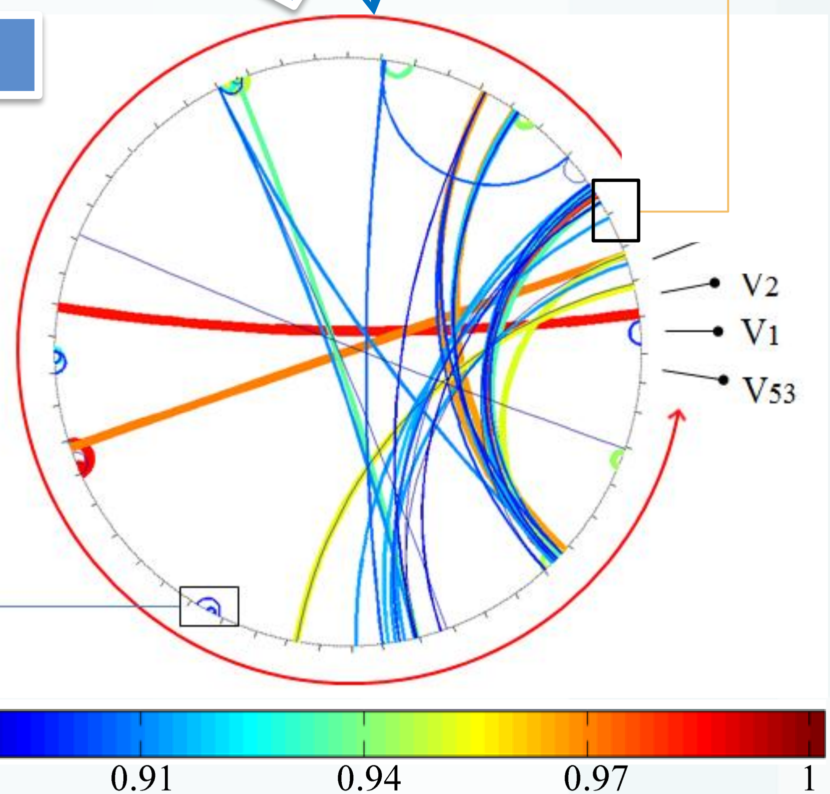


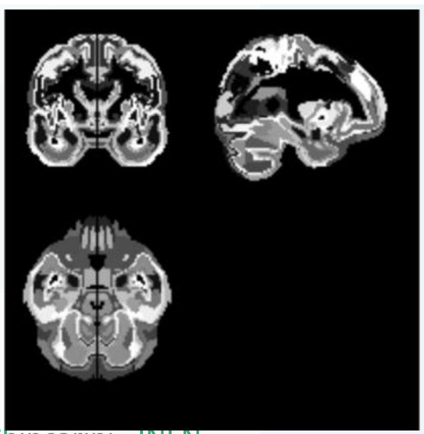
$|c_{\mu\nu}|$

Connectogram representation

Matrix representation

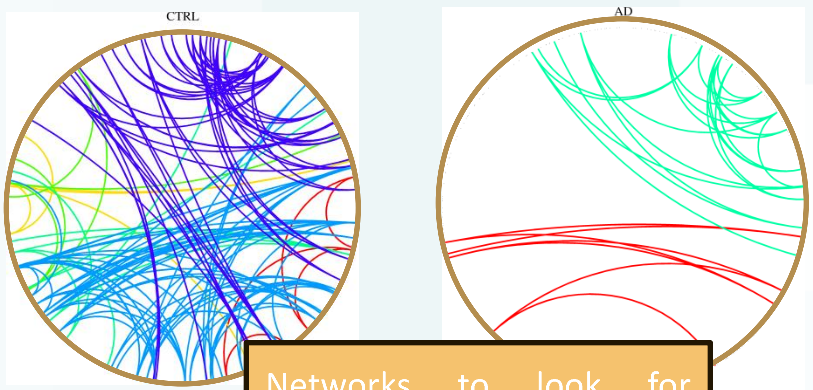




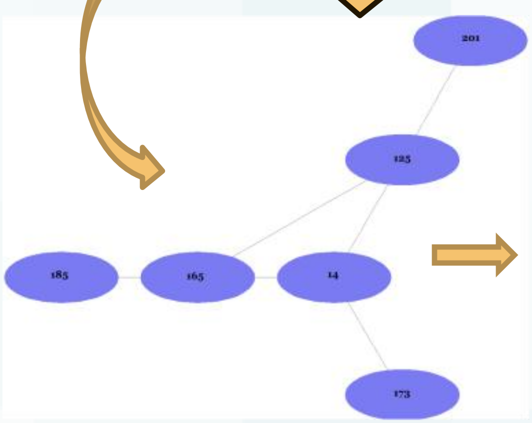


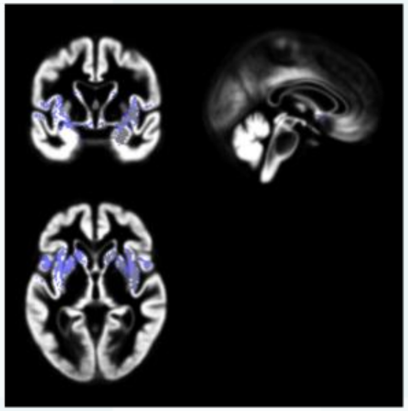
Data driven ROIs

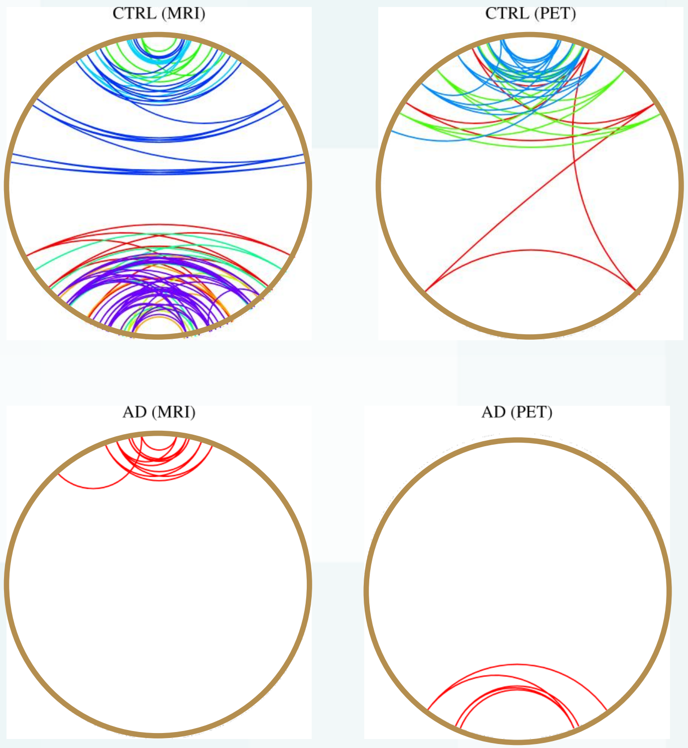
Complex patterns: specificity and multimodality



Networks to look for pathology patterns

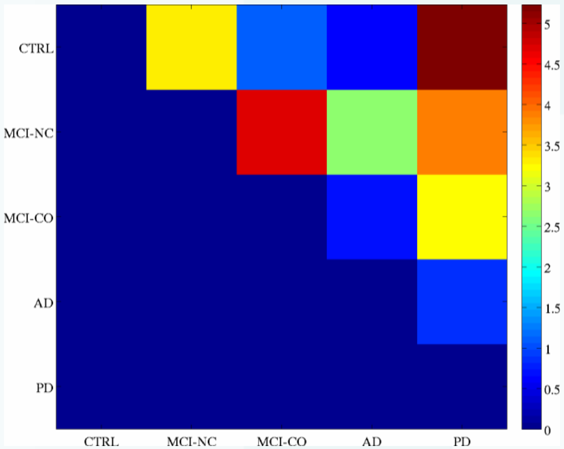






MRI & PET works just the same

Coherence distance



$$D_{coherence}(Cp_1, Cp_2) = \frac{D_M(Cp_1, Cp_2) - \overline{D_M(Cp_{1eq}, Cp_{2eq})}}{\sigma_{D_M(Cp_{1eq}, Cp_{2eq})}}$$

$$D_M(Cp_1, Cp_2) = \sum_{i=1,N^2} (|Cp_{1i} - Cp_{2i}|) * max(|Cp_1|, |Cp_2|)^2$$

- Monte Carlo-type distance:

take any two partitions of a set and ask how likely is it, that the two partitions have a distinct pattern with respect to a random choice?

Distance between partitions

C_{p1}, C_{p2} → adjacency matrices of 2 groups

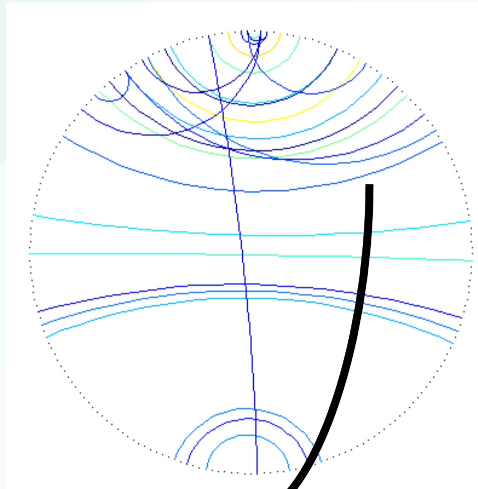
σ_{DM} → std on random-sampled matrices

C_{p1eq}, C_{p2eq} → random-sampled matrices (with same number of subjects)

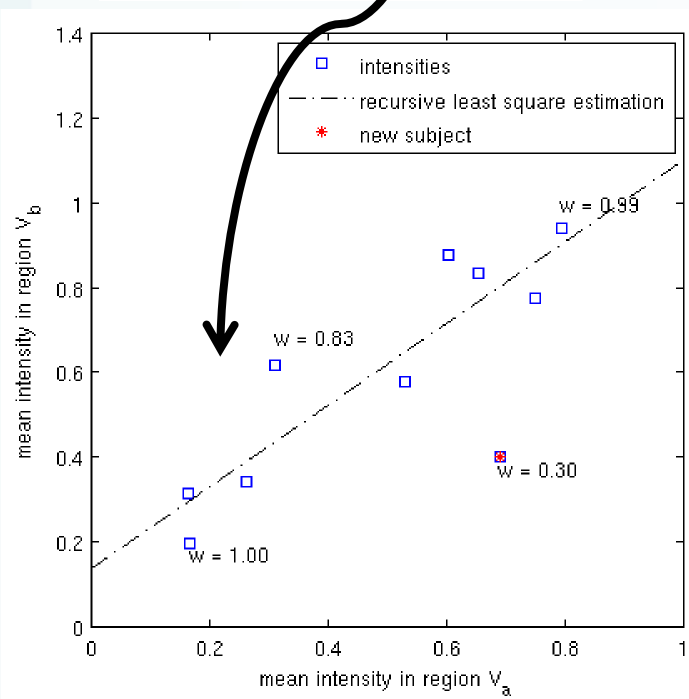
- Cohorts are macro-classes of smaller and otherwise highly similar entities. → Clusterization procedure to "refine" grouping
- Not statistically different if $D_{coherence} < 3\sigma$ → no specific patterns

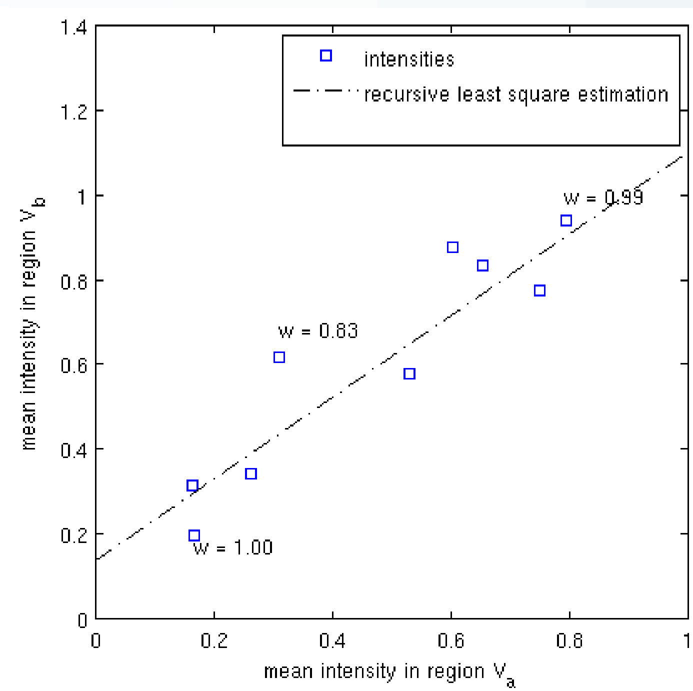
Robust regression and weights

- A line in the connectogram is the representation of a 2D scatterplot
- Subjects are represented by squares

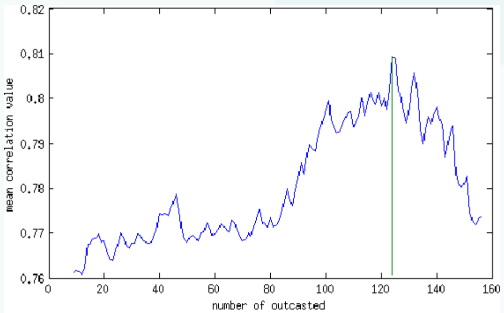


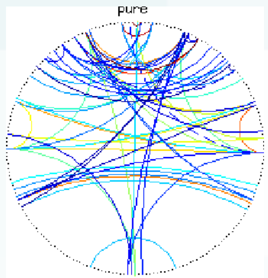
- Robust least square methods are used to rank the contribution of a new subject to the best linear estimator

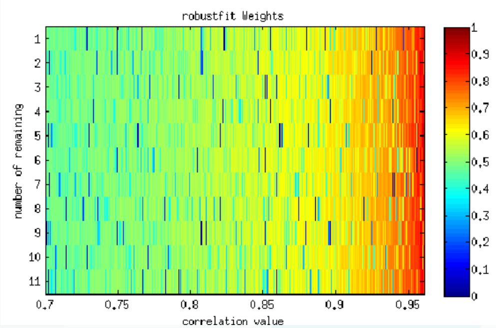


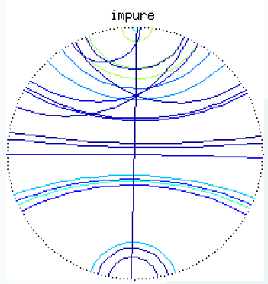


If a metric is defined on a domain, partitioning is at hand…



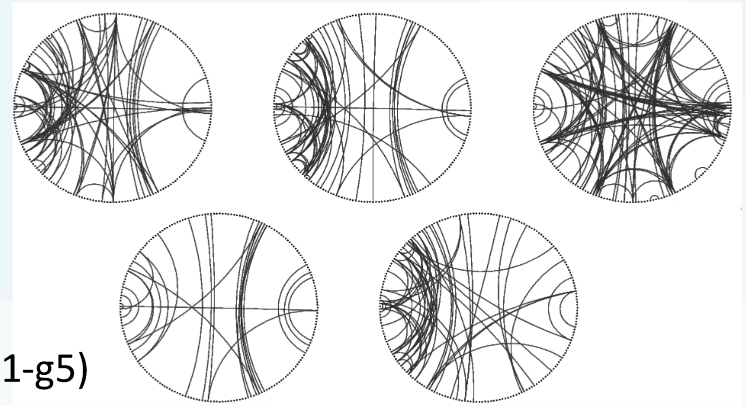






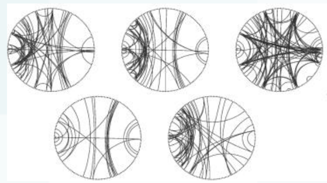
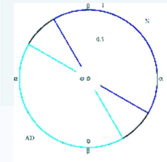
- "Recursive" partitioning looking for highest coherence distance
- Subjects rank, remove less relevant → the group is left more "homogeneous"
- At each step new matrices are computed
- Stop when high num of subjects are involved in strong correlations
- → [Repeat on remaining subjects] →

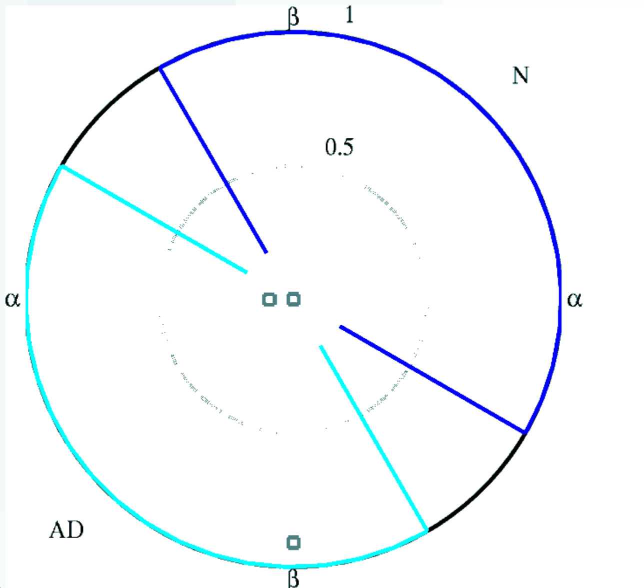
More complex, distinct & naked eye visible patterns

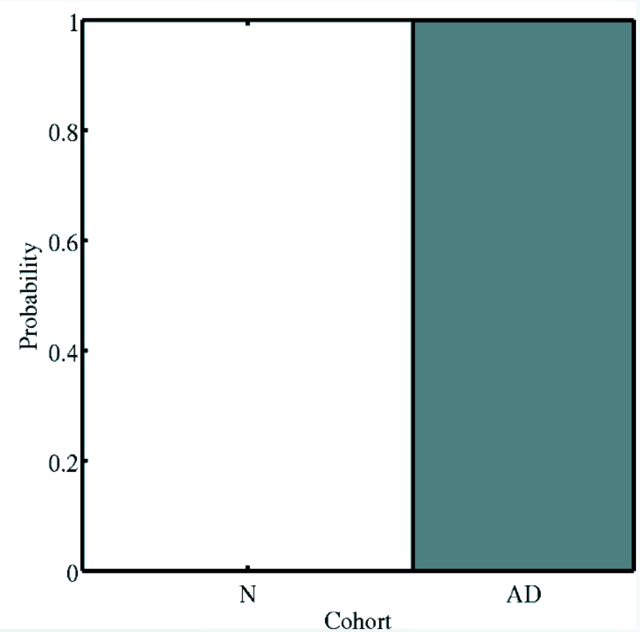


Controls patterns (g1-g5)

Single subject classification

Feature vector X  =  Similarity measure





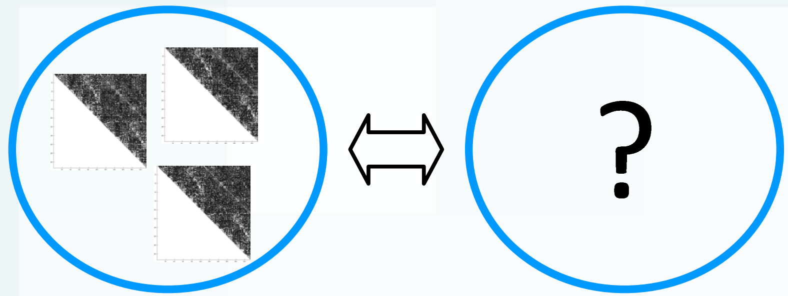
Affinity plot

- Subgroups (greek letters)
- Radius → "Affinity" value (≈ membership probability)
- Final label → highest affinity (classification)

Clinical counterpart

Is coherence clustering only a mathematical tool? Have we stepped onto something with clinical significance

Feature space



Clinical space

We looked for **specific profiles** of clinical features of each clustered sub-group.

Meta-data from ADNI (chemical measurements, neuropsychological evaluations, ematic data, …) → 257 features

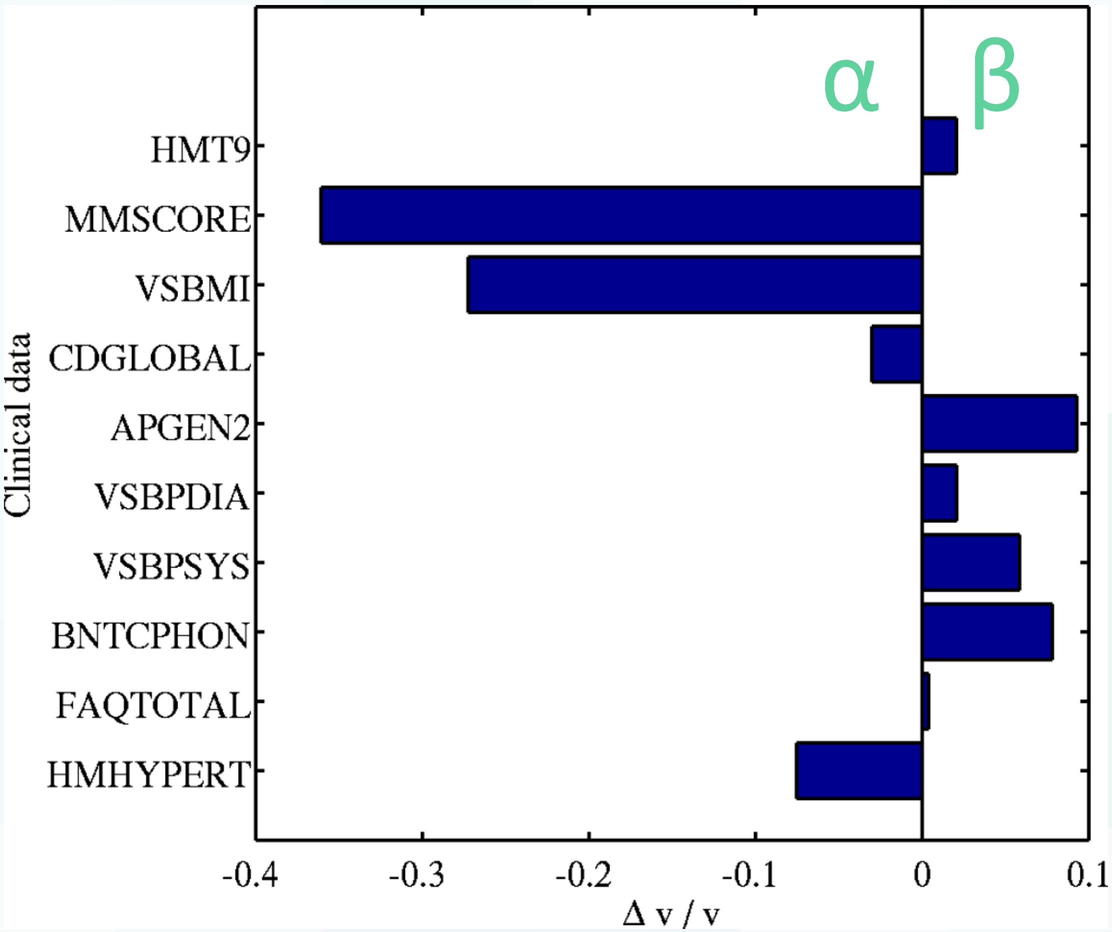
Blood pressure, APOE, MMSE/ADAS/MoCA/FAQ tests, Hachinski scale,Geriatric Depression scale, plasma cells/lymphocytes count, urine values, height/weight, TAU, …

Requirements: scale, ordering, objectivity, “continuous index”

- Decisional trees (RF) → list features discriminating subgroups
  – features whose value significantly differ with respect to other families

Phenotypes

Sample descriptive statistics of the two main CTRL subgroups (α,β)



HMT9 (Laboratory Test HMT9),
Lymphocytes count

MMSCORE (Neuropsychological test),
Mini Mental State Exam total score

VSBMI (Vital Signs),
Body mass index

CDGLOBAL (Neuropsychological test),
Clinical Dementia Rating

APOGEN2 (Genetic Data),
ApoE Genotyping Allele 2

VSBPDIA (Vital Signs),
Diastolic

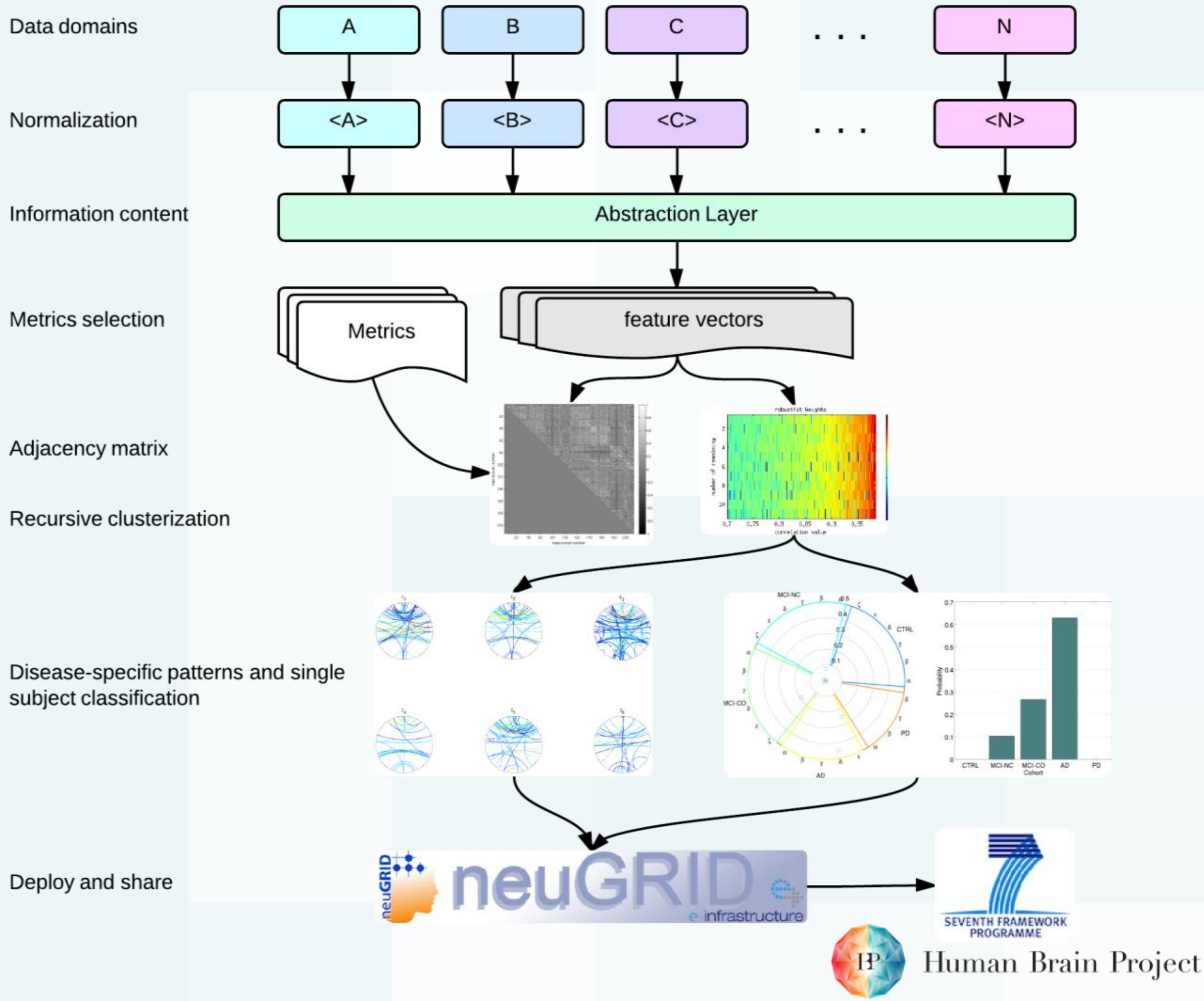
VSBPSYS (Vital Signs),
Systolic

BNTCPHON (Neuropsychological Battery)
Number of correct responses following a phonemic cue

FAQTOTAL (Functional Assessment Questionnaire),
Total Score

HMHYPERT (Modified Hachinski Test),
History of Hypertension

Coherence at a glance

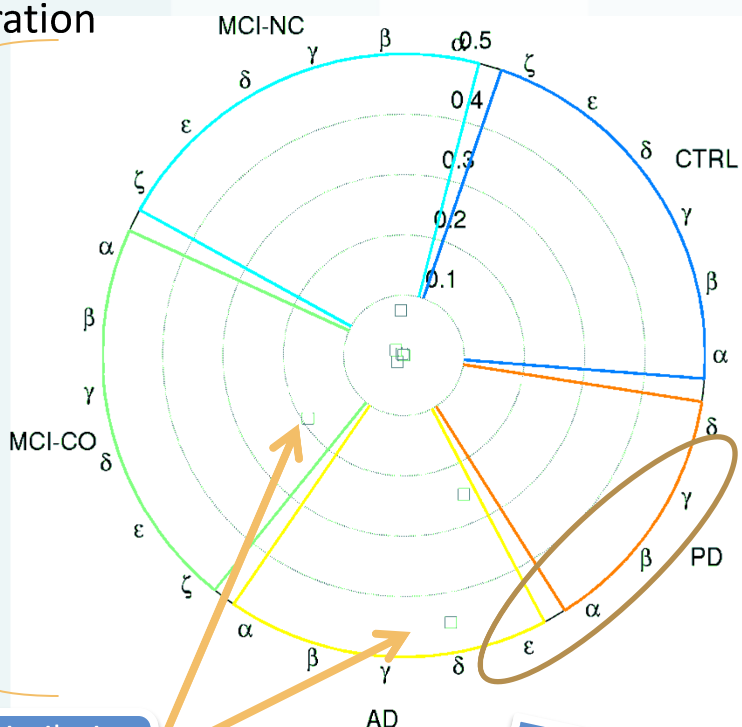


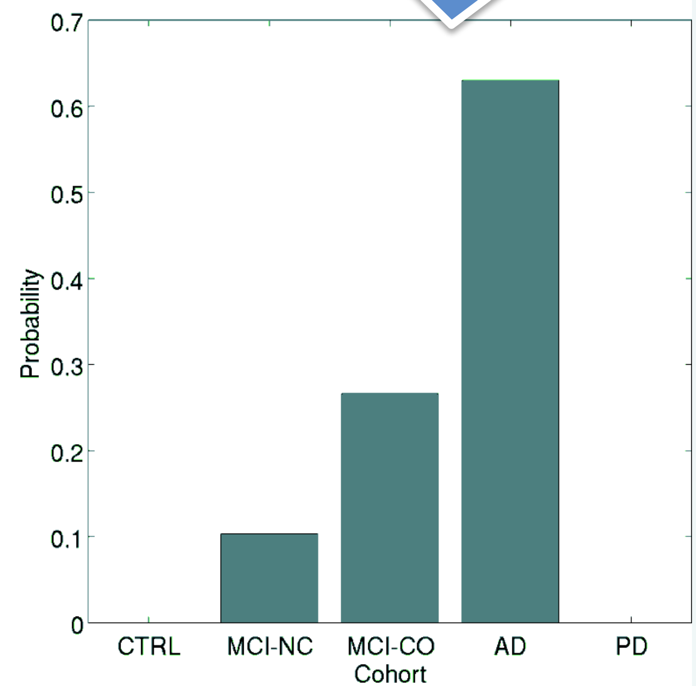
Towards differential diagnosis

- Very flexible analysis. Many pathologies can be included
- Multi modal analysis embedded
- Currently testing Alzheimer & Parkinson diseases
- Studying: AD+PD+FTD+LBD
- Paper in preparation

Single subject classification via affinity measure
(probability of belonging to a specific cohort vs. the whole population)

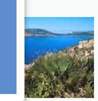
Affinity plot





Subject similarity scores

Maximally similar subgroups within a clinically homogeneous cohort. Towards endo-phenotypes description.



BEYOND DATA ANALYSIS

Probabilistic medicine

What do we need from biomarkers?

Clinical aspects

- Easy implementation in everyday practice
- Low-cost, widely available
- Minimally invasive

Medical research

- Continuous index, suitable for follow-up tests
- Significant for pharma trials

Base science

- Etiology and progression of the disease
- Differential discrimination

Prevention & risk factors

- to be used in population screening and drug trials

Best practices

- Avoid unnecessary tests and treatments

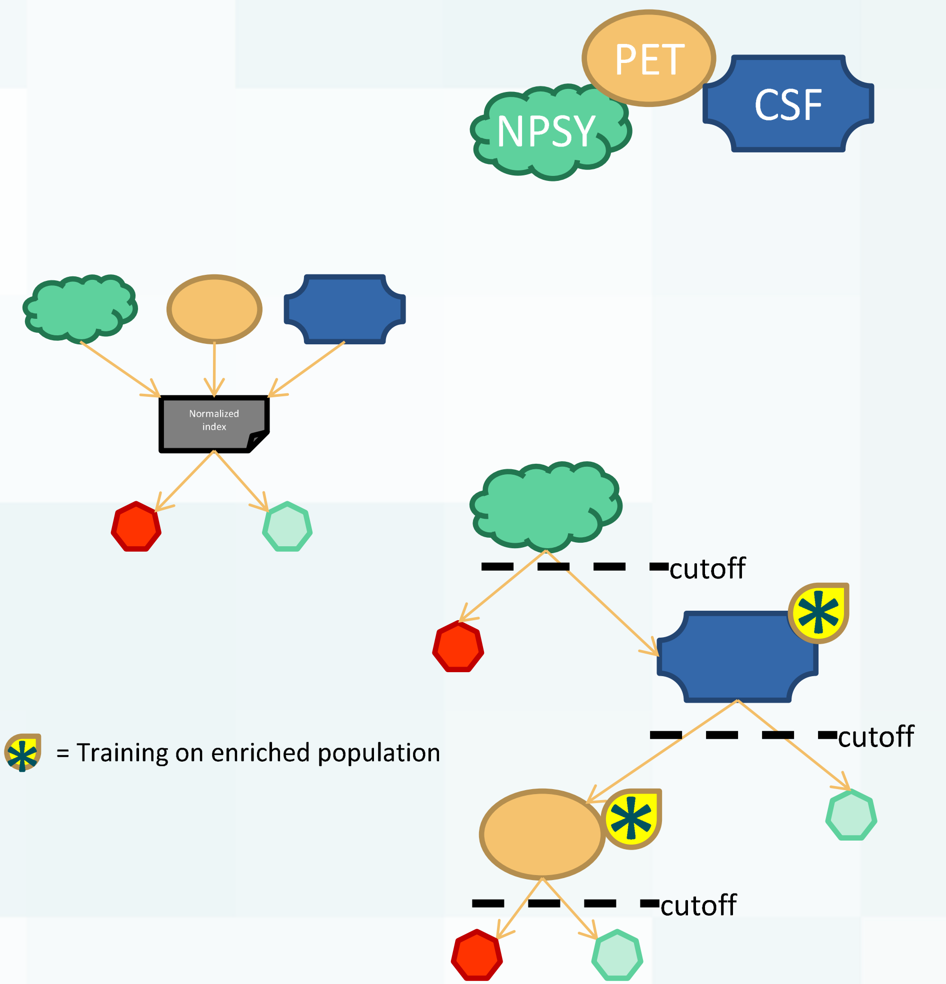
Ethical implication

- How do we convey the true meaning of a probabilistic result to the general public
- prognostic value in risk prevention

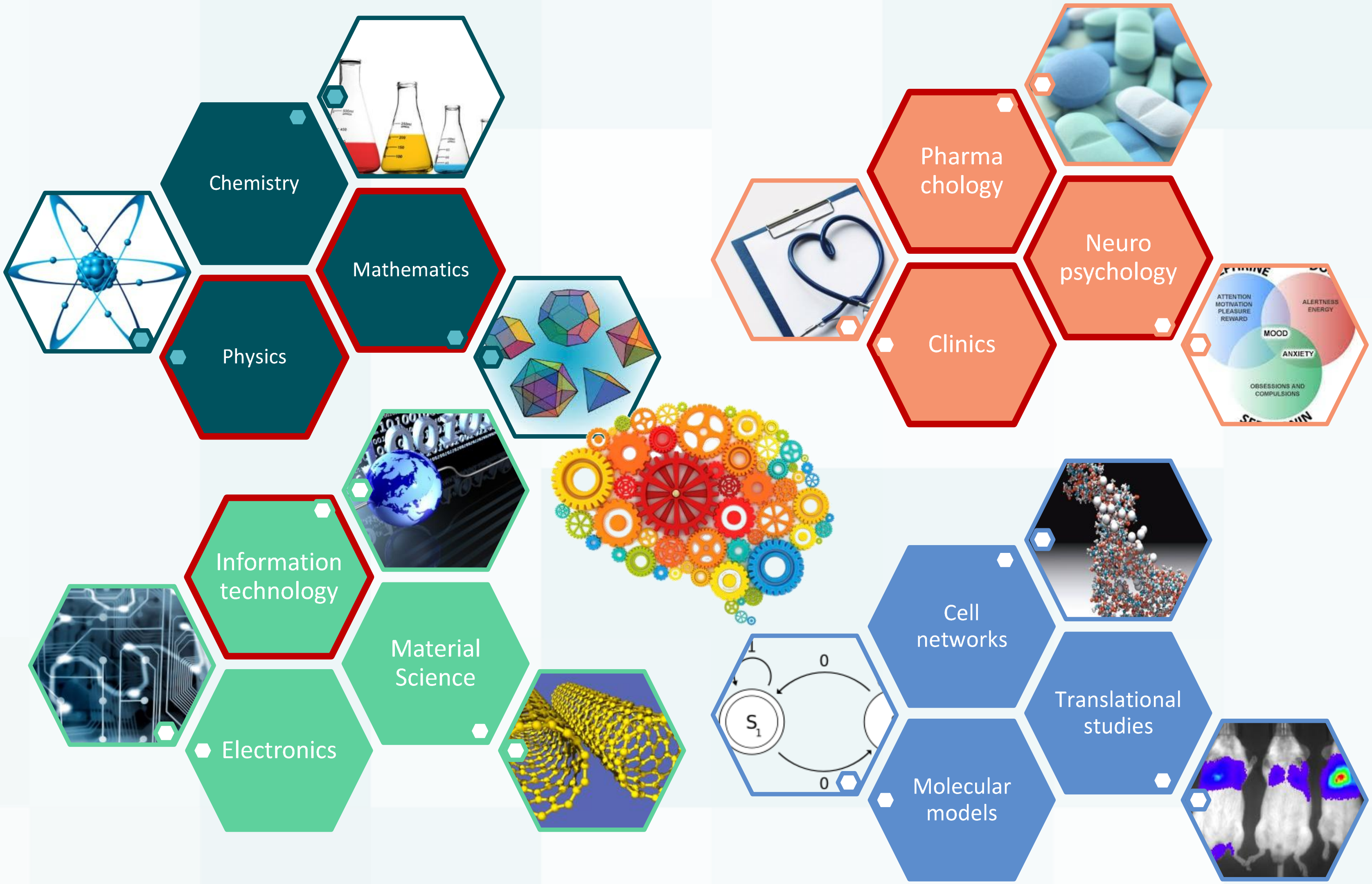
<u>Warning on:</u>
invasive tests, specificity, standardization, data analysis, prognostic value, costs, …

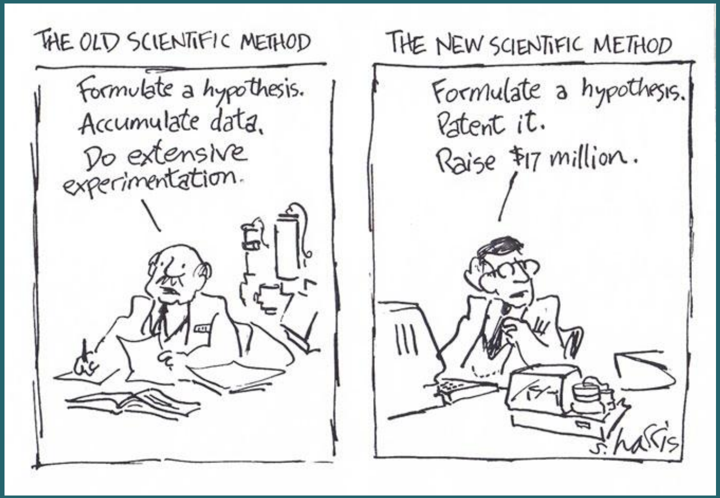
Biomarker guided best practice

- Three information domains
  - Neuropsych.
  - FDG-PET
  - CSF
- Two approaches
  - Full data
    - All three domains available to each subject
    - This [standard] analysis will be used as benchmark
  - Decision tree
    - Information flow depends on test order: not all subjects need to be tested on the three domains
    - Classifiers are trained on enriched population from previous steps
    - Many variants possible: tree order/number of nodes/pruning rules…
    - Expected results:
      - Lower total cost
      - Hints on best practice & optimization



A tight, multidisciplinary approach




THE OLD SCIENTIFIC METHOD
Formulate a hypothesis.
Accumulate data.
Do extensive experimentation.
THE NEW SCIENTIFIC METHOD
Formulate a hypothesis.
Patent it.
Raise $17 million.
S. harris

THANK YOU